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Quick Pulse

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DRUG-ELUTING STENT UPDATE

Twelve interventional cardiologists, cath lab directors, and cath lab managers/ supervisors in the U.S. were interviewed to see if drug-eluting stent (DES) use is changing due to concerns about late stent thrombosis. Sources were well aware of the stent thrombosis issue; doctors are concerned about it, and they have been discussing it among themselves. DES use remains relatively unaffected. Although some cath labs cut their use slightly over the summer, there is no continuing shift from DES to bare metal stents (BMS). However, doctors are prescribing longer use of dual antiplatelet therapy – Sanofi-Aventis/Bristol-Myers Squibb's Plavix (clopidogrel) and aspirin.

Background

Stent thrombosis has been an issue haunting drug-eluting stents for some time. Initially, much of the debate centered on whether Johnson & Johnson's Cypher was safer than Boston Scientific's Taxus, or vice versa. Then, fingers were pointed at the durable polymers as the likely culprit, piquing interest in bioerodable polymers, bioerodable stents, and polymer-less DES.

In addition, doctors became less convinced that the whole late stent thrombosis was due to durable polymers. The possible causes of stent thrombosis with DES now being discussed include: polymer, drug, duration of antiplatelet therapy, lack of re-endothelialization, stent expansion, stent fractures, and stent malapposition.

Concern rose a notch at the EuroPCR meeting in Paris in June 2006, but it reached a crescendo at the World Congress of Cardiology (WCC) meeting in Barcelona in early September. At WCC, late stent thrombosis was referred to as "the Cox-2 story of interventional cardiology." A non-interventional cardiologist 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."

At WCC, the concern was heightened by these presentations:

- Two meta-analyses of registries from the Netherlands ((RESEARCH and T-RESEARCH) and Switzerland (SIRTAX and POST-SIRTAX), covering 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. There was almost a linear increase between 30 days and 3 years. However, there was no statistically significant difference in stent thrombosis between Cypher and Taxus. These researchers also performed a

nested case-control study, using historic controls for BMS, and they found no significant difference between BMS and DES from 0-30 days, a non-significant advantage to BMS from 30-180 days, and a clear trend in favor of BMS beyond 180 days.

- An independent meta-analysis of the safety of first generation drug-eluting stents, based on published or presented randomized Cypher and Taxus clinical trials. Researchers found:
  - An excess of clinical events with both Cypher and Taxus.
  - A 38% increase in the relative risk of serious adverse events (death or MI) with Cypher and a 16% increase with Taxus vs. BMS.
  - A trend to increased mortality with DES over time. However, this trend was not statistically significant concerning total mortality.
  - No statistically significant difference between DES and BMS in ***cardiac mortality***.
  - No statistically significant difference between DES and BMS in non-cardiac mortality, but preliminary evidence suggesting that Cypher – but not Taxus – may lead to increased ***non-cardiac mortality***.

Current DES usage

On average, drug-eluting stents account for 91% of all stents used (range 70%-98%), and this is generally holding steady. Over the past three months, eight hospitals reported the DES share of their stent mix has been flat (unchanged). One hospital said there has been a traditional "summer slump" in overall stent usage due to physician and patient vacations, but no change has occurred in the mix between DES and BMS. Comments included:

- *Midwest cath lab manager:* "They (interventional cardiologists) are concerned, but they haven't changed their practice right now. They want to wait and see (how the situation develops)."
- *Illinois cath lab manager:* "Even with all the publicity surrounding the Boston Scientific Taxus stent (and stent thrombosis), there hasn't been too much of a change that we've seen…Everything is status quo."
- *Minnesota cath lab manager:* "Doctors are concerned, but there haven't been any changes (in DES use)."
- *Indiana cardiologist*: "At the recent European meetings there was a lot of hullabaloo about an increased thrombosis rate and mortality rate with DES…It created a stir, and I think maybe it raised awareness about things we already knew as interventional cardiologists."
- *Oklahoma:* "We are not doing anything differently."
- *Ohio cardiologist:* "I am moderately concerned, but it hasn't yet affected our usage."
- *Pennsylvania*: "Our DES use hasn't changed. It's pretty flat. There isn't even a slight trend either way."

Three hospitals have increased their BMS use and cut DES use, but all only made slight shifts, and that change from DES to BMS has already occurred, and sources insisted it is not a continuing trend.

- *New York:* "Until April or May, our DES use was 90%-92%. In July, August, and September, it was 84%-85%, which is a 6%-7% decline. And it's going to stay there (at that level)…The large decrease is because, for patients who we know won't take Plavix for a long time, or who may have non-cardiac surgery, in the past we gave them Plavix for three to six months and then stopped. Now, those groups are eliminated, and they are getting BMS."

- *Florida:* DES use averaged 96% for 2005, but year-to-date is 94%, and July, August, and September 2006 were all 90%, indicating about a 6% drop in DES use. "I talked to a couple of doctors about the European data, and they don't really think all of that is true. My guys don't think there is much to the stent thrombosis issue, at least not yet."

- *California:* "Our DES use is 70%-75%...We've gone down a little bit, mostly because everyone is very keyed into not putting DES in patients who are unlikely to take prolonged clopidogrel…It seems reasonable to put a non-DES in patients at low risk for restenosis, and if it's a short lesion in a big artery, maybe a non-DES would be the way to go. But for people with long lesions and medium sized arteries, BMS was no panacea…You definitely lose some of the benefits of DES if you reserve their use for treatment of in-stent restenosis in a bare metal stent."

The California doctor went on to explain: "You can't just throw a DES in there any more and say, 'Good luck,' because you have to have ***long*** discussions with patients. These reports of late stent thrombosis are sort of making everybody look twice at the utilization of DES. I think that because the U.S. embraced them so fully, there isn't much place to go but down. For me personally, I don't think it is going to be a huge difference (in DES use), but that's because I'm very paranoid from the get-go about making sure that patients can take prolonged clopidogrel and aspirin…We will continue to use DES. The people who say restenosis is benign don't do interventional cardiology or never had a stent themselves. The people we used to see – the 'frequent fliers' who used to come back and get 3-4-5 procedures on the same lesion – don't come back any more. They're not getting restenosis (with a DES)…We get the worst of the worst patients…and you can see a dramatic difference (in in-stent restenosis with DES). With balloons, it was pretty bad, and with DES, it is only mildly bad."

Usage outlook

In October and November 2006 – and for the foreseeable future – sources predicted that DES use will remain flat, but many will be watching what develops at the TCT meeting in Washington DC October 22-27, 2006, or at the FDA Advisory Committee meeting on stent thrombosis in December 2006. One source said, "It depends on what the next series of reports show. When we get better quantification of the risk, the big thing will be looking at the differences between the stents in terms of late outcomes."

DES choices

Sources also reported no real shifts in use between Johnson & Johnson's Cypher and Boston Scientific's Taxus drug-eluting stents. On average, Cypher accounts for 58.8% of DES use at these hospitals, and Taxus has 41.2% share. Comments on specific stents included:

- "Our doctors believe that Cypher is a better product."
- "We push for 80% Cypher use because of our purchasing agreement."
- "We use 98%-99% Cypher because our doctors like it, and we have a relationship with J&J on pricing."
- "We are 95% Taxus."
- "We have a contract with Boston Scientific to use more Taxus and get a better price, but our doctors prefer Cypher, so we are using more Cypher than Taxus."
- "There is no difference between the two. The Cypher people would have you think it is a Taxus problem, and the Taxus people think it's a generic problem. I fall into the latter category. I've seen late thrombosis occur with both stents. We use 60% Cypher, 40% Taxus."

Dual antiplatelet therapy

While concerns about stent thrombosis are generally not affecting overall DES use, they are leading to more and longer use of dual antiplatelet therapy. More than half the sources said they are keeping patients on Plavix longer than before, and the others said dual antiplatelet therapy recommendations have been unchanged. In one case, the recommendation is now for ***three years*** of Plavix. Comments included:

- *Midwest cath lab manager:* "We are keeping patients on Plavix a little longer."
- *New England:* "We are starting to pre-medicate ***all*** elective cases with 600 mg of Plavix prior to the procedure, and for the most part even patients that come from emergency rooms that get transferred here…get 600 mg of Plavix as well as full-strength aspirin unless it is contraindicated. Also, they get Plavix and aspirin after the procedure for at least six months, or longer, depending on whether it was a small vessel, etc."
- *Illinois cath lab manager:* "Generally, doctors are advising patients to stay on it (dual antiplatelet therapy) as long as they can afford it."
- *Indiana cardiologist:* "We do know that you have to give more prolonged use of Plavix and aspirin – way more than 30 days. The Cypher (package insert) says three months, and the Taxus (package insert) says six months, but many of us have seen thromboses much later than six months, nine months, or 12 months, and now the literature is bearing that out. Many of us interpret that as meaning: Keep patients on indefinite aspirin and Plavix…We tell patients the risks (with DES). If, in the first year the patient might want elective surgery, we ask, 'Can you postpone it? With DES it's committing you to lifelong aspirin and Plavix. Can you do that?' Some patients may opt for a BMS; they'd rather have the risk of restenosis than thrombosis. The literature says that you have a 1 in 200 per year – about 0.5% per year – late thrombosis rate, which is not very high, but if it happens, you have a 30%-40% chance of dying. So it is our practice to do aspirin and Plavix indefinitely. Whether that is right or wrong, I don't know, but it makes some intuitive sense to me."
- *New York cardiologist:* "We instituted a policy…starting in late June to recommend patients be on Plavix for ***three years*** – no longer one year – and baby aspirin for life."
- *California cardiologist:* "I'm telling everyone a year minimum – if they can afford the therapy. The risk is still fairly low, and it's a trade-off…I try to continue (the Plavix) indefinitely as well as aspirin the rest of their life…But there are (stent thrombosis) cases out there years later…There are a lot of reasons why late stent thrombosis may occur – allergic reactions, poorly opposed stents, complex lesions with multiple stents – but clearly one of the big things is non-compliance with clopidogrel. And there are conflicting data on the consequences of premature discontinuance of clopidogrel. In a JAMA (***Journal of the American Medical Association***) article a year and a half ago on a European registry, one out of three patients suffered stent thrombosis when clopidogrel was stopped prematurely – and 45% of them died. That's a huge issue. But on the other hand, there is David Cohen's analysis of an unrelated issue (not a stenting trial) but which had pretty good data about one month compliance with medications, and about a third of patients weren't taking their clopidogrel at one month much less three months. There's a disconnect here. If a third aren't taking their clopidogrel…we ought to see people dropping like flies, and it ought to be obvious…I know the truth is somewhere in between."

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