

# 20 Late Stent Thrombosis with Drug Eluting Stents—Is it End of the Road for Drug Eluting Stents?

The introduction of drug-eluting coronary stents as a means of preventing restenosis, has rapidly and profoundly affected the field of interventional cardiology. Met with widespread enthusiasm by the clinical community, drug-eluting stents are now used in a majority of intracoronary stenting procedures, justifying their characterization as a “transforming technology.” Drug-eluting stents have been implanted in nearly 6 million patients worldwide since they were introduced 3 years ago.

## **Drug Eluting Stents: Pathophysiologic Mechanism of Restenosis Prevention and Stent Thrombosis**

In percutaneous coronary interventions (PCI) the gain in luminal diameter is the result of splitting of the atherosclerotic plaque and by stretching of media and adventitia. The endothelial lining is often disrupted during PCI. The arterial response to this injury is a sequence of events that try to repair the site of injury. Within 72 hours, platelets and fibrin deposition starts associated with migration of acute inflammatory cells. Over the next 2 weeks, these are replaced by chronic inflammatory cells and proliferating smooth muscle cells that migrate from media and intima. These smooth muscle cells synthesize collagen and proteoglycans to form the neointima.<sup>1,2</sup>

Restenosis after Balloon angioplasty occurs as a result of: (1) formation of neointima and (2) Vessel recoil and adventitial fibrosis induced constriction of the vessel (Negative remodeling). Deployment of Bare Metal Stents (BMS) prevents vascular recoil and arterial constriction but it does not prevent neointimal proliferation resulting in considerable restenosis rates after bare metal stenting (approximately 25%). Success in inhibiting the neointimal proliferation was achieved with the discovery of Drug Eluting Stents (DES) which deliver antimitogenic agents (such as sirolimus and paclitaxel) locally at the site of injury and inhibit cellular proliferation.

*Stent thrombosis:* Deployment of a metallic foreign body within the artery creates a thrombosis risk. Antiplatelet therapy prevents thrombosis in the vast majority of cases until the stent struts are covered by an endothelialized neointima. Drug eluting stents by inhibiting smooth muscle cell proliferation and extra-cellular matrix synthesis may also inhibit re-endothelialization of injured arterial surface. The benefit of restenosis prevention is thus accompanied by a delay in arterial healing resulting in a prolongation of the window of risk for stent thrombosis.

## **Drug Eluting Stents—Clinical Application**

On the basis of the results of two pivotal studies SIRIUS and TAXUS IV, FDA approved CYPHER (Sirolimus-eluting stent by Cordis, Johnson & Johnson) in 2003 and Taxus Express (Paclitaxel eluting stent by Boston Scientific) in 2004 for clinical use. In both these pivotal studies drug eluting stents successfully met their primary endpoints (significant reduction in 9 months target

vessel failure for CYPHER and 9 months target vessel revascularization for TAXUS), and reduction in major adverse cardiac event (MACE) rates (mainly driven by reduced revascularization rates).<sup>3-4</sup> Since then DES have been shown to be significantly superior to BMS in reducing restenosis rates in various studies (RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, TAXUS studies).

### Labeled Indications

Based on the results of these pivotal studies the CYPHER and TAXUS stents were approved for the following limited anatomic indications:

- 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  $\leq 30$  mm on native coronary arteries with reference vessel diameter  $\geq 2.5$  mm to  $\leq 3.5$  mm.
- The TAXUS Express Paclitaxel-eluting coronary stent is indicated for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete *de novo* lesions of length  $\leq 28$  mm on native coronary arteries with reference vessel diameter  $\geq 2.5$  mm to  $\leq 3.75$  mm.

But use of DES in clinical practice, across the world has not been limited to above-mentioned indications. Majority (>60%) of the current use of DES is for non-labeled indications like more complex lesions and patient subsets (e.g. bifurcation lesion, multiple stents, diabetics, acute MI, renal dysfunction, multivessel disease, etc.).

### Concerns About Increased Late Stent Thrombosis

At the European Society of Cardiology (ESC) scientific congress, September 2006, Dr. Edoardo Camenzind of University Hospital Geneva presented his study entitled "Safety of drug eluting stents: a meta-analysis of 1st generation DES programs". In this study he compared the results of all published or presented trials comparing the Taxus or Cypher stents with a bare-metal stent. Results of this meta-analysis as shown in Figure 1.

Figure 1 shows the rate of death or Q-wave MI was 0.9% for BMS versus 1.7% for SES at 6-9 months ( $p=0.21$ ), 1.4% for BMS versus 2.3% for SES at 1 year ( $p=0.30$ ), 2% for BMS versus 3.7% for SES at 2 years ( $p=0.09$ ), 4% for BMS versus 6% for SES at 3 years ( $p=0.06$ ).

The rate of death or Q-wave MI was 1.5% for BMS versus 1.6% for TAXUS at 6-9 months ( $p=0.88$ ), 1.6% for BMS versus 1.7% for TAXUS at 1 year ( $p=0.80$ ), 2.8% for BMS versus 2.6% for TAXUS at 2 years ( $p=0.78$ ), 3.1% for BMS versus 3.5% for TAXUS at 3 years ( $p=0.6$ ) as shown in Figure 2.

Figure 3 shows the last available follow up, death or Q-wave MI was significantly higher in the SES group compared with the BMS group (6.3% Vs 3.9%, RR 1.38,  $p=0.03$ ). The rate of death or Q-wave MI at last follow-up did not differ significantly for PES compared with BMS (2.6% vs. 2.3%, RR 1.16,  $p=0.68$ ).

In summary, the Camenzind meta-analysis reported outcomes through three years post stent implantation and suggested a small but significant increase in death or Q-wave MI in patients treated with CYPHER stents possibly due to stent thrombosis compared to those treated with bare metal stents (increased rates not reaching statistical significance was also noticed with TAXUS stents).

At the Transcatheter Cardiovascular Therapeutics (TCT) Symposium in Washington, DC in October 2006, Drs Stone and Leon presented a meta-analysis of patient-level data which showed a significant increase in the incidence of stent thrombosis among patients with DES that had been implanted more than 1 year earlier: stent thrombosis occurred in five such patients in the Cypher group, as compared with none in the bare-metal group, and in nine such patients in the Taxus group, as compared with two in the bare-metal group. For the Taxus trials the cumulative

increase in stent thrombosis rate was 0.5% between one and four years after stent implantation (approximately 0.15% per year) and for the CYPHER trials it was 0.6% between one and four years (approximately 0.2% per year).

BASKET-LATE study followed the patients of BASKET study (in which 826 patients received DES Vs BMS and were followed up for 6 months for the cost effectiveness of DES) for additional 12 months and looked into late events between 7-18 months (defined as any cardiac death and documented nonfatal MI occurring between 7 and 18 months). Authors concluded that after the discontinuation of clopidogrel (6 months after stent implantation), the benefit of DES in reducing Target vessel revascularization is maintained; however, this benefit is mitigated by an increase in the rate of late cardiac death or nonfatal MI, possibly related to late stent thrombosis.<sup>5</sup>

Peter Wenaweser in his study (done at Bern and presented at ESC scientific congress 2006), found that the rate of stent thrombosis were 1.2% at 30 days, 1.7% at one year, 2.3% at two years, and 2.9% at three years, corresponding to a stent thrombosis rate of 0.6% per year between 30 days and three years.

### **DES: Decreased Stent Restenosis vs Increased Stent Thrombosis**

In contrast to restenosis stent thrombosis has a more acute presentation and carries a very high mortality. In a recent study, it was noticed that 29 of 2229 (1.3%) patients with DES implantation had stent thrombosis by 9 months of follow up. Of these, 14 patients (0.6%) had subacute thrombosis and 15 patients (0.7%) had late stent thrombosis (more than one month post-stenting). Seven patients (24%) presented with death, 20 patients (69%) presented with nonfatal MI and 2 (7%) with unstable angina. At follow up, of these 29 DES stent thrombosis patients 13 died, corresponding to a case fatality rate of 45%.<sup>6</sup> Similar rates of mortality and morbidity have been observed in other studies. On the other hand, stent restenosis is expressed as a relatively 'benign' clinical condition. Most of these patients present with exertional angina (64%), some with unstable angina (26.4%) and rest with acute MI (9.5%)<sup>7</sup> (Fig. 4).

The difference in the outcomes of DES Vs BMS is essentially due to a reduction in the rate of ischemia driven repeat revascularization. No differences in death and MI rates have been shown with these two types of stents at 9 to 12 months post-stenting. Data from multiple randomized clinical trials provide convincing evidence that the DES significantly reduce the rate of repeat revascularization but recently there has been an increasing concern of small but significant increase in late stent thrombosis. Reduction in the restenosis rate at the cost of increased stent thrombosis rate (as compared to BMS) has made some researchers to state, "We've traded a short-term benefit on a relatively benign disorder, namely restenosis, for a long-term mortality disadvantage." While others believe that as the event rates are very low therefore the benefits of this very effective strategy for coronary disease outweigh safety questions and it does not justify decreasing their use till more data is available.<sup>9,10</sup>

Concerns about mid and long term safety of drug eluting stents have stimulated rethinking as putting DES use into perspective and to find solutions that can decrease the sub-acute and late stent thrombosis, while maintaining the anti-restenosis benefit. Endeavor<sup>11</sup> (Zotarolimus-eluting phosphorylcholine polymer based) was shown to have lower rates of target vessel failure at nine months as compared to BMS (15.1% with BMS Vs 7.9% with Endeavor, p=0.0001) and lower MACE (major adverse cardiac events) (14.4% with BMS Vs 7.3% with Endeavor, p=0.0001). Restenosis rates were also significantly less with Endeavor. Rate of stent thrombosis was 0.5% with Endeavor, which was not different from BMS (1.2%).<sup>8</sup>

Author's strategy is to prolong the dual antiplatelet therapy to longer period than the current 6 months to 1 year. It is also clear that indiscriminate use of DES in all patients undergoing percutaneous coronary intervention is not justified.

At the St. Stephen's hospital, we have had a subacute stent thrombosis rate of roughly 1.5% (7 per 500 stents used) with the first generation DES. Roughly 80% of these have been associated

with discontinuation of clopidogrel use; generally without prior consultation with the physician. We have addressed this issue with the following steps: 1) Re-emphasize the meticulous continuation of clopidogrel therapy in all patients receiving DES. 2) Prolonging clopidogrel therapy beyond one year. 3) Using triple antiplatelet therapy that includes clopidogrel, aspirin and cilostazol, for the first month after DES implantation. We also have increasing experiences with the second generation DES that are either polymer free or have less polymer. Of 123 patients who received Costar (paclitaxel coated polymer based stent) in last one year ,one had stent thrombosis and one had in-stent restenosis. Of 60 patients receiving Endeavor stent one had stent thrombosis and one had in-stent restenosis. 32 patients received Yukon (non-polymer based sirolimus eluting stent) and there was no stent thrombosis or restenosis among these patients.

### **Areas of Uncertainty**

- Most of these studies, which have shown increased rates of death or MI with DES, are Meta-analysis based on the published literature. In contrast Meta-analysis based on patient-level data from DES manufacturers have not shown increased risk with these stents.
- As mentioned above the labeled indication for DES use are relatively few, whereas most of the patients where DES are implanted have a more complex coronary anatomy. Increased rates of stent thrombosis have been observed in more complex lesion and patient subsets (e.g. bifurcation lesion, multiple stents, diabetics, acute MI, renal dysfunction, multivessel disease). Data on this subset of patients is limited at present. Valuable information on DES thrombosis, death and MI rates in more complex setting is expected from ongoing registry studies.
- Multiple studies indicate increased rates of DES thrombosis, MI or mortality associated with premature discontinuation of dual anti-platelet therapy. The optimal duration of dual antiplatelet therapy particularly in more complex lesion is unknown.
- It is not known whether an extended course of dual antiplatelet therapy will prevent late stent thrombosis.
- It is not known whether non-polymer based DES or DES based on non-inflammatory polymers will have some effect on reducing late stent thrombosis.

As occurs with many clinical advances, the initial exuberance generally gives way to the realities presented by real world findings, particularly as indications expand beyond the package insert. As the issue of late stent thrombosis crops up many new treatment modalities are sure to appear. Issues of optimal duration of antiplatelet therapy, use of nonpolymer based stent / novel stents / stents coated with antibodies that attract endothelial cells will be addressed in detail in near future.

### **Possible Solutions**

1. Change in the antiplatelet regimen: to include additional agents or newer agents, given for a longer period of time.
2. Intravascular ultrasound guided stent implantation: to ensure uniform stent apposition against the arterial wall.
3. Use of new stent technology: use of nonpolymer based stents and biodegradable stents.

### **CONCLUSION**

That Drug Eluting Stents have been a major advance in medical therapeutics is beyond doubt. However, the initial enthusiasm should be tempered with caution regarding indiscriminate use. The current knowledge should be taken as the beginning of a new era in stent technology, rather than the end.

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