Journal Club Member

The first 2 cardiac surgery articles (authors E. Camenzind and S. Yusuf) for this Thursday’s journal club need to be viewed on a web page as they are not yet published. The 3rd (BASKET trial) follows in abstract form

These 3 presentations on stents from the 2006 World Congress of Cardiology – European Society of Cardiology and 2006 ACC have really shaken up the cardiology world and prompted an FDA investigation. These should be viewed by each of us! especially the discussion by Dr. Salim Yusuf which I found shocking. Of note he is a Rhodes Scholar, NIH trained now at McMaster University in Canada and author of Evidenced-based Cardiology).

To view these short talks (5 min and 7 min) click on the link below and select the last two presentations listed below:


Safety of drug-eluting stents: insights form meta analysis.
E Camenzind (Geneve 14, CH) J Nordmann (Basel, CH)
17 slides
5 min 29 sec

Discussant
Dr Salim Yusuf
6 slides
7 min 29 sec

The following is the 3rd article: The BASKET trial presentation from the 2006 ACC:

BASKET-LATE: Late Clinical Events Related to Late Stent Thrombosis After Stopping Clopidogrel: Drug-Eluting vs Bare-Metal Stenting

Disclosures
Luis Gruberg, MD, FACC
"The results of this small study and the conclusions reached by the authors are certainly a cause for concern."

Presenter: Matthias E. Pfisterer, MD (University Hospital Basel, Switzerland), for the BASKET-LATE Investigators

Subacute and late stent thrombosis are rare but feared complications following percutaneous coronary intervention. Whereas acute stent thrombosis usually occurs while the patient is still in the hospital and is quite dramatic, subacute and late stent thrombosis usually occur after the patient has been discharged home. Therefore, rapid restoration of normal coronary blood flow is often not possible, and the patient may sustain an acute myocardial infarction, which confers a high risk of mortality.

Because of the growing concern that delayed endothelialization after implantation of a drug-eluting stent (DES) may cause late stent thrombosis, prolonged dual antiplatelet therapy is currently recommended for at least 3 months after sirolimus-eluting stent placement and 6 months after paclitaxel-eluting stent placement.

The BAsel Stent Kosten Effektivitäts Trial - LAte Thrombotic Events (BASKET-LATE)\(^1\) trial was conducted to determine the incidence of late clinical events (> 6 months following intervention) related to stent thrombosis in patients treated with DES vs bare-metal stent (BMS) after patients discontinued clopidogrel therapy. The study was also designed to identify the predictors, timing, and outcome of such thrombotic events in relation to type of implanted stent.

**Study Design**

Between May 2003 and May 2004, patients treated with percutaneous coronary intervention and stenting were enrolled in the BASKET\(^2\) trial and randomized in a 2:1 fashion to receive DES or BMS. Patients who remained event-free at 6-month follow-up were subsequently enrolled in the BASKET-LATE trial. Patients were followed for an additional 12 months to determine the incidence of cardiac death or nonfatal myocardial infarction (MI) (primary endpoint) and clinically driven restenosis-related target vessel revascularization. Dual antiplatelet therapy was administered for 6 months in all patients regardless of stent type, and clopidogrel was discontinued in all patients after 6 months.

**Results**

In the BASKET trial, a total of 826 patients were randomized in a 2:1 fashion to receive either DES (n = 545) or BMS (n = 281). From this cohort, BASKET-LATE included 502 patients treated with DES (data are available for 499 patients) and 244 patients treated with BMS. Baseline clinical and lesion characteristics are shown in Table 1.
### Table 1. BASKET-LATE: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DES (n = 499)</th>
<th>BMS (n = 244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>63</td>
<td>64</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>77</td>
<td>77</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>67</td>
<td>66</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>S/P MI (%)</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>S/P PCI (%)</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>S/P CABG (%)</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Unstable angina (%)</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>ST-elevation MI (%)</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Stable angina (%)</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Culprit vessel (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>LCx</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>RCA</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Bypass graft (%)</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitors (%)</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Stents/patient (%)</td>
<td>1.5 ± 0.7</td>
<td>1.5 ± 0.7</td>
</tr>
</tbody>
</table>

BMS = bare-metal stent; CABG = coronary artery bypass graft; DES = drug-eluting stent; GP = glycoprotein; LAD = left anterior descending; LCx = left circumflex; MI = myocardial infarction; RCA = right coronary artery; S/P = status-post

The rates of nonfatal MI and cardiac death/nonfatal MI during 7-18 months of follow-up were significantly higher in the DES group than in the BMS group; however, the overall rate of major adverse cardiac events did not differ between the 2 groups (Figure 1).

![Figure 1. BASKET-LATE: major cardiac events during 7- to 18-month follow-up.](image)
Angiographically documented thrombosis rates were also similar between the 2 groups (Figure 2). Cardiac death, nonfatal MI, and the combined endpoint of cardiac death and MI were more frequently related to late stent thrombosis (Figure 3). These events occurred at a median of 116 (range, 15-362) days after stopping clopidogrel. By multivariate analysis, prior MI (odds ratio [OR] 3.0, \( P < .007 \)), need for glycoprotein IIb/IIIa inhibitor use (OR 3.4, \( P < .003 \)), and DES (OR 3.9, \( P < .03 \)) were independent predictors of late cardiac death/nonfatal MI.

**Figure 2.** BASKET-LATE: rate of late-stent thrombosis.

**Figure 3.** BASKET-LATE: outcomes related to late-stent thrombosis.

**Conclusions**

1. After clopidogrel discontinuation, late-stent thrombosis-related events:
• were 2-3 times more frequent among those who had received DES than among those who had received BMS;

• carried 4 times higher risk of cardiac death/MI vs non-thrombosis-related events;

• occurred up to 1 year after clopidogrel discontinuation; and

• were more frequent in patients with prior MI, those who needed glycoprotein IIb/IIIa inhibitors initially, or those who had received DES.

2. From these results, the authors calculated that real-world DES use in 100 patients avoids 5 target vessel revascularization events at 6 months but leads to 3.3 late deaths or MI.

**Viewpoint**

The results of this small study and the conclusions reached by the authors are certainly a cause for concern. As has been demonstrated by previous studies, the rate of late stent thrombosis after DES implantation was not significantly higher than the rate associated with BMS, but, nevertheless, the consequences are dire.

What I find especially troublesome is the fact that we cannot predict with certainty which patients are prone to develop late stent thrombosis and when stent thrombosis is likely to occur -- the latter of which is extremely variable in relation to clopidogrel discontinuation. I am not completely convinced that we should advise all patients treated with a DES to continue dual antiplatelet therapy indefinitely, especially when considering high costs and the potential for bleeding complications. This issue generated plenty of debate at the ACC meeting and is far from being resolved.

**References**

1. Pfisterer ME, Kaiser CA, Bader F, Brunner-La Rocca HP, Bonetti PO, Buser PT. Late clinical events related to late stent thrombosis after stopping clopidogrel: prospective randomized comparison between drug-eluting versus bare-metal stenting. Program and abstracts from the American College of Cardiology 55th Annual Scientific Session; March 11-14, 2006; Atlanta, Georgia. Abstract 422-11.

The following is the abstract for the Camenzind presentation (1st article) and the slides from a follow up presentation by J. Nordmann. (Watch the videos it's worth it.)
Safety of drug-eluting stents: insights from meta analysis.

A meta-analysis of first generation drug eluting stents - including both first generation drug eluting stent extent of both mortality and Q-wave Myocardial Infarction in comparison to bare metal stents. Here the presenter Edoardo Camenzind (Geneva, Switzerland) and the discussant Alain Nordmann (Basel, Switzerland) provide an overview of the results.

Introduction

First generation drug eluting stents (1stg-DES: sirolimus eluting stent [SES] have been widely accepted and are used for a large spectrum of clinical indications.

Recently case reports and autopsy reports have been published on single cases as well as on series of cases which experienced stent thrombosis more than 30 days after stent deployment, so called late stent thrombosis. Delayed healing and diminished antiplatelet therapy could be demonstrated as relevant precipitating factor.

The global incidence of ‘in-1st g-DES’ thrombosis according to the literature remains uncertain. According to some single center registries and post-marketing surveillance registries as well as meta-analysis the incidence of late angiographic stent thrombosis does not seem to be higher in 1st g-DES as compared to bare metal stents (BMS). However according to the recently presented BASKET-Late trial, a small randomized trial designed to evaluate cost effectiveness of 1st g-DES versus BMS, severe cardio-vascular events were significantly higher in patients with 1st g-DES as compared to BMS in the year following the interruption of dual antiplatelet therapy.

Methods

The current analysis embraced both 1st g-DES clinical programs (SES and PES) and included all available data concerning company supported randomized double-blind clinical trials comparing 1st g-DES to the respective BMS control. Of the SES program the following trials were included: RAVEL, SIRIUS, E-SIRIUS and C-SIRIUS and for the PES program: TAXUS II, IV, V and VI accounting for a total of n=878 SES vs n=870 BMS and n=1685 PES vs n=1675 BMS. Available randomized trials’ data within a specific study program (SES or PES) were stratified by trials and data of the same time-periods of follow-up were pooled as well as data of the latest available follow-up.

The clinically oriented analysis focuses on death, Q-wave MI and death and Q-wave MI combined thought to reflect the incidence of stent thrombosis best instead of using restrictive thrombosis definitions (e.g. late angiographic stent thrombosis).

Results

The incidence - up to the latest available follow-up - of total mortality and Q-wave MI combined were 38% (SES) and 16% (PES) higher in 1st g-DES as compared to control BMS (p-value: SES vs BMS: 0.03 ; PES vs BMS. 0.68).

Conclusion

Death and Q-wave myocardial infarction have a higher incidence in 1st generation drug eluting stents as compared to the bare metal control stents.

Thus the indiscriminated use of 1st g-DES should be avoided and the use of bare metal stent may still be maintained awaiting for safer 2nd g-DES.
SAFETY OF DRUG-ELUTING STENTS: INSIGHTS FROM A META-ANALYSIS

Alain J. Nordmann, Matthias Briel, Heiner C. Bucher
Basel Institute for Clinical Epidemiology
Switzerland

HOT LINE SESSION ESC Sep 3, 2006
BARCELONA
PURPOSE

- Meta-analysis of randomised controlled trials comparing sirolimus- or paclitaxel-eluting stents to bare metal stents to evaluate their effect on total, cardiac and non-cardiac mortality.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Follow-up years</th>
<th>N</th>
<th>Cause of death</th>
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<tbody>
<tr>
<td>NAVAL</td>
<td>4</td>
<td>10</td>
<td>4× cancer (lung, prostate, pancreas, gastrointestinal)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3× stroke, 2× hemorrhage, 1× ischemia</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>2× pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1× pulmonary embolism</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>4</td>
<td>466</td>
<td>4× cancer (renal, 1× colon, 1× unspecified)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4× respiratory failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2× stroke, 1× hemorrhage, 1× ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2× sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1× lymphoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1× car accident</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1× septic disorder (Alzheimer's disease)</td>
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<tr>
<td>C-SIRIUS</td>
<td>3</td>
<td>1</td>
<td>1× cancer (lung)</td>
</tr>
<tr>
<td>T-SIRIUS</td>
<td>3</td>
<td>2</td>
<td>1× cancer (lung)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1× stroke</td>
</tr>
<tr>
<td>SES-SMART</td>
<td>1</td>
<td>1</td>
<td>1× pancreatic cancer</td>
</tr>
<tr>
<td>DIABETES</td>
<td>1</td>
<td>5</td>
<td>1× septic shock</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1× stroke</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1× pulmonary embolism</td>
</tr>
<tr>
<td>BASNET</td>
<td>1</td>
<td>3</td>
<td>1× cancer, 1× cancer (lung, prostate, pancreas, gastrointestinal)</td>
</tr>
</tbody>
</table>

No non-cardiac deaths in patients randomized to drug-eluting stents so far in the SCANOSTENT trial.
CONCLUSIONS

• DES for the treatment of coronary artery disease do not reduce total mortality when compared to bare metal stents.
• Preliminary evidence suggest that sirolimus-, but not paclitaxel-eluting stents may lead to increased non-cardiac mortality.
• Long-term follow-up and assessment of cause-specific deaths in patients receiving DES are mandatory to determine long-term safety of these devices.
The following press articles point to the significance of these presentations:

ROCKVILLE, Md., Sept. 14 -- The FDA said today it will hold a special meeting of a device advisory committee to assess new data about "small but significant" increases in the rates of death and myocardial infarction among patients treated with drug-eluting coronary stents. The agency said that its Circulatory System Devices Advisory Panel will meet before the end of the year to consider the implications of a meta-analysis reported in Spain and earlier data that suggested late-stenosis safely concerns with the devices. In a statement, the agency added that it has already discussed safety concerns with the makers of the two FDA-approved drug-eluting stents-Cypher, a sirolimus-eluting stent sold by Cordis, a Johnson & Johnson company, and Taxus, the paclitaxel-eluting stent sold by Boston Scientific. The FDA cited two recent studies, BASKET (Basel Stent Cost Effectiveness Trial), first reported in March at the American College of Cardiology meeting, and the Camenzind meta-analysis reported this month in Barcelona at the European Society of Cardiology meeting. The BASKET study found that at 18 months, the rate of death or myocardial infarction was 8.4% for patients treated with drug-eluting stents and 7.5% for bare-metal stents, but that difference was not statistically significant. \( P=0.63 \). By contrast, the Camenzind meta-analysis, which included three-year data, found a 2.4% increase in the incidence of death or MI in patients who received Cypher stents compared with patients treated with bare-metal stents \( P=0.03 \). The FDA said it will review those data and other pertinent information at the advisory panel meeting. It also signaled that it is seeking more information about the possible mechanism of the excess mortality and MI in patients with drug-eluting stents. The hypothesis is that the events are caused by late stent thrombosis due to a failure of the stent to re-endothelialize, but that has yet to be proven. The FDA statement said the agency is continuing to evaluate information related to the duration of dual antiplatelet therapy with aspirin and Plavix (clopidogrel).

"Although the duration of [Plavix] 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 [Plavix] in more complex patients has not been defined," the FDA said. The current American College of Cardiology/American Heart Association guidelines recommend an minimum of three months of Plavix plus aspirin for patients who receive Cypher stents and six months of dual therapy for those who have Taxus stents implanted. The ACC/AHA also
recommends extending dual therapy for a year for patients with no known excess bleeding risk. The FDA said more clinical studies will probably be needed to determine the ideal duration of dual antiplatelet therapy. Meanwhile, the FDA offered reassurances about the safety of drug-eluting stents and said it "believes that coronary [drug-eluting stents] remain safe and effective when used in patients having clinical and coronary anatomic features similar to those treated in the pivotal trials conducted by the manufacturers for FDA approval."

Those approved indications are:

- The CYPHER Sirolimus-eluting Coronary Stent is indicated for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete de novo lesions of length ≤ 30 mm in native coronary arteries with reference vessel diameter of ≥ 2.5 mm to ≤ 3.5 mm.

- The TAXUS Express Paclitaxel-Eluting Coronary Stent System is indicated for improving luminal diameter for the treatment of de novo lesions ≤ 28 mm in length in native coronary arteries ≥ 2.5 to ≤ 3.75 mm in diameter.

Finally, the FDA said that for "thousands of patients each year, these devices have resulted in a significant reduction in the need of second procedures to treat restenosis." An estimated one million drug-eluting stents have been implanted in patients in the United States.

The drug eluting stents debate - Hot Line Session Results

TWO SEPARATE, independent meta-analyses - presented in Hot Line session I at the World Congress of Cardiology 2006 - bring the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) hailed the data as one of the most important presentations to come out of this year’s meeting.

"Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is unknown,” said Yusuf. “I've a feeling the data we're seeing today is only the tip of the iceberg. We need to encourage more public access to the data.”
Presenter, Edoardo Camenzind (Geneva, Switzerland), said recent case reports had flagged up the problem of in-stent thrombosis resulting from DES. The BASKET-LATE data showed that the rate of cardiac death and nonfatal myocardial infarction (MI) was higher in patients with DES than in those with bare metal stents (BMS) (p=0.01). “The problem is likely to be significantly under-reported, since if people die on the street they don’t fulfil the angiographic criteria to be classified as in-stent thrombosis.”

The second presenter, Alain Nordmann (Basel, Switzerland), had concerns that DES accounted for more than 90% of stents used in the USA and Switzerland now. Camenzind undertook a meta-analysis looking at death and Q-wave MI in all randomised DES trials where data were available. Results at the latest available followup (four years) showed the incidence of death or MI was 6.3% for the sirolimus stent and 3.9% for the control BMS stent (p=0.03). For the paclitaxel stent, rates were 2.6% compared to 2.3% for the BMS stent (p=0.68). He concluded that death and Q-wave MI were higher in firstgeneration DES than BMS. He stressed that the problem was in first-generation DES – sirolimus and paclitaxel – and might not arise in the second-generation.

In the second study, Nordmann undertook a meta-analysis of all randomised, controlled, first-generation DES trials comparing cardiac and non-cardiac deaths in DES versus BMS. At four years overall mortality was higher for both cardiac and non-cardiac deaths in DES patients. Of the 36 non-cardiac deaths identified, 15 were due to cancer, including lymphoma and cancers of the lung, prostate, pancreas, GI, kidney and rectum.

“At this time, we can’t prove a causal relationship, only a statistical association. What makes me concerned is how difficult it was to obtain this data from the manufacturer,” said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

Yusuf widened the debate to include percutaneous coronary intervention (PCI). “The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed,” he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

“There’s no beneficial influence on mortality – PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest pain. It’s not re-stenosis that kills but the thousands of lesions you can’t see. Stable angina can be controlled with full medical management.” Yusuf said vested interests included pharmaceutical companies, who have invested billions of dollars in DES, and cardiologists in the US and Canada who are reimbursed according to PCI procedures undertaken. He called for Euro Heart Surveys to provide clear evidence on when PCI was needed, predicting the majority of indications would be uncertain.

Jean Marco, chairperson of the PCI Euro Heart Survey, said that the Euro Heart Survey had outlined evidence-based indications for PCI. “These meta-analyses shouldn’t be viewed as detracting from the value of PCI and DES, but promoting a precautionary attitude towards the indiscriminate use of first generation DES.”

Reference:
Source:
Thrombosis is the price for the success of drug-eluting stents

Seldom has a medical product been introduced to greater enthusiasm than the announcement of the RAVEL study results at the Stockholm 2001 ESC Congress. To packed lecture halls, data was presented showing the Cypher sirolimus-eluting coronary stent had zero restenosis at six months. At the time Marie-Claude Morice, the chief investigator of the study, commented: “We are probably witnessing a new revolution in the treatment of coronary disease.”

Five years on, with around four million drug-eluting stents (DES) implanted worldwide, the future does not appear so rosy. Experience has shown that the success of DES comes at a price – patients using DES could be trading restenosis, which is seldom life-threatening, for instent thrombosis, which may lead to death and myocardial infarction (MI). Presentations to the 2006 World Congress will explore the problems and benefits of DES and highlight innovations that could be important to the future of this technology.

First introduced in 1979, percutaneous transluminal coronary angioplasty (PTCA), or balloon angioplasty, rapidly became the main method of coronary revascularisation. But restenosis – where trauma to the vessel wall results in proliferating smooth muscle cells migrating to the intima (the innermost layer of the blood vessel), causing the vessel to constrict again, sometimes within the stent (instent restenosis) – remained the Achilles heel, occurring in up to 30% of cases (J Am Coll Cardiol 2001; 37:2215–39). Two drug-eluting stents, the Cypher stent (Cordis/Johnson & Johnson) and Taxus stent (Boston Scientific) were introduced to overcome the problem, with many others in development. The Cypher and Taxus stents are produced by coating a stainless-steel stent with a thin layer of a non-erodable synthetic polymer containing either sirolimus or paclitaxel respectively.

In the landmark RAVEL study (N Engl J Med 2002; 346 1773-80), the angiographic rate of restenosis for the coated stent at six months was a stunning 0%, compared to 26% for the control bare metal stents (BMS). A second study, by Antonio Colombo, demonstrated that the Taxus stent reduced angiographic restenosis to 2.3% at six months compared to 17.9% for the BMS (Circulation 2003; 108:798-794).

However, the SIRIUS study, by Jeffrey Moses, which looked at patients who approximated more closely to everyday practice (including those with diabetes, longer lesions, and multi-vessel disease), did not produce such dramatic benefits for the Cypher stent (N Engl J Med; 2003:349;1315-23). The study, which randomised 1,058 higher risk patients to the Cypher stent or a BMS, showed a restenosis rate of 8.9% in the stented segment for DES patients compared to 36.3% for BMS patients.
Edoardo Camenzind (University Hospital of Geneva, Switzerland) said: “The studies demonstrate the difference between highly selected patients and more complex cases, showing that in real life situations the binary restenosis rate after DES deployment may be less spectacular.”

The studies were reassuring about the risk of instent thrombosis with DES. In two subsequent meta-analyses, one showed no difference in survival or MI rates between DES and BMS, despite a significantly lower rate of restenosis in DES patients, and the other showed no increased incidence of instent thrombosis up to a one year for DES (Bapapulle, Lancet 2004; 364:583-91 and Raul Moreno, J Am Coll Cardio; 2005 45:954-9).

In addition, a post-marketing surveillance registry, the e-Cypher Registry, by Philip Urban (Circulation. 2006; 113:2152-2163), found that at one year the rate of in-stent thrombosis in patients with the Cypher stent was 0.87%, which was comparable to data for BMS stents.

Matthias Pfisterer (University Hospital Basel, Switzerland) said: “Taken together, these studies indicate that DES reduce restenosis and target vessel revascularisation without significant effects on death or non-fatal MI over a period of up to 12 months.” But the real concerns centre on what happens at one year and beyond, where increasing evidence suggests that more late stent thromboses occur with DES than BMS.

Stephan Windecker (University Hospital Bern, Switzerland) said: “The issue of late angiographic stent thrombosis (LAST) is reason for considerable concern, with some cardiologists believing the incidence of thrombosis to be higher in DES than BMS after one year, and others saying you can’t be certain.”

The first indication something might be seriously amiss came in 2003 when the FDA issued two warnings to clinicians linking Cypher stent implantation to a total of 290 incidences of thrombosis 30 days after the device had been fitted, and to more than 60 deaths.

Around the same time, clinical and autopsy reports described late instent thrombosis occurring between 12-18 months after implantation, with one case caused by a hypersensitivity reaction probably related to the polymer (Circulation 2004; 109:701-705).

Renu Virmani (CV Path, Gaithersburg, MD) was not surprised. She has long been a lone voice, warning of dire consequences for DES after demonstrating both the sirolimus and paclitaxel-eluting stents showed delayed healing at one month in the arteries of pigs and rabbits. Delayed healing was characterised by persistent fibrin deposition, variable inflammation and incomplete endothelialisation.

Further cause for concern came from the Basel Stent Cost-effectiveness Trial – Late Thrombotic
Events (BASKET-LATE) data, which showed that among 746 DES or BMS patients who had dual antiplatelet therapy discontinued after the first six months, the rate of cardiac death or non-fatal MI over the following year was higher in patients with DES than BMS (4.9% versus 1.3%; p=0.01), and that this was likely to be related to late stent thrombosis, which presented as death or MI in 88% of cases.

"While patient numbers are low and the study design is observational, the results showed a disturbing trend in the wrong direction for DES," commented Windecker.

A non-statistically significant result of pooled analyses of the four SIRIUS and the four TAXUS studies showed that DES appeared to be associated with a higher risk of thrombosis at three years than BMS.

A clue to what is happening comes from a study by Michael Joner comparing autopsies of 23 people implanted with DES for more than 30 days, with 25 matched autopsies implanted with BMS (JACC 2006; 48:193-202). Results showed DES patients had greater delayed healing, characterised by persistent fibrin deposition and poorer endothelialisation compared to BMS stent patients.

Such studies suggest instent thrombosis may be caused by delayed or no re-endothelialisation. "The biggest problem is delayed healing," said Virmani. "Initially, there's little difference between BMS and DES, but after 14 days you start to see smooth muscle appearing in BMS, which you don't see in DES."

This is partly due to the eluted drugs that are not specific for smooth-muscle cells, and also prevent endothelialisation. "It's also likely that polymers on drug-eluting stents induce chronic inflammation that further delay healing," said Virmani. An additional contributory factor was the stoppage of dual antiplatelet therapy.

Camenzind said that the current definition of LAST was leading to an underestimate of the extent of instant thrombosis. In the Hot Line I session on Sunday there will be two dedicated presentations on this topic: "safety of drug-eluting stents" and "insights from meta-analysis".

The concerns surrounding LAST appear to be reaching a wider audience. On 22 June 2006 The Wall Street Journal quoted a number of cardiologists saying that they had seen "small, but nevertheless meaningful" reductions in the use of DES in their hospitals.

While there may be a temporary downturn in use of first generation DES, most cardiologists believe they are here to stay, but that new strategies are required. One simple approach might be to continue dual antiplatelet therapy long-term, but Camenzind warned this could cause bleeding complications.

Gabriel Steg (Hôpital Bichat-Claude Bernard, Paris) suggested that first generation DES use could be restricted to patients who were most likely to benefit from prevention of restenosis, such as diabetics, or those with multiple long lesions in small vessels, rather than indiscriminate use. During the Hot Line Session III, Christoph Kaiser (University Hospital Basel, Switzerland) will present an algorithm for a targeted stent use based on evidence from the BASKET trial, including a full 18-month follow-up.

Another solution might be to provide coatings that are more "biologically friendly" to promote natural healing processes. But, as Ron Waksman (Washington Hospital Center, Georgetown University, Washington DC) said, why choose a permanent prosthesis to solve a temporary healing problem? Significant advances in material engineering are poised to produce biodegradable stents. Some of these advances will be described in the "Bioresorbable stents: issues to be resolved" symposium at ESC on Monday. Current biodegradable stents include MediVas (San Diego) amino acid-based polyesteramides (PEA) and Reva (also based in San Diego) a poly DTE carbonide, which...
have the advantage of being CT and MRI compatible.

In the session, Waksman will explain the advantages of metallic biodegradable stents over polymer stents, focusing on radial strength and time to complete degradation, while Wim J van der Giessen (Erasmus Medical Center, Rotterdam) will counter that strategies, such as light energy and temperature, can be used to cure polymers and make them almost equally strong.

In the history of stent devices, Barcelona 2006 could prove as memorable as 2001.
James P. Greelish, MD
Assistant Professor
Director of Research and Education
Department of Cardiac Surgery
Vanderbilt University

Office: (615) 343-9195
Direct: (615) 343-9183
Cell: (615) 400-3484

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