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Treatment of coronary artery disease from the inside: Light at the end of the tunnel?

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ABSTRACT

Surgical treatment of coronary heart disease has shown its life saving benefits in millions of patients for more than half a century. Attempts to create less invasive ways to achieve similar results have attracted great attention since the introduction of balloon angioplasty in 1977. The fascination with such techniques was hampered by a 30% recurrence rate and a 5% rate of abrupt closure, requiring emergency bypass surgery in most instances.

Angioplasty lost much of its unpredictability with the introduction of stents in 1986. The use of potent anti-platelet regimes added further safety, but recurrence remained a definite thread until the introduction of anti-mitotic coatings during the early years of this century. Very late thrombosis, however, continues to haunt interventionist and patients. Vanishing poly-lactic acid stents time still fail to exhibit comparable mechanical properties at present. So far bypass surgery has not yet lost its attraction in complicated and diffuse disease, despite its much higher patient discomfort.

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Having observed the often devastating sequelae of acute and chronic coronary artery disease, heart surgeons were suggesting – even in the mid-nineteenth century – relatively aggressive revascularization procedures. When it became clear that the benefits of the so called Vineberg-procedure[1] – an open chest operation which involved tunneling the periphery of the left mammary artery into the surface of the left ventricle – failed to hold its promise in the late 1940's, patch plasties were tried to enlarge stenotic areas with slightly better results. From 1962 to 1967, open chest coronary artery bypass surgery using autogenous saphenous vein grafts was performed by D. Sabiston (1962). H. Garrett (1964), D. Kahn (1966), and was popularized by R. Favaloro (1967) at the Cleveland Clinic.[2]

Saphenous vein grafting became the most common revascularization technique for the next two decades. In 1977 Andreas Grüntzig proposed a much less invasive approach using the natural routes of the circulation. The first balloon angioplasty of coronary artery stenosis was done in September 1977 in Zürich using a homemade balloon catheter which he advanced to the point of the obstruction and, hoping for the best, dilated a significant proximal left anterior descending artery lesion, thus reducing the degree of obstruction to the point that the patient became asymptomatic.[3] This patient is still alive and well after a number of further procedures (B. Meier, personal communication).

Having adopted this procedure a few months after the initial attempts, it soon became clear to me that the Grüntzig's optimistic view about the ability to reliably flatten atherosclerotic plaques by the application of pure pressure was not met by lasting results in many cases. Recurrence was observed in one-third of such angioplasty cases, and abrupt closure requiring bypass surgery occurred in some 5% of the procedures. This is why I decided to approach an industrial partner in Lausanne (Switzerland) with the aim of developing a self-expanding stent, which became the first intravascular scaffold used in 1986 (Figure 1).[4] This stent was made from a 316 L stainless steel wire braid of 60 micron thickness retained by a retractable membrane which could be released when the scaffold was the correct position (Figure 2). Numerous other models, all using stainless steel, were developed in the years to come. Most of them were passively expanded using regular angioplasty balloons. By the year 2000, stenting had become the mainstay in the treatment of coronary heart disease.

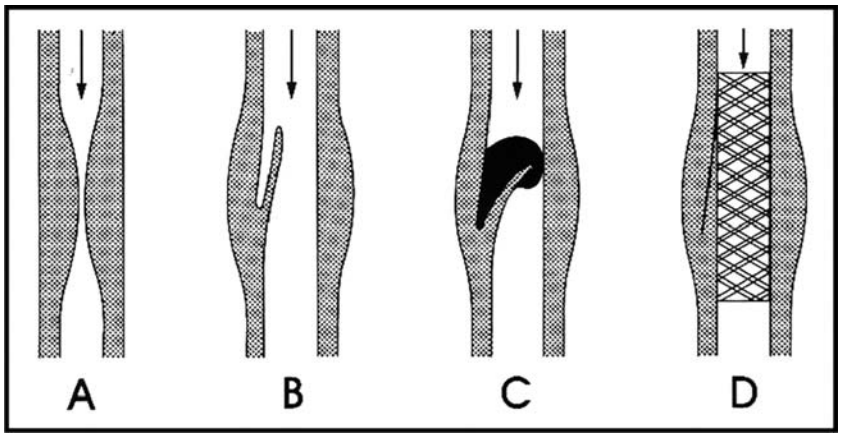

Figure 1. Schematic drawing illustrating the mode of action of the first clinically used stent in 1986.

Metal is foreign to the human body. Stent thrombosis, early and late after implantation of metal stents, was not infrequently observed and led to the development of different drug treatments.[4] Also, there was concern about vascular motion being permanently inhibited by the presence of metal stents.

Internal hyperplasia following implantation of permanent stents became such an issue that drugs were added to the metal by coating it with different polymers containing drugs – mainly anti-mitotics - meant to inhibit intimal proliferation. This method became very popular at the turn of the century and reduced the in-stent restenosis rate significantly. On the other hand, the delayed 'domestication' of metal stents through inhibition of neo-intimal ingrowth required long term antithrombotic treatment, mainly with various platelet inhibitors.[5]

The dream of a stent that disappears once the artery had healed crossed the minds of many interventional cardiologists. The first attempt to use a "vanishing stent" was performed in Japan by Doctors Igaki and Tamai who published the results of a small, preliminary series in Circulation in the

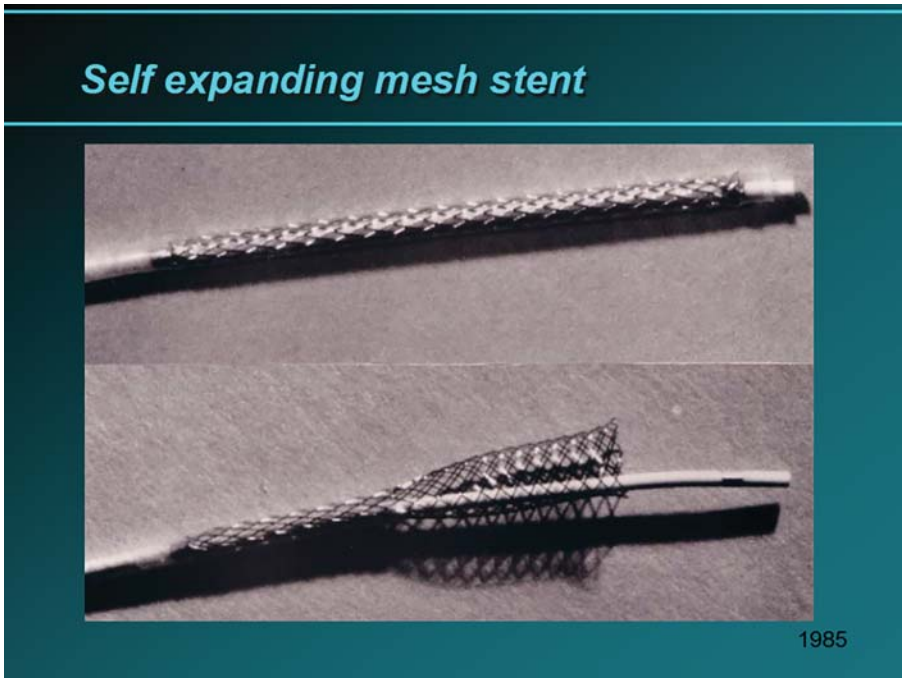

Figure 2. Self expanding mesh stent used in 1986.

year 2000.[6] Their biodegradable poly-L-lactic acid coronary stents clearly lacked the radial strength of currently used metal stents. This is why Biotronik created a bio-absorbable metal stent made out of a magnesium alloy. This stent, however, in its initial form created an unacceptably high number of recurrences.[7]

The industry became obsessed with attempts to use stents that did not leave anything behind a few months after implantation. In animal experiments, high molecular weight polymers – in particular high molecular weight poly-L-lactic acid (PLLA) – caused less inflammation than the low molecular weight polymers.[8] Most modern "vanishing stents" use this material (Figure 3), mainly because of its tendency to induce lesser inflammatory response while maintaining a relatively acceptable radial force.[8] On the other hand no current polymer stent can compete with metal regarding mechanical properties, in particular radial strength, which is a major determinant preventing restenosis.

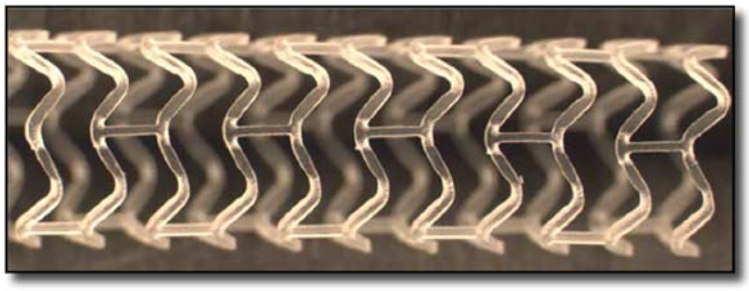

Figure 3. Poly-lactic acid "vanishing" stent.

Despite their shortcomings, bio-absorbable vascular scaffolds (BVS) - as they are called, to distinguish them from permanent stents - have now entered the clinical arena. A number of randomised trials have started or have even been finished. The first randomised trial of the ABSORB stent showed results similar to permanent metal stents, at least in relatively short-term observational or randomised studies. There is, however, a suspicion of a possible increased risk of stent thrombosis with bioresorbable scaffolds. In the ABSORB III and ABSORB IV trials a slightly higher rate of stent thrombosis was observed in the bioresorbable scaffold group (0.6% versus 0%).[9] This observation has been described as a "genuine clinically worrisome signal". Whereas restenosis is a relatively benign condition, stent thrombosis may result in myocardial infarction or even death.

In clinical trials to date, shorter lesions have been stented with bioresorbable scaffolds. This is in contrast to the rather liberal use of drug-eluting metal stents, which have often being used to cover long segments and even entire arteries.

Bio-absorbable scaffolds are something of a dream solution for the treatment of coronary artery disease. Many goals have been achieved, but the ultimate equipoise of BVS compared to drug-eluting metal stents, has not yet been reached (Figure 4). Further research is needed regarding the materials and the geometry of vanishing scaffolds. Bio-absorbable stents at this time have a much larger strut thickness compared to metal stents. This is clearly detrimental in view of intravascular flow dynamics. Stronger, malleable materials are urgently needed. At the same time they must not induce an inflammatory response.

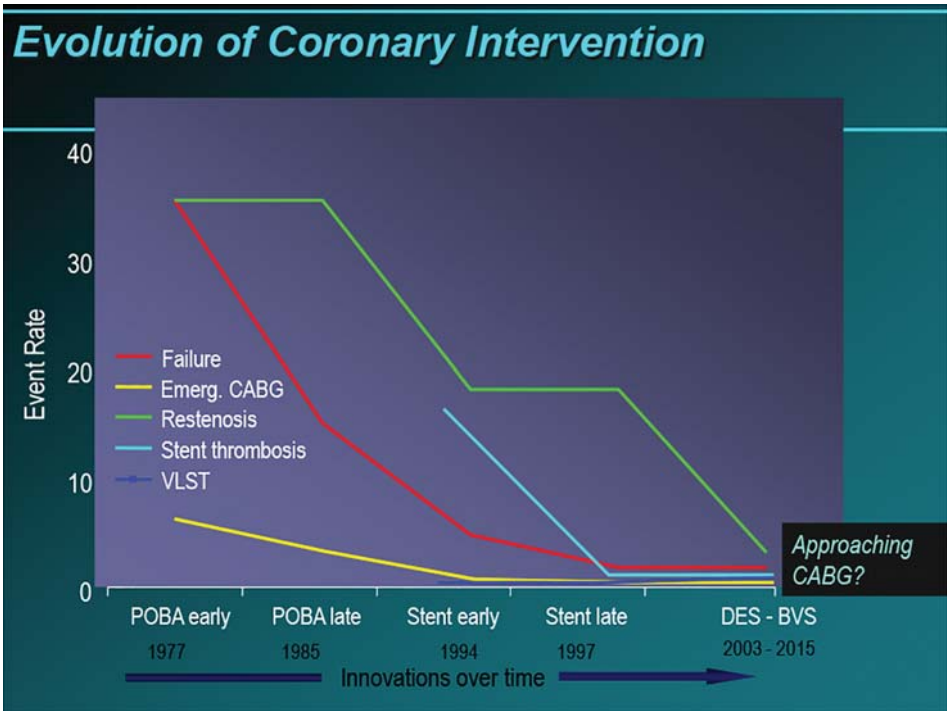

Figure 4. Schematic drawing of the evolution of coronary revascularisation since the inception of balloon angioplasty (POBA) in 1977. The advent of drug eluting stents (DES) has significantly reduced the rate of restenosis without being able to eliminate very late stent thrombosis (VLST). Biodegradable scaffolds (BVS) may overcome this problem only if their physical properties can be improved; they may then make bypass surgery (CABG) a last resort.

Despite the enormous progress made, the light at the end of the tunnel when it comes to treatment of coronary artery disease *from the inside* is still some way away. For the time being bypass surgery still has its attraction as it uses natural components. A recent randomised trial comparing the outcome of 880 patients after bypass surgery or everolimus-eluting stent implantation in 27 centres in East Asia, reported slightly better results in the bypass group when it came to repeat revascularization, although the surgical patients had a marginally higher rate of peri-procedural strokes. No bioresorbable scaffolds, however, were used in this trial.[10] There were problems with this trial, due to the fact that it was underpowered (recruitment was stopped early, the patients were of Asian descent - which implies smaller coronary arteries), but the overall conclusions seem to point to the fact that strictly biological – albeit quite invasive – revascularization has its merits and that stenting needs to be improved further.

The downside of bypass surgery, of course, is the comparably higher discomfort for patients. As a rule all randomized trials, as well as the resulting guidelines, are already obsolete once they are being published. Clinical and scientific wisdom should always dominate any medical decision. The two treatment options, angioplasty or surgery, must be carefully weighed against each other in each individual case.

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