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HeartFacts

Southern California Cardiovascular Consultants

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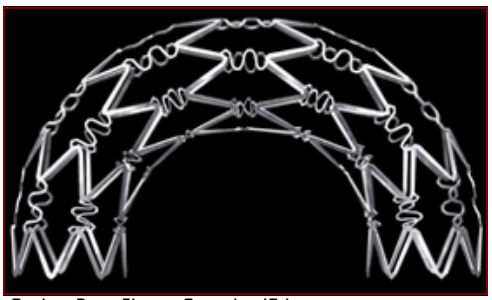
Drug Eluting Stents

Drug eluting stents (DES) are the latest weapon in the interventional arsenal. Available in Europe since 2001, this device has now been implanted in approximately 440,000 human beings worldwide. The Cypher stent from Johnson & Johnson is the first DES released in the U.S. Why DES?

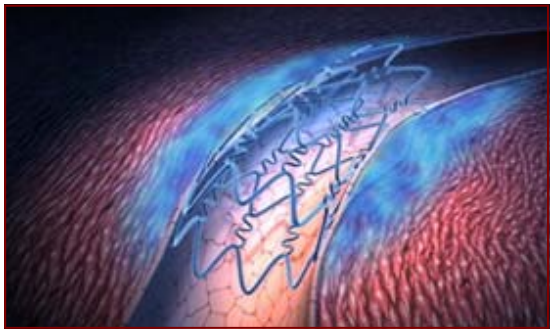
At the dawn of coronary intervention it became apparent that reobstruction of the treated coronary artery occurred in as many as 40 percent of patients undergoing balloon angioplasty. Coronary stents were developed in major part to deal with this phenomenon. The best metal stents reduced restenosis to about 20 percent of patients treated but did not eliminate the problem.

In-stent restenosis (ISR) seemed to be an irreducible problem. This was a new iatrogenic disease consisting of scar tissue build up inside the stent. Histologically, the tissue was identical to that found in keloids. Scientists began to suspect that trauma to the arterial media occurring at the time of implantation triggers the transformation of smooth muscle cells into fibroblasts. The fibroblasts then lay down voluminous quantities of collagen and elastin within and adjacent to the device. Over months this gradually chokes off the newly reconstructed lumen.

Early on it was noted that the incidence of the phenomenon was directly proportional to the length of the stent implanted and inversely proportional to its diameter. "Shorter and fatter" became the holy grail of stenting and this strategy was shown to reduce ISR. Making the stent struts thinner also seemed to reduce ISR and this led to a search for newer materials with greater radial strength, e.g. cobalt chromium. (Some scientists have suggested that the incidence of ISR may be related to the quantity of nickel in a given manufacturer's stainless steel. Patients who have experienced ISR appear to have a higher prevalence of contact dermatitis when challenged by nickel. Lastly, oral medications including valsartan and folic acid have been reported to reduce ISR.



Cypher Drug Eluting Stent by J&J



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A number of treatment strategies to deal with patients who develop ISR have evolved. Conventional balloon angioplasty pushes the scar outside the struts but unfortunately the tissue frequently prolapses back into the lumen. Atherectomy, rotablator, and laser have all been tried in an effort to debulk tissue. (Nothing is quite as exciting as getting a rotablator burr trapped in a stent strut!). The current technique for dealing with ISR involves scoring the tissue with a cutting balloon and pushing it outside the struts with further balloon expansion. This is followed by the delivery of low dose beta radiation transluminally using a special catheter connected to a hot source. The treatment takes about three minutes and is called vascular brachytherapy or VBT.

All of this led to a search for some method that might **prevent** ISR. Focusing on the transformation of smooth muscle cells (SMC) to fibroblasts, scientists proposed coating bare metal stents (BMS) with antimitotic chemotherapeutic agents. Initial results in animals were promising and every manufacturer rushed to find its own unique agent. In general a BMS is coated with a polymer that embeds

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Drug Eluting Stents (continued)

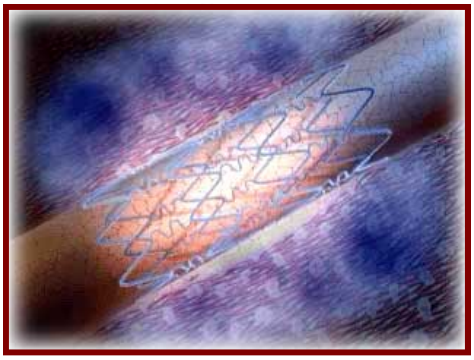
"Focusing on the transformation of smooth muscle cells (SMC) to fibroblasts, scientists proposed coating bare metal stents (BMS) with antimitotic chemotherapeutic agents." •

the drug and releases it slowly over weeks. The drug inhibits SMC transformation triggered by the trauma of implantation. The stent not only reconstructs the lumen but also serves as a slow release drug delivery system.

The initial trials of the Johnson & Johnson Cypher stent were remarkable. There was no ISR in the pilot trial of approximately 100 patients. Angiographic ISR was reduced to 9 percent in the qualifying trial of approximately 500 patients. The stent was released with great fanfare and expectation. Enthusiasm was quickly dampened.

J. & J. chose to build their DES on an older stent design. This "platform" is bulky and not as deliverable as more sleekly profiled current BMS. Moreover, the stent is somewhat stiff and does not have much lateral flexion. When implanted on a curve it tends to straighten the segment and create torsion points at the inlet and outlet. It was soon noted that these areas were foci for a new form of restenosis occurring outside the stent margins. A characteristic angiographic appearance was quickly dubbed the "edge effect" or "candy wrapper effect". It has been postulated that torsion occurring with each ventricular systole creates trauma at these points, which results in SMC transformation just proximal and distal to the stent. Our experience suggests that the 9 percent restenosis rate may be slightly higher in the real world because clinicians are forced to deal with complex disease that is traditionally an exclusion in stent trials.

A further concern is newly available basic science research in animals which suggests that drug eluting stents delay endothelialization of the device and may simply postpone scar tissue formation not prevent it. At about the same time, a small number of cases of subacute thrombosis in patients has caused a torrent of case solicitations by trial lawyers. (Check out "Cypher stent" on the Internet using any search engine). Citing the animal data, their brief claim that non-endothelialization of bare metal creates a nidus for clot deposition. Preliminary analysis by the FDA, however, reveals this rate to be no higher than with traditional stents.



Artists rendering of DES

A second manufacturer is poised to release its DES. The Boston Scientific stent will likely become available in the first quarter of 2004. In the TAXUS IV trial this stent had an in segment restenosis rate of 7.9 percent and an ISR of 5.5 percent. The REALITY trial will pit the two companies' stents in a head-to-head comparison. Stay tuned. The Stent Wars have begun. •

L.R. O'Connor, M.D., F.A.C.C.

"A second manufacturer is poised to release its DES. The Boston Scientific stent will likely become available in the first quarter of 2004." •

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Y. Joseph Wen , M.D.

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