# Future devices: bioabsorbable stents

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**Abstract**

**There are many advantages to bioabsorbable stents, including the potential to inhibit intimal hyperplasia by avoiding prolonged foreign body reaction and/or releasing antiproliferative drugs during degradation. The bioabsorbable polymer poly-l-lactic acid (PLLA) is used as a biodegradable coating of permanent metallic stents but can also be used to manufacture complete stents, at the expense of a greater recoil. Clinical, angiographic and intravascular ultrasound results at four years with the first stent tested (Igaki Tamai, Igaki, Japan) show patency rates similar to the rates expected with stainless steel stents and full reabsorption. Magnesium stents are another, perhaps more encouraging, development because they retain mechanical properties similar to conventional metallic stents. Full degradation of the magnesium alloy used to manufacture the Biotronik Lekton Magic stent requires 6–8 weeks. In man, initial clinical experience with this stent has been gained in patients with critical lower limb ischaemia. An ongoing study is testing its safety and efficacy in human coronary arteries.**

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## Introduction

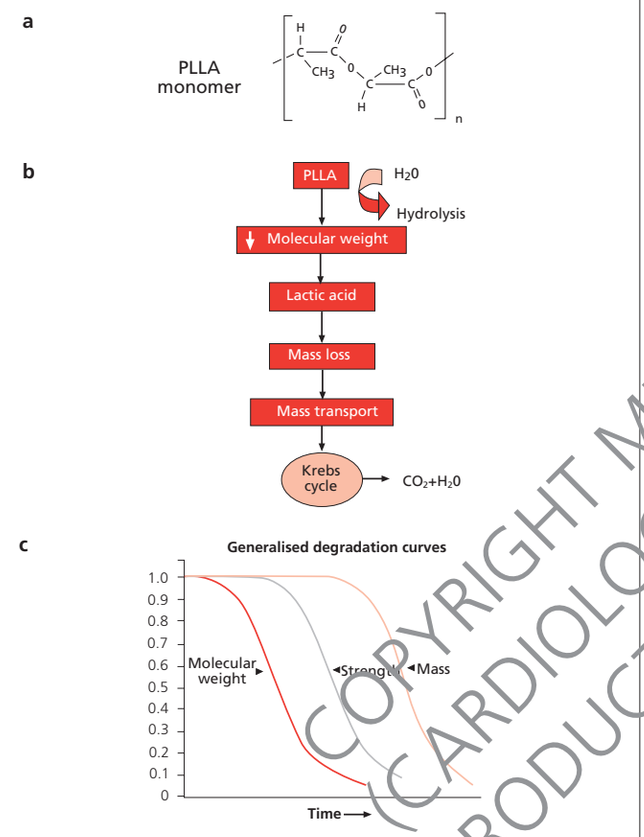
Stainless steel stents have revolutionised percutaneous coronary intervention (PCI) since their inception in 1987.[1] By virtue of their scaffolding property, they reliably re-appose dissection flaps and virtually eliminate elastic recoil after balloon angioplasty, thereby significantly reducing re-stenosis.[2] Concerns regarding high rates of stent thrombosis, chronic inflammation, late re-stenosis and long-term compatibility have proved to be unfounded; the enthusiasm that existed in the early 1990s for developing a bioabsorbable stent largely died down by the second half of that decade.[3] However, an increase in the complexity of cases being performed together with a desire to exploit the advantages of local delivery of drugs inhibiting intimal hyperplasia without the need to implant a permanent intracoronary device, has now led to a resurgence of interest in biodegradable stents.[4]

There are many potential practical advantages to a bioabsorbable stent.[5] While covering a side branch with a stent, it would no longer be necessary to open routinely any stent struts traversing the ostium of an uncompromised side branch. Following ostial stenting, struts protruding into the aorta or the parent vessel would no longer be a permanent potential source of embolism and of obstruction to future vessel instrumentation. Degradation of struts would remove the inflammatory stimulus for ongoing intimal hyperplasia, and late positive remodelling would no longer be prevented from offsetting lumen encroachment.[6] Within the field of paediatric interventions, a biodegradable stent would permit normal arterial growth. Arterial straightening and hinge point effects would be eliminated and no longer would a 'full metal jacket' preclude subsequent coronary surgery. Cardiac magnetic resonance (CMR) imaging, the likely future non-invasive alternative to angiography for coronary imaging, will not be prevented.

In the current era of drug elution, a bioabsorbable substance represents the ideal vehicle to ensure complete drug delivery, and the temptation may arise to extend treatment to 'normal' or 'near normal' vessel segments with minimal lumen narrowing

* Since this article was submitted, the editors are sorry to report that Dr Bernhard Heublein died in September 2004.

**Figure 1.** Structure (a), metabolism (b) and mechanical properties (c) of poly-L-lactic acid (PLLA). PLLA undergoes hydrolysis and its molecular weight is decreased, resulting in lactic acid, mass loss, mass transport and finally metabolism into carbon dioxide and water. It undergoes complete metabolism, making it an attractive vehicle for drug elution. The degradation curves demonstrate a progression over time with first a reduction of polymer molecular weight, then strength, and finally mass




but with severe atherosclerotic burden at risk of progression or destabilisation (rupture). At the human level, how often do our patients ask us about the long-term fate of stents and whether they can be removed?

There may, of course, be a down side. The integrity of the stent must persist until endothelialisation has occurred in order to avoid the risk of fragment embolism, and the bioabsorbable stent must possess sufficient radial strength throughout the period during which recoil may occur. Two main classes of devices have been investigated.

## Bioabsorbable polymeric stents

Van der Giessen and colleagues reported the pathological sequelae of implantation of the Wiktor coil stent coated with five different polymers in porcine coronary arteries.[7] All polymers were associated either with marked inflammation leading to intimal hyperplasia or with thrombotic occlusion. Clearly, not all bioabsorbable compounds prove to be biocompatible but subsequently one polymer was found which produced more encouraging results. A coating of the high molecular weight (≈321 kDa) form of poly-L-lactic acid (PLLA) induced no inflammation, did not increase the degree of intimal hyperplasia over that observed with an uncoated Wiktor stent and no subacute thrombosis was reported (figure 1).[8] Lincoff and colleagues were able to deliver dexamethasone from this PLLA polymer coat, although it had no inhibitory effect on re-stenosis. Three weeks after implantation of a prototype PLLA stent in normal porcine coronaries, inducing injury with a stent: artery ratio of 1.3:1, biocompatibility once again was excellent: there was no inflammation, but a prominent intimal hyperplasia (47% diameter stenosis) was present within the stent.[9]

The Igaki-Tamai coil stent is constructed entirely from PLLA (183 kDa), with strut thickness 170 µm, and is therefore potentially bioabsorbable. It has temperature-sensitive self-expanding properties and is completely radiotransparent, visualised only by means of radio-opaque gold markers at each end. It is balloon-mounted and then delivered by balloon inflation, using contrast warmed at 80°C (50°C at the stent site). The stent is maintained at 37°C and continues to expand gradually to its original size.

The only report of the use of this stent in human coronary arteries was published in the year 2000.[10] Twenty-five stents were implanted electively in 18 *de novo* lesions and one re-stenotic lesion in a total of 15 patients, including three diabetics. Adjunctive treatment included nifedipine, nitrates and a dextran infusion during the procedure, intravenous heparin for three days following the procedure, ticlopidine 500 mg daily for one month and aspirin 81 mg daily for six months. Quantitative coronary angiography and intravascular ultrasound were performed at one day, three months and six months. Reference vessel diameter was 2.85 mm and the average lesion length was 13.4 mm. Three lesions were American Heart Association/American College of Cardiology (AHA/ACC) type C and atherectomy was performed in four cases. Acute stent recoil was much greater than with conventional stainless steel stents (22%) but no further recoil occurred after the first minutes. At six months, there were no deaths, myocardial infarctions or bypass grafts (CABGs), but one patient underwent repeat PCI because of in-stent restenosis. The intra-vascular ultrasound (IVUS) data demonstrated enlargement of stent area from 7.42 $mm^2$ to 8.18 $mm^2$ at three months, with no further enlargement thereafter. Stent struts continued to be detectable at six months. Intimal hyperplasia occurred and the loss index (late loss as a proportion of initial gain) was 0.48, similar to or greater than the late loss observed with most metallic stents. The angiographic and ultrasound follow-up study at four years, recently reported by Dr Tamai at CCT 2004 (Complex Coronary Therapeutics, Kobe, Japan) showed absence of further hyperplasia or vessel enlargement and complete disappearance of the stent struts.

Whilst this report is reassuring, and suggests outcomes following use of the PLLA Igaki-Tamai stent to be equivalent to a stainless steel stent, it nevertheless raises a number of important

**Figure 2.** Corrosion kinetics of magnesium alloys. Different formulations of magnesium alloy have different corrosion kinetics. These images were obtained after immersion of stents in 0.9% saline solution at 37ºC at pH 7.0. Alloy E, with the slowest kinetics, was chosen for production of the Lekton Magic stent

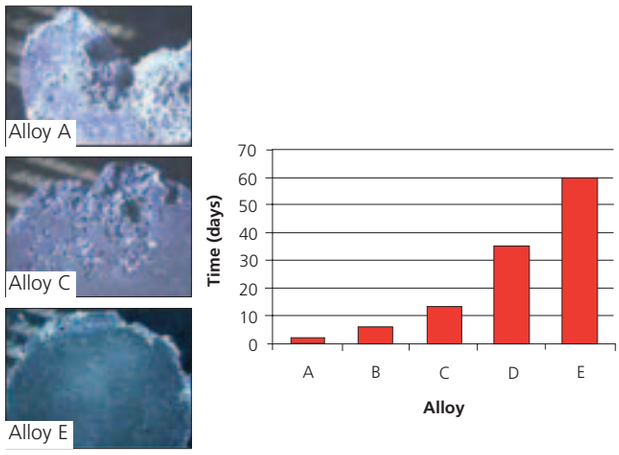
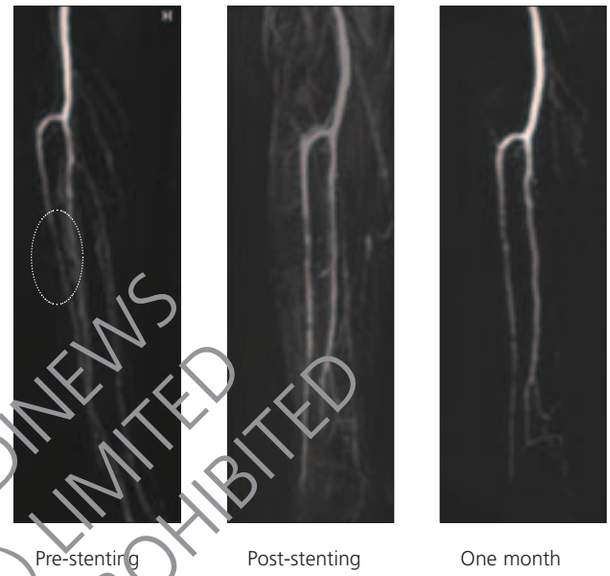



**Figure 3.** Magnetic resonance (MR) images of Lekton Magic stents implanted in a lower limb artery. The newly implanted Magic stent produces very little degradation of MR images. Following biocorrosion for one month, there is further improvement in the image quality of the stented segments






issues. First, heating of the vessel wall to 50ºC, initially recommended for stent implantation but no longer used, causes smooth muscle cell proliferation and platelet adherence.[11,12] Second, because of the poor mechanical properties of PLLA the stent undergoes significant recoil immediately after balloon deflation despite a bulky construction which might impact on its deliverability. Third, the uncontrolled stent expansion in the days and weeks following deployment could result in deep injury to the arterial wall, thus further promoting the restenotic process or perhaps, in an extreme case, inducing perforation.[13] With the use of a drug previously tested to prevent restenosis (tranilast), promising animal results have been recently reported, prompting a new clinical trial of the Igaki Tamai stent with stents up to 20 cm in length implanted in superficial femoral arteries (Biamino *et al.*, Dresden, personal communication).

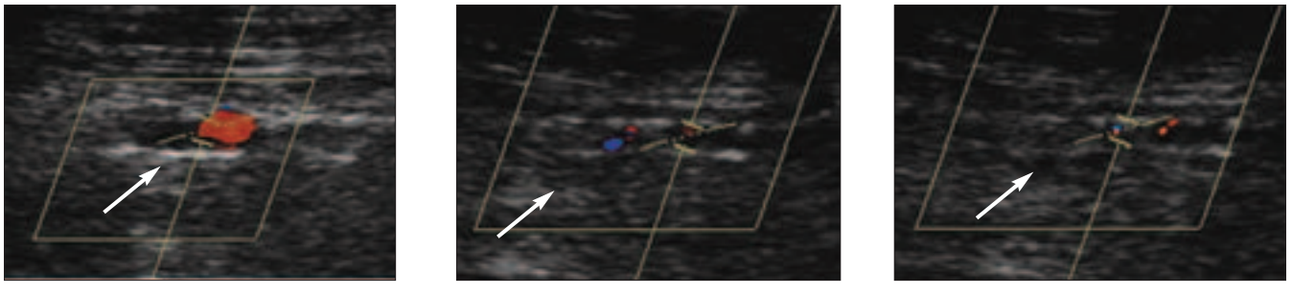
Guidant and Biosensors are currently conducting large clinical coronary studies using a new PLLA drug-eluting bioabsorbable coat for a metallic stent. This consists of a thin film of polylactic acid, breaking down to lactic acid, a natural metabolite, and which can load drugs for greater than 50% of its mass. This will eliminate the possibility of persistent quantities of drug remaining within a permanent polymer and has achieved outstanding inhibition of late hyperplasia with the use of everolimus but will not confer the advantages of an entirely biodegradable stent.

## Biocorrodible metallic stents

Two biocorrodible materials have been evaluated in animal studies. The NOR-I stent is a slotted tube design constructed from pure iron, with a strut thickness of 100–120 µm and recoil of 2.2%. This stent was implanted in 16 rabbit aortas with a reference diameter of 3.4 mm and with a stent: artery ratio of 1.13:1.[14] No stent thrombosis or death was encountered. Angiographic follow-up over 18 months demonstrated no more than 5% loss of stent area. Histological examination demonstrated no significant inflammation but stent degradation products produced slight elevation and brownish discolouration of the intimal surface. Stent struts remained detectable even 18 months after implantation. The internal elastic lamina was frequently destroyed, with severe indentation and compression of the media. There are no reports of the use of this stent in coronary arteries but this degree of injury might be expected to produce intimal hyperplasia in muscular arteries. Only limited conclusions regarding iron coronary stents can therefore be drawn from this study.

A magnesium alloy, AE21, containing also 2% aluminium and 1% rare earth metals (Ce, Pr, Nd) has been assessed in pig coronary arteries (figure 2).[15] Twenty slotted tube stents with a length of 10 mm and uneven strut thickness of 150–200 µm were implanted in 11 pig coronary arteries of reference diameter 2.5–3.5 mm. An overstretch injury was produced with a stent: artery ratio of 1.3:1. There was no stent thrombosis or myocardial infarction but there was one unexplained death four days following the procedure. Follow-up angiography, IVUS and histology were performed at 10, 35 and 56 days. Expansion of this uneven stent was asymmetrical, and struts positioned within the adventitia caused inflammation and exaggerated intimal hyperplasia. More pronounced inflammation was observed in some

**Figure 4.** Ultrasound images after implantation in a distal popliteal artery proved progressive disappearance (right panels) of the bright artefacts induced by the stent struts, well visible at day one after implantation (left panel)



Day one Day 30 Day 90

areas, with the greatest concentration of degradation products corresponding with corroding struts of greater thickness. Mean neointimal area was 1.41 $mm^2$ at 35 days and 2.71 $mm^2$ at 56 days. Strut biocorrosion had begun at 35 days and it was estimated by extrapolation that this would be complete by 98 days. The natural process of arterial growth expected in young pigs was not prevented by the stent and the in-stent area increased from 3.28 $mm^2$ at 35 days to 6.15 $mm^2$ at 56 days.

This report is the first in which a bioabsorbable stent has been shown to reach an advanced stage of biodegradation within a few months after implantation. Construction of stents with thinner struts might accelerate degradation kinetics but it should be avoided to reach the point of permitting recoil of a diseased coronary segment. Magnesium is an attractive material for further evaluation as its degradation generates an electronegative, and therefore thrombosis-resistant, surface.[16]

Biotronik have recently developed the Lekton Magic coronary stent, constructed from a magnesium alloy (WE43) containing also zirconium (< 5%), yttrium (< 5%) and rare earths (< 5%). The stent has a novel design characterised by circumferential noose-shaped elements connected by unbowed cross-links along its longitudinal axis; it is balloon-expandable and mounted on a 6F compatible rapid exchange delivery system. *In vitro* studies have indicated that the stent undergoes biocorrosion within two months.

In a pre-clinical study, 33 minipigs were each implanted with two Lekton Magic stents and one control stent (Lekton Motion®; Biotronik). After four weeks, the angiographic minimal lumen diameter (MLD) (corrected for reference diameter) of the Mg group was higher than in the control group (1.49 mm *vs.* 1.34 mm). During the following two months, the MLD in the control group remained nearly unchanged (1.33 mm at 12-week follow-up) whereas the MLD in the Mg group revealed significant remodelling: the MLD increased from 1.49 mm at week four to 1.68 mm at week 12 ($p<0.001$). Despite the observed inhibitory effect of the absorbable metal stent on smooth muscle cell growth, homogenous and rapid endothelialisation of the Mg stent was observed in the animal model. Necroscopy after six days showed a nearly complete thin layer of neointima already covering the struts of the magnesium alloy stent.

Initial clinical experience with the absorbable metal stent has been gained in a peripheral application. A total of 20 patients (10 diabetics) with a mean age of 76 years have been treated with absorbable metal stents for critical lower limb ischaemia. A total of 23 stents were used to treat lesions with reference diameter of 2.7 mm and lesion length of 11 mm. Angiographic and IVUS guidance were used. No adverse events were reported during the procedures. Post-procedural colour flow Doppler (figure 3) and MR demonstrated accurate positioning and expansion of the stents despite angiographically visible calcifications in 14 cases; unobstructed blood flow indicated the absence of early recoil. The ultrasound images proved the compatibility of this stent material with MR imaging procedures (figure 4). One-month follow-up with Doppler and MR is now complete. Normal flow was present in 18 patients whilst indices suggested 30-40% stenosis in two patients. One patient died on day 24 of pneumonia unrelated to the stent.

Late follow-up was incomplete at the time of writing but two late occlusions have been reported. In one patient, this was the result of occlusion of a femoro-fibular venous bypass graft and the stent in the receiving vessel remained patent at histology. No patient showed any symptoms of allergic or toxic reactions to the stent material.

This stent will soon be evaluated for the first time in human coronary arteries in the PROGRESS study. This will be a prospective, multicentre, consecutive, non-randomised study of 63 patients with a single *de novo* native coronary lesion. Follow-up will be performed by means of angiography, IVUS and CMR. The primary end point will be a composite of major disease cardiac end points major adverse cardiac end points (MACE) defined as death, non-fatal myocardial infarction or ischaemia-driven target lesion revascularisation (TLR) at four months.

## Practical limitations

The Lekton Magic stent is completely radiolucent. This property will create difficulty in detection of stent embolisation, confirma-

### Key messages

- Bioabsorbable polymeric stents using poly-L-lactic acid (PLLA) may have long-term outcomes similar to those with stainless steel stents but are unlikely to enjoy widespread use because of marked recoil
- Stents using two biocorrodible materials, iron and magnesium, have been evaluated in animal studies. Current data suggest some advantages when compared against conventional stents
- There is some early clinical experience with the absorbable magnesium stent in patients with critical lower limb ischaemia
- This stent has been implanted for the first time in human coronary arteries in 11 patients

tion of complete stent expansion and apposition and in precise placement of overlapping stents. The risk of embolisation will be minimised by the presence of sleeves on the delivery balloon at either side of the crimped stent. If the Lekton Magic stent were to pass into everyday interventional practice, optimal lesion preparation and more liberal use of IVUS would be necessary.

## Conclusion

The animal and limited human data described here have provided some insight into the potential of biodegradable coronary stents. Having acknowledged the pioneering role of the Igaki-Tamai stent, the mechanical properties of this PLLA stent render it unattractive for widespread clinical application. The magnesium stent appears to have scaffolding properties, radial strength and thickness of the delivery system similar to those of the first generation metallic stents. Scaffolding for the minimum necessary period and degradation before provoking the signal for intimal hyperplasia is a tantalising possibility but is unlikely to be attainable as the stent must remain for the first crucial weeks and the degradation process itself may stimulate an intimal reaction. Still, current data show 50% reduction in intimal area compared with conventional stents and suggest an antiproliferative effect on smooth muscle cells. If there is to be a continuing role for local drug delivery to inhibit the re-stenotic process, this can be easily achieved by adding a biodegradable polymer for drug release.

After the promising initial results of below-the-knee implantations, the long-term clinical results and repeated ultrasound and magnetic resonance examinations of PROGRESS will reveal whether this stent is fully bioabsorbable and can fulfil its potential in treatment of coronary atherosclerosis.

## Conflict of interest

HG, RR and VK have no interests to declare. CI and CDiM received a research grant from Biotronik AG for the PROGRESS Trial. NP, JV, MB and KD received a research grant from Biotronik AG for the biodegradable stent in the below-the-knee lesions pilot trial. The late Bernhard Heublein was a medical director of Biotronik AG, Bülach, Switzerland.

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