Coronary-Artery Stent

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The use of percutaneously introduced prosthetic devices to maintain the luminal integrity of diseased blood vessels was proposed by Dotter and Judkins in 1964 (2), well before the introduction of coronary angioplasty by Gruntzig et al 1997.(3)

Palmaz et al introduced the use of balloon-mounted stents (as used in coronary arteries today) in peripheral arteries in 1985.(4)

Schatz et al subsequently modified the palmaz-stent, which led to the development of the first commercially successful stent, the palmaz-schatz stent.(5) One such device was a metal tube or" Scaffold" that was inserted. Puel and Sigwart were the first to implant a stent in humans after balloon angioplasty in March 1986.

Sigwart and colleagues were also the first to describe the use of this stent in 1987 for emergency vessel closure during balloon angioplasty.(6)

In 1994 the first Palmaz-Schatz stent was approved for use in the United States.(7)

Over the next decade, several generations of bare metal stents were developed, with each succeeding one being more flexible and easier to deliver to narrowing.(7)

Early observation trials highlighted problems associated with the use of stents, in particular, a high incidence of subacute occlusion, despite aggressive anticoagulation regimens that prolonged hospital stays and that were difficult to control and occasionally led to serious events.(1)

In 1993 two important randomized trials compared the Palmaz-schatz stent with angioplasty, establishing the elective placement of coronary stents as a standard treatment. (BENESTENT, STRESS)

Although the implantation of an intracoronary stent prevents the acute recoil and post-injury arterial shrinkage associated with balloon angioplasty, it increases the risk of subacute thrombosis (3.7 percent of patients, a value higher than that seen with balloon angioplasty alone) and, more importantly, replaces the atherosclerotic coronary disease with the more severe iatrogenic condition of in-stent neointimal hyperplasia, that is, the growth of scar tissue inside the stent through the cell-cycle pathway, and as a result, the proliferation and migration of vascular smooth-muscle cells.(1) This in-stent restenosis occurs in about 25% of cases of bare metal implantation, typically at six months, necessitating a repeat procedure.(7) A recent meta-analysis of 29 published, randomized studies involving 9918 patients and comparing balloon angioplasty with routine coronary stenting with bare stents confirmed that stenting reduces restenosis and repeat intervention, but dose not reduce mortality or MI.(8)

Once a role for elective stent implantation was established, the next goal was to overcome the compplications of subacute thrombosis and neointimal hyperplasia through pharmacologic and physical means.

Various biologically inert surfaces coatings, such as carbon, platinum, phosphorylcholine, and gold, have been

applied to stainless-steel stents in an attempt to reduce thrombosis and restenosis, but the effectiveness of these strategies has not been proven in clinical trials. Significat reduction of stent thrombosis with heparin-coated stents has been reported from a single center study.(9)

Drug-Eluting Stents

Sometimes referred to as "coated"or "medicated" stent, a drug-eluting stent is a normal metal stent that has been coated with a pharmacologic agent (drug) that is known to interfere with the process of restenosis.

The components of a drug-eluting stent can be divided into a platform (the stent), a carrier (usualy a polymer), and an agent (a drug) to prevent restenosis.

Stents are ideal delivery systems because they allow the local delivery of the active agent to the area of vascular injury, averting the need to deliver high doses systemically.

A drug that is successfully eluted should inhibit the complex cascade of events that leads to neointimal formation after stent implantation. Different drug-eluting stents vary in their ability to inhibit neointimal growth. However, in the data gathered so far, the drug-eluting stent has been extremely successful in reducing restenosis from a 20%-30% range to single digits.

In addition to the drug-eluting stent itself, there are several decisions made by the interventional cardiologist that result in a successful placement:

-Correct sizing of the stent length

-Correct sizing of the stent diameter

-Sufficient deployment of the stent; once placed at the optimum site in the blocked artery, it is expanded fully to the arterial wall.

Successful Drug-Eluting Stents

The first positive clinical data on drug-eluting stents came from trials examining Sirolimos-Coated stents. The Cypher Sirolomus-eluting stent (Cordis, Johnson and Johnson), first implanted in Brazil and the Netherlands.Paclitaxel is a potent antiproliferative agent that inhibits the disassembly of microtubules. There were a lot of studies that led to FDA approval of Cypher (Sirolimus-euting stent) in April 2003 and Taxus in March 2004 (Paclitaxel-eluting stent). The approved indications according to the FDA statements were: (10)

■ The Cypher Sirolimus-eluting coronary stent is indicated for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete denovo lesions of lengths ? 30mm in native coronary arteries with reference vessel diameter of ?2.5 mm to ?3.5mm.

■ The Taxus Express Paclitaxel-eluting stent system is indicated for improving luminal diameter for the treatment of denovo lesions ?28 mm in length in native coronary arteries ? 2.5 mm to ? 3.75 mm in diameter.There are a lot of comparative trials of Cypher with Taxus stents; some of these trials show superiority of one over the other and some show no difference, but the major positive for drug-eluting stents is that both the TAXUS and CYPHER stents have shown a significant reduction of restenosis(7) and the need for reintervention in the treated vessel. In spite of reduction of restenosis, the new data suggested a small but significant risk of stent thrombosis in patients who have been treated with the CYPHER and TAXUS stents.(12)

On the other hand, the Swiss reseachers in their January 2 issue of the Journal of American College of cardiology highlighted another potential problem with drug-eluting stents. They found that the drug-eluting stents seem to inhibit the growth of collateral coronary circulation and after six months of implantation of drug-eluting stents, coronary collateral function is 30% to 40% lower than that obtained equally long after bare metal-stent implantation.(13) The Swiss team concluded, considering the protective nature of collateral vessels, this could lead to more serious cardiac events in the presence of abrupt coronary occlusion.(13)

Drug - Eluting Stents Thrombosis

Thrombosis within the stent may occur early, within the first 30 days after implantation, or late, if after this period, with differing causes. The most common cause of early stent thrombosis is mechanical (unrecognized dissection or underexpansion of the stent), whereas late stent thrombosis is potentially due to a mismatch

between the stent and the vessel (stent malposition), hypersensitivity, or abnormal rendothelialization. A recently recognized potential predisposing factor for stent thrombosis is resistance to aspirin and Clopidogrel; this association requires more investigation.(1)

Several presentations made at the World Congress of Cardiology/European Society of Cardiology annual meeting (2006) in Barcelona are once again highlighting some physicians'and patients' concerns about the long-term safety of drug-eluting stents (DES)(14). Several recent analyses that tracked patient outcomes for four to five years after stent placement showed that blood clots were slightly more likely to form inside a drug-eluting stent than inside a bare metal stent.(15) In one of the studies from the Thorax Center in Rotterdam, Dr. Peter Wenaweser reported that over three years the cumulative rate of thrombosis was 2.9%, but what was disturbing was that the rate was linear?starting at 1.2% at 30days (similar to bare-metal stents) and then 0.6% each year thereafter. Unlike bare-metal stents, thrombosis did not seem to wane with time, but continued to increase at the same rate, confirming concerns that drug-eluting stents suppress cell growth too much in some individuals, opening the door to blood clots (thromboses) which have serious consequences. (14) In another study by Dr. Eduardo Camenziad of University Hospital of Geneva, outcomes of patients in bare-metal stents were compared with those with drug-eluting stents.The results were dramatic: the incidence of death and heart attack was higher in patients who received drug-eluting stents?30%- 40% higher in Cypher studies; about 5% higher in Taxus group. Dr.Camenziad concluded that these increases were "the clinical presentation of stent thrombosis".(14)

Even though stent thrombosis occurs at low rates, new data suggested that it is significant(12) and extremely dangerous; fatal in over one third of cases.(7) As for concerns about adverse events related to coronary drug-eluting stents, FDA issued an initial statement on September 14, 2006. The statement noted that there is a small but significant risk of stent thrombosis in patients who have been treated with Cypher and Taxus stents. On December 7 and 8, The Circulatory System Devices Advisory Panel met in an effort to fully characterize the risks, timing and incidence of drug-eluting stent thrombosis, and in response to specific questions posed by FDA, the panel supported the continued use of these devices especially as on-label use (use of device inside the FDA- approved indications), with awareness of increased risks of stent thrombosis, death or MI with off-lable use (use of device outside the FDA-approved indications). It should be noticed that at least 60% of current drug-eluting stent use is off-label.(12) In conclusion, in order to minimize the risk of late stent thrombosis the following, recommedations has been proposed by the Society for Cardiovascular Angiography and Interventions (SCAI).(15)

- Prior to any stent implantation, patients should meet accepted criteria for coronary intervention as described in guidelines jointly published by the ACC, AHA, and SCAI.
- The decision to treat a patient with a drug-eluting stent-rather than a bare metal stent or bypass surgery-must be made on an individual patient basis, considering the relative risks and benefits of each therapy. This determination will vary according to each patient's medical history, coexisting illnesses, and lesion characteristics.
- Patients must be carefully evaluated for their ability to adhere to long-term therapy with dual anti-clotting medications.
- Careful attention must be paid to stent implantation technique, including the use of intravascular ultrasound, screening for arterial calcification, and pretreatment of complex lesions in some cases.
- Patients should take dual anti-clotting medication for at least three to six months, preferably for 12 months unless there is a high risk for bleeding. In patients with a higher-than average risk for late stent thrombosis-for example, those with diabetes- physicians should consider not only continuing dual anti-clotting medication for longer than 12 months, but also testing responsiveness to these medications and adjusting dosages as needed.
- Discontinuation of dual anti-clotting medication requires careful consideration and must be individualized for each patient.

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