

Bioabsorbable Stents: The Future Is Near

A review of the breakthroughs and challenges of bioabsorbable stents as a potential solution to the risks associated with available drug-eluting stents.

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Coronary stents have revolutionized the treatment of obstructive coronary artery disease by improving immediate and late complications of balloon angioplasty. In general, these goals are achieved within weeks after the procedure, leaving the bare-metal stent (BMS) platform permanently in the artery. Despite significant advances in the metallic stent materials and widespread use of drug-eluting stents (DES), there are several limitations to the current technology. These limitations include occasional mismatch of stent-to-artery sizing, implantation of a permanent metallic intravascular prosthesis, hypersensitivity reactions, and delayed vessel wall healing, all potentially culminating in late DES thrombosis. Some complications may arise from continued biological interaction of the metal stent, polymer, or drug with the surrounding tissue. Metallic stents are also known to cause artifacts on noninvasive tests, such as cardiac computed tomography (CT) and magnetic resonance imaging (MRI). Bioabsorbable stents may provide an exciting potential alternative to address the limitations of the current technology. In this article, we discuss the latest preclinical and clinical research, as well as future roles of this technology.

Percutaneous transluminal coronary angioplasty (PTCA), first preformed in 1977 by Andreas Grüntzig, has revolutionized therapy for coronary artery disease. Since then, the field of interventional cardiology has witnessed vast improvements in techniques and mounting research designed to address the limitations associated with PTCA. Coronary stents demonstrated significant reductions of major adverse cardiac events (MACE) and procedure-related myocardial infarction; they have become the standard of care in interventional cardiology.^{1,2} Previously, the prevalent use of BMS gave rise to a new problem—luminal renarrowing within the stent

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from neointimal proliferation, the process known as in-stent restenosis (ISR).

Stent-based local drug delivery, namely DES, was developed to combat ISR. DES can achieve a further decrease in angiographic restenosis and target lesion revascularization rate^{3,4} but have generated concerns regarding the possible sequelae of late stent thrombosis from late malapposition, hypersensitivity reaction, and long-term impairment of endothelial response.⁵⁻⁸ Additionally, permanent DES deployment may reduce vasomotion within the stented segment and impair endothelial response in adjacent vessel segments.⁹ Nevertheless, the crucial benefits of stenting may be limited to immediate scaffolding and shortly thereafter until healing and re-endothelialization have occurred. Beyond that period, no utility for stents has been demonstrated, and their presence may represent a nidus for late thrombosis and chronic inflammation. These issues have prompted aggressive research in the novel concept of bioabsorbable stents.

THE NEED FOR BIOABSORBABLE STENTS

Stents composed of bioabsorbable/biodegradable materials represent an attractive alternative revascularization modality; the justification stems from the short-term need for vessel scaffolding and avoidance of the potential long-term complications of metallic stents.^{10,11}

Compared with metallic stents, there are several potential advantages, including complete absorption of stent material, a phenomenon that may facilitate repeat treatments to the same site, allow restoration of vasomotion, as well as improve lesion imaging with cardiac CT and MRI. Some less common but troublesome complications of current stent technology, such as stent-strut fracture and delayed allergy to polymer,¹² would be less problematic. Additionally, if the artery is not splinted, lumen size may later improve (positive remodeling).¹³ Other potential limitations of metallic stents are distortion of vessel geometry, side branch occlusion, and mismatch of the stent to the vessel size. The latter may result in smaller luminal size after stent implantation. In many respects, a temporary device, which dissolves after completion of its role, is preferable over a permanent intracoronary metallic prosthesis.

Thus, the goal was to design a bioabsorbable stent that once dissolved would leave behind only the healed natural vessel, allowing for restoration of vasoreactivity with enhanced potential for vessel remodeling. Late stent thrombosis would no longer be a concern, and prolonged antiplatelet therapy would thus likely not be required. Furthermore, these stents can be used as delivery vehicles for agents such as drugs and gene therapy, as in treatment of vulnerable plaque. Bioabsorbable stents can also be suitable for complex anatomy in which flexion/extension articulations predispose to stent crush and fracture, such as in superficial femoral and tibial arteries. Because bioabsorbable stents are less rigid than their metallic counterparts, device delivery through tortuous or calcified anatomies may be less challenging, perhaps improving the procedural success rates in these cases (Table 1).

TYPES OF BIOABSORBABLE MATERIALS AND STENTS

Although exciting research in biodegradable stents has been ongoing, the emergence of a viable degradable stent has been relatively sluggish. This problem is largely due to difficulties in development of an adequate biodegradable material that is compatible with the vessel wall, while not evoking a significant inflammatory response. If the latter were to occur, the potential restenosis implications may be even more problematic than with the metal stent. Some theoretical limitations of this technique have to be considered. The duration of mechanical stability required after stent deployment in a diseased artery is unknown. Moreover, alterations of stent degradation dynamics at a major branch, such as for kissing aortoiliac stents, or across the common external iliac arteries remain unknown. Furthermore, the

TABLE 1. BIOABSORBABLE STENTS: OBJECTIVES

- Perform the vessel scaffolding function of metallic stents (best acute result)
- Leave no chronic foreign body implant
- Deliver therapeutic agents
- Provide large matrix reservoir for therapeutics
- Potential treatment for vulnerable plaque
- Increased ability to re-treat target vessel
- No interference with CT and MRI
- Possibly no need for prolonged antiplatelet therapy to prevent late stent thrombosis
- Restoration of vasoreactivity at the stented site

short- and long-term local intramural biocompatibility and bioreactivity of the constituents of biodegradable materials during degradation need to be assessed.

Ideally, degradable implants should afford superior physiologic repair, reconstitution of local vascular compliance, and a temporary longitudinal and radial strengthening effect, as well as offer the possibility for growth and late positive remodeling.^{14,15} They should be compatible with follow-up MRI and intravascular ultrasound (IVUS) procedures and not restrict surgical revascularization. Biodegradable implants should also offer the possibility for integration with local drug delivery and gene transfer technologies.

Several considerations exist in the selection of a polymer or alloy for bioabsorbable stents. The strength of the polymer and its ability to expand with sufficient radial force are essential for successful stent deployment and avoidance of immediate recoil. Other considerations include the overall time and rate of degradation/corrosion (a very rapid degradation rate can be associated with inflammation), biocompatibility with the vessel wall, and lack of toxicity. The change in the mechanical properties and the release profiles of drugs from bioabsorbable stents directly depends on the degradation rate of the stent, which can be controlled by selection of the polymer or the alloy, passivation agents, or the manufacturing process (Table 2). Currently, such materials fall into two general categories: polymeric-based and metallic-based.

Polymers have been widely incorporated into cardiovascular devices and are primarily used as delivery vehicles for drug coatings.^{16,17} The first polymeric material proposed for a bioabsorbable stent was poly-L-lactic acid (PLLA).¹⁸ The PLLA stent was reported to hold up to 1,000 mm Hg

TABLE 2. ISSUES WITH BIOABSORBABLE STENTS

- Radial strength
- Acute, subacute, and chronic recoil
- Time and rate of degradation
- In vivo elution of drug from biodegradable stent
- Radiopacity of the stents

crush pressure and to maintain its radial strength for 1 month. This stent was almost completely degraded by 9 months, with minimal evidence of thrombosis, moderate neointimal growth, and a limited inflammatory response in porcine coronaries. Other proposed polymers include polyglycolic acid (PGA), poly (D, L-lactide/glycolide) copolymer (PDLA), and polycaprolactone (PCL). The metallic alloys utilized for bioabsorbable stents are iron and magnesium, in combination with some rare metals.

PRECLINICAL RESEARCH

The prototype of a temporary stent was a bioabsorbable, self-expanding PLLA stent introduced by Stack and colleagues of Duke University for the reduction of experimental post-PTCA restenosis.^{19,20} Although minimal inflammation was observed in a canine model, other biodegradable polymers, including polyglycolic acid/poly-lactic acid, polycaprolactone, polyhydroxybutyrate valerate, polyorthoester, and polyethyleneoxide/polybutylene terephthalate, were subsequently tested in a porcine model and found to induce significant inflammatory response and arterial proliferation.²¹ These adverse tissue responses may be attributable to a combination of parent polymer compound properties, biodegradation products, and possibly implant geometry.

A subsequent stent (Igaki-Tamai, Kyoto Medical Planning Co., Ltd., Kyoto, Japan), composed of high molecular weight (321 kDa) PLLA and a novel zigzag helical coiled design (as opposed to a mesh design), produced acceptably low inflammatory and scarring responses after experimental²² and clinical implantations.²³ However, concerns have been raised regarding the stent's slow absorption kinetics, as well as possible thrombosis arising from thermal vessel wall damage incurred during initial stent expansion. Moreover, continued stent expansion may result in trauma-induced neointimal hyperplasia from chronic swelling.

Drug-loaded polymer stents have also been tested in porcine coronary arteries. Both a tyrosine kinase antagonist (ST638)-coated Igaki-Tamai stent²⁴ and a double helical PLLA stent, containing the antiproliferative substance paclitaxel,²⁵ were shown to reduce the degree of in-stent

TABLE 3. BIOABSORBABLE STENTS

- Igaki-Tamai: PLA
- REVA: Tyrosine-Polycarbonate
- BVS: PLA
- Biotronik: Magnesium
- BTI: Salicylate-based

restenosis, although concerns regarding inflammation remained. A variety of polymer-based absorbable stents are currently under investigation and development. The bioabsorbable everolimus-eluting stent (BVS, Abbott Vascular, Santa Clara, CA) has a backbone of PLLA that provides the support and a coating of poly-D,L-lactic acid that contains and controls the release of the antiproliferative agent everolimus. Bioabsorbable Therapeutics, Inc. (Menlo Park, CA) has developed a family of potentially unique anti-inflammatory polymers. These compounds are comprised partly of salicylic acid, the active ingredient in aspirin, which has well known anti-inflammatory and antiplatelet properties. Based on encouraging results with this novel bioabsorbable salicylate-based polymer as a DES coating in porcine coronary artery model,²⁶ a fully bioabsorbable sirolimus-eluting stent was synthesized entirely from this unique material (Table 3).

Nevertheless, important drawbacks of polymer stents relate to their intrinsic mechanical properties. Polymers are not able to guarantee the same radial force and limited recoil compared with metal platforms, and their relative bulkiness may limit application in small vessels.

CLINICAL RESEARCH

In the ABSORB trial, the feasibility of a fully bioabsorbable everolimus-eluting stent (BVS, Abbott Vascular) in 30 patients with ischemia and a single de novo coronary lesion was investigated.²⁷ Some important concerns about the efficacy of this device were raised by this study.²⁸ The in-stent late loss with the BVS (0.44 mm) was comparable to that seen with some DES currently on the market, and the late lumen loss was primarily due to reduction in stent area. At 2 years after implantation, the stent had dissolved. The data regarding vasomotion, restenosis, and freedom from late thrombosis were encouraging.²⁹

The PROGRESS-AMS study³⁰ was a prospective, multicenter clinical trial of 63 patients with coronary artery disease who underwent implantation of the fully absorbable magnesium stent (AMS, Biotronik, Berlin, Germany). Angiography and IVUS were conducted immediately after AMS deployment and at 4 months. The AMS was well expanded upon deployment, without immediate recoil.

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The major contributors to restenosis, as detected by IVUS at 4 months, were decrease of external elastic membrane volume (42%), extrastent neointima (13%), and intrastent neointima (45%). From 4 months to late follow-up (28 months), paired IVUS analysis demonstrated complete stent degradation, with durability of the 4-month IVUS indices. Slower degradation was suggested to provide sufficient radial force to improve long-term patency rates of the AMS.

SUMMARY

Although the concept of fully degradable stents, which provide luminal scaffolding for the required duration and subsequently dissolve, is not new, many novel materials and designs have been proposed and evaluated. The specter of late DES thrombosis and requirement of prolonged dual-antiplatelet therapy have further fueled accelerated recent research in this arena. The realization of this goal continues to be pursued by many research groups and medical device manufacturers. Thus far, various permutations of this design have met with mixed clinical and preclinical results. We believe that the future is near for the fully bioabsorbable DES era; however, further studies are needed before this technology can be declared mainstream in the treatment of patients with coronary artery disease. ■

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1. Kimmel SE, Localio AR, Krone RJ, et al. The effects of contemporary use of coronary stents on in-hospital mortality. Registry Committee of the Society for Cardiac Angiography and Interventions. *J Am Coll Cardiol*. 2001;37:499.
2. Kimmel SE, Localio AR, Brensinger C. Effects of coronary stents on cardiovascular outcomes in broad-based clinical practice. *Arch Intern Med*. 2000;160:2593.
3. Moses JW, Leon MB, Popma JJ, et al, for the SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315-1323.
4. Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation*. 2003;107:38-42.
5. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48:193-202.
6. Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol*. 2006;47:175-181.
7. Chen JP, Crisco LVT, Jabara R, et al. Late Angiographic Stent Thrombosis: the LAST straw for drug-eluting stents? *Angiology*. 2009;59:676-681.
8. Chen JP, Hou D, Pendyala L, et al. Drug-eluting stent thrombosis: the Kounis hypersensitivity-associated acute coronary syndrome revisited. *JACC: Cardiovasc Interv*. (In press).
9. Hofma SH, van der Giessen WJ, van Dalen BM, et al. Indication of long-term endothelial dysfunction after sirolimus-eluting stent implantation. *Eur Heart J*. 2006;27:166-170.
10. Zidar J, Lincoff A, Stack R. Biodegradable stents. In: Topol EJ, ed. *Textbook of Interventional Cardiology*. 2nd ed. Philadelphia, PA: Saunders; 1994:787-802.
11. Colombo A, Karvouni E. Biodegradable stents: Fulfilling the mission and stepping away. *Circulation*. 2000;102:371-373.
12. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation*. 2004;109:701-705.
13. Ormiston JA, Stewart FM, Roche AHG, ET AL. Late regression of the dilated site after coronary angioplasty: a five year quantitative angiographic study. *Circulation*. 1997;96:468-474.
14. Regar E, Sianos G, Serruys PW. Stent development and local drug delivery. *Br Med Bull*. 2001;59:227-248.
15. Wintermantel E, Mayer J, Ruffieux K, et al. Biomaterials, human tolerance and integration. *Chirurgie*. 1999;70:847-857.
16. Hastings GW, Ed. *Cardiovascular Biomaterials*. London, UK: Springer-Verlag; 1992.
17. Murphy JG, Schwartz RS, Huber KC, et al. Polymeric stents: modern alchemy or the future? *J Invas Cardiol*. 1991;3:144-148.
18. Stack RE, Califf RM, Phillips HR, et al. Interventional cardiac catheterization at Duke Medical Center. *Am J Cardiol*. 1988;62(Suppl F):3F-24F.
19. Labinaz M, Zidar JP, Stack RS, et al. Biodegradable stents: the future of interventional cardiology? *J Intervent Cardiol*. 1995;8:395-405.
20. Tanguay JF, Zidar JP, Phillips HR 3rd, et al. Current status of biodegradable stents. *Clin Cardiol*. 1994;12:699-713.
21. van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation*. 1996;94:1690-1697.
22. Lincoff AM, Furst JG, Ellis SG, et al. Sustained local delivery of dexamethasone by a novel intravascular eluting stent to prevent restenosis in the porcine coronary injury model. *J Am Coll Cardiol*. 1997;29:808-816.
23. Tamai H, Igaki K, Kyo E, et al. Initial and 6-month results of biodegradable poly-L-lactic acid coronary stents in humans. *Circulation*. 2000;102:399-404.
24. Yamawaki T, Shimokawa H, Kozai T, et al. Intramural delivery of a specific tyrosine kinase inhibitor with biodegradable stent suppresses the restenotic changes of the coronary artery in pigs in vivo. *J Am Coll Cardiol*. 1998;32:780-786.
25. Vogt F, Stein A, Rettemeier G, et al. Long-term assessment of a novel biodegradable paclitaxel-eluting coronary polylactide stent. *Eur Heart J*. 2004;25:1330-1340.
26. Jabara R, Chronos N, Robinson K. Novel bioabsorbable salicylate-based polymer as a drug-eluting stent coating. *Cathet Cardiovasc Intervent*. 2008;72:186-194.
27. Ormiston JA, Serruys PW, Regar E, et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. *Lancet*. 2008;371:899-907.
28. Macaya C, Moreno R. Bioabsorbable drug-eluting stents: the future of coronary angioplasty? *Nat Clin Pract Cardiovasc Med*. 2008;5:598-599.
29. Serruys PW, Ormiston JA, Onuma Y, et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. *Lancet*. 2009;373:897-910.
30. Waksman R, Erbel R, Di Mario C, et al; PROGRESS-AMS (Clinical Performance Angiographic Results of Coronary Stenting with Absorbable Metal Stents) Investigators. Early- and long-term intravascular ultrasound and angiographic findings after bioabsorbable magnesium stent implantation in human coronary arteries. *JACC Cardiovasc Intervent*. 2009;2:312-320.