

## CHAPTER

# 9

# Coronary Stents- Safety Issues and Current Status

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## Introduction

Restenosis following plain balloon angioplasty, largely due to elastic recoil and negative remodeling was thought to have been taken care of by the introduction of Stents which are metal scaffoldings. However as time passed it became apparent that stents too became restenotic due to intimal proliferation. These Bare metal stents (BMS) were made up of medical stainless steel and several modifications in their design were made in an attempt to conquer restenosis. Gold coated, carbon coated and heparin coated stents were introduced to name a few, however all attempts proved futile and restenosis rates remained at a frustrating 25-40 %.<sup>1</sup>

*Restenosis was crowned as the “Achilles heel of Angioplasty”.*

Hope came through with the introduction of drug Eluting stents (DES)-stents which are coated with polymers which instead helped elute in a controlled fashion cytotoxic drugs over a period of 2-4 weeks. These drugs by interfering with cell division at the molecular level can favorably alter neointimal proliferation responsible for instent restenosis. These new additions to the armamentarium have helped bring Restenosis rates below 10%. The two prototype 1<sup>st</sup> generation DES which have been available since 2002 in Europe and Asia and from

2003 in the USA, are the Sirolimus eluting Cypher (Cordis, J&J) and paclitaxel eluting Taxus (Boston Scientific) and much data available today pertains to these two stents . Several randomized studies have proven the efficacy of both these stents upto a follow up period of 4 to 5 years. A new problem that seems to have cropped up with the use of DES is stent thrombosis especially late and very late stent thrombosis (Figure 1). Stent thrombosis can be classified as acute, subacute, late and very late when

**Figure 1 : Left coronary angiogram showing abrupt cutoff at inflow of the Cypher stent implanted 22 months ago. The patient at this time was on aspirin and this time subject to thrombus extraction and PCI**



**Table 1 : Proposed mechanisms of stent thrombosis with DES**

- Delayed Endothelialization
- Dysfunctional endothelialization
- Malapposition
- Aneurysm formation
- Premature cessation of antiplatelets
- Polymer related hypersensitivity

it occurs within 24 hours, 24 hours-30 days, 30 days to 1 year and beyond 1 year after implantation respectively. The magnitude of the problem of late and very late stent thrombosis has been worked out to be 0.2 % per year in patients with on label use and upto 0.6% per year for patients with off label use based upon the data from randomized studies and large registries.<sup>2,3</sup> This problem is seen very rarely with bare metal stents.

So just what is it that makes these DES which are otherwise technical marvels thrombogenic. Several proposals have been made as enlisted in Table 1 and are discussed below.

1. **Delayed Endothelialization:** The cytotoxic drugs though used in miniscule amounts arrest cell cycle and thus impair and delay the endothelialization within the stent which helps prevent restenosis. However this leads to less mature neointimal and greater number of bare stent struts when compared to DES without thrombosis. This along with other procedural and/or pathological risk factors including localised hypersensitivity, ostial and/or bifurcation stenting, malapposition/incomplete apposition of struts, increased stent length, overlapping stents, restenosis and penetration of struts into the necrotic core may promote stent thrombosis. Penetration of the necrotic core is frequently documented at autopsy in patients with acute MI. Autopsy stent studies suggest that healing is further impaired at sites of plaque rupture with DES as compared to BMS.<sup>4</sup>
2. **Dysfunctional Endothelialization:** Recent reports<sup>5</sup> have highlighted the issue of endothelial dysfunction 6 months after DES implantation. While the subgroup which received BMS had normal exercise induced vasodilatation, the DES group demonstrated paradoxical vasoconstriction in the peri stent region as well as the vessel portion well away from the distal stent margin. The authors proposed that this may contribute towards increased rates of delayed stent thrombosis.
3. **Polymer Related Hypersensitivity:** Human pathological specimens have shown that persistent fibrin deposition and eosinophilic infiltration in patients who had died of late stent thrombosis. The histopathological picture is one of localised hypersensitivity vasculitis which is thought to be polymer related and plays a pivotal role in stent thrombosis.<sup>6</sup> Newer generation polymer free DES are a step in this direction as discussed below.
4. **Premature cessation of antiplatelet therapy:** Stent implantation may induce platelet adhesion and activation of the coagulation cascade, both of which are recognized factors for stent thrombosis. Recent observations reveal that discontinuation of antiplatelet therapy is particularly with DES thrombosis. However there is a lack of randomized clinical trials that assess the appropriate duration of long term antiplatelet therapy for prevention of DES thrombosis. At present a course of 12 months of dual antiplatelet therapy may be considered, especially in high risk patients. Several experts feel that even longer term dual antiplatelet therapy may be logical as very late stent thrombosis is being increasingly reported.<sup>1</sup>
5. **Malapposition and aneurysm formation:** Both are believed to stem from delayed endothelialization. Late stent malapposition was seen in 21% Cypher stents in the RAVEL study as compared to 4% in the control arm.<sup>7</sup> Malapposition is also implicated in stent thrombosis. Similarly

**Figure 2 : Aneurysm developing 6 months after implantation of DES**



aneurysms may develop and at times these may leak and cause tamponade (Figure 2 & 3)

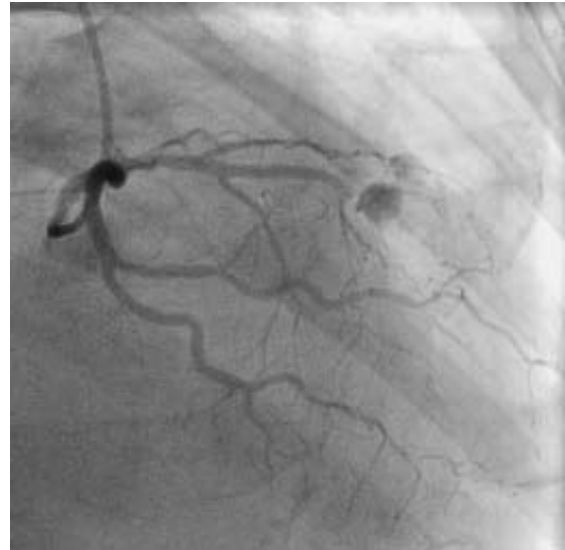
These findings have led to a growing concern and have caused a decline in DES sales all over the world. The problem is largely because of the rampant use of DES, especially off Label use and “DES for all approach”. Corrective measures are on the way and several newer and innovative stent designs have been developed. The current status of these is discussed below.

**1. Safer Drug Polymer combinations with thinner strut Cobalt chromium platforms**

Newer Generation Stents made of Chromium Cobalt, with thinner struts, better deliverability and coated with newer and safer drugs and polymers have been developed.

**Endeavor (Medtronic) :** It is a phosphorylcholine based cobalt alloy Driver coronary stent which elutes zotarolimus. In ENDEAVOR I a first in man (FIM) study the 48 month Target Lesion Revascularization (TLR) free survival was 96.9% and the stent thrombosis rate was very low (1%). In the ENDEAVOR II trial (Endeavor vs. Driver) the Major Adverse Coronary Event (MACE) event free survival rates at 3 years

**Figure 3 : Leaking aneurysm developing 4 months after DES implant. The patient presented with chest pain, pericardial rub and tamponade**



were 88.3% and 79.6% in the DES and BMS groups respectively.<sup>8</sup> The stent thrombosis rate was < 1% at 3 years of follow up.

The ENDEAVOR III trial though failed to meet its non inferiority end point in terms of late lumen loss as compared to Cypher possibly due to differences in drug elution, showed a significant higher freedom from death and MI for Endeavor versus Cypher (97.8% vs. 92.9%,  $p = 0.015$ ), indicating a superior safety profile for Endeavor at 2 years. The stent is in use in Europe and Asia.

**Xience V stent (Abbot Vascular, Calif):** It is an Everolimus eluting cobalt chromium stent with a durable fluoropolymer. The 14 days rabbit iliac artery model data showed 78% strut endothelialization as compared to 38% with Endeavor, 20% with TAXUS and 7% with Cypher. This makes it a very promising stent from the safety point.

The series of trials with this stent- SPIRIT I, SPIRIT II and III have shown excellent safety record for the Xience V stent. SPIRIT V a large international registry is ongoing to assess the safety and efficacy in real world cases. The

**Table 2 : Making New Generation Drug Eluting Stents safer- Current Directions of Development**

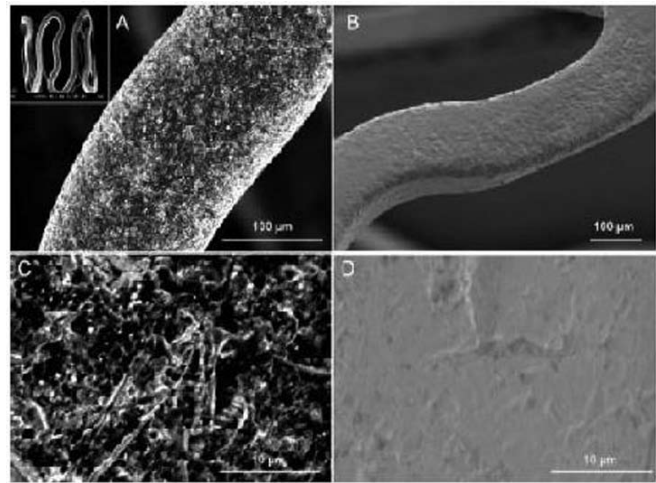
- Safer, drug polymer combinations with new generation thinner strut Cobalt Chromium platforms.
- Biodegradable polymers with special designs allowing multiple drug delivery capabilities.
- Surface Modification with drug delivery without use of polymer.
- Bioengineered Stents
- Bioabsorbable Stents

stent is already available in Europe and Asia for commercial use.

- 2. Newer Coatings:** To overcome problems due to the synthetic polymers newer coatings have been developed which are bioactive, biocompatible and bioresorbable or biodegradable. These include Hydroxyapatite (HAp), Glycocalix (GC) and Heparin. HAp is highly porous; forms bone mineral and matrix of teeth and is used as a bone substitute material and in dental implants. It is expected that these coatings will be safer than the existing ones. Glycocalix used biomimicry as the basis for it being less thrombogenic. Medtronic recently developed a novel co-polymer, the “Endeavor Rolute”, for extended release of zotarolimus in their next generation DES. Porcine implants show 100% re-endothelialization. Four month follow up human data in the first 30 patients revealed an in-stent late loss of 0.12 mm and no TVR or stent thrombosis. Larger randomized studies have been initiated.

### Biodegradable Polymers with special Designs

**The Conor MedStent and CoStar stent (Conor MedSystems, Calif):** These are stainless steel and Cobalt chromium stents respectively with reservoirs (wells) along the stent struts that are filled with a matrix of fully resorbable polymer (PLGA) and the drug Paclitaxel. The wells allow for potential unidirectional delivery of a drug (or drugs) to the luminal or mural sides of the vessel wall, as well as bidirectional delivery

**Figure 4: Scanning electron Microscope Picture of the unique microporus PEARL surface of the Yukon stent seen before and after coating with Sirolimus**

of the drug(s) to both sides simultaneously or different drugs to either side.

The major trials with this stent system PISCES (stainless steel) and COSTAR I<sup>o</sup> (chromium cobalt) were dose finding trials while EuroSTAR and COSTAR II were two pivotal clinical trials. The combined data of PISCES, COSTAR I, SCEPTER and EUROSTAR showed no case of late and very late stent thrombosis up to a period of 2 years follow up, highlighting the safety of this platform.

The COSTAR II trial compared the CoStar stent with the Taxus Express Paclitaxel eluting stent, and was designed to demonstrate non-inferiority at eight-month follow-up with respect to major adverse cardiac events (MACE) in patients with multi-vessel or single-vessel disease. At follow-up, the CoStar stent had significantly higher MACE rate than the Taxus stent (11.0% vs. 6.9%). This difference was largely due to a significantly higher incidence of clinically driven TVR (8.1% vs. 4.3%). COSTAR thus did not meet the non inferiority criteria. The stent thrombosis rate was however very low.

After failure of the COSTAR II to show non-inferiority, it is planned to use a limus drug

instead of Paclitaxel in the newer generation Costar stent in order to enhance its efficacy.

### 3. Surface Modification with drug delivery without Polymer

#### *Yukon, Translumina (GmbH, Germany)*

It is a polymer free, microporous, Sirolimus coated stent. The special stent surface known as PEARL has more than 1 million micropores per square centimeter of the stent surface which helps the drug to get adsorbed and spread uniformly on the stent surface creating a smooth layer (Fig 4). The drug is released predictably within 2 to 3 weeks leaving a bare stent in place. The drug can be coated in the cardiac catheterization laboratory using a specialized stent coating machine. These stents can be used up to 4 months after coating as per the release patterns studied in vitro.

Data from ISAR TEST<sup>10</sup> and TRANSIT registry<sup>11</sup> have shown that these stents to be efficacious and safe. The stent is commercially available for use in Europe and several countries in Asia.

### 4. Bioengineered Stents

**Genous Stent: :Orbus Neich, (Fort : Lauderdale, Fla)** has developed a stent system coated with a functional matrix loaded with immobilized antibodies against CD 34 antigens found on the surface of endothelial progenitor Cells (EPC). The EPC cells derived from the bone marrow are found in circulation and are preprogrammed to transform into mature endothelial cells at sites of endothelial damage which in the case of PCI is the site of stent implantation. Endothelial cells inhibit platelets and subsequent thrombus formation and have modulating effects on vascular wound healing by inhibiting smooth muscle cell migration, proliferation, and expression of extracellular matrix material.

The HEALING I and HEALING II<sup>12</sup> trials have shown promise for these stents. EPCs can be increased by pre treating patients with a high dose of statins

A DES-EPC combination is being developed. The drug would be eluted on the abluminal side to inhibit neointimal proliferation while the EPC homing on the endoluminal side would ensure proper re-endothelialization. This very innovative concept is likely to be evaluated in clinical trials shortly.

### 5. Bioabsorbable Stents

These are stents which disappear completely over a period of three to four months. The first stent to become available in this category was the Igaki-Tamai stent made of poly-L-lactic acid. The FIM study was carried out in a small cohort of 15 patients. The angiographic restenosis rate and TLR was 10.5%, which proved the stents efficacy, safety and effectiveness of this stent.

#### **Magnesium Based Bio absorbable stent**

Magnesium with its antithrombotic and antiproliferative properties has been evaluated as the main component of a bio absorbable stent. A recently reported study showed that magnesium based bio absorbable stents are safe but the restenosis rates are unacceptably high possibly because of an early dissolution in less than 4 months.<sup>13</sup> Modifications of stent characteristics with prolonged degradation and drug elution are currently in development.

#### **Everolimus Eluting Bioabsorbable Stent**

The stent has a bioabsorbable structure and polymer made of polylactic acid that controls the release of Everolimus. The 'ABSORB Trial' using this stent revealed very promising results. At 180 days the MACE continued to be low at 3.3% with no cases of stent thrombosis. However at 90 days the late stent malapposition rate as seen by intravascular ultrasound was 25% possibly due to recoil of the stent. Changes in the stent design are underway to eliminate the problem of recoil. Bio absorbable stents are in an early stage of development but hold considerable promise to overcome many of

the limitations of the current generation of permanent metal implants.

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