

# DRUG-ELUTING STENTS

## an end to restenosis as we know it?

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### A history of intervention

It's hard to believe that selective coronary angiography is only 44 years old—first accidentally performed during aortography by Sones et al. in 1958 in the Cleveland Clinic [1]. An initially primitive procedure was rapidly refined by various pioneers. In parallel with this was the development of a therapeutic procedure for stenosed lower limb arteries. In 1964, Charles Dotter, in collaboration with Judkins, used catheters of increasing diameter, percutaneously, in a method somewhat analogous to oesophageal dilatation as performed today [2].

One limitation of this procedure was the need for an access port larger than the maximum diameter achieved in the target vessel. A solution eventually emerged with the first prototype balloon catheter. Latex balloons were disappointing, but in 1974, Andreas Gruntzig, under advice from a local Swiss expert in plastics, used polyvinyl chloride (PVC) to produce a balloon catheter which remains the basic design for angioplasty catheters today.

The first patient to undergo coronary angioplasty was a 38-year-old businessman in Zurich, who presented with unstable angina and anterior ST elevation on a subsequent exercise stress test [3]. Coronary angiography revealed a tight proximal left anterior descending (LAD) lesion, and the patient was introduced to Gruntzig, who offered balloon PTCA as an alternative to the then unavoidable bypass graft operation. Some 23 years on, the dilatation site was pristine at repeat coronary angiography (performed for atypical chest pain). Unfortunately, the outcome was not so favourable for many of the subsequent patients undergoing PTCA. Numerous practitioners have published on the incidence of restenosis in the treated segment, usually in the first six months, including Patrick Serruys of the Thorax Centre in Rotterdam, who reported in 1988 a 25-50% restenosis rate, depending on the criteria for defining restenosis.

### Coronary stenting

Coronary stents had emerged in 1986 — first implanted in Toulouse, France by Jacques Puel [4]. Around this time, several series of stent implantation in dogs were published by US groups, including Palmaz and Schatz [5]. While initially useful in scaffolding inadvertent dissections, stent use was limited by coagulation problems, requiring anticoagulation with heparin and warfarin before the advent of the newer

oral anti-platelet agents, such as clopidogrel (Plavix), which helped to liberate stenting as a procedure.

Over the last six years, the rate of stent implantation in most interventional units has risen to 70–90% of all cases. Indeed, in the UK, the National Institute for Clinical Excellence (NICE) guidelines for 2000 recommended all coronary lesions undergoing angioplasty be stented, if at all feasible, for safety and cost reasons [6].

### A history of restenosis

The advent and increased usage of stenting has reduced the risk of restenosis and the need for re-intervention, but only to a less-than-acceptable rate of between 20 and 30%. Restenosis occurs almost exclusively as a result of neointimal hyperplasia. It represents an extreme form of the healing response which occurs in all interventional sites. To some extent, the number of patients who develop re-narrowing can be reduced by acutely achieving the largest possible vessel diameter (e.g., stenting with an intravascular ultrasound guide). However, further therapies are required to reduce this rate even further.

Brachytherapy (refined to local delivery of  $\gamma$  or  $\beta$  emitting radiation) has shown promise in reducing intimal cell proliferation. A number of drawbacks are emerging, such as the need for both interventional cardiologists and radiation therapists to be present, increasing procedure costs and complexity. There is an obvious concern with regard to radiation exposure, of both the patient and close contacts. Even more disappointing is the tarnishing of initially promising results with the probability that radioactive stents delay, but do not prevent neointimal hyperplasia, and in some studies, late occlusion has occurred.

Investigators have spent many years now seeking the elusive holy grail: an anti-proliferative drug that can be mounted on a stent to eliminate restenosis.

Early efforts included the use of gold stents, which had no significant influence on thrombotic events in the first 30 days, but were associated with a considerable increase in the risk of restenosis over the first year after stenting, when compared to non-coated steel stents.

The first obstacle to overcome was the requirement for a safe, effective delivery vehicle for the selected drug. Any polymer stent coating had to fulfil two important criteria:

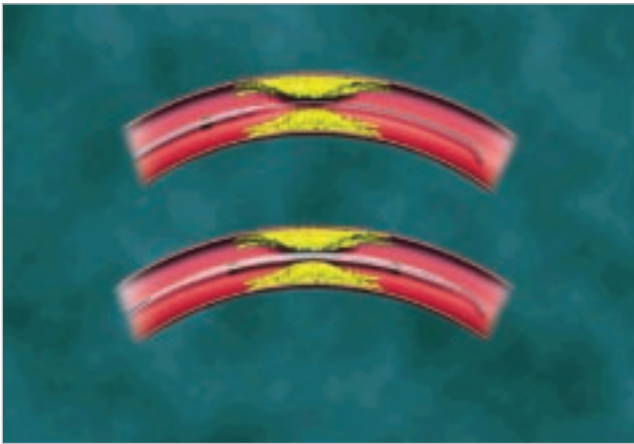


Figure a.

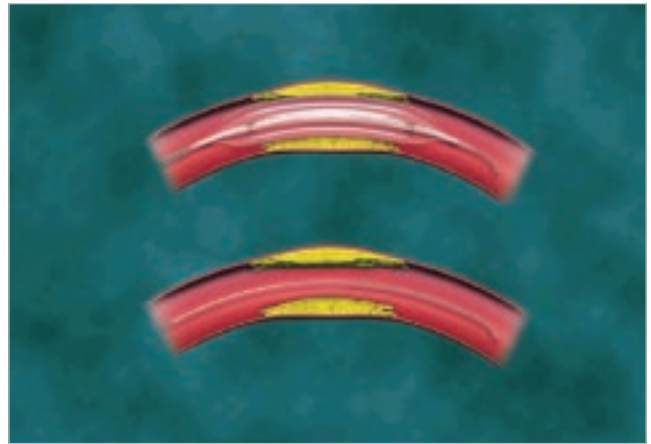


Figure b.

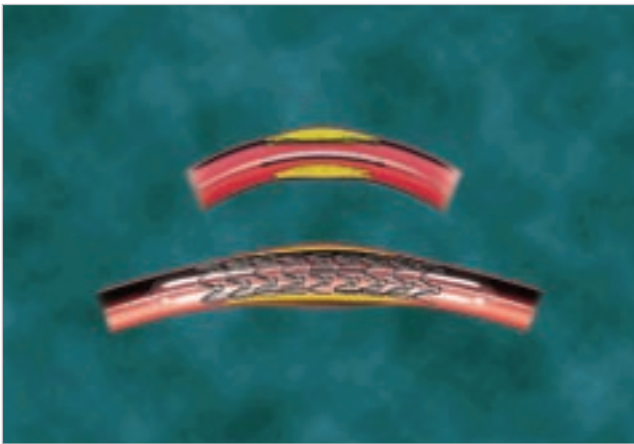


Figure c.

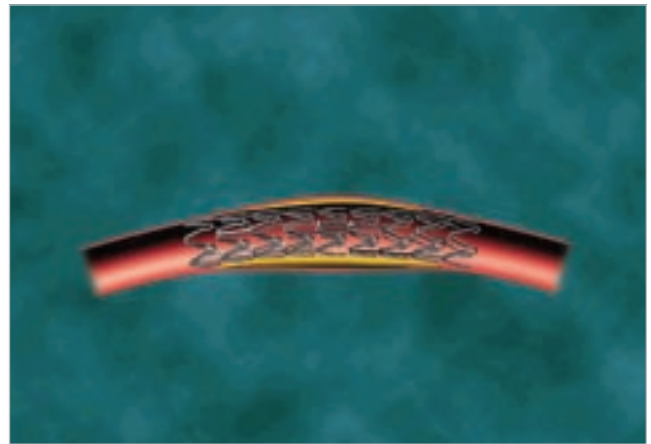


Figure d.

Figures (a) through (d) illustrate balloon angioplasty to a stenosed coronary artery with deployment of a metallic stent to maintain arterial patency.

firstly, it had to be capable of releasing drugs in appropriate doses over a specified period, and secondly, the coating itself had to be relatively inert, avoiding either local or systemic reaction. An early breakthrough was the publication of a large prospective multicentre trial of a polymer-clad stent versus a conventional stainless steel stent. This coated stent was not associated with thrombotic events and had a similar number of end-points reached as the conventional stent.

Once a delivery system had emerged, work intensified in many centres on the identification of a safe, effective, anti-proliferative drug. Early animal, and now human, usage of several agents has been promising. The highest profile publications have been from the RAVEL study investigators. Presentation of their 6-month results at the European Society of Cardiology meeting in Stockholm, 2001 literally had people running to phone their stockbrokers. The RAVEL Study (Randomised study with sirolimus-coated Bx VELOCITY balloon-expandable stents in the treatment of patients with *de novo* coronary lesions) used sirolimus (originally Rapamycin). This drug was initially in development for antimicrobial properties in the 1970s, but was quickly abandoned because its anti-fungal benefits were outweighed by its immunosuppressive side effects. It came back into use in the renal transplant programme for the prevention of graft rejection. Animal studies of heart transplant recipients on

sirolimus treatment revealed an unexpected absence of coronary intimal proliferation. Human studies of sirolimus have thus far exceeded expectations. RAVEL was a randomised double-blind study of coated vs. uncoated Bx Velocity stent in 238 patients at 19 centres in Europe and South America. At six months, there was 0% restenosis in the sirolimus group compared with 26% in the bare stents group. Major adverse events at seven months in the treatment group were 3.3%, compared with 27.1% of controls ( $p < 0.0001$ ).

Forty-five patients were subsequently studied in Brazil and Rotterdam by Dr E. Sousa and Dr P. Serruys [7]. The patients were given either fast or slow-release stents and followed out to one year. Angiographic and intravascular ultrasound (IVUS) follow-up was obtained at 4 and 12 months in Brazil and at six months in Rotterdam. No patient achieved >50% diameter restenosis at one year and IVUS-detected neointimal hyperplasia was virtually absent. Studies are now underway on their use for in-stent restenosis.

Other drugs and studies with potential include Taxus, which used paclitaxel-coated stents in a 3-centre study in Germany. Paclitaxel is an antiproliferative and cytostatic agent without toxicity. It prevents smooth muscle cell migration and reduced inflammation and apoptosis. The dose used is very small compared with chemotherapy doses. The restenosis rate was 0% in the coated stent versus 10% in

the NIR stent group (control group results were better than average, possibly because it was IVUS-guided). There were no major adverse cardiac events and no incidence of thrombosis. Taxus II, III and IV are in progress.

The Asian Paclitaxel-Eluting stent Clinical Trial (ASPECT) reported six-month outcomes of 177 patients in a triple-blinded multi-centre trial. The high dose arm of the study was associated with a 4% binary restenosis rate at six months compared with a 27% rate in the control group.

All the above trials used standard anti-platelet regimens.

Other drugs currently in trials include actinomycin-D, titanium nitric oxide and QP2, and all show promise. The near future of stenting looks exciting, and interventionists may be able to implant sirolimus-coated stents (Cordis, Johnson & Johnson) as early as April 2002. In the future however, the goal is a drug-coated 'smart' biodegradable stent, or even a polymer stent that the physician dips in his/her preferred cocktail of antiproliferative drugs just prior to deployment.

The wise will, however, advise caution and scepticism, as the studies are small, and long-term potential difficulties with the phenomenon of zero neointimal proliferation have yet to be evaluated. Word on the street is watch those share prices!

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