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Review

Bioresorbable polymeric stents: current status and future promise *

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Abstract—Metal stents and, more recently, polymer-coated metal stents are used to stabilize dissections, eliminate vessel recoil, and guide remodeling after balloon angioplasty and other treatments for arterial disease. Bioresorbable polymeric stents are being developed to improve the biocompatibility and the drug reservoir capacity of metal stents, and to offer a transient alternative to the permanent metallic stent implant. Following a brief review of metal stent technology, the emerging class of expandable, bioresorbable polymeric stents is described, with emphasis on developments in the authors' laboratory.

Key words: Stent; bioresorbable polymer; drug delivery; gene therapy; in-stent restenosis.

INTRODUCTION

Percutaneous transluminal coronary angioplasty (PTCA) is a standard treatment for focal arterial stenosis. Use of this 'noninvasive' treatment has rapidly expanded, since its introduction in 1977, to more than 500 000 cases per year in the United States alone. There has been a high restenosis rate of the treated segment following PTCA, up to 30%, with an estimated cost of $3.5 billion per year in the United

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States alone in 1997 [1]. Metallic intracoronary stents were introduced to prevent arterial dissection, elastic recoil, and intimal hyperplasia associated with PTCA treatment. However, metal stents themselves induce an inflammatory response which can contribute to intimal hyperplasia [2, 3]. This problem has led to the intensive development of radiation-emitting stents and polymer- and ceramic-coated metal stents that can be loaded with various drugs, both strategies intended to reduce the inflammatory response to the metal stent.

METAL STENTS

Metal stents have evolved from relatively stiff, difficult to deploy structures designed to prevent wall dissection and collapse, to more flexible, open architectures which can negotiate tortuous channels and also overlay vessel branches whilst maintaining their patency. Early designs, including the Wallstent (Schneider), Palmaz-Schatz (Johnson & Johnson), Wiktor (Medtronic) and Gianturco-Roubin (Cook) stents, have given way to the Micro (AVE), Multilink (ACS) and other designs [4–7]. The metals from which these stents are made are selected for strength, elasticity, and malleability or shape memory. Commonly used materials include stainless steel, tantalum and nitinol alloys [6, 8, 9]. Nitinol offers superelastic and thermal shape memory properties, which allow stent self-expansion at deployment, and thermally-induced collapse for theoretical removal procedures [10].

Several clinical trials have shown the benefit of stenting compared with PTCA alone. BENESTENT and STRESS, two major trials, were designed to assess the clinical outcome following PTCA with *de novo* (primary) stenting [6, 11, 12]. The BENESTENT trial found a reduction in the 6-month restenosis rate for the stent group compared with the control PTCA group (22% vs. 32%, respectively). The STRESS trial demonstrated a similar reduction; the rate of restenosis was 30% in the stent group and 42% in the control group. More recent trials, analyzing newer stents with those used in BENESTENT and STRESS, such as WEST, MUSIC and FINESS, have demonstrated lower restenosis rates [13]. Despite the improved results, stent-induced intimal hyperplasia and restenosis remain problematical, especially in complex procedures, with long lesions and multiple stent deployments [3]. Furthermore, the long-term (> 10 years) effects of metallic stents in humans are still unknown. Thus, other measures are required to resolve the restenosis issue.

Two approaches to the management of residual stent-induced restenosis have emerged: stent polymer or ceramic coatings loaded with various pharmacologic agents [14–18] and beta- or gamma-emitting radioisotopes, delivered via the stent itself or at stent implantation. Early clinical results suggest that pactitaxel, sirolimus, GPIIb/IIIa inhibitors, and other agents reduce short-term stent restenosis rates almost to zero (Table 1) [3, 13, 19]. These encouraging early results must be verified in longer-term trials. Low-dose radioisotope treatments with metal stents loaded with beta (^{90}Sr, ^{90}Y, ^{32}P) or gamma (^{192}Ir) emitters have also improved the

Table 1.
Clinical trials and animal studies via coated stents and use of drugs with stenting

Agents	TRIALS/studies	References
Paclitaxel, microtubular inhibitor	TAXUS I, ASPECT	[81, 82]
Sirolimus, immunosuppressive agent	RAVEL, US trial	[83, 84]
Actinomycin D	Pig coronary arteries	[85]
Metalloproteinase inhibitor[a]	Porcine coronary arteries, porcine femoral arteries	[86, 87]
Cytochalasin D, inhibitor of the actin microfilament formation	Porcine coronary model	[88]
Oligodeoxynucleotides to human transcription factor EGR-1	Pig coronary arteries	[89, 90]
Antisense morpholino compound (AVI-4126)	Porcine coronary model	[91]
GPIIb/IIIa inhibitors:		
Abciximab	TARGET, ADMIRAL	[92, 93]
Eptifibatide	CRUISE, ESPRIT	[94–96]
Methylprednisolone, anti-inflammatory	Porcine coronary model	[97]
Dextrose albumin microbubles containing c-Myc antisenses	Pig coronary arteries	[98]
Cross-linked hyaluronan or chitosan	Pig coronary arteries	[99]
Gold film coating	NUGGET	[100, 101]

[a] Opposing responses were observed.

restenosis rate [19–21]. Such stents have also been proposed for the local treatment of tumors and the prevention of excessive granulation tissue formation [22, 23].

Improvements in the restenosis rate notwithstanding, metal stents have other important limitations, including thrombogenicity, permanence, a limited potential for local drug delivery, and, for isotope-loaded stents, continuing radiation-induced damage [3, 12, 24]. Metal stent surfaces are moderately thrombogenic, requiring short-term antiplatelet or anticoagulant therapy. Metal stents are permanent implants. It is practically impossible to remove a metal stent, despite claims to the contrary for shape memory alloy stents that, in theory, can be narrowed *in situ* by application of heat or cold. Surgical revision of a stented vessel is also a practical impossibility, due to the difficulty of freeing the metal fiber impacted in the neointima. Coated metal stents have been introduced recently to provide controlled drug release, with very good short-term results (Table 1). Current practice is to use a bioresorbable phosphoryl choline polymer, or other polymer coating. However, the small reservoir capacity of the polymer film limits the amount of drug that can be loaded and eluted. Radiation-emitting stents have also been effective in reducing stent-induced restenosis; these, however, may induce radiation damage to the vessel wall. Finally, although not reported to date, there is the theoretical possibility of erosion of the arterial wall, due to compliance mismatch between the stent and arterial tissue. Given the difficulties with further development of metal stents, consideration of bioresorbable polymeric stents is attractive, as they may avoid the cited limitations of metal stents and offer other advantages as well.

POLYMERIC STENTS

Several reports of resorbable and nonresorbable polymeric stents have recently appeared [12, 24–29]. The rationale for the nondegradable stent is improved biocompatibility over the metal stent and convenient drug loading. Nonresorbable polymers being investigated for stent use include polyethylene terephthalate, polyurethane urea, and polydimethyl siloxane. The rationale for the bioresorbable stent is support of the arterial wall only during vessel healing, with gradual transfer of the mechanical load to the tissue as the stent mass and strength decrease over time, longer-term delivery of drug and/or gene therapy to the vessel wall from an internal reservoir, and no need for a second surgery to remove the device. Bioresorbable polymers under investigation include aliphatic polyesters, polyorthoesters, and polyanhydrides. Recently, bioresorbable, linear, multiblock copolymers with shape memory capability have been introduced [30]. Controlled incremental heating of this thermoplastic material has been used to shrink sutures, making graded tissue approximations feasible in minimally invasive surgery applications. The same concept is also valuable for bioresorbable stent applications. Following balloon expansion, heat (approx. 5°C temperature change) applied to shape memory elements in the stent could reinforce designs that might not otherwise have sufficient recoil resistance.

Poly-L-lactic acid (PLLA), poly-D,L-lactic acid (PDLA), poly ε-caprolactone (PCL) and polyglycolic acid (PGA), all aliphatic polyesters, are the most frequently used materials for bioresorbable stents [12, 24, 25]. PLLA and PDLA have a high tensile strength, permitting robust mechanical design, but requiring long degradation times. PGA and PCL have less strength, but faster degradation rates. Useful combinations of these materials (copolymers and blends) can be made to improve flexibility. These materials degrade principally by simple hydrolysis of the ester bond in the polymer backbone. Partial chain scission degrades the polymer to 10–40 μm particles, capable of being phagocytosed and metabolized to carbon dioxide and water, which are of course fully resorbed. The degradation time is a function of the chemical structure of the polymer and its molecular weight. In typical formulations, PGA degrades over a time period of 6–12 months, while PLLA degrades over months to years (Table 2).

The long-term behavior of biodegradable polymers in blood vessels has not been well established. Van der Giessen *et al.* [31], testing strips of five different biodegradable polymers, PGA/PLA, PCL, polyhydroxybutyrate valerate, polyorthoester and polyethylene oxide/polybutylene terephthalate, found extensive inflammatory responses within the coronary arterial wall. The observed tissue responses might be due the parent polymer compound, additives to the polymer, intermediate biodegradation products, the implant geometry, or combinations thereof. On the other hand, the authors noted that the implants were cleaned but not sterilized; therefore, bacterial or nonbacterial contamination might also have accounted for the inflammatory response. We have also observed a similar inflammatory response to sterilized PLLA stents implanted in the porcine femoral artery [32]. This

Table 2.
Characteristics of typical bioresorbable polymers[a]

Polymer	Melting point (°C)	Glass transition temperature (°C)	Modulus (Gpa)	Degradation time (months)
PGA	225–230	35–40	7.0	6–12
PLLA	173–178	60–65	2.7	>24
PDLA	Amorphous	55–60	1.9	12–16
PCL	58–63	−65 to −60	0.4	>24

PGA = poly(glycolic acid); PLLA = poly(L-lactic acid); PDLA = poly(D,L-lactic acid); PCL = poly(ε-caprolactone).
[a] Adapted from Ref. [102].

may have been due to the original polymer formulation, which was not intended for medical applications and contained an epoxide functionality of unknown quantity. More recent, purified formulations appear to induce a much less intense inflammatory response, as determined both by studies in the progress of PLLA fiber implantation into the rat aortic wall over 1–4 weeks and by PLLA stent implantation in the pig femoral artery for 2 weeks. In the same vein, long-term study of polylactide copolymer, PLLA/PDLA (PLA96) stents in a rabbit abdominal aorta model found that the stents degraded with minimal tissue response within 24 months, with suitable encapsulation of polymer fragments in a thin neointima, leading the authors to suggest PLA96 as a promising stent core material [33].

Several early calls for expandable bioabsorbable stents have been published as alternatives for metallic stents [12, 24, 25]. These led to bioresorbable stents from Duke University [34], Tianjin/Beijing University [35], Kyoto University [28], Igaki/Tamai [36] and the University of Texas at Arlington/Southwestern Medical School (UTA/SW) [32, 37]. The first biodegradable stent was developed and investigated at Duke University. This PLLA stent, based on a slotted polymer fiber design, was reported to withstand up to 1000 mmHg compression pressure; *in vivo* studies demonstrated minimal thrombosis and inflammatory responses, and moderate neointimal growth. The Tianjin/Beijing stent, made of PDLA/PCL copolymer with an inner heparin layer, was deployed with a balloon catheter, employing heating and pressurization. This stent produced mild neointimal proliferation in swine carotid artery models at 2 months. The Kyoto University PGA coil stent exhibited thrombus deposition in canine implant studies, but no subacute closure. The Igaki/Tamai stent, a bioresorbable PLLA zigzag coil thought to be derived from the Kyoto design, was studied in the first clinical report of a bioresorbable stent in the human coronary artery. This stent also required a combination of heating and pressurization for expansion. The preliminary (6-month) results suggest that this stent is safe and effective for human use. Long-term studies are anticipated.

THE MULTIPLE LOBE STENT

This PLLA stent is designed using a linear, continuous coil array principle, by which multiple furled lobes (four in the present design) convert to a single large lobe upon balloon expansion (Fig. 1). Melt-extruded PLLA fibers (drawn 6 : 1) with a diameter of 0.14 mm and an ultimate stress of 350 ± 40 MPa are woven continuously around a four-mandrel array (one central, three peripheral) into a four-lobe configuration. Three longitudinal fibers are interwoven and glued to the coil for mechanical support. After fabrication, a conventional angioplasty balloon catheter is inserted in the central lobe and the stent can be deployed at the target site. The structure of the fully expanded stent is that of a helical coil with three longitudinal reinforcing fibers. The initial and final diameters of stents are adjustable by various combinations in sizes of central and peripheral rod mandrels. Stents with furled diameters ranging from 1.6 to 2.4 mm were fully expanded by 3 atm pressure, to 2.3–4.7 mm: the corresponding expansion ratios ranged from 1.4 to 1.9. Collapse pressure under radial compression was adequately high, ranging from 0.4 to 2.4 atm, depending on the fiber ply and other design parameters.

Preliminary results from various *in vitro* and *in vivo* studies of this expandable bioresorbable stent suggested that the design principles and fabrication technique were sufficiently robust and versatile, thus meriting further investigation [37, 38].

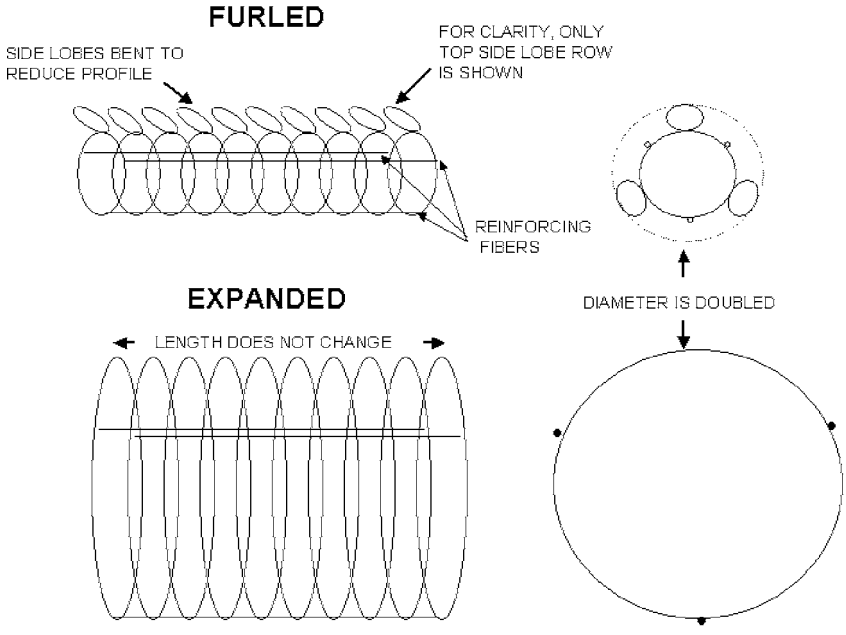

Figure 1. Schematic diagram of the helical coil polymeric stent design (external version). The fiber is wound continuously over four mandrels to obtain the multiple lobes. The side lobes are flattened passively, or by use of a sheath during delivery. These lobes can also be wound inside the primary coil to reduce the profile during delivery. Both designs open readily with balloon expansion.

In 1- and 2-week implant studies in the porcine common femoral artery, stents did not migrate; however, the vessel lumen was markedly reduced at 2 weeks, due to a strong inflammatory response. Stents, like other implants, elicit a range of host responses, which interfere with the patency of the device [31, 39]. Various approaches have been investigated to improve the biocompatibility of these stents, including surface plasma treatment and drug incorporation. Pulsed RF plasma treatment with di(ethylene glycol) vinyl ether significantly reduced platelet adhesion in a 1 h porcine arteriovenous shunt model to less than 10% of untreated control values [37]. Curcumin (diferoyl methane), a non-steroidal anti-inflammatory drug, was melt-extruded with PLLA to generate curcumin-loaded PLLA fiber (C-PLLA). The curcumin was uniformly distributed within the fibers and a stable curcumin release rate for 36 days was observed. *In vitro* studies of mouse peritoneal phagocytes indicated significant reductions in the adhesion of these cells to C-PLLA compared with PLLA controls. These results suggested that C-PLLA has anti-inflammatory properties, which may benefit the implants. Other non-steroidal anti-inflammatory agents with sufficiently high melting points can be introduced into the polymer bulk in the same way.

We have also investigated the bulk loading of aqueous drugs that cannot tolerate melt extrusion, using a wet spinning technique that permits the incorporation of large amounts of drug (up to 20 wt%) in the PLLA fiber. In addition, hollow PLLA fiber spinning processes that allow loading drugs, genetic vectors, or radioisotopes into PLLA accessories have been examined.

STENTS AS RESERVOIRS FOR LOCAL DRUG AND GENE THERAPY

Efforts have been directed towards developing stents coated with a biodegradable drug-impregnated polymer, capable of gradually releasing therapeutic agents into the vessel wall to reduce thrombosis and restenosis [2, 3, 39, 40]. The use of antithrombotic drugs such as heparin and hirudin is one strategy [41]. Other agents include prostacyclin analogy Iloprost [42], glycoprotein IIb/IIIa receptor antibodies or inhibitors [43], and antiproliferative agents such as nitric oxide donors, corticosteroids and taxanes that inhibit neointima and local tumor proliferation [18, 39, 40]. Drugs or peptides contained within polymers can be in a non-chemically bonded configuration (physical entrapment) or chemically bonded to the polymer side-chains [26]. Stents coated with drug-eluting polymers such as hirudin, prostacyclin, and nitrosylated albumin were shown to reduce neointima formation [39, 42]. Decreased early thrombosis and neointima formations were also observed in stents loaded with glycoprotein IIb–IIIa inhibitors [44, 45] and with nitric oxide donors [46, 47]. Furthermore, intramural delivery of an antiproliferative agent, a specific tyrosine kinase inhibitor, using biodegradable stents has suppressed the restenotic changes of coronary arteries of treated pigs [28].

In addition to local drug delivery, stents can also serve as carriers for gene therapy delivery. Stents seeded with cells transfected with the desired gene, stents loaded

with recombinant adenovirus gene transfer vectors, and stents loaded with naked DNA impregnated in various matrices have been proposed [2, 29, 48–50]. The introduction of an interested gene into the arterial wall can be achieved either by *in vitro* genetic manipulation of cells before their seeding onto stents or by direct *in vivo* gene transfer. Cell-based gene transfer using stents as platforms has been shown a major advantage in terms of site-specific gene expression. However, cell-based gene delivery has several limitations, including removal or injury of cells from the stent after balloon expansion and a significant time delay required for cell harvest, expansion, gene transfer, and subsequent selection prior to stent seeding. Yet seeding the stents with genetically engineered endothelial cells (ECs) to produce agents such as tPA has been shown to inhibit smooth muscle cell (SMC) proliferation [51]. A recent study has shown that a mesh stent coated with fibronectin is an excellent platform for adherent gene transduced SMCs [52].

Similar to the advantage of cell-based gene transfer, site-specific gene delivery, gene-stent therapy has been applied to reduce thrombosis and in-stent restenosis. Genes that encode enzymes of the prostacyclin synthetic pathway, nitric oxide synthase, the thrombin inhibitor, and thrombomodulin have been studied and demonstrated a significant reduction in thrombosis and restenosis in animal models [29, 50, 53–55]. We successfully demonstrated local gene transfer and expression from PLLA stents impregnated with a recombinant adenovirus carrying a nuclear localizing βGal reporter gene into the carotid and renal arteries in the rabbit. Liver transfection was negligible in both cases, suggesting that gene delivery was local, not convected to remote sites to a significant degree [48]. In spite of promising results in animal models, to date no effective human gene therapy has been found to prevent restenosis [29, 50, 56]. In addition, potential side effects of the gene therapy approach such as subsequent malignant transformation due to oncogene activation with utilization of retroviral gene vectors and subsequent expression in other organs need to be further evaluated. In order to prevent potentially dangerous distal spread of viral vectors, a recent study has developed stent-based anti-viral antibody tethering of vectors onto the collagen coating surface of stents as a suitable platform for local gene delivery [57]. Another promising strategy for gene therapy delivery involves the introduction of antisense oligonucleotides into cells in order to inactivate the mRNA encoding proteins important in the restenotic process [58]. Uses of synthetic oligonucleotides to suppress proto-oncogenes including c-myb and c-mbc, proliferating cell nuclear antigen, and cell cycle-specific proteins cdc2 and cdk2 kinases were reduced protein expression and cell proliferation [12, 58].

NON-CORONARY USES OF STENTS

The range of stent applications has expanded with increases in experience and encouraging results in the treatment of vascular diseases. Stents have been used for the treatment of urethral obstruction from benign prostatic hyperplasia; for the treatment of tracheobronchial obstruction of benign or malignant origin; for the

treatment of benign and malignant strictures of the esophagus, the gastrointestinal (GI) tract, and the bile duct; and for the treatment (stents and stent-grafts) of arterial dissections, aneurysms and various neurovascular diseases.

STENTS IN UROLOGY

Stents have been used to prevent postoperative urine retention following thermal treatment of benign prostatic hyperplasia (BPH) by various means, including direct vision laser ablation of the prostate and transurethral microwave therapy. Several stent designs, including the Nissenkorn, Barnes, Finnish biodegradable self-reinforced polyglycolic acid (SR-PGA) spiral and Trestle, were shown to prevent obstruction of the prostatic urethra and restricture of the anterior urethra [27, 59, 60]. Biodegradable stents have been studied clinically in the treatment of BPH and are claimed to provide superior results to suprapubic catheters [61–65]. Self-reinforced PLLA bioresorbable spiral stents are also undergoing evaluation for use in the anterior urethra, posterior urethra and upper urinary tract, to prevent urinary retention and repair of local ureteral trauma or defects [66, 67]. Surface modification of these biodegradable stents, by grafting with hydroxyethylmethacrylate or by incorporation of biologically active compounds, is claimed to be an efficient approach to improve biocompatibility and cell adhesion properties [68, 69].

STENTS FOR THE MANAGEMENT OF TRACHEOBRONCHIAL OBSTRUCTION

Tracheobronchial obstruction from either benign or malignant disease causes significant morbidity and mortality. Metal stents, developed originally for the vascular system, have been adapted for lesions involving the tracheobronchial tree. These include the Palmaz (Johnson & Johnson), Strecker (Boston Scientific), Gianturco-Z (William Cook Europe), Wallstent (Boston Scientific) and Ultraflex (Boston Scientific) stents [70]. These stents were successfully used to treat patients with inoperable bronchogenic cancer, esophageal tumors, primary tracheal tumors, and metastatic malignancy. Bioresorbable tracheal stents have been investigated in the setting of pediatric tracheal malacia, to solve the problem of limited tracheal growth in children with rigid external fixation and to avoid the necessity of a second procedure to remove the synthetic material [70–72]. The general results from these studies suggest that stenting is a promising method to treat tracheal obstruction.

STENTS IN THE ESOPHAGUS AND GASTROINTESTINAL (GI) TRACT

Many malignant and benign strictures in the esophagus and GI tract can be treated by minimally invasive alternatives to surgery, including the use of stents. Most

commonly used in the esophagus and GI tract are the Wallstent (Boston Scientific), Ultraflex (Boston Scientific), Gianturco-Z (William Cook Europe), Esophacoil (Instent) and Flamingo stents (Boston Scientific). In general, these stents have been shown to be effective in relieving esophageal dysphagia [22, 73, 74]. This success has led to the employment of stents to manage lesions of the GI tract, including the stomach, pylorus, upper small intestine, duodenum, and colon [22, 73]. The use of bioresorbable material is currently being explored for the esophageal stent. First results in the placement of a PLLA stent (Instent) for the management of benign esophageal stricture suggest that a bioresorbable stent offers a new treatment modality [75]. In addition, bioresorbable stents were recently used in pancreaticojejunal anastomoses [76].

STENTS IN THE MANAGEMENT OF NEUROVASCULAR DISEASE

Stents and stent-grafts have been used for the management of arterial and venous sinus stenosis, arterial dissection, arterial aneurysm and arteriovenous fistulae [77, 78]. A number of case reports have been published describing the significant reduction in carotid stenosis with the use of stents in the treatment of carotid stenosis, recurrent carotid stenosis, vertebral artery stenosis, and venous sinus stenosis [78]. As cited in this review, Shawl *et al.* [79] reported a series of 124 stented vessels in which carotid stenosis was reduced from $86 \pm 7\%$ to $2 \pm 2\%$; the major postprocedural stroke rate was 0.8% and the minor stroke rate was 2%. Three cases of basilar artery stenosis have been successfully treated with coronary stents at our institution [80]. Other unpublished reports from our institution have demonstrated the effectiveness of stents in bridging side-wall aneurysmal ostia, suggesting that stents are a promising means for the management of arterial dissection and pseudoaneurysm. Unfortunately, no large studies have yet been published, so the effectiveness of stents in this application remains to be determined.

CONCLUSION

Stents play an increasingly important role in percutaneous coronary interventions. Various metal stents have been shown to reduce the restenosis rate compared with angioplasty alone. This success has prompted the expansion of stent usage to peripheral arteries, the urethra, trachea, esophagus and GI tract. Stents do not eliminate the problem of coronary arterial restenosis and may contribute to it by inducing neointimal hyperplasia. Thus, isotope-loaded metal stents and polymer- and ceramic-coated metal stents, using the coating as a vehicle for local anti-inflammatory drug delivery, have been introduced, with promising results. Several bioresorbable stent designs are in development for temporary mechanical support combined, in some cases, with drug and/or gene therapy delivery. Such temporary, bioresorbable stents that match the expandability and recoil resistance

of metal stents in the coronary arterial setting have been reported. These stents are theoretically superior for arterial wall healing, but face challenges in their application to smaller, more tortuous channels. Radioisotope-loaded metal or polymeric stents are also appealing for the local treatment of tumors and for the prevention of excessive granulation tissue formation in non-coronary settings. Stent design and development is currently a very active area of bioengineering practice. The expanding range of applications and new designs, materials, and surface treatments suggest that more effective, less invasive therapies may be anticipated in the near future.

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REFERENCES

1. G. Belli, S. G. Ellis and E. J. Topol, *Prog. Cardiovasc. Dis.* **40**, 159 (1997).
2. H. Bult, *Trends Pharmacol. Sci.* **21**, 274 (2000).
3. R. Hoffmann and G. S. Mintz, *Eur. Heart J.* **21**, 1739 (2000).
4. A. J. Carter, D. Scott, D. Rahdert, L. Bailey, J. De Vries, K. Ayerdi, T. Turnlund, R. Jones, R. Virmani and T. A. Fischell, *J Invasive Cardiol.* **11**, 127 (1999).
5. J. M. Dumonceau and J. Deviere, *Baillieres Best Pract. Res. Clin.* **13**, 109 (1999).
6. Y. Ozaki, A. G. Violaris and P. W. Serruys, *Prog. Cardiovasc. Dis.* **39**, 129(1996).
7. A. G. Violaris, Y. Ozaki and P. W. Serruys, *Int. J. Cardiac Imaging* **13**, 3 (1997).
8. T. Nicholson, *Hosp. Med.* **60**, 571 (1999).
9. T. J. Cleveland and P. Gaines, *Hosp. Med.* **60**, 630 (1999).
10. C. D. J. Barras and K. A. Myers, *Eur. J. Vasc. Endovasc. Surg.* **19**, 564 (2000).
11. D. R. Ramsdale, *Hosp. Med.* **60**, 624 (1999).
12. J. F. Tanguay, J. P. Zidar, H. R. Phillips and R. S. Stack, *Cardiol. Clin.* **12**, 699 (1994).
13. A. H. Gershlick, *Heart* **86**, 104 (2001).
14. C. von Birgelen, M. Haude, J. Herrmann, C. Altmann, W. Klinkhart, D. Welge, H. Wieneke, D. Baumgart, S. Sack and R. Erbel, *Catheter Cardiovasc. Interv.* **47**, 496 (1999).
15. C. Stefanandis, E. Tsiamis, C. Vlachopoulos, K. Toutouzas, C. Stratos, I. Kallikazaros, M. Vavuranakis and P. Toutouzas, *Cathet. Cardiovasc. Diagn.* **40**, 217 (1997).
16. C. Herdeg, M. Oberhoff and K. R. Karsch, *Semin. Interv. Cardiol.* **3**, 197 (1998).
17. W. J. van der Giessen, H. M. van Beusekom, M. H. Eijgelshoven, M. A. Morel and P. W. Serruys, *Semin. Interv. Cardiol.* **3**, 173 (1998).
18. J. Gunn and D. Cumberland, *Eur. Heart J.* **20**, 1693 (1999).
19. A. W. Chan and D. J. Moliterno, *Cleve. Clin. J. Med.* **68**, 796 (2001).
20. J. Kotzerke, H. Hanke and M. Hoher, *Eur. J. Nucl. Med.* **27**, 223 (2000).
21. C. Hehrlein and W. Kubler, *Semin. Interv. Cardiol.* **2**, 109 (1997).
22. R. Lamber, *Endoscopy* **32**, 322 (2000).
23. S. Balter, *Cathet. Cardiovasc. Diagn.* **45**, 292 (1998).
24. M. Labinaz, J. P. Zidar, R. S. Stack and H. R. Phillips, *J. Int. Cardiol.* **8**, 395 (1995).
25. A. Colombo and E. Karvouni, *Circulation* **102**, 371 (2000).
26. T. Peng, P. Gibula, K. Yao and M. F. A. Goosen, *Biomaterials* **17**, 685 (1996).
27. M. Talja, T. Valimaa, T. Tammela, A. Petas and P. Tormala, *J. Urol.* **11**, 391 (1997).

28. T. Yamawaki, H. Shimokawa, T. Kozai, K. Miyata, T. Higo, E. Tanaka, K. Egashira, T. Shiraishi, H. Tamai, K. Igaki and A. Takeshita *J. Am. Coll. Cardiol.* **32**, 780 (1998).
29. C. Indolfi, C. Coppola, D. Torella, O. Arcucci and M. Chiariello, *Cardiol. Rev.* **7**, 324 (1999).
30. A. Lendlein and R. Langer, *Science* **296**, 1673 (2002).
31. W. J. van der Giessen, M. Lincoff, R. S. Schwartz, H. M. M. van Beusekom, P. W. Serruys, D. R. Holmes, S. G. Ellis and E. J. Topol, *Circulation* **94**, 1690 (1996).
32. S. Su, *Biomedical engineering*, Doctoral dissertation, University of Texas at Arlington, Arlington (2000).
33. E. Hietala, U. Salminen, A. Stähls, T. Välimaa, P. Maasilta, P. Törmälä, M. S. Nieminen and A. L. J. Harjula, *J. Vasc. Res.* **38**, 361 (2001).
34. C. M. Agrawal and H. G. Clark, *Invest. Radiol.* **27**, 1020 (1992).
35. R. Gao, R. Shi, S. Qiao, L. Song and Y. Li, *J. Am. Coll. Cardiol.* **27**, 85A (1996).
36. H. Tamai, K. Igaki, E. Kyo, K. Kosuga, A. Kawashima, S. Matsui, H. Komori, T. Tsuji, S. Motohara and H. Uehata, *Circulation* **102**, 399 (2000).
37. S. Su, R. Y. Chao, C. L. Landau, K. D. Nelson, R. B. Timmons, R. S. Meidel and R. C. Eberhart, *Ann. Biomed. Eng.* (2003) (in press).
38. S. Su, C. L. Landau, R. Y. N. Chao, R. B. Timmons, R. S. Meidel, L. Tang and R. C. Eberhart, *Circulation* **104**, II-507 (2001).
39. O. F. Bertrand, R. Sipehia, R. Mongrain, J. Rodés, J. Tardif, L. Bilodeau, G. Côté and M. G. Bourassa, *J. Am. Coll. Cardiol.* **32**, 562 (1998).
40. D. Brieger and E. Topol, *Cardiovasc. Res.* **35**, 405 (1997).
41. R. Herrmann, G. Schmidmaler, B. Märkl, A. Resch, I. Hähnel, A. Stemberger and E. Alt, *Thromb. Haemost.* **82**, 51 (1999).
42. E. Alt, I. Haehnel, C. Beiharz, K. Prietzel, D. Preter, A. Stemberger, T. Fliedner, W. Erhardt and A. Schömig, *Circulation* **101**, 1453 (2000).
43. A. Colombo and C. Briguori, *Am. Heart J.* **138**, S153 (1999).
44. R. Aggarwal, D. Ireland, M. Azrin, D. De Bono and A. Gershlick, *J. Am. Coll. Cardiol.* **29**, 353A (1997).
45. R. Aggarwal, D. Ireland, M. Azrin, M. Ezekowitz, D. De Bono and A. Gershlick, *Circulation* **94**, 3311 (1996).
46. J. Folts, N. Maalej, J. Keaney and J. Loscalzo, *Circulation* **92**, I-670 (1995).
47. J. Folts, N. Maalej, J. Keaney and J. Loscalzo, *J. Am. Coll. Cardiol.* **27**, 86A (1996).
48. Y. Ye, C. Landau, J. E. Willard, G. Rajasubramanian, A. Moskowitz, S. Aziz, R. S. Meidell and R. C. Eberhart, *Ann. Biomed. Eng.* **26**, 398 (1998).
49. B. D. Klugherz, P. L. Jones, X. Cui, W. Chen, N. F. Meneveau, S. DeFelice, J. Connolly, R. L. Wilensky and R. J. Levy, *Nature Biotechnol.* **18**, 1181 (2000).
50. M. D. Feldman, B. Sun, B. J. Koci, C. C. Wu, J. R. Kneller, H. S. Borovetz, S. Watkins, A. Nadeem, L. E. Weiss, M. L. Reed, A. J. Smith and W. D. Rosenblum, *J. Long Term Eff. Med. Implants* **10**, 47 (2000).
51. D. A. Dichek, R. F. Neville, J. A. Zwiebel, S. M. Freeman, M. B. Leon and W. F. Anderson, *Circulation* **80**, 1347 (1989).
52. C. J. Panetta, K. Miyauchi, D. Berry, R. D. Simari, D. R. Holmes, R. S. Schwartz and N. M. Caplice, *Hum. Gene Ther.* **13**, 433 (2002).
53. P. Vermeersch, Z. Nong, E. Stabile, O. Varenne, H. Gillijns, M. Pellens, N. Van Pelt, M. Hoylaerts, I. De Scheerder, D. Collen and S. Janssens, *Arterioscler. Thromb. Vasc. Biol.* **21**, 1604 (2001).
54. L. M. Akyurek, S. Nallamshetty, K. Aoki, H. San, Z. Y. Yang, G. J. Nabel and E. G. Nabel, *Mol. Ther.* **3**, 779 (2001).
55. O. Varenne and P. Sinnaeve, *Curr. Interv. Cardiol. Rep.* **2**, 309 (2000).
56. L. Gruberg, R. Waksman, L. F. Satler, A. D. Pichard and K. M. Kent, *Exp. Opin. Invest. Drugs* **9**, 2555 (2000).

57. B. D. Klugherz, C. Song, S. DeFelice, X. Cui, Z. Lu, J. Connolly, J. T. Hinson, R. L. Wilensky and R. J. Levy, *Hum. Gene Ther.* **13**, 443 (2002).
58. N. Kipshidze, J. Moses, L. R. Shankar and M. Leon, *Curr. Opin. Mol. Ther.* **3**, 265 (2001).
59. R. Kapoor, E. N. Liatsikos and G. Badlani, *Curr. Opin. Urol.* **10**, 19 (2000).
60. B. A. Kletscher and J. E. Oesterling, *Urol. Clin.* **22**, 423 (1995).
61. J. J. M. C. H. de la Rosette, H. P. Beerlage and F. M. J. Debruyne, *J. Endourol.* **11**, 467 (1997).
62. E. Kemppainen, M. Talija, M. Riihelä, T. Pohjonen, P. Törmälä and O. Alfthan, *Urol. Res.* **21**, 235 (1993).
63. A. Pétas, M. Talja, T. Tammela, K. Taari, K. Lehtoranta, T. Välimaa and P. Törmälä, *J. Urol.* **157**, 173 (1997).
64. A. Pétas, T. Isotalo, M. Talja, T. L. J. Tammela, T. Välimaa and P. Törmälä, *Scand. J. Urol. Nephrol.* **34**, 262 (2000).
65. A. Pétas, P. Kärkkäinen, M. Talja, K. Taari, M. Laato, T. Välimaa and P. Törmälä, *Br. J. Urol.* **80**, 903 (1997).
66. J. Lumiaho, A. Heino, T. Pietiläinen, M. Ala-Opas, M. Talja, T. Välimaa and P. Törmälä, *J. Urol.* **164**, 1360 (2000).
67. J. Lumiaho, A. Heino, V. Tunninen, M. Ala-Opas, M. Talja, T. Välimaa and P. Törmälä, *J. Endourol.* **13**, 107 (1999).
68. A. Brauers, P. K. Jung, H. Thissen, O. Pfannschmidt, W. Michaeli, H. Hoecker and G. Jakse, *Tech. Urol.* **4**, 214 (1998).
69. A. Brauers, H. Thissen, O. Pfannschmidt, H. Bienert, A. Foerster, D. Klee, W. Michaeli, H. Höcker and G. Jakse, *J. Endourol.* **11**, 399 (1997).
70. A. L. Rafanan and A. C. Mehta, *Int. Chest Radiol.* **38**, 395 (2000).
71. T. C. Robey, P. M. Eiselt, H. S. Murphy, D. J. Mooney and R. A. Weatherly, *Laryngoscope* **110**, 1936 (2000).
72. H. Lochbihler, J. Hoelzi and H. Dietz, *J. Pediatr. Surg.* **32**, 717 (1997).
73. R. Morgan and A. Adam, *J. Vasc. Interv. Radiol.* **12**, 283 (2001).
74. T. Nicholson, *Hosp. Med.* **61**, 97 (2000).
75. S. W. Fry and D. E. Fleischer, *Gastrointest. Endosc.* **45**, 179 (1997).
76. M. Parviainen, J. Sand, A. Harmoinen, H. Kainulainen, T. Välimaa, P. Törmälä and I. Nordback, *Pancreas* **21**, 14 (2000).
77. H. A. Gray and A. W. Crane, *Am. J. Roentgenol.* **175**, 289 (2000).
78. M. B. Horowitz and P. D. Purdy, *Neurosurgery* **46**, 1335 (2000).
79. F. Shawl, W. Kadro, M. J. Domanski, F. L. Lapetina, A. A. Iqbal, K. G. Dougherty, D. D. Weisher, J. F. Marquez and S. T. Shahab, *J. Am. Coll. Cardiol.* **35**, 1721 (2000).
80. M. B. Horowitz, G. L. Pride, D. F. Graybeal and P. D. Purdy, *Neurosurgery* **45**, 925 (1999).
81. E. Grube, S. M. Silber and K. E. Hauptmann, *Circulation* **104**, II-463 (2001).
82. S. Park, W. H. Shim, D. S. Ho, A. E. Raizner, S. W. Park, J. J. Kim, M. K. Hong, C. W. Lee, S. Y. Cho, Y. S. Jang, D. H. Choi, C. P. Lau, R. Lam and Y. Wang, *Circulation* **104**, II-464 (2001).
83. J. W. Moses, M. B. Leon, J. J. Popma and R. E. Kuntz, *Circulation* **104**, II-464 (2001).
84. J. E. Sousa, M. Morice, P. W. Serruys, J. Fajadet, M. Perin, E. B. Hayashi, A. Colombo, G. Schuler, P. Barragan and C. Bode, *Circulation* **104**, II-463 (2001).
85. K. A. Robinson, N. A. Chronos, J. Royal, L. Suh, G. D. Cipolla, R. Virmani and R. S. Stack, *Circulation* **104**, II-506 (2001).
86. F. Gobeil, M. Laflamme, M. Bouchard, Campbell E., M. Wood, P. St-Jacques, J. Vincent and G. Leclerc, *Circulation* **104**, II-388 (2001).
87. H. M. Van Beusekom, M. J. Post, B. J. De Smet, M. G. Put, M. S. Harteveld and W. J. Van der Giessen, *Circulation* **104**, II-506 (2001).
88. K. J. Salu, H. Yanming, J. M. Bosmans, L. Xiaoshun, I. K. Scheerder and C. J. Vrints, *Circulation* **104**, II-506 (2001).

89. H. C. Lowe, R. Fahmy, C. N. Chesterman and L. M. Khachigian, *Circulation* **104**, II-265 (2001).
90. H. C. Lowe, R. G. Fahmy, M. M. Kavurma, A. Baker, C. N. Chesterman and L. M. Khachigian, *Circ. Res.* **89**, 670 (2001).
91. H. Kim, H. A. Yazdi, R. Seaborn, P. Iversen, G. S. Roubin, S. S. Lyer, M. B. Leon, J. W. Moses and N. Kipshidze, *Circulation* **104**, II-545 (2001).
92. T. A. Swierkosz, S. Kapoor, D. C. Tardiff, J. W. Hirshfeld, B. D. Klugherz, D. M. Kolansky, K. Magness, N. Valettas, R. L. Wilensky and H. C. Herrmann, *Circulation* **104**, II-385 (2001).
93. G. Montalescot, P. Barragan, O. Wittemberg, P. Pinton, S. Elhadad, X. Deboisgelin, A. Akesbi, B. Jouve, M. Amor and F. Funck, *Circulation* **104**, II-386 (2001).
94. G. Amoroso, A. J. van Boven, D. J. van Veldhuisen, R. A. Tio, C. P. Balje-Volkers, A. S. Petronio and W. van Oeveren, *J. Cardiovasc. Pharmacol.* **38**, 633 (2001).
95. D. L. Bhatt and A. M. Lincoff, *Circulation* **104**, II-384 (2001).
96. A. G. Rebeiz, K. S. Pieper, J. C. O'Shea, I. C. Gilchrist, B. Chandler, J. Slater, J. B. Muhlestein, T. J. Loenz, D. Joseph, M. M. Kitt and J. E. Tcheng, *Circulation* **104**, II-386 (2001).
97. Y. Huang, L. Wang, I. Vermeire, E. Verbeken, E. Schacht and I. D. Scheerder, *Circulation* **104**, II-665 (2001).
98. T. R. Porter, P. Iversen, F. Xie, D. Kricsfeld, S. J. Radio, J. Lof and S. Flynn, *Circulation* **104**, II-589 (2001).
99. R. Rohde, B. Heublein, S. Ohse, E. Evagorou, K. Pethig and A. Haverich, *Circulation* **104**, II-666 (2001).
100. G. B. Danzi, C. Capuano, M. Sesana, A. D. Blasi and D. Antoniucci, *Circulation* **104**, II-625 (2001).
101. S. Silber, N. Reifart, M. Morice, J. V. Dahl, E. Benit, K. Hauptmann, J. E. Sousa, J. G. Webb, U. Kaul and C. Chan, *Circulation* **104**, II-623 (2001).
102. J. C. Middleton and A. J. Tipton, *Med. Plast. Biomater* **30** (March) (1998).