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by Lynne Peterson

SUMMARY

The concern about stent thrombosis with drug-eluting stents dominated the meeting this year, and it was referred to as the "Cox-2 story of interventional cardiology." ♦ Cardiologists, cardiac surgeons, and interventional cardiologists were all talking about stent thrombosis, and that discussion is likely to continue for many months if not longer. ♦ There was no consensus about the level of risk, the cause, or what to do about this problem. However, the FDA plans an advisory committee meeting sometime later this year to discuss the issue.

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WORLD CONGRESS OF CARDIOLOGY (WCC)

Barcelona, Spain
September 2-6, 2006

The World Congress of Cardiology 2006 was a joint meeting of the European Society of Cardiology (ESC) and the World Heart Federation (WHF). This report is divided into two parts – devices and drugs – though devices, and specifically drug-eluting stents, dominates.

DEVICES

LATE STENT THROMBOSIS WITH DRUG-ELUTING STENTS

Late stent thrombosis was referred to as "the Cox-2 story of interventional cardiology." Whether the problem will rise to that level remains questionable, but the issue certainly dominated the WCC meeting. An expert said, "We have a major problem on our hands with patients who already have drug-eluting stents…Keeping patients on Plavix for life is one answer, but we can't do that because of cost, side effects, compliance, potential surgeries, etc…The message is we've gone too fast on drug-eluting stents…We should at least return to only using drug-eluting stents for the limited indications where they have been tested…(But) I'm not saying we should stop using drug-eluting stents and go back to bare metal stents."

Dutch/German registry

Dr. Peter Wenaweser, who works with Dr. Patrick Serruys at the Thoraxcenter in Rotterdam, the Netherlands, presented the results of an analysis of four drug-eluting stent (DES) registries: 2 from Rotterdam (RESEARCH and T-RESEARCH) and 2 from Bern, Switzerland (SIRTAX and POST-SIRTAX). The registries covered 8,146 consecutive patients from April 2002 to December 2005. Angiographic stent thrombosis was found to be 2.9% at 3 years, with incident density of 1.3 per 100 patient-years, with almost a linear increase between 30 days and 3 years. However, he said there was no significant difference in stent thrombosis between Cypher and Taxus.

- Use of a non-randomized cohort from just two tertiary care centers.
- Analysis limited to angiographic stent thrombosis.
- IVUS not routinely performed in stent thrombosis patients.
- No direct comparison with bare metal stent patients.

These researchers also performed a nested case-control study, using historic controls for bare metal stents, and they found: No significant difference between bare metal stents and drug-eluting stents from 0-30 days, a non-significant advantage to bare metal stents from 30-180 days, and a clear trend in favor of bare metal stents beyond 180 days.

Asked how DES use will be affected after this data, Dr. Wenaweser said, "At this time we don't have enough evidence to change our clinical practice. For the time being we are using drug-eluting stents."

Patients who developed late stent thrombosis tended to be younger and were more frequently smokers. Their mean time to stent thrombosis was 451 days. The only independent predictor of stent thrombosis was acute coronary syndrome (ACS) at the time of the index procedure; all the other variables – bifurcation, number of stents used, total stent length, etc. – were not independently associated with stent thrombosis. But there did appear to be a strong association to antiplatelet therapy (or lack of it).

Dr. Ray Gibbons of the Mayo Clinic, President of the American Heart Association (AHA), commenting on these findings, said "Late outcomes are not perfect, and there remains a potential problem that continues beyond where people were worried."

Meta-analysis

An independent meta-analysis of the safety of first generation drug-eluting stents, based on published or presented randomized clinical trials, was presented at WCC, and the news was not good for drug-eluting stents in general and Cypher in particular. The trials included in the first part of this meta-analysis were:

- Cypher: RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS.
- Taxus: TAXUS I, II, IV, V, and VI.

For an additional safety analysis comparing Cypher and Taxus several other trials were included in the meta-analysis – SES-SMART, DIABETES, and BASKET. Researchers found that:

- The combination of death and Q-wave MI was higher with DES than with bare metal stents.

Two Institution Cohort Study of Stent Thrombosis with Drug-Eluting Stents

Location	Cypher	Taxus	p-value
Bern patients	2,775	1,336	---
Rotterdam patients	1,100	2,905	---
Hypertension	51%	41%	<.05
Diabetes	18%	14%	N/A
Stent length per patient	33.6 mm	38.0 mm	N/A
Measurement	**Stent thrombosis**	**No stent thrombosis**	**p-value**
Age	60	63	0.007
ACS at time of index procedures	71%	59%	0.03
Average stent diameter per patient	2.8 mm	2.9 mm	0.46
Bifurcations	28%	17%	0.0005
Average stent length per patient	43.4 mm	35.8 mm	<.05
Stent thrombosis at 3 years	2.9%		---

Stent Thrombosis over Time

Stent thrombosis	9 days	30 days	365 days	730 days	1,065 days
Overall	1.1%	1.2%	1.7%	2.3%	2.9%
Cypher	1.0%	1.1%	1.3%	1.9%	2.5%
Taxus	1.2%	1.3%	2.0%	2.7%	3.2%

Association of Antiplatelet Use and Stent Thrombosis

Antiplatelet use	Early stent thrombosis patients	Late stent thrombosis patients
No antiplatelet therapy	4%	26%
Single antiplatelet therapy	9%	51%
Dual antiplatelet therapy	87%	23%

Meta-Analysis: Incidence of Death and Q-wave MI

Death and Q-wave MI by time period	Bare metal stent	DES	p-value	Relative difference
RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS				
6-9 months	0.9%	1.7%	0.21	+47%
1 year	1.4%	2.3%	0.30	+39%
2 years	2.0%	3.7%	0.09	+46%
3 years	4.0%	6.0%	0.06	+33%
Serious adverse events (death or MI)	3.9%	6.3%	**0.03**	Absolute increase 2.4%
TAXUS I, II, IV, V, VI				
Death and Q-wave MI by time period	**Bare metal stent**	**DES**	**p-value**	**Relative difference**
6-9 months	1.5%	1.6%	0.88	+6%
1 year	1.6%	1.7%	0.80	+6%
2 years	2.8%	2.6%	0.78	-7%
3 years	3.1%	3.5%	0.60	+11%
Serious adverse events (death or MI)	2.3%	2.6%	0.68	Absolute increase 0.3%

Safety of Cypher vs. Taxus

Measurement	Overall DES	Cypher	Taxus
Overall mortality (all Nss)			
1 year	0.94	0.86	0.98
2 years	1.11	1.35	0.97
3 years	1.25	1.48	1.10
4 years	N/A	1.46	N/A
Cardiac mortality (all Nss)			
1 year	0.84	0.79	0.89
2 years	0.73	0.64	0.80
3 years	1.00	1.11	0.89
4 years	N/A	1.24	N/A
Non-cardiac mortality (all Nss)			
1 year	1.07	0.94	1.11
2 years	1.72	**2.74**	1.21
3 years	1.45	**2.04**	1.17
4 years	N/A	1.65	N/A

- An excess of clinical events appeared to be seen with both Cypher and Taxus stents, but their magnitude seems uncertain.
- There seems to be a trend to increased mortality with DES over time, however this trend is not statistically significant concerning total mortality.
  - **Cardiac mortality** – no statistically significant difference between DES and bare metal stents.
  - **Non-cardiac mortality** – no statistically significant difference between DES and bare metal stents, but at two and three years, there was an association between Cypher and non-cardiac mortality. The cause-specific reasons for the Cypher non-cardiac deaths were cancer, stroke, and lung disease. The preliminary evidence suggests that Cypher but not Taxus stents may lead to increased ***non-cardiac*** mortality.
- The relative risk of serious adverse events (death or MI) was increased 38% with Cypher and 16% with Taxus.

Dr. Salim Yusuf of McMaster University in Canada was the discussant for the meta-analysis presentation, and he called it perhaps the most important presentation at the meeting, "The new studies raise concerns. I do not believe they are convincing, but they are disconcerting."

He suggested percutaneous coronary intervention (PCI) is being overused and referred to drug-eluting stents as a "Trojan horse." He commented, "PCI is inferior to CABG on mortality and angina relief in multivessel disease, and yet it continues to be done…There is no evidence that PCI in stable coronary disease prevents cardiac events, and it may have long-term cardiac adverse consequences, and it is hugely cost-ineffective…We should perform PCI sparingly and use stents judiciously, not in practically every case. As clinicians, we seem to have lost our clinical judgment. We need a thoughtful and selective PCI complementing full medical therapy and CABG surgery…I call on ESC…to have a balanced and independent working group, not just interventional cardiologists, to evaluate the role of PCI and devices, including drug-eluting stents – and keep industry out of it."

Dr. Yusuf called the non-cardiac mortality – cancer, sepsis, stroke, etc. – with drug-eluting stents "very strange," adding, "It may be there is rapid impairment of the immune system, both locally and systemically, that causes conditions that we do not fully understand…Are the agents being released from the stent for much longer than planned? Do the anti-mitotic agents have a systemic adverse effect? I don't know…We need more data on clinical events…There is a significant excess in non-cardiac deaths (in the meta-analysis), and we need to see if this is real…It is true the paclitaxel data are not statistically significant, but do you need statistically significant harm to stop a therapy for which there is no evidence of benefit?"

At a press conference after the presentation, Dr. Yusuf was even more animated in his call for more conservative use of drug-eluting stents. Asked if he thinks people will listen to his message, he responded, "My fear is they won't. There are too many intertwines in PCI. It is part of the culture of cardiology to do PCI, to open up a narrowed artery. How can it be bad for you? Yet the data are that it certainly is no good in stable coronary disease…PCI of the target lesion is almost like doing surgery to remove a tumor but leaving the metastasis behind …There is no doubt it (PCI) is helpful for angina…but the majority of patients don't get full medical therapy…and there is some feeling that PCI may be a reasonable alternative to medical therapy.

Among other comments made by Dr. Yusuf and the investigators were:

- *Dr. Alain Nordmann:* "Most of the studies (used in the meta-analysis) were industry-sponsored. It was very difficult to get the data for this…All the original TAXUS trials didn't report mortality as a separate endpoint. They reported a combined endpoint...There is a problem with industry selectively reporting the outcomes most beneficial to them. We need some neutral assessment of all these trials to tell you, the patients, what exactly is the benefit or harm of drug-eluting stents."
- *Dr. Yusuf:* "PCI doesn't prevent heart attacks or death… So, what does PCI do? It creates problems. We are chasing our tail with it. The fundamental question is maybe the (PCI) procedure was not necessary in the first place."
- *Dr. Yusuf:* "My caution is on widespread, indiscriminate use of PCI…Many people (doctors) are doing patients who would go to surgery…I would urge limited use of drug-eluting stents…Let's not have cowboys deciding what gets done."
- *Dr. Nordmann:* "I'm pretty much confident that it is not the antiplatelet regime that makes the difference…I question that it is clopidogrel that makes the difference… When you look at cardiac death, there is no difference between bare metal stents and drug-eluting stents, making a strong point that it is not clopidogrel that is the driving factor."
- *Dr. Edoardo Camenzind:* "You have an intrinsic milieu where, indeed, if you stop antiplatelet therapy, you will trigger thrombosis…but there may be other triggers. Don't search for triggers."
- *Dr. Gabriel Steg, France:* "This is a major red flag."

Some interventional cardiologists were vocal in their criticism of Dr. Yusuf, saying he went too far in his attack on drug-eluting stents:

- *Italy:* "Yusuf is Yusuf, and we all know his message."
- *Belgium:* "I don't think it is appropriate to throw the baby, the nurse, and the mother out with the water…I

don't think it is appropriate to use drug-eluting stents indiscriminately in all patients, but it is important to make sure that the patients will be compliant, and in a condition where they will be able to continue dual antiplatelet therapy for some period of time."

The AHA's Dr. Gibbons cautioned that, though the meta-analysis will catch a lot of attention, it needs to be carefully scrutinized. He pointed out that the PREMIER registry, published in ***Circulation*** in June 2006, found that 1 in 7 DES patients (13.6%) had stopped their dual antiplatelet therapy (aspirin + Plavix) by one month – and the patients who stopped were much more likely to die during the next year." He said, "I would not be critical at all of the FDA here." He added, "This kind of study only raises questions; it can't answer them. We don't know for example that the heart attacks in the (DES) patients were in the stented vessel, so patients who get DES are sometimes chosen because their physician thinks they are more likely to have restenosis."

AHA Chief Science Officer Dr. Rose Marie Robertson said, "There are no new data here. This is not a new trial. This meta-analysis indicates a need to see that data published before we change our current recommendations." She called the Cypher data "provocative" but said that a study not prospectively designed to look at Cypher vs. Taxus "raises eyebrows."

German/Italian data

At a Boston Scientific off-site event, Dr. Antonio Colombo of Italy presented preliminary new data from a study of German and Italian DES use. The final data will be presented at TCT 2006 and published in the ***Journal of the American Medical Association***. The data were fairly provocative, suggesting that perhaps six months of Plavix (Sanofi-Aventis, clopidogrel) is sufficient. He said, "This data is kind of reassuring because most probably after one year, the situation is not so bad." He cautioned, "Old concepts such as final optimal results and optimal drug therapy remain important if not more important in the DES era." In patients who develop a stent thrombosis, Dr. Colombo would place a bare metal stent, not a DES.

Dr. Colombo disputed the findings of the Serruys/Windecker study that found a steady increase in stent thrombosis of 0.6% per year, "I really think if we had this constant rate – even after three or four years…that we would see it, considering how many drug-eluting stents are implanted worldwide. This would become an alarming phenomenon."

German/Italian Stent Thrombosis Study

Stent thrombosis in patients on:	0-180 days n=2,160	181-360 days n=2,120	361-540 days n=2,100
Aspirin + Plavix	0.4%	0.3%	0.4%
Only aspirin	7.5%	0.2%	0.1%
Neither aspirin nor Plavix	14.3%	4.5%	0
Stent thrombosis with sudden cardiac death included			
Aspirin + Plavix	0.5%	0.3%	0.5%
Only aspirin	11.3%	0.2%	0.3%
Neither aspirin nor Plavix	17.8%	4.5%	0

European Stent Thrombosis

Country/Site	Overall stent thrombosis	Subacute stent thrombosis 30 days - 6 months	Late stent thrombosis (>6 months)
Italy	1.3%	0.6%	0.7% 0.5% Cypher 0.8% Taxus
Netherlands (Thoraxcenter)	---	1.03%	0.3% 0.3% Cypher 0.4% Taxus
Washington Hospital Center	1.27%	1.0%	0.25% No difference between Cypher and Taxus
Spain (one site 100 consecutive patients with 3 months Plavix)	---	---	2%
Spain (one site 300 consecutive patients with 6 months Plavix)	---	2% Cypher 0 Taxus 0 BMS	0 Cypher 0 Taxus 1% BMS
Spain (one site 200 Cypher patients followed 2 years)	---	---	2% Cypher
Spain (one site 1,675 patients)	1.2% overall 1.48% Cypher 1.1% Taxus	0.48%	0.77% overall 1% Cypher 0.6% Taxus
Preliminary results of Spanish ESTROFA study (17 sites with 9,000 patients)	1.15% overall 1.4% Cypher 0.95% Taxus	N/A	~0.2% per year

Spanish data

At the same Boston Scientific event, Dr. Jose de la Torre of Spain presented a new look at real-world DES use in Spain. He said his analyses found that the risk factors for DES stent thrombosis were younger age, STEMI, and LAD lesions.

Of the stent thrombosis patients in the preliminary results of the ESTROFA study:

- 83% presented as STEMI.
- 35.5% had early discontinuation of antiplatelet therapy.
- Average duration of dual antiplatelet therapy was an average of 6 months (ranging 3-12 months). But he noted that some centers are moving to 12 month therapy.

- 14% presented with cardiogenic shock.
- The significant predictors for late stent thrombosis were: STEMI, LAD, and age.
- Stent thrombosis was numerically but not significantly slightly higher with Cypher than Taxus.
- Compared to BMS, the benefits of DES outweigh the risk, in his opinion.

BASKET trial update

An 18-month update was presented of the prospective, randomized, real-world BASKET trial, which compared the efficacy of bare metal stents and drug-eluting stents in reducing restenosis and preventing repeat revascularization procedures in patients at the University Hospital of Basel, Switzerland enrolled from May 2003 to May 2004.

18-Month Results of BASKET Trial

Measurement	Bare Vision	Cypher or Taxus	p-value
Cardiac death and MI	7.5%	8.4%	0.63
Non-infarct related TVR	11.6%	7.5%	0.05
MACE	18.9%	15.8%	0.26

The only predictors of an event were: Bypass graft disease or use of at least one stent <3.0 mm. In those patients, there was a highly significant benefit to drug-eluting stents, in terms of death/MI, TVR, and MACE. Researchers concluded, that stenting of larger native vessels with drug-eluting stents has no significant benefit – and possibly even causes small late harm. They recommended drug-eluting stents be restricted to small vessels/stents (<3 mm) and to bypass grafts for optimal cost-effectiveness and long-term benefit, challenging the idea that every patient should receive a drug-eluting stent.

The industry perspective

Both Boston Scientific and Johnson & Johnson have prepared their own, new meta-analyses of their respective drug-eluting stents.

➢ **Johnson & Johnson.** Dr. Dennis Donohoe, Vice President of Worldwide Regulatory and Clinical Affairs at Cordis, said the J&J analysis found no statistically significant increase in stent thrombosis with Cypher, "We looked at total mortality over four years, and it was 5.1% with bare metal stents, and 6.5% with Cypher, an absolute difference of 1.4% (p=0.22), representing a relative difference of 22%. MI was 6.1% with bare metal stents and 6.3% with Cypher (p=0.92)."

Dr. Donohoe questioned the findings of both studies, pointing out that there is no universal definition of stent thrombosis and different DES analyses have looked at different time periods. He said, "Doctors have already changed their DES use to the degree they are going to do so. The discussion of drug-eluting stents is not news. Physicians have a concern (about stent thrombosis), and they are making decisions based on individual patients – not using them in patients who are older (over age 80) or with surgery planned. I've seen no evidence of interventional cardiologists moving away from use of DES in complicated patients, but they are increasing their use of dual antiplatelet therapy."

The FDA was described by several sources as "in a data-finding mood." About a week before WCC, J&J updated the FDA on its meta-analysis of DES stent thrombosis. Dr. Donohoe said J&J suggested the FDA consider the overall mortality and MI rates of DES – what the real risk:benefit is.

Asked about the impact of the studies presented at WCC on regulatory approval of newer drug-eluting stents, Dr. Donohoe said, "European doctors are having more discussion about how much data are needed for a C.E. Mark. Xience was approved on 27 patients, and I've heard doctors talking about regulators requiring more data (in the future). The challenge is whether the data clearly point to the issue – late stent thrombosis or very late stent thrombosis."

➢ **Boston Scientific.** Officials at WCC were emphasizing the benefits of drug-eluting stents, insisting that stent thrombosis is a DES class issue, and that Plavix should be given at least 6-12 months. Dr. Donald Baim, Boston Scientific's Executive Vice President and Chief Medical and Scientific Officer, said, "The essential equivalence of clinical results (of Cypher and Taxus) has now been borne out in the broadest available data (with no cherry-picking)."

At WCC, Boston Scientific experts said they had looked at all the pooled data from Taxus II (3 years), IV (3 years), V (1 year), and VI (2 years). They reported: Taxus stent thrombosis from 6-36 months in 1,718 patients was 0.46% vs. 0.57% for Cypher. Dr. Baim said, "You will hear claims from other stent manufacturers…that they don't have late stent thrombosis, but right now only Taxus and Cypher have clinical trials with enough patients over a long enough time to make that claim, given that we are talking about events with a 0.2% per year rate…I'll leave it to J&J to address why there is 2.4% absolute increase (in stent thrombosis) with Cypher (in the Swiss meta-analysis)."

Summary of Boston Scientific Presentations on Stent Thrombosis

Measurement	Cypher	Taxus
WCC meta-analysis: 6-36 months stent thrombosis	0.57%	0.46%
BASKET-LATE: late stent thrombosis	2.6% (vs. 1.3% bare, Nss)	
BASKET and BASKET-LATE: increased risk of death	1.2%	
BASKET and BASKET-LATE: increased risk of MI	2.8%	

Dr. Baim warned doctors that they can't ignore the stent thrombosis issue just because they haven't personally had a case of late stent thrombosis: "Just because you haven't yet

recognized the problem with your DES doesn't mean that you don't have it. Everything points to late and very late stent thrombosis being a class effect and similar for Cypher and Taxus."

However, just a day after the WCC meeting, Boston Scientific announced that a new internal analysis of 3,500 Taxus patients shows a "slightly" increased risk of stent thrombosis but no increase in death or MI. A Boston Scientific official said the analysis was completed on June 24, 2006, and the company met with the FDA about the results on August 1st and also shared the findings with European regulators.

What can be done about this late stent thrombosis issue? Dr. Baim said, "One of the strongest predictors of stent thrombosis is premature discontinuation of Plavix. ESC guidelines now recommend Plavix for 6-12 months for patients who tolerate the drug well. There is no firm evidence why these drugs should be stopped arbitrarily at 3 or 6 months. If some patients heal their stents more slowly, we may promote healing by prolonging Plavix out closer to 1 year."

Other points Dr. Baim made included:

- He gave Boston Scientific's Odyssey program a plug. This is the Barracuda stent using a biodegradable abluminal polymer combined with a pro-healing luminal surface and neither a polymer nor a drug.
- Boston Scientific has a bifurcation stent in development. This is going into first-in-man studies early in 2007.
- "Long-term follow-up shows no increased death or MI for Taxus vs. BMS…Taxus continues to have a very favorable long-term benefit:risk balance…We must reinforce six months of dual antiplatelet therapy (or more when clinically indicated) in drug-eluting stent patients."

Physician reaction to the stent thrombosis data

Interventional cardiologists spoke out strongly in defense of drug-eluting stents, emphasizing their benefits. Their comments included:

➢ *Spain (Dr. Eulogio Garcia):* "It isn't that simple to…say this is the risk of stent thrombosis. You have to take into considera-tion what drug-eluting stents have changed in real practice – and they have changed two things: (1) They have stopped debate about restenosis recurring, and (2) The spectrum of treatable patients has expanded, not only from surgery but also from medical therapy…Rather than going back to more bare metal stents, we need to work harder and invest more money on solving the late stent thrombosis problem."

➢ *France (Dr. Christian Spaulding):* "These were only oral presentations, and what's important in medicine is to get them published in a peer-reviewed journal so we can have a look at the data and have a statistical review. For the moment, it is only a concern that has to be confirmed by a peer-reviewed publication. What I came home with is: There ***could*** be an issue with late stent thrombosis, but it remains to be validated by more long-term follow-up on the trials we have right now, and that, even if there is an issue with late stent thrombosis, the numbers are relatively small…And whether stent thrombosis is more frequent with drug-eluting stents than bare metal stents remains to be determined."

➢ *U.S. (Dr. Steven Nissen of the Cleveland Clinic, president of the American College of Cardiology):* He called the stent thrombosis data at WCC potentially "explosive," saying, "It may indicate the need to keep patients on dual antiplatelet therapy, perhaps for life. The hypothesis is that drug-eluting stents are never re-endothelialized." On the other hand, he noted that there are limitations to meta-analyses, calling them "a poor man's randomized trial." He continued, "We need to look at both the quality of the data and the quality of the analysis...If it is real, it's big. Back in the U.S. the trend – and it's been subtle – has been back toward bare metal stents…I'm suspicious of the registry data. There is always the possibility of bias. If the meta-analysis is based on randomized clinical trials, that is more compelling…I think this (stent thrombosis in the meta-analysis) is probably a case of unintended consequences…I think we have tilted too far away from bypass anyway, especially since there are no data to prove that (PCI) saves lives…We send patients home four days after bypass, so why not have bypass?"

However, some European doctors raised new questions about the cost-effectiveness of drug-eluting stents in light of this data. An Irish doctor noted that drug-eluting stents definitely reduce restenosis but he questioned both the cost-effectiveness of that and the importance of it:

- "We can say without equivocation that the efficacy of drug-eluting stents is confirmed to reduce restenosis."
- "Cost-effectiveness may not concern regulators, but it concerns those of us introducing a new technology to financially constrained health systems…RAVEL (the first randomized trial of Cypher) suggested drug-eluting stents could almost be cost-saving…The BASKET trial last year showed the incremental cost-effectiveness is €18,000, with <€10,000 acceptable, and a QALY >€50,000. So, you can say the data don't favor use from a cost-effectiveness perspective."
- "In June in the ***Annals of Internal Medicine***, they summarized: We overestimate the restenosis benefit by the design of the trials, underestimate the risk of stent thrombosis by an over-reliance on soft endpoints, and overestimate the cost-effectiveness of drug-eluting stents."

Several cardiologist called for other changes to drug trials and reporting. A French doctor said, "I think we (journal reviewers) should encourage the editorial boards of the major journals to require mortality data from all major trials." A Dutch doctor said, "We had a heart failure drug that improved quality of life, but decreased life expectancy…Total mortality

should be reported in every trial. If a combined endpoint is used, all components of the endpoint should be reported and should go in the same direction…I hate MACE as an endpoint because different definitions are used." A third cardiologist predicted, "In a few years, clinical trials will be very different from today."

Shortly after Dr. Yusuf returned from the WCC meeting, he made a presentation to his whole cardiology department, and it was packed. He said, "There was a general consensus that we need local guidelines on what to do. A group will re-evaluate this, and the interventional cardiologists will take the lead. And the trainees will decrease the number of patients they refer to the cath lab." His slides can be accessed at: **www.phri.ca/presentations.htm**

The cause(s) of stent thrombosis

Interventional cardiologists just don't know what is causing late stent thrombosis with drug-eluting stents. Until recently, most fingers were pointing at the polymer, but experts now are less certain of this, and several other possible culprits are being explored and discussed.

In the August 2006 issue of ***Proceedings of Transcatheter Cardiovascular Therapeutics***, Dr. Marty Leon of Columbia Hospital pointed to several "predictors" of late stent thrombosis: discontinuation of dual antiplatelet therapy, prior brachytherapy, renal failure, diabetes, bifurcations, decreased left ventricular ejection fraction, total stent length, and in-stent restenosis. However, he noted that the cause of this phenomenon has been harder to identify. He concluded, "This increased risk is doubtless multifactoral, but unfortunately, the majority of events appear related to biologic or DES (drug-polymer) responses, which cannot be modified by improved procedural technique."

The possible causes of stent thrombosis with drug-eluting stents being discussed at the WCC meeting included:

➢ **Polymer.** Dr. Serruys said, "Where you do a (bifurcation) crush, and have three layers of metal and three layers of a 15 μg coating, that might be a source of trouble."

Is there anything manufacturers can do to lower the risk of stent thrombosis with existing polymers? A J&J official said, "That question assumes the underlying problem is the polymer, and that is mostly based on autopsy data. We are not convinced it is all a polymer issue." And J&J is not the only one defending polymers. While pathologist Dr. Renu Virmani has long suggested that it is polymers which are at least one of the problems, there was a lot of discussion at WCC that it may be the nature of immunosuppressant drugs as well or instead.

➢ **Drug.** Both Taxus and Cypher have now been shown, in different analyses to have a statistically significant increase in risk of stent thrombosis. In the meta-analysis presented at WCC, sirolimus performed significantly worse than paclitaxel, and some experts suggested that immune modulators, such as the limus drugs which affect mTOR, may be more thrombogenic either by delaying re-endothelialization or other methods. After the WCC, Boston Scientific said their own internal analysis found a statistically significant increase with paclitaxel. Dr. William Wijns of the Netherlands said, "It looks as if with sirolimus, there is a 38% increased risk…We've seen some data on total mortality and MI from paclitaxel that do not seem to indicate there is an increased risk…I don't think it is appropriate to lump all drug-eluting stents in one pile. I don't think there is a class effect…We have to look at each drug separately." Meta-analysis author Dr. Camenzind emphasized that his findings apply only to first-generation drug-eluting stents, saying, "It is not a class effect. You need to look at each stent particularly and state if it is clinically beneficial or not. Clearly, sirolimus has a significant trend to have more Q-wave MI and death, and there is a trend for Taxus. This is not necessarily applicable for all other drug-eluting stents that will come out in the future."

If it is the drug, would everolimus and zotarolimus be more or less dangerous? Dr. Serruys said, "If you look at the (everolimus) molecule, the only small change is in the binding site, so I don't think intrinsically, you will have a different effect on mTOR (with everolimus vs. sirolimus)."

➢ **Duration of antiplatelet therapy.** A speaker said, "It is important that, along with industry, we look at the freedom from antiplatelet therapy curve. There might be very different curves for sirolimus and more recent programs, so the possibility exists that, with some more recent programs the device is not much safer than sirolimus, but the antiplatelet therapy was continued longer than in the sirolimus program."

➢ **Lack of re-endothelialization**, which could be due to many different factors. Dr. Wijns said, "With sirolimus, instead of dilatation (researchers) found an exercise-induced vasoconstriction 12% proximal to -15% distal, and that was in the ***Journal of the American College of Cardiology*** in 2005. I have a hard time understanding that…Rotterdam confirmed long-term endothelial dysfunction six months after sirolimus implantation, and that was published in the ***European Heart Journal*** in 2006."

➢ **Stent expansion.** Xience investigator Dr. Garcia suggested, "Not all the stents expand the same way, and we know Cypher is a very tough stent to expand. You need very high pressures to expand it. How many of the thrombosis patients were under-expanded? We don't know."

➢ **Stent fractures.**

➢ **Stent malapposition.** Dr. Wijns said, "Malapposition was reported in up to 40% of cases, with a void behind the stent struts that originally were well-opposed, and this is potentially a subset for altered hemodynamics and thrombosis." Dr. Serruys said Dr. Peter Fitzgerald at Stanford has looked by IVUS at stent malapposition and normal stent placements and hasn't been able to say malapposition is

responsible for stent thrombosis, but another study by Dr. Alexandre Abizaid in Brazil found a malapposition in stent thrombosis, though that "may be two different things." Dr. Gregg Stone of Columbia University said, "I think if it is related, it is probably a low frequency event."

Change in DES usage patterns

At the meeting, it appeared that stent thrombosis issues would cause only a slight slowing of drug-eluting stents use in Europe, perhaps not a drop off in use but just a slowing in penetration, and little or no change in the U.S., at least until after TCT – but a lot of discussion. The stent thrombosis issue appeared unlikely to drive market share shifts in Europe in the near term, but if the issue doesn't get resolved, it may give more of a boost to Xience/Promus, Endeavor, and CoStar in the U.S. when and if those stents become available.

Without more definitive data, sources all agreed that the FDA will not pull drug-eluting stents from the U.S. market without more definitive data, and neither Johnson & Johnson nor Boston Scientific is likely to withdraw their product as Merck did with Vioxx. The FDA could strengthen warnings, but it cannot control off-label use. The question, however, is what the insurance carriers will do. Will they stop paying for off-label use of drug-eluting stents? A week after WCC, Kaiser Permanente, a big U.S. health system, started its own study of the safety of drug-eluting stents, and Kaiser studies have often had great sway with the FDA.

Interventional cardiologists generally were circling the wagons as they now face "attacks" from two fronts – surgeons who are expected to see this issue as a way to defend CABG and medical cardiologists in the U.S. as well as Europe who are already calling for a reduction in the use of drug-eluting stents.

- *France:* "I don't think use of drug-eluting stents will change very much in my practice or in France. The only thing I may change is to give clopidogrel for a longer period of time. I currently give clopidogrel for six months, and I will probably go to one year."
- *New England:* "There won't be a change in any dramatic way. There may be more discussion on using drug-eluting stents where there is clearly a proven benefit. Before this meeting, I heard some interventional cardiologists were inclined to put bare metal stents in large vessels. The data at this meeting may stimulate more discussion…Personally, I believe we have swung too far (towards drug-eluting stents) and need to find a middle ground. I think the pendulum has swung too far and needs to swing back somewhat…I see this as a call to action for drug-eluting stent makers to provide much more organized long-term data, and the American Heart Association can support that data collection."
- *Netherlands #1:* "There are no data to change DES use."
- *Netherlands #2:* "I think penetration will slow a bit – and the issue will promote dual antiplatelet use."
- *Sweden:* "Stent thrombosis will decrease use of drug-eluting stents. If you add the restenosis rate and the stent thrombosis rate together, the number is close to bare metal stents. DES efficacy will be questioned because of the cost."
- *Illinois:* "Everyone will want to try the next new stent, and if someone (manufacturer) blinks early and comes out with a wildly lower price, they might get a surge in use, though I don't think that will happen…If a product really is more deliverable, it will find a special niche."
- *North Carolina:* "DES use will go down slightly…I think we should go back to bare metal stents. I would only get a BMS myself."
- *Illinois:* There will be no change in DES use (in the U.S.). Any comparison now with bare metal stents has a couple of gigantic deficiencies. In my own practice, most interventions today are in patients in whom I wouldn't imagine using a bare metal stent because of the prospect of an intermediate or poor outcome – e.g., a total occlusion in the right coronary artery, where there is a small likelihood of it staying open with a bare metal stent. But the controversy will continue to rage because (a) practice is evolving faster than we can study it, and (b) even if we stood still long enough for a snapshot, there are no resources to fund a trial large enough to study this."
- *U.S.:* "I think European use of DES will go down."
- *Dr. Ron Waxman of the Washington Hospital Center:* He called the data "another stent thrombosis wave." He predicted that the data would slow DES penetration in Europe but would have minimal impact in the U.S., "There is more fear in Europe, partly because of the cost issue." He also said new data from his hospital will be presented at TCT which will show that there is significantly more stent thrombosis with Cypher than Taxus.
- *Massachusetts:* "I think use of DES will remain the same – but new drug-eluting stents will be helped."

The impact on newer drug-eluting stents

Several experts at WCC were predicting that approval of new drug-eluting stents will be delayed as a result of the stent thrombosis issue, but, while some European countries may move slower in the future on DES applications, that may not be true of all countries. It is not at all clear yet what the FDA will do, but most sources agreed that the FDA is unlikely to require two-year or longer data before approving new drug-eluting stents.

Comments included:

- *Dr. Yusuf, Canada:* "There may not be a new drug-eluting stent."

- *Meta-analysis lead author Dr. Camenzind* said he believes that more animal data should be required by regulators before any new DES is approved, but he stopped short of calling for additional human data.
- *AHA President Gibbons* said he doesn't believe regulatory approval of new drug-eluting stents will be impacted by the WCC stent thrombosis data.
- *Dr. Waxman* predicted that the stent thrombosis data would expedite, not slow, regulatory approval of new drug-eluting stents, "Overall, this is good news for Medtronic."
- *A Medtronic official* said, "It is too early to say stent thrombosis will delay new stents."
- *Dr. Steg, France* said there are serious implications for drug-eluting stents in development. He said talks have already begun with regulatory agencies in Europe and the U.S., and he said those agencies will require more hard endpoints and patient-related outcomes – not late loss or IVUS – for approval. He commented, "This will not be popular with industry or all of the interventional cardiology community."

Trends in dual antiplatelet therapy – Sanofi-Aventis's Plavix (clopidogrel) + aspirin

If there was any consensus on the stent thrombosis issue it was that use of Plavix will go up worldwide. However, Dr. Maarten Simoons, Chief of Cardiology at the Thoraxcenter in the Netherlands and a former president of the European Society of Cardiology, pointed out that Plavix use is off-label; it is not approved for preventing stent thrombosis in patients getting a drug-eluting stent. A Spanish doctor also pointed out that the number needed to treat with Plavix is very high, "If you treat patients with aspirin + clopidogrel, you need to treat 300 patients to prevent one stent thrombosis, but you have 299 patients with a bleeding risk, etc."

The AHA's Dr. Gibbons said a working group has been formed and within the next 60-90 days will craft an advisory about dual antiplatelet use post-DES. He added, "I am not by any means suggesting the need for lifetime dual antiplatelet therapy (after DES)."

What will doctors be telling patients who already have a drug-eluting stent and are worried about stent thrombosis? Should they continue their dual antiplatelet therapy indefinitely, and if they have stopped it, should they restart it? The consensus is growing that patients should continue dual antiplatelet therapy for at least a year (perhaps longer in some complex patients), and some patients should restart Plavix. That is the current recommendation of the American College of Cardiology and the American Heart Association.

Comments on this issue included:

- *The AHA's Dr. Robertson:* She said there is not enough data to say a person who already has a drug-eluting stent and has stopped Plavix should restart it, "No, there is not enough data to say that."
- *Illinois:* "If the patient had one stent for focal disease and was off Plavix for 4-12 months, I doubt there is a compelling argument to put him back on it, but in complex patients a compelling argument could be made that you should restart it. Patients who need surgery after 4 months of dual antiplatelet therapy should either (1) find a surgeon who will operate on clopidogrel, or (2) be treated like a heart valve patient: Put on Lovenox (Sanofi-Aventis, enoxaparin, a low molecular weight heparin), then heparin, then that stopped for the operation, then the process reversed right after the surgery with either clopidogrel or Lovenox followed by clopidogrel."
- *Australia:* "I'll tell patients to stay on Plavix if they are on it now. If they've been off Plavix for six months and are fine, they probably don't need to go back on it, but if they are not fine, they should go back on it…I don't think the (hospital) ethics committee will agree that a patient has re-endothelialized so now we can stop Plavix because we don't yet have a (simple) test to prove it." However, he said there will be data at AHA 2006 on a test that may help show re-endothelialization.
- *Massachusetts:* "I will tell patients that if they haven't completed a year on Plavix, to restart it until they have a total of 12 months."
- *Midwest U.S.:* "Many cardiologists already scale clopidogrel therapy to the complexity of the disease they are stenting…I treat patients with diffuse disease or bifurcations with lifelong clopidogrel, but in the Ravel-type patient, a few months of clopidogrel seems fine – Ravel patients have still shown no stent thrombosis."
- *Netherlands Taxus user:* "The issue will promote dual antiplatelet use…Right now we prescribe 12 months dual antiplatelet therapy, and we are not allowed to give it longer, but I think we will do that anyway."
- *Boston Scientific's Dr. Donald Baim:* "As manufacturers of drug-eluting stents, it is our job to say it shouldn't take lifelong Plavix and to develop devices like (our bio-degradable stent) that will be completely endothelialized in about six months."
- *Dr. Colombo, Italy:* "I was in favor of lifelong dual antiplatelet therapy, but now with the new data (*see page 4*)…most of the time, 1 year is sufficient. Maybe insulin-using diabetics may need it lifelong, but for the standard patient, I think one year…Worldwide I doubt many patients are taking dual antiplatelet therapy after one year. In Germany, most physicians stop after six months…I think one year unless there is a real concern of some side effects, and then maybe you shouldn't implant a drug-eluting stent."

REGULATORY ISSUES:
The impact of stent thrombosis on new stent approvals

It is unlikely there will be drastic regulatory changes any time soon, but regulators are concerned. About a week after WCC, the FDA said it is watching the situation and gathering information, but the agency said it remains convinced that DES are safe and effective when used for FDA-approved indications, "For thousands of patients each year, these devices have resulted in a significant reduction in the need of second procedures to treat restenosis…While the new data are of interest to the FDA and raise important questions, we do not have enough information yet to draw conclusions. It's unclear, for example, what causes drug-eluting stent thrombosis, how often it occurs, under what circumstances it occurs, or what the risk of occurrence is in a given patient."

The FDA confirmed that it has been meeting with Johnson & Johnson and Boston Scientific "to discuss any information and perspectives they have that may be pertinent to this issue," adding, "We remain keenly interested in the long-term follow-up of patients enrolled in the original pivotal DES randomized trials as well as those in the more complex patient and lesion subsets…who are currently being treated in 'real world' randomized and registry studies."

The FDA also announced it would convene a meeting of its Circulatory System Devices Advisory Committee "in the near future" – at least before the end of this year – "to improve our knowledge regarding the incidence and timing of stent thrombosis as well as the appropriate duration of clopidogrel use in patients who receive DES." The Agency will look to the advisory panel for recommendations on how to address this issue, "such as possible changes to device labeling or the need for additional clinical studies."

The FDA noted a suggestion of "a small but significant increase in the rate of death and MI possibly due to stent thrombosis in patients treated with DES…While the studies presented at the Atlanta (American College of Cardiology, 2006) and Barcelona meetings have raised important questions, the data we currently have do not allow us to fully characterize the mechanism, risks, and incidence of DES thrombosis. A more formal evaluation of the data in these studies is necessary, and any conclusions are dependent upon a thorough peer review…Stent thrombosis in patients who receive DES is a primary area of interest for the agency because of the potential for serious adverse outcomes – even though stent thrombosis occurs at low rates."

The FDA also is closely evaluating information related to the duration of treatment with Plavix, noting, "Although the duration of clopidogrel appeared to be adequate for the selected patients in the original clinical trials conducted to support FDA approval, the agency recognizes that the optimal duration of clopidogrel in more complex patients has not been defined. The recommended duration of clopidogrel administration and patient compliance with the prescribed regimen are likely interrelated with patient and anatomical factors that are associated with DES thrombosis. Additional clinical data are likely needed to reach conclusions regarding the optimal antiplatelet therapy regimen for DES patients."

A member of the Medicines Evaluation Board in the Netherlands, which is currently one of the key countries for drug-eluting stent C.E. Mark approvals, said he has noted significant differences in the amount and quality of clinical and non-clinical data being submitted on drug-eluting stents, "It is clear guidance is needed on the non-clinical and clinical data required for drug-eluting stents…We think there should be full-blown applications…With pharmaceuticals (drugs), we are generally extremely reluctant (to rely on post-marketing studies) because if the additional studies are negative, should we withdraw the product from the market? And that is legally difficult. A product (like drug-eluting stents) with a short life is a different situation…That could be part of the discussion (of new guidelines)."

The Dutch regulator said he was aware of the stent thrombosis issue before WCC. He commented, "Now, we have to be more careful (in DES approvals). More extensive data will be required – human data and improved animal data. Long-term follow-up and even animal data could help." He also suggested the limus DES stents may have a higher hurdle: "I was very surprised that sirolimus is worse. I had always thought that it was better than paclitaxel, but it looks worse now…I think it is a limus class effect."

Sources reported that FDA officials, European regulators, industry officials, representatives of the European Society of Cardiology, and key interventional cardiologists have been meeting over the past few months to clarify the regulatory path for drug-eluting stents. One expert commented, "It is clear that more regulatory data will be required." He predicted regulatory approvals will be delayed going forward, noting, "With the pioneering products (Cypher and Taxus), we made the leap, the major progress, and now we can concentrate more on safety."

Other points experts made included:

- European doctors and industry want a kind of European FDA, but European regulators balked, preferring the current country-autonomous systems.
- Some European regulators want to make the European process even more stringent than the FDA.
- Regulators in the Netherlands want five-year outcome data with stent thrombosis and deaths measured, but whether this would have to be pre-approval is still unclear.
- The FDA reportedly has referred to post-marketing studies as "a joke." Going forward, they may require 30% monitoring, which a source said would be very, very expensive.
- The FDA is expected to change the vocabulary used, standardizing definitions of things like MACE, TLR, and stent thrombosis.

In addition, the Medical Device Directive, voluntary guidelines used by the Ministry of Health officials in individual European countries is in the process of review, Dr. Alexander (Sandy) Geddes, Director of Regulatory EHQ for Boston Scientific, said. He commented, "We know the clinical requirements will be strengthened. Where you do not meet them, you will be required to do a more robust document review process.

Dr. Geddes said the expertise to review drug-eluting stents varies by country, "Not each is skilled or has the background or resources to do the review. The key (submission) countries include the U.K. and Holland, with France up and coming. Not every country has that expertise."

According to Dr. Geddes, the challenges relating to the drug component of drug-eluting stents include a lack of:

- Certainty on review time.
- Communication between regulators and manufacturers.
- Transparency of the procedure.
- Guidance on documentation (extent and format) required.
- Understanding of the extent and scope of the review.

Dr. Geddes said the rule of thumb has been a 100-patient trial for European approval of a bare metal stent and generally 300 patients for a drug-eluting stent, or fewer for a "very benign" drug. A Belgian doctor responded, "I think the question today is if we should raise those standards."

The Agency for Healthcare Research and Quality (AHRQ) has the DECIDE project underway and it will issue its recommendations on what to do with stents "soon" – probably sometime between TCT (October 22-26, 2006) and AHA (November 12-15, 2006). They will not be presented at a meeting, but will be put on the website (**www.ahrq.gov**).

A position paper is likely to come out soon in the ***European Heart Journal***, with Dr. Don Cutlip of Beth Israel Deaconess Medical Center in Boston the first author. FDA officials reportedly are making improvements to the manuscript, which is an indication that they are participating in this. The article is expected to outline two types of drug-eluting stent trials:

1. Device-oriented, which will start with small trials.
2. Patient-perspective, where they don't die, get an MI, etc.

Dr. Robert Califf of Duke said he believes there needs to be more human data for drug-eluting stent approvals in the future, and the ACC's Dr. Nissen (former chairman of the FDA's Cardiovascular and Renal Drugs Advisory Committee) had the same message. However, sources at the meeting generally were not predicting a near-term shift away from Cypher and Taxus to Medtronic's Endeavor, Conor's CoStar, or any other drug-eluting stent.

Physician comments on the likely impact of the stent thrombosis issue on approval of new drug-eluting stents included:

- *U.S. #1:* "I think there should be more stringent or long-term follow-up, but post approval. The long-term data we have is potentially confounding."
- *U.K.:* "We may need to follow-up patients longer, and regulators may delay the newer stents."
- *U.S. #2:* "There is a chance the FDA may require longer trials, and I favor that approach. I'd like to see a compromise – two years for an approval and five years post-marketing…You have to take this seriously. Late loss is not enough going forward…There has to be different weight given to the components of a combined endpoint. Restenosis is not the same as late stent thrombosis. If death goes the wrong direction, you need to ask hard questions. You have to ask if the reduction in restenosis is enough to warrant accepting increased death …Would you rather have a second procedure or die?"
- *Netherlands #1:* "I think the same long-term follow-up of drug-eluting stents will be required as for drugs – possibly 3-4 year follow-up before approval but certainly long-term mandatory post-marketing studies…The change will be very slow because it is a complex process, but I will make a plea (for change)."
- *Netherlands #2:* "We probably have to change to a long-term follow-up system like there is for drugs…Long-term drug registration requires large and long-term trials. I don't understand why we can't do that with drug-eluting stents. Long-term follow-up is appropriate and should be required. The question is whether pre-registration or post-marketing, and I think before registration."
- *France #1:* This source said there have already been meetings with FDA and European regulators on requiring new clinical endpoints – death, MI, and symptomatic TVR – instead of surrogate endpoints in DES trials. He also said there is a call for a public repository for the results of device trials, as with drug trials, and companies should be forced to publish all device trial data.
- *France #2:* "I currently use about 60% Cypher and 40% Taxus, and I don't plan to start using Endeavor or CoStar. It hasn't been proven that there is less late stent thrombosis with these stents than the first generation stents, and practically, I don't think we will ever have that data because stent thrombosis is a very rare event."

Comparison of Drug-Eluting Stents *

Measurement	Cypher	Taxus	Xience	Endeavor
Polymer thickness	7.2 µm	15.6 µm	5.3 µm	N/A
Dosing	140 µg/cm^2	100 µg/cm^2	10 µg/cm^2	10 µg/mm
Stent	Stainless steel	Stainless steel	Cobalt chromium	Cobalt alloy
Drug	Sirolimus	Paclitaxel	Everolimus	Zotarolimus

*** Source mostly Abbott Vascular**

ABBOTT'S Xience V/BOSTON SCIENTIFIC'S Promus

Abbott's Xience V, which will be sold by Boston Scientific under the private label Promus, is a Guidant Multi-Link Vision cobalt chromium stent coated with a durable acryil and fluorinate combination polymer that elutes everolimus on a Guidant Multi-Link Vision delivery platform. The Xience V polymer was acquired outside Abbott; it was not developed in-house at either Abbott or Guidant.

Xience V received a C.E. Mark in Europe based on the results of the 60-patient patient SPIRIT-I trial (with 28 patients getting Xience). Both companies plan to launch this stent in October 2006. Principal investigator Dr. Patrick Serruys declared, "Today a major new player is born."

Dr. Gregg Stone described it as "inert, flexile, ductile, with a high drug loading capacity, and quite non-tacky to the touch." He said, "(Everolimus) basically stops the cell cycle in its tracks. Everolimus and sirolimus are almost identical…There is very, very little differences in cell studies…It seems there is less webbing with this than other (drug-eluting stents). You can crimp this very tightly, which should lead to high retention…I think it will be one of the most deliverable stents on the market…We expect a very low rate of periprocedural MI just based on the thinness of the polymer."

There is no polymer top coat, but the elution profile was described as "very similar to Cypher." Dr. Stone said 80% of the drug is released by 28 days, with none detectable at 120 days, "There is very consistent drug release, so we expect a very consistent response."

A Boston Scientific source indicated that sales reps will focus on selling Promus into Cypher accounts "because that's what our market research indicates is the best market." Taxus reportedly will be the focus, but Promus is "an option" – and perhaps a way to take market share from Cypher.

2-Year SPIRIT-I Results

Measurement	Xience n=28	Control n=32	p-value
Evaluable patients at 2 years	26	28	---
Efficacy at 6 months			
Primary endpoint: In-stent late loss	0.10 mm	0.84 mm	<.0001
Restenosis	0	0	---
Late loss	0.23	0.81	<.001
% volume obstruction	8.6%	29.0%	---
Efficacy at 2 years			
Restenosis	4.5%	28.0%	0.05
Proximal late loss	0.14	0.43	---
Distal edge late loss	0.03	N/A	---
% volume obstruction	10.7%	26.9%	---
MACE at 1 year			
Cardiac death	0	0	---
Q-wave MI	3.8%	0	---
MACE	15.4%	21.4%	---
MACE at 2 years			
MACE	15.4%	25.0%	---

SPIRIT-I

Dr. Didier Carrie of France presented the IVUS from the 17-site, 152-patient trial, which served as the basis for the C.E. Mark for Xience.

SPIRIT-II results

Dr. Patrick Serruys presented the 6-month results of the Phase II SPIRIT-II pilot trial of Xience V, an everolimus-eluting ML Vision stent. This was a 300-patient, prospective, randomized, non-inferiority trial conducted in Europe, India, and New Zealand. The stents used were 2.5-4.5 mm x ≤28 mm. The delta for non-inferiority was 0.16 mm. Xience V was shown to be not only non-inferior to Taxus, but it was clearly ***superior in terms of late loss***. Xience V also had significantly less restenosis. Dr. Serruys said, "It is clear that SPIRIT-II met its primary endpoint, which was a modest endpoint. As a matter of fact, it achieved superiority…Xience is more effective than Taxus in reducing neointimal hyperplasia and has lower MACE…The trial confirmed exactly what was seen in the first-in-man study – 0.11 in-stent late loss."

Asked if, in the light of the stent thrombosis data at this meeting, if lower late loss is a positive or a negative, Dr. Serruys indicated the jury is out, saying, "It is clear we have to find the right balance. It is clear that 0.2 mm to 0.3 mm late loss will be very beneficial on neointimal hyperplasia, but if you go too far in either direction, you will run into trouble. It will take a few years…to find the (answer)…What everolimus will achieve is unclear. It is mechanistically similar to sirolimus, and we may expect the same change (in the endothelium), though all the analogs (of sirolimus) are modified, and sometimes the impact on mTOR is reduced somewhat. It is too early to make a statement."

Asked what antiplatelet regimen he would advise with this stent in light of the recent late stent thrombosis data, he said, "We recommended three months (in this trial), but the (recent) EuroHeart survey indicated 70% of doctors are now recommending 12 months."

The discussant after the formal presentation of the SPIRIT-II data, Dr. Robert Harrington of Duke University, noted that a nice correlation has been shown between late loss and restenosis, but he argued that we need to know more about late cardiac events, "As a community, we need to consider the tradeoff of thrombosis vs. restenosis…Before we embrace new technology enthusiastically until subsequent studies demonstrate not just (reduced) restenosis but the risk of thrombotic events."

Other reaction to the Xience data included:

- *U.S. #1:* "It was very impressive that there is a more powerful drug to prevent restenosis, but the trial was small, and we need more patients and more long-term follow-up."
- *U.S. #2:* "The results are very impressive…but we really don't know the incidence of stent thrombosis without long-term data."

6-Month SPIRIT-II Results

Measurement	Xience n=223	Taxus n=77	p-value
Diabetics	23%	24%	Nss
Insulin dependent diabetics	5%	7%	Nss
2 lesions	17%	18%	Nss
Type C lesions	13%	13%	Nss
Pre-procedure RVD	2.70	2.82	0.099
Post procedure RVD	2.86	3.00	---
Pre-procedure MLD	1.06	1.14	---
Post procedure MLD	2.49	2.62	0.031
Primary endpoint			
In-stent late loss	0.11 mm	0.36 mm	<.0001 for non-inferiority <.001 for superiority
***Secondary endpoints* and other efficacy results**			
In-segment late loss	0.07 mm	0.15 mm	N/A
Late loss proximal edge	0.12 mm	0.16 mm	---
Late loss distal edge	0.02 mm	-0.01 mm	---
% DS	16%	21%	<.001
Restenosis in-stent	1.3%	3.5%	.194
Restenosis in-segment	3.4%	5.8%	N/A
Neointimal volume in-stent	3.8 mm (73% reduction)	14.4 mm	<.0001
Volume obstruction	2.5% (66% reduction)	7.4%	<.001
Safety			
Late stent thrombosis	1 patient at 53 days *	1 patient at 50 days **	---
Incomplete apposition	6.5%	5.6%	---
Incomplete apposition resolved	3 patients	2 patients	---
MACE	2.7%	6.5%	---
TLR	1.8%	3.9%	---
Acute stent thrombosis	0	0	---
Subacute stent thrombosis	0	0	---
Late stent thrombosis (LaST)	0.5%	1.3%	---
Cardiac death	0	1.3%	---
Q-wave MI	0	0	---
Non-Q-wave MI	0.9%	2.6%	---

* 1 patient with complex disease at 53 days on dual antiplatelet therapy, treated and still alive

** 1 patient at 50 days on dual antiplatelet therapy who died

- *Belgium:* "It looked very good. Obviously, there were not a huge number of patients. It was better than I expected…I prefer Xience to Cypher because I always liked Vision and its deliverability. Guidant was always very good with stents, catheters, and balloons."

Dr. Eulogio Garcia of Spain, a SPIRIT-II investigator, has used the Xience V stent outside of clinical trials on about 30 "challenging" patients so far to evaluate it on a pre-marketing basis. He said, "I've been really impressed with it. We had a lot of experience with (the bare) Vision, so we knew how that behaves…I've been impressed because the performance of the Xience V is slightly better than Vision. I don't know if that has to do with the polymer, which really acts as a sort of a lubricant."

Dr. Garcia said his cath lab's breakdown in stent use has been about: 30% Taxus, 30% Endeavor, 20% Cypher, and 20% bare metal stents. In six months, he expects his DES usage will be about: 30% Xience, 30% Endeavor, 20% Taxus, and 20% bare. "With these results, probably the advantage of Cypher over the others is gone…Xience will mostly replace Cypher and part of Taxus…We choose Endeavor in cases where we think there is a lesser risk of restenosis, trying to avoid very diffuse disease. Xience will allow us to treat challenging lesions with predictable results."

How does Xience V compare to the other drug-eluting stents? Dr. Garcia praised the Xience platform, "Why go to church in a small truck if you can go in a Cadillac or a Mercedes?"

Asked about stent fractures with Xience V, an investigator said, "Stent fractures are not uncommon with Cypher, and they can happen with Taxus but less often. I think they are uncommon with Xience, but we will have to see…Stent fracture is not something like stent thrombosis that has emerged (as a major clinical issue)."

Xience availability

At WCC, Abbott officials insisted the manufacturing issues that came up in April have been largely resolved, but their comments were in line with statements by more senior officials in the U.S. who said the rollout would be "controlled." Abbott's Vice President of EMEA (European) Marketing said, "We delayed the launch in April, and now we need to build units for trials and the European launch. Manufacturing is going well. There are no outstanding manufacturing issues…We are pleased with our manufacturing capacity and will be able to fulfill the needs for a ***staged*** European launch. I don't anticipate any (availability) issues with the U.S. launch."

Asked why planned live Xience V cases were pulled from both EuroPCR and WCC, she offered this explanation, noticeably avoiding the WCC part of the question: "PCR was too soon after the April issue. Now, we are doing product evaluations in several countries."

First-in-Man Xience data updated

Dr. M. Wierner of Germany presented the two-year follow-up on 60 patients who were in the Xience first-in-man study.

Ongoing and planned Xience program

- **SPIRIT-III.** Data from this 1,380-patient (from 80 U.S. sites and 12 Japanese sites) trial will be presented at the American College of Cardiology in 2007. The primary endpoint is in-segment late loss at 240 days.
- **SPIRIT-IV.** This is a 1,125-patient, single-blind randomized, U.S. trial comparing Xience V to Taxus. Dr. Gregg Stone is the principal investigator. The primary endpoint is TVF at 270 days. The first patient was enrolled in August 2006.
- **SPIRIT-V.** This is a 3,021-patient, 100-site two-part study:
  1. A registry that will begin when Xience V is launched in Europe.
  2. A prospective, randomized, multicenter, single-blind, parallel two-arm study in 321 diabetic patients, comparing Xience V to Taxus Liberté.

ABBOTT'S bioabsorbable stent program

This program uses the BVS bioabsorbable stent with a ML Vision balloon delivery system and elutes everolimus from a bioabsorbable poly lactic acid (PLA) polymer coating. The drug's release kinetics were described as the same as Xience and Abbott's zotarolimus-eluting ZoMaxx. Dr. Leif Thuesen of Denmark said the polymer has been safely used in numerous medical applications since the 1960s, and approximately 200 products are made from PLA or a co-polymer containing PLA, "It breaks down to lactic acid. No drug is left behind…During degradation, the molecular weight, strength, and mass will all go down…The radial strength is approximately the same as the Multi-Link Vision and seems a bit higher than the old Multi-Link…The strut thickness is 0.0060 mm, which is higher than Multi-Link."

Dr. Thuesen said the preclinical animal data have been good, demonstrating good safety and effectively reducing neointimal response in both the porcine and rabbit models, "There was a thin, well-healed neointima, complete luminal endothelialization, no evidence of medial necrosis, and no evidence of inflammation."

Are there any advantages to this stent? Dr. Thuesen thinks so: "The advantage might be a potential return of vasomotor function as the stent degrades and loses its scaffolding capability. That was demonstrated in the preclinical model after 12 months. And it is potentially MR and CT compatible …These stents seem to solve many of the problems we have with stents today."

The ABSORB trial, using a 3.0 mm x 12 mm stent, has already begun, with the first 30 patients enrolled at six sites outside the U.S. The principal investigators are Dr. Patrick Serruys of the Netherlands and Dr. John Ormiston of New Zealand. Asked about the likelihood of bioabsorbable stents replacing metal stents in the future, Dr. Stone said, "Laymen would say it doesn't make sense to put metal in a coronary artery. (Pathologist Dr. Renu Virmani) would say you need at least a good four months of scaffolding before you can reduce the scaffolding structures. With bioabsorbable stents, there will certainly be new enemies. We don't know what they will be, but we have to be very careful, and in the ABSORB trial, we are using several technologies, including multislice CT, etc., to try to pick up any signal…Our concern with bioabsorbable is that you will have chronic inflammation, but I'm impressed from the (Abbott) animal studies that there is less inflammation with BVS, but this stent takes more than a year to go away, so these patients will take extended follow-up." The 30-day results from the ABSORB trial will be presented at TCT 2006.

ABBOTT'S ZoMaxx

Abbott's ZoMaxx – the TriMaxx stent coated with Pharmacoat (phosphorylcholine) that elutes zotarolimus – program is not dead; it is continuing.

- ZoMaxx-I trial is, according to an Abbott official, "going well," with results expected at TCT 2006.
- ZoMaxx-I is the pivotal Phase III trial for European approval. Abbott hopes to launch ZoMaxx in 4Q06, but the U.S. timeline is "not defined."
- ZoMaxx-II is still enrolling.
- ZoMaxx-Europe is a ~900-patient, single-arm study that started enrolling patients in May 2006. The primary endpoint is TLR at 9 months.

CONOR'S CoStar

Paclitaxel

At a session sponsored by Biotronik (which co-markets CoStar in Europe), Dr. William Wijns of Belgium reviewed CoStar, a cobalt chromium stent coated with a fully bioresorbable PLGA polymer that elutes paclitaxel from reservoirs (wells). Among the features of this stent are:

- 492 reservoirs per 16 mm stent.
- Strut thickness of 0.0035 inches.
- Crossing profile of 0.038 inches.
- Good radioopacity.

- Currently, the recommendation is for six months of dual antiplatelet therapy, but Dr. Wijns noted, "Obviously, we need to look longer term, but because the polymer is virtually gone by six months…One would not expect very late stent thrombosis to occur, but that remains to be demonstrated."

The U.S. pivotal trial is the COSTAR-II, comparing CoStar (900 patients) and Taxus (600 patients). The primary investigators are Dr. Dean Keriakes of the Ohio Heart Health Center in Cincinnati, Dr. Mitchell Krucoff of Duke University, and Dr. Wijns. The primary endpoint is 8-month MACE, and the primary angiographic endpoint is 9-month late loss. The trial is fully enrolled, and the data are expected at the American College of Cardiology 2007. So far, 831 patients have 1-year follow-up, with 0.12% stent thrombosis (in the 31-180 day period).

Users appear very happy with CoStar, but they are not easy to find. One doctor said he likes it because it is "more deliverable than Taxus." Dr. Stephan Verheye of Belgium, who is the principal investigator for the randomized, multicenter GENESIS trial comparing CoStar to Corio (pimecrolimus-eluting) and SymBio (dual elution of pimecrolimus and paclitaxel), also claims CoStar is very deliverable, saying "CoStar is more deliverable than all the drug-eluting stents on the market, except Endeavor). In his lab, drug-eluting stents are only used for diabetic patients (20%-25% of stent patients), and he uses CoStar and Cypher, no Taxus and no Endeavor. He used to use Taxus but replaced it because of the profile, delivery, and stickiness. Asked how he chooses between Cypher and CoStar, he said, "In difficult, long-lesions, small lesions, and tortuous vessels, I use CoStar. In easy lesion, I use Cypher or CoStar."

How does CoStar and Xience compare? Dr. Verheye said, "I believe in CoStar because it opens so many opportunities. It does the job, the polymer is gone and it behaves like a bare metal stent after six months, so we won't see late stent thrombosis."

What antiplatelet regimen does he use with CoStar? Dr. Verheye said, "Patients get six months Plavix with CoStar, three months at least with Cypher, though he prefers six months."

Pimecrolimus

Conor also is working on a CoStar that elutes a limus drug, Novartis's pimecrolimus. The Pro-Limus program utilizes the same cobalt chromium stent, but with a Probio (silicone carbine) coating with a PLLA (poly L lactide) degradable carrier. For stents, pimecrolimus is licensed to Biotronik, Avantec, and Conor; Aventec and Conor are already in clinical development.

The first-in-man Pro-Limus trial is expected to start in 4Q06. This will be basically a safety and clinical performance in 60 patients in Belgium and Germany. That will be followed by:

- PRO-LIMUS-I will be a 900-patient European safety trial.
- PRO-LIMUS-II will be a 300-patient study in Europe.
- PRO-LIMUS-III will be a 100-patient efficacy study in Japan.

JOHNSON & JOHNSON

Future stent programs

J&J's U.S. stent development program is:

1. **Cypher Select Plus** – a modified version of the original Cypher, with some design changes for better handling – a shorter, flexible tip, a hydrophilic coating, and elongated stent segments. A J&J official commented that both of these stents are for outside the U.S., and the company does not plan to bring either Cypher Select or Cypher Select Plus to the U.S., though some of the features of Cypher Select Plus will be part of newer stents that do come to the U.S.
2. **Python** – a stainless steel stent with the same Surmodics polymer as Cypher.
3. **Firefox** – a cobalt chromium stent which right now is expected to have the same Surmodics polymer as Cypher, but J&J is talking about the possibility of "modifying" this.
4. **Biodegradable** – a stent which itself is a polymer, developed internally at J&J, that erodes away. Preclinical studies are to begin later this year, with human trials starting some time in 2007.

2-Year REALITY data

REALITY was a prospective, randomized, 1,386-patient trial conducted in Europe, Asia, and Latin America, and sponsored by J&J. The results suggested a lower stent thrombosis rate with Cypher than Taxus in the 8-month results, but the statistical significance of the difference depended on how one stent thrombosis patient was counted. By an intent-to-treat analysis, there was no statistically significant difference in stent thrombosis <30 days (0.6% Cypher vs. 1.6% Taxus), but in patients actually treated, the stent thrombosis rate met statistical significance in favor of Cypher (0.4% vs. 1.8% with Taxus). At two-years, however, there was a clearly lower stent thrombosis rate with Cypher.

2-Year Safety Results of REALITY Trial

Measurement	Cypher n=684	Taxus n=669	p-value
Stent thrombosis	0.9%	2.5%	0.02
MACE (cardiac death, MI, and TLR)	13.2%	14.9%	Nss
Total MI	4.8%	6.9%	Nss
Q-wave MI	0.1%	1.5%	0.006
Non-Q-wave MI	4.7%	5.4%	Nss
Cardiac death	1.9%	1.9%	Nss
TVF	14.3%	16.6%	Nss
TLR	6.4%	6.1%	Nss

4-year E-SIRIUS data

The benefits of Cypher over a bare metal stent continue held up over four years in E-SIRIUS, a European, 352-patient, double-blind, multicenter, randomized trial sponsored by J&J which compared restenosis in Cypher vs. bare metal stents.

4-Year Results of E-SIRIUS Trial

Measurement	Cypher n=175	Bare metal stent n=175	p-value
Death	5.7%	5.6%	Nss
TLR	7.4%	27.1%	<.001
MACE (all cause death, MI, and TLR)	16%	34.5%	<.001
Stent thrombosis overall	2.3%	0	Nss (p=0.060)
Late stent thrombosis	2 patients	0	Nss

SIRTAX-Diabetes

One-year data from the pre-specified diabetic subset of the SIRTAX trial, an independent, head-to-head comparison of Cypher and Taxus trial found that MACE (cardiac death, MI, or TLR) was 50% lower with Cypher.

1-Year Results of SIRTAX-Diabetes

Measurement	Cypher	Taxus	p-value
MACE overall	10.2%	20.4%	0.04
MACE in non-insulin dependent diabetics	54% reduction	N/A	N/A
MACE in insulin-dependent diabetics	44% reduction	N/A	N/A
TLR	5.6%	12.9%	0.06
Restenosis	3.0%	13.6%	0.03
In-stent late loss	0.11	0.33	0.02

MEDTRONIC'S Endeavor

A European source said a European doctor has seen two cases of stent thrombosis with Endeavor and may or may not have reported them to the company, but he is supposed to be considering publishing them. The company has not acknowledged any stent thrombosis, so this could just be rumor.

D R U G S

GENERIC STATINS

European cardiologists said they are making wide use of generic simvastatin, often when they would prefer to use higher potency statins, but higher potency statins such as Pfizer's Lipitor (atorvastatin) are generally available for patients who do not reach goal on simvastatin. A Swedish doctor said, "There are strict rules on doctors prescribing statins that say we must use the least expensive statin. Only in special situations will they allow other statins."

ASTRAZENECA'S Crestor (rosuvastatin) *in combination with* SCHERING-PLOUGH'S Zetia (ezetimibe)

The 12-week, 469-patient EXPLORER trial found that adding 10 mg Zetia to 40 mg Crestor resulted in significant drops in C-reactive protein (CRP) and LDL. CRP fell as much as 46% over 6 weeks, and combination therapy helped 58% of patients achieve dual CRP/LDL-C goals – (LDL-C <100 mg/dL or <70 mg/dL (depending on risk category) and CRP <2 mg/dL – especially for patients in whom target levels were CRP <2 mg/dL.

6-Week EXPLORER Trial Results

Measurement	40 mg Crestor	40 mg Crestor +10 mg Zetia
Patients achieving dual LDL/CRP goals	24%	58%
CRP reduction	29%	46%
LDL reduction	N/A	70%
Patients achieving LDL goal of <100 mg/dL	79%	94% (p<.001)
Increase in HDL	8.5%	10.8%

CV THERAPEUTICS' Aceon (perindopril)

Perindopril is an ACE inhibitor made and sold in Europe by Servier, and marketed in the U.S. by both Solvay and CV Therapeutics. CV Therapeutics has hoped to make Aceon a top seller much the way King did for Altace (ramipril) after the HOPE data.

At WCC, researchers reported on a trial where perindopril failed to show a benefit in elderly heart failure patients. The results of the 3-year, 850-patient, PEP-CHF trial of perindopril in elderly people with chronic heart failure failed to meet the primary endpoint, showing no statistically significant reduction in all-cause mortality or heart failure-related hospitalizations. Primary investigator Dr. John Cleland of the U.K. said the trial had several problems: It was slow to recruit patients, and even with a longer enrollment period, only 850 of the planned 1,000 patients were enrolled. In addition, many patients dropped out after 12-18 months of treatment, moving to open label ACE inhibitors.

Even during the first year of the trial, in which most patients remained on therapy, perindopril failed to show a statistically significant effect on all-cause mortality or heart failure-related hospitalizations.

PEP-CHF Trial Results with Perindopril

Measurement	Perindopril n=474	Placebo n=476	Hazard ratio	p-value
Primary endpoint: All-cause mortality or heart failure-related hospitalizations at 3 years	Down 31%	Down 31%	0.92	0.545

However, several previous trials have given the companies a strong marketing message for perindopril, so this trial is not a major negative issue:

- The PROGRESS trial showed perindopril has a stroke prevention benefit.
- The 12,218-patient EUROPA trial found that ACE inhibitors (specifically perindopril) are beneficial in low risk patients.
- The 1,500-patient PERSUADE trial presented at ESC last year, demonstrated a benefit in diabetics. PERSUADE researchers estimated that treating 27 patients with 8 mg Aceon daily over four years would prevent one cardiovascular death or MI.
- The 1,259-patient PREAMI trial indicated perindopril is effective and safe in elderly patients, showing a statistically significant reduction in risk of cardiac remodeling, but no significant effect on mortality or hospitalization for heart failure.
- The ASCOT-BPLA trial, a substudy of the EUROPA trial showed that the combination of perindopril and Pfizer's calcium channel blocker Norvasc (amlodopine) ***is*** more effective in reducing CV events (e.g., heart attacks and strokes) than atenolol + a diuretic. 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.

LILLY'S prasugrel

Marketing against generic clopidogrel could be a challenge

Doctors asked about the outlook for Sanofi-Aventis's Plavix (clopidogrel) if U.S. courts allow Apotex to begin selling its generic clopidogrel again. All agreed that many, but not all, patients would switch to the generic because of cost. They also predicted that a generic would boost overall clopidogrel use as well. A U.S. doctor said, "Some of my patients say their list of medication is several hundred dollars a months. If they had clopidogrel 15%-30% cheaper, that might make a difference to them."

What would generic clopidogrel mean for a launch of prasugrel? Doctors said it depends on how well it can differentiate itself. An investigator said, "We know prasugrel has a higher level of platelet inhibition. The bottom line is it is more efficient (than clopidogrel). Whether it overcomes generic clopidogrel depends on the degree of superiority. I'll need to see an overall substantial reduction in events and an acceptable bleeding profile." An Australian cardiologist said, "As much as I'd like to think the brand is better, the generic is as good. If patients are happy with the brand, they'll probably stay on the brand…There is an urgent need for a test of clopidogrel response…Prasugrel could do well if it shows better control." A Swedish doctor said, "Patients will be switched from brand to generic, but usage will expand as well because of the debate on the duration of treatment for Plavix. Industry wants us to use it for 12 months, but the hesitancy is price post-stenting or post-ACS…Prasugrel would need to show not only non-inferiority but also some advantage, or it would have only limited use."

A paper on a new test for clotting response will be presented at the American Heart Association meeting in November 2006.

NOVARTIS'S Diovan (valsartan)

Japanese patients respond better to the angiotensin receptor blocker (ARB) valsartan than other therapies for blood pressure control. That was the finding of the JIKEI Heart Study, which was conducted by independent researchers but with an unrestricted grant from Novartis. JIKEI was a 3,081-patient trial designed to compare valsartan to non-ARB therapy, looking at blood pressure control (<140/90 mmHg) as well as cardiovascular outcomes, including angina, stroke, and heart failure. Researchers said the trial was halted early because valsartan showed an unequivocal benefit on cardiac events, though there were no differences in blood pressure or heart rate control between the two groups. Study co-chair Dr. Bjorn Dahlof of Sweden said, "For the first time, the clinical value of valsartan…are extended to an Asian population."

JIKEI Heart Study

Measurement	Events with valsartan	Events with non-ARB therapy	p-value
Cardiac events	92	149	0.0002
Stroke	28	48	0.028
Angina	19	53	0.0001
Heart failure	18	36	0.029

NUVELO'S rNAPc2

Researchers from Brigham & Women's Hospital presented a poster on the ANTHEM-TIMI-32 trial of rNAPc2, a recombinant, modified form of NAPc2, derived from the hookworm, that provides Factor Xa-dependent inhibition of Factor VIIa complex. In Phase II elective knee and PTCA studies, it prevented new thrombin generation. The hope is that it will inhibit ischemia without increasing bleeding when compared to heparin and the low molecular weight heparin enoxaparin (Sanofi-Aventis's Lovenox).

In this trial, 203 patients with nSTE ACS – who were at high risk of recurrent ischemia or recurrent MI and for whom early catheterization was planned – were given either enoxaparin or unfractionated heparin (UFH), then randomized to either placebo (continuation of the heparin or enoxaparin) or rNAPc2 in 8 escalating dose groups (from 1-10 µg/kg). Both arms got their drug by IV bolus every 48 hours. Patients could also receive a GP IIb/IIIa and/or clopidogrel. Ischemia was measured by 3-lead continuous ECG (Holter monitor).

Then, another 26 patients were enrolled in an open-label phase at the highest rNAPc2 dose (10 µg/kg) plus ½ dose heparin, followed by a second open-label phase of 26 patients of 10 µg/kg rNAPc2 plus no heparin.

Demographics of ANTHEM-TIMI-32 Trial of rNAPc2

Measurement	rNAPc2 n=215	Placebo (heparin or enoxaparin) n=40
nSTE-MI	53%	50%
Diabetes	34%	33%
Mean TIMI risk score	3.5	3.7
Got 1 dose of study drug	85%	83%
Got 2 doses of study drug	14%	18%
Got 3 doses of study drug	1%	0
Enoxaparin	71%	75%
UFH	33%	33%
GP IIb/IIIa use	53%	53%
PCI	45%	58%
CABG	11%	3%

The 4 major hemorrhages with rNAPc2 were all at the 10 µg/kg:

- None occurred in the patients also taking ½ dose UFH.
- 3 of these were in patients taking full-dose UFH and were all CABG-related.
- 1 occurred in the patients getting no concomitant UFH, but this group had four procedure-related thromboses.

Principal investigator Dr. Robert Giugliano of Brigham & Women's Hospital said the data have not yet been submitted for publication, but he hopes to get it published soon. More data will be at TCT 2006 in an oral presentation (with antibody and MI data) and two posters on the angiographic findings. He offered these comments on – and explanations of – the data:

- *On why there is more ischemia with the low dose groups than the high dose groups:* "It is numerically higher but not a statistically significant difference. Why there isn't a step-wise function, I don't know. Maybe this has to do with the small sample size."
- *On what he would like to see in a Phase III trial:* "It would need 4,000-15,000 patients, and if it is 4,000, there would need to be two trials. There is no way Nuvelo can do that alone; it will need a partner." He suggested the primary endpoint should be either death or MI or a 3-way combination of death, MI, or recurrent revascularization.
- He believes a Phase IIb trial should be done before a pivotal Phase III in order to better determine the best way to dose rNAPc2 with UFH/enoxaparin. He'd like to see a Phase IIb trial looking at 7.5 µg/kg rNAPc2 + half dose heparin vs. 10 µg/kg with no heparin (except in the cath lab) vs. placebo, measuring ECG by Holter monitor and clinical endpoints. He'd also like to continue the drug after discharge for a month.
- At this point, he thinks the best dosing may be either:
  - 7.5 µg/kg rNAPc2 + full dose heparin in patients going to the cath lab immediately, or
  - 10 µg/kg rNAPc2 + half dose heparin in the cath lab.
- There has been no sign of any liver abnormalities, as were seen with AstraZeneca's Exanta (ximelagatran).
- Non-neutralizing antibodies are formed, but in this trial, it was not much different from preliminary antibody data shown at the American Heart Association meeting in

Efficacy and Safety of rNAPc2 in ANTHEM-TIMI-32 Trial

Measurement	Placebo	Low dose rNAPc2					High dose rNAPc2		p-value
		1.5 µg/kg	2.0 µg/kg	3.0 µg/kg	4.0 µg/kg	5.0 µg/kg	7.5 µg/kg	10.0 µg/kg	
Ischemia	21%	33%	21%	26%	37%	17%	11%	9.0%	Trend 0.013
Ischemic events per patient	7 of 34	6 of 18	4 of 19	5 of 19	7 of 19	3 of 18	2 of 18	7 of 78 overall 1:23 on no heparin 3:24 on half dose heparin 3:31 on full heparin	
Incidence of ischemia	20.6%	26.9% (p=0.064 vs. placebo)					9.4% (p=0.013 vs. placebo) (p=0.002 vs. low dose rNAPc2)		3-way p=0.008
Mean number of episodes per patient	0.59	1.02					0.30		3-way p=0.06
Average duration of ischemia per patient	23 min.	34 min.					4.9 min		3-way p=0.02
Average ST-product per patient *	29	54					9.2		3-way p=0.02
Safety									
Minor hemorrhage	2.5% (1 patient of 40)	2.9% (3 patients of 103)					0.9% (1 patient of 112)		3-way p=0.77 Trend 0.49
Major hemorrhage	0	0					3.6% (4 patients of 112)		

* ST-product = maximal extent of STD (in mm) x duration of ischemia (min)

2005. There will be a little more data on antibodies during the oral TCT presentation.

- rNAPc2 is given by a slow (~1 minute) IV push, which he tells patients "is a big non-event," but it can also be given subcutaneously. He said he gives it IV to get it on board right away.
- The half-life of rNAPc2 is 50-60 hours, probably closer to 60 hours. Dr. Giugliano said this means it can be dosed every 2 days, but they are considering dosing it two or three times a week, "That would really distinguish it."
- Compared to clopidogrel, he said it has the same bleeding risk but lasts for a shorter time (clopidogrel lasts 5-7 days). And there is an antidote for rNAPc2, Factor VIIa, that completely reverses its action.
- rNAPc2 also may have utility in other indications, including cancer, DVT, and sepsis. Dr. Giugliano said he used it in a lung cancer patient with refractory DVT at the 7.5 µg/kg dose (for the DVT, not the cancer), and the results were limb-sparing.
- *On where rNAPc2 might be more useful than enoxaparin:* "In patients going to the cath lab early, medically managed patients, a large percentage of high risk patients. Why would patients who are low risk for events need a fancy, expensive drug?"

NOVARTIS/SPEEDEL'S Rasilez (aliskiren, SPP-100)

Data from a 1,625-patient, open-label study found that once-daily Rasilez, an oral rennin inhibitor, given either as monotherapy or in combination with HCTZ (hydrochlorothiazide), provides safe, long-term (12-month), sustained 24-hour blood pressure control without the risk of rebound hypertension. In the trial, patients were randomized to receive Rasilez 150 mg or 300 mg QD. Patients taking Rasilez 300 mg whose blood pressure was not controlled were allowed to add HCTZ. After 11 months, 261 patients on Rasilez monotherapy were randomly assigned to continue on the drug or receive placebo during a four-week randomized, double-blind, placebo-controlled withdrawal phase. The most commonly reported adverse events included diarrhea, back pain, headache, dizziness, and nasopharyngitis.

After 12 months patients in both Rasilez groups achieved similar reductions in blood pressure – down an average of 4.1 mmHg with monotherapy and 6.6 mmHg with combination therapy. During the 1-month withdrawal period, patients taking placebo experienced a gradual rise in blood pressure, while patients remaining on Rasilez maintained their blood pressure reductions.

A separate, 6-week study of 762 patients with mild-to-moderate hypertension found that adding Rasilez to amlodipine significantly lowered blood pressure without the increased edema usually associated with a doubling of the amlodipine dose. All patients started treatment with a 5 mg amlodipine dose, and if they were inadequately controlled, then they were randomized either to add 150 mg Rasilez or to double the dose of amlodipine. At the end of the study, patients taking Rasilez + amlodipine had statistically significant reductions in mean sitting SBP and DBP vs. patients taking low dose amlodipine alone. Significantly more patients on combination therapy responded to treatment and reached blood pressure targets than those taking low dose amlodipine. Outcomes were similar when comparing combination therapy to a double dose of amlodipine.

6-Week Rasilez Study

Measurement	Rasilez + amlodipine	Low dose amlodipine	Double-dose amlodipine
Reduction in mean sitting SBP	11.0 mmHg	8.5 mmHg	---
Reduction in mean sitting DBP	5.0 mmHg	4.8 mmHg	---
Edema	2.1%	3.4%	11.2%

DATA TO WATCH

TCT, October 2006:

- Final data by Dr. Colombo on a German/Italian study of stent thrombosis.
- Results of Abbott's ZoMaxx-I trial.
- 30-day results from Abbott's ABSORB trial of its BVS absorbable drug-eluting stent.
- Oral presentation and 2 posters on Nuvelo's rNAPc2.

American Heart Association, November 2006:

- A paper on a new test for clotting response will be presented.

American College of Cardiology, March 2007:

- Results of the U.S. pivotal trial COSTAR-II, comparing CoStar and Taxus.
- SPIRIT-III results.
- Data on a test to determine stent re-endothelialization.

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