

Does the Metal Matter?

An overview of next-generation stent platforms.

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Originally used to scaffold an artery that was destined to close (secondary to coronary dissection or elastic recoil), the stent has become a mainstay of interventional cardiology. Early stents were simple, rigid, stainless steel systems covered with a sheath to prevent embolization off of the catheter during the sometimes tortuous and long path to the culprit area. The metal component has varied, including gold, stainless steel, tantalum, and various amalgams. Polymers and drugs were later added to prevent the growth of fibrointimal hyperplasia and restenosis. In this article, we review the three major components of drug-eluting stent (DES) design (including platform, drug, and polymer types [Figure 1]), with a focus on the metal and scaffold and a brief overview of pharmaceutical agents and polymers applied to the stent.

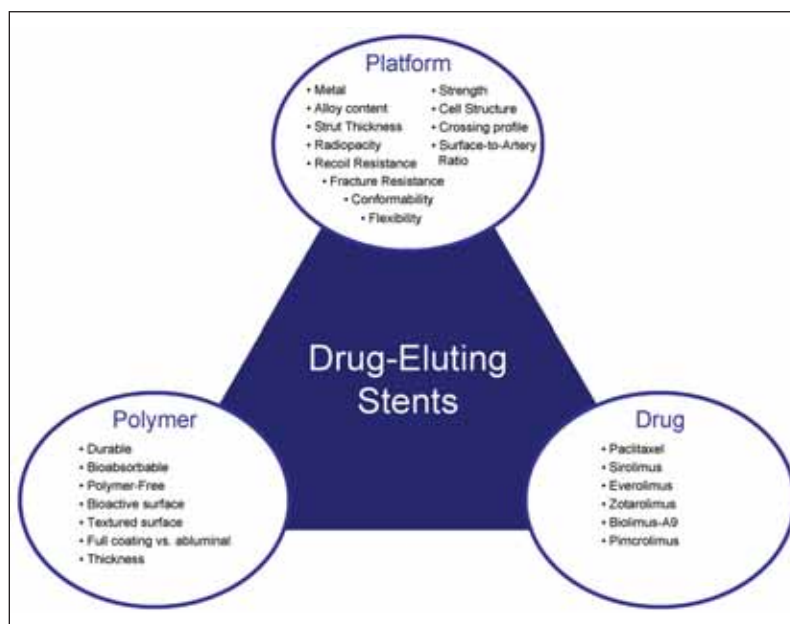


Figure 1. DES components.

THE PLATFORM

Metal Alloy

The type of metal used for the stent scaffold may have an impact on the effectiveness and safety of the stent.¹ First-generation stents, including the first stent implanted into a human coronary artery by Puel and Sigwart,² were made of stainless steel. Although stainless steel provides corrosion resistance and vascular biocompatibility, visualization of stainless steel stents under x-ray fluoroscopy may be challenging, particularly when implanting stents with thin struts.³ The thinner the strut, the greater the flexibility; however, as strut thickness diminishes with stainless steel, so does the visualization on fluoroscopy. The addition of more

radiopaque materials, such as tantalum⁴ or gold, was initially explored; however, gold-coated stents were associated with increased restenosis and mortality risk.^{5,6}

Cobalt-chromium-based alloys, such as L605 used in the Multi-Link Vision stent (Abbott Vascular, Santa Clara, CA) and MP35N used in the Driver stent (Medtronic Inc., Minneapolis, MN), have been successfully implanted.^{7,8} More recently, Boston Scientific Corporation (Natick, MA) has developed platinum-chromium stents,⁹⁻¹¹ the first alloy specifically developed for coronary stenting. Because it is more dense than stainless steel or cobalt-chromium,¹² the radiopacity of platinum-chromium is higher (Figure 2), which allows the use of thinner struts without sacrificing

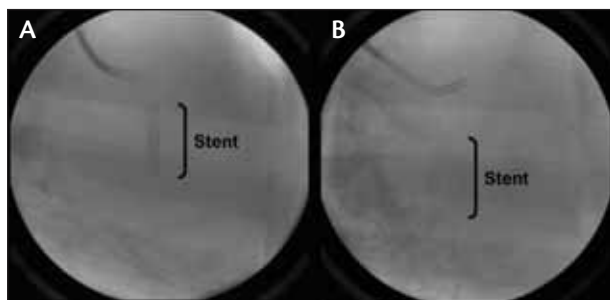


Figure 2. Radiopacity comparison of platinum-chromium versus 316L stainless steel. Platinum-chromium, 81- μ m strut thickness, left circumflex lateral view (A). 316L stainless steel, 97- μ m strut thickness, left circumflex lateral view (B). Fluoroscopy with OEC 9900 portable C-arm (GE Healthcare, Wauwatosa, WI).

visibility⁹ (the importance of thin struts will be described later in this article). The incorporation of platinum also increases the strength of the alloy.¹⁰ Bench studies have demonstrated that the platinum-chromium alloy used in the Element stent (Boston Scientific Corporation) has increased radial strength and increased fracture resistance compared to the 316L stainless steel Taxus Express stent (Boston Scientific Corporation).¹³

Plastic deformation (elastic) recoil is a measure of the stent's ability to maintain its initial expanded diameter and minimize the risk of late malapposition to the vessel. Stents produced from cobalt-chromium alloys may have higher acute recoil (high plastic deformation) due to the yield strength properties of the alloy. Recent studies have challenged this widely held belief in noncomplex lesions after intravascular ultrasound and have found no compromise in acute stent expansion between stainless steel and cobalt-chromium when the Xience V/Promus stent (Abbott Vascular/Boston Scientific Corporation) is compared with earlier-generation stainless steel stents.¹⁴ Plastic deformation recoil of the platinum-chromium Element stent has been reported to be 3.6% compared to 4.6% and 5%, respectively, for the Xience V/Promus and Endeavor cobalt-chromium (Medtronic, Inc.) stents.^{13,15}

In addition, nickel content (Table 1), which has been incriminated in both metal hypersensitivity reactions and restenosis after bare-metal stent (BMS) deployment,^{16,17} is less in the platinum-chromium alloy (9%) compared with 316L stainless steel (14%) or cobalt-chromium stent alloys (L605 = 10%;¹⁸ MP35N = 35%^{7,8}). Some recent innovations in design include replacement of the core content of metal with drug, creating a so-called drug-filled stent, or using a core wire of differing composition to enhance radiopacity with a continuous sinusoidal pattern to enhance delivery while continuing to allow smaller strut diameters (continuous sinusoid technology line; Figure 3).

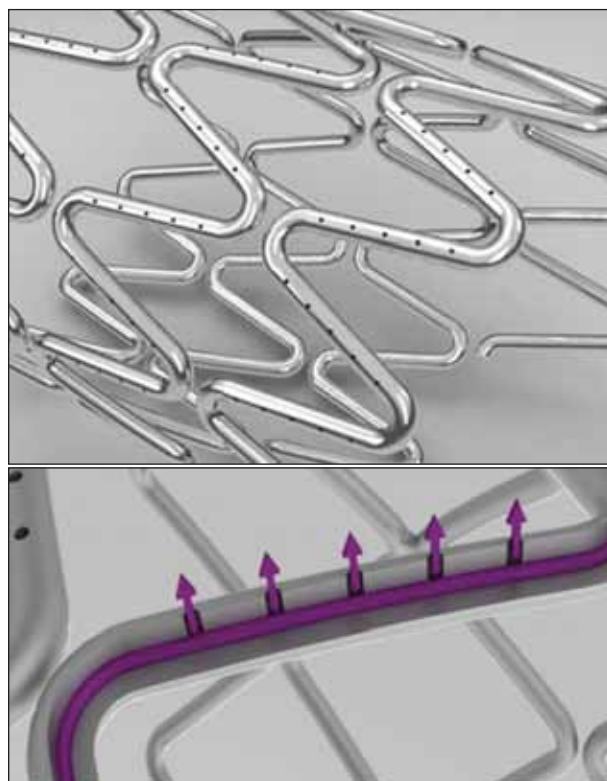


Figure 3. Continuous sinusoid technology and drug-filled stent (Medtronic, Inc.).

Strut Thickness

In addition to the type of metal used, strut thickness may also affect vascular response. It has been postulated that thinner stent struts result in lower restenosis rates and improved healing, possibly due to less stent-induced arterial injury and inflammation. In the ISAR-STERO studies, thinner-strut stents were associated with significantly less angiographic and clinical restenosis after stenting, regardless of the architectural design of the stent.^{19,20} Thinner struts also result in increased flexibility, reduce the stent profile, and allow lower-pressure deployment.²¹ Because thinner-strut stents require less neointima coverage, endothelialization and healing may be facilitated, possibly resulting in a reduced risk of late stent thrombosis.²²⁻²⁴

Because both the radial strength and radiopacity of first-generation stainless steel stents depended on the thickness of the stent strut, the development of thin-strut stents was limited, necessitating strut thicknesses of 132 μ m (Taxus Express) to 140 μ m (Cypher BX Velocity, Cordis Corporation, Bridgewater, NJ). The use of stronger, more radiopaque metals, such as cobalt-chromium (Multi-Link Vision, Driver) and platinum-chromium (Element), has allowed the incorporation of thinner struts without sacrificing strength or visibility (Figure 4). In a preclinical study, luminal coverage of stent struts correlated with strut thick-

TABLE 1. NOMINAL ELEMENTAL COMPOSITION BY WEIGHT (%)^a

	316L Stainless Steel	L605 (Cobalt-Chromium Alloy)	MP35N (Cobalt-Chromium Alloy)	Platinum-Chromium Alloy
Iron	64 ^b	3 maximum	1 maximum	37 ^b
Platinum	NA	NA	NA	33
Cobalt	NA	52 ^b	34 ^b	NA
Chromium	18	20	20	18
Nickel	14	10	35	9
Tungsten	NA	15	NA	NA
Molybdenum	2.63	NA	9.75	2.63
Manganese	2 maximum	1.5	0.15 maximum	0.05 maximum
Titanium	NA	NA	1 maximum	NA

Abbreviations: NA, not available.

^aReprinted with permission from Trials.¹³

^bDesignated as balance value calculated from nominal values of other elements.

ness in three BMS models: endothelialization was highest in the 81- μ m, platinum-chromium Element stent; lower in the 97- μ m, stainless steel Taxus Liberté stent (Boston Scientific Corporation); and lower still in the 132- μ m, stainless steel Taxus Express stent.¹¹

Clinical studies have supported the suggestion that reduced strut thickness results in lower restenosis rates after stent placement. The SPIRIT family of studies has demonstrated that the revascularization rates of the 81- μ m, cobalt-chromium Xience V/Promus stent are significantly less than the 132- μ m Taxus Express platinum-chromium stent.^{25,26} Although drug type was also different between these two stents (see The Drug section), the PERSEUS clinical trials have suggested that target lesion revascularization (TLR) rates are numerically lower (although not statistically significant) in the thin-strut Taxus Element stent compared to the Taxus Express stent, which use the same drug, dose, and polymer but have different stent designs.²⁷

Architecture

The specific architecture of the stent is also believed to be an important determinant of flexibility, deliverability, homogeneity of drug distribution, and fracture resistance. Resistance to stent fracture also depends on the geometric design of the stent, which affects flexibility through tortuous lesions. In challenge focal bend fatigue tests, the next-generation Element stent can

withstand significantly more bend cycles before fracture compared to the earlier-generation Taxus Express or Taxus Liberté stents.²⁷

The number of available stent models across the range of diameters is important to ensure homogenous drug distribution. Stent platforms such as Taxus Express, Multi-Link Vision, Cypher BX Velocity, and Driver have only two stent models to cover the range of diameters. For example, in these first-generation stents, 2.25-mm-diameter stents used the same stent platform as a 3-mm-diameter stent mounted onto a smaller balloon. In contrast, the next-generation, platinum-chromium Element stent includes four stent models to optimize the surface-to-artery ratio and provide more uniform drug distribution and scaffolding. In addition, second- and third-generation stents now include specifically designed small-vessel options, such as the Taxus Liberté Atom 2.25-mm stent (Boston Scientific Corporation), the Cypher 2.25-mm stent, and the Xience Nano 2.25-mm stent (Abbott Vascular). The Element stent has a specific model for the 2.25-mm-diameter size that incorporates a lower system profile and more segments per stent than the larger models, which is expected to facilitate

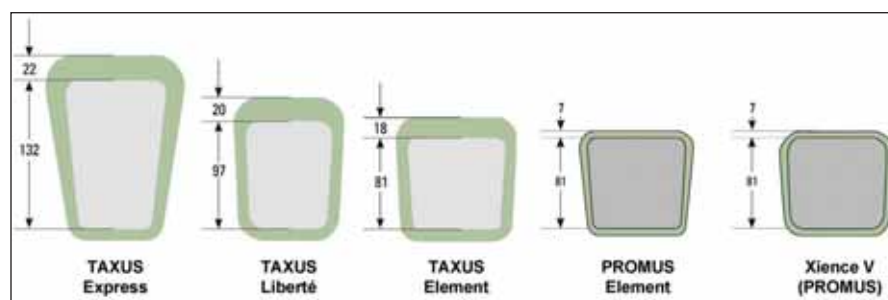


Figure 4. Examples of DES strut thickness (μ m).

TABLE 2. NEXT-GENERATION STENTS AS OF MAY 2010 (UNITED STATES MANUFACTURERS)²⁸

Product Name	Manufacturer	Metal/Platform	Strut Thickness	Drug	Polymer	Clinical Studies (Clinicaltrials.gov NLM Identifier) ²⁹
BVS	Abbott Vascular	Fully bioabsorbable stent	150 μ m	Everolimus	Bioabsorbable	ABSORB A (NCT00300131), ABSORB B (NCT00856856), ABSORB-EXTEND (NCT01023789)
Synergy (Evolution)	Boston Scientific Corporation	Platinum-chromium/Element	81 μ m ^a	Everolimus	Bioabsorbable	EVOLVE
Jactax	Boston Scientific Corporation	Stainless steel/Taxus Liberté	97 μ m	Paclitaxel	Bioabsorbable	JACTAX HD(NCT00754728), JACTAX LD (NCT00754975), OCTDESI (NCT00776204)
Nevo	Cordis Corporation	Cobalt-chromium/RES (reservoir) technology	99 μ m	Sirolimus	Bioabsorbable	NEVO RES I (NCT00606333), NEVO RES II (NCT00714883), CYNERGY (NCT01106378)
Promus Element	Boston Scientific Corporation	Platinum-chromium/Element	81 μ m	Everolimus	Durable	PLATINUM (NCT00823212), PLATINUM QCA (NCT00824434)
Resolute	Medtronic, Inc.	Cobalt-chromium/Driver	91 μ m	Zotarolimus	Durable	Medtronic RESOLUTE trials (NCT00726453, NCT00248079)
Taxus Element	Boston Scientific Corporation	Platinum-chromium/Element	81 μ m	Paclitaxel	Durable	PERSEUS Workhorse (NCT00484315), PERSEUS Small Vessel (NCT00489541)
Xience Prime	Abbott Vascular	L605 Cobalt-chromium/Multi-Link 8	81 μ m	Everolimus	Durable	SPIRIT PRIME
Xience "Thinman"	Abbott Vascular	Ultrathin/Novel	Unknown	Everolimus	Durable	TBA
Xience V/Promus	Abbott Vascular (Promus distributed by Boston Scientific Corporation)	L605 Cobalt-chromium/Multi-Link Vision	81 μ m	Everolimus	Durable	SPIRIT studies (NCT00180453, NCT00180310, NCT00180479, NCT00307047, NCT00402272)
Xience Nano (2.25-mm stent)	Abbott Vascular	L605 Cobalt-chromium/Multi-Link Vision	Unknown	Everolimus	Durable	SPIRIT Small Vessel

^aCompany plans a 71- μ m stent for commercial release.

deliverability and conformability in small, tortuous vessels. The 38-mm Taxus Liberté Long stent (Boston Scientific Corporation) is also now available. Longer stents reduce the need for multiple overlapping stents in long lesions, which has been correlated with increased non-Q-wave myocardial infarction events in paclitaxel-eluting stents.³⁰

THE DRUG

Given a strong yet flexible scaffold matrix and geometric architecture, an appropriate alloy composition, and a thin-strut design, DES are often further distinguished by the drug and polymer applied to the stent. First-generation, FDA-approved DES, such as the Cypher sirolimus-eluting stent³¹ and the Taxus Express paclitaxel-eluting stent³² demonstrated reduced clinical and angiographic revascularization rates compared to BMS that were maintained out to 5 years after implantation.^{33,34} However, the potential for increased inflammation and delayed healing compared to BMS presents continuing challenges,³⁵ prompting developers of next-generation stents to focus on optimizing the polymer and the drug, in addition to the metal platform.

An overview of the next-generation stents that are currently available or in development in the United States is shown in Table 2. Many more next-generation DES are available in the European market and have been described in previous reviews.^{22,28}

Two major drug classes are used to inhibit restenosis in DES. The -olimus (rapamycin) drugs, including sirolimus (Cypher), everolimus (Xience V/Promus), biolimus A9, and zotarolimus (Endeavor), act on mTOR, a key intermediary in the phosphatidylinositol 3-kinase pathway.³⁶ Paclitaxel (Taxus) acts downstream of these pathways by inhibiting microtubular function, which is required for cell migration and proliferation.³⁷ Results of the SPIRIT family of studies suggest that the everolimus-eluting, cobalt-chromium, 81- μ m Xience V/Promus stent inhibits restenosis to a greater extent than the paclitaxel-eluting, stainless steel, 132- μ m Taxus Express stent in general populations.^{26,38} However, in patients with diabetes, the 1-year TLR rates were similar between Xience V/Promus (6.4%) and Taxus Express (6.9%) in the SPIRIT IV study²⁶ and numerically lower with the Taxus Liberté paclitaxel-eluting stent (3.8%) than with Xience V/Promus stent (8.4%; $P = .16$) in the SPIRIT V diabetic randomized controlled trial³⁹ (although late loss was significantly higher with the Taxus Liberté than with the Xience V/Promus stent). Although still inconclusive, these results potentially suggest a unique role for paclitaxel in the diabetic metabolic state that is consistent with its mechanism of action downstream of metabolic pathways affected by diabetes. This also highlights the ability of the stent composition and thickness to ameliorate or accentuate the

effects of the drug and polymer. It is possible that paclitaxel may be a better agent for diabetic patients (considerable controversy exists here); however, the larger stent diameter may have ameliorated the effect in SPIRIT IV.

In the PERSEUS clinical study, the 81- μ m, platinum-chromium, paclitaxel-eluting Taxus Element stent group had a 1-year TLR rate of 3.8%,²⁷ which compares favorably to the 3.4% TLR rate observed in the SPIRIT III study with the Xience V/Promus stent.³⁸ The Taxus Element might be a better comparator for the Xience V/Promus stent than the Taxus Express because the strut thickness is more similar and both incorporate a chromium alloy, allowing a better potential “drug-versus-drug” comparison, albeit with differing polymers.

A comparison of the results of the next-generation Element stent series, which includes both everolimus- (Promus Element) and paclitaxel- (Taxus Element) eluting varieties using the same metal and stent platform, will yield important information as to the relative importance of the antirestenotic drug versus the stent metal and design. An analogue to sirolimus, zotarolimus is an antiproliferative agent used on the Resolute stent (Medtronic, Inc.) and the Endeavor thin-strut platform.⁴⁰ However, the Endeavor polymer has been replaced with the BioLinx polymer system, which is a blend of the hydrophobic C10 polymer (controls drug release), hydrophilic C19 polymer (supports compatibility), and polyvinyl pyrrolidinone (increases initial drug burst and elution rate).⁴⁰ The RESOLUTE trial, a prospective, nonrandomized, multicenter, first-in-human study included 139 patients and demonstrated a 0% stent thrombosis rate at 9 months, and TLR, target vessel revascularization, and target vessel failure rates of 1.4%, 1.4%, and 7.9%, respectively, at 2-year follow-up.^{40,42} Other considerations, such as full-drug coating (conformal) versus abluminal only, polymer type (durable or bioabsorbable), drug release pharmacokinetics, and the simultaneous addition of prohealing compounds, are also being assessed in novel DES studies (Table 2).

THE POLYMER/CARRIER

Most DES incorporate the antirestenotic drug into an elastomeric polymer or combination of hydrophobic and hydrophilic agents (as noted previously with the BioLinx polymer), which allows controlled release of the drug over a defined (usually limited) time period. However, problems with the polymer have been implicated in cases in which DES fail. These problems include nonuniform coating, webbing of the polymer surface, polymer delamination, and biocompatibility issues. Such difficulties are believed to provoke inflammatory reactions, potentially leading to late stent thrombosis, which unfortunately does not seem to be eliminated over the course of time.^{24,43}

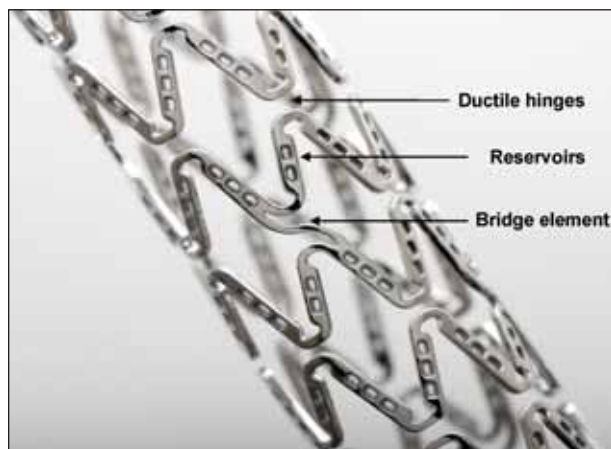


Figure 5. The Nevo sirolimus-eluting coronary stent (Cordis Corporation). Reprinted from *EuroIntervention*,⁴¹ Copyright (2009), with permission from Europa Edition.

Although thinner polymer and bioactive or textured surfaces can be used to promote healing, many next-generation stent manufacturers are also developing stents with bioabsorbable polymers, or no polymer at all, in order to address this issue. Several bioabsorbable polymer-coated stents are currently in development or under clinical investigation (Table 2), such as the Nevo stent (Cordis Corporation), which incorporates a fully bioabsorbable polymer, a thin-strut cobalt-chromium platform, and a novel reservoir technology for controlled drug release (Figure 5).⁴¹ Promising 6-month angiographic and 12-month clinical results have been reported for the Nevo stent in the RES-ELUTION I study, a randomized controlled trial comparing Nevo to the Taxus Liberté stent.^{45,46} The Synergy (Evolution) stent (Boston Scientific Corporation) incorporates an everolimus-eluting, bioabsorbable polymer applied to the abluminal surface of a platinum-chromium stent. This stent will be studied in the EVOLVE clinical trial.

METAL NO MORE?

Fully bioabsorbable stents, such as the BVS stent (Abbott Vascular),^{47,44} are also under development. Bioabsorbable stents are intended to provide immediate scaffolding support to open the stenosed artery but then to biodegrade within 6 months to 2 years, leaving behind a naturally healed vessel similar to absorbable sutures routinely placed into tissue to approximate edges. Fully bioabsorbable stents may reduce the chronic inflammation associated with a metallic platform and possibly shorten the duration of dual-antiplatelet therapy needed. Challenges to fully absorbable stents remain, including degradation rates, vascular compatibility, particulate debris, and scaffold strength. Recent findings from the

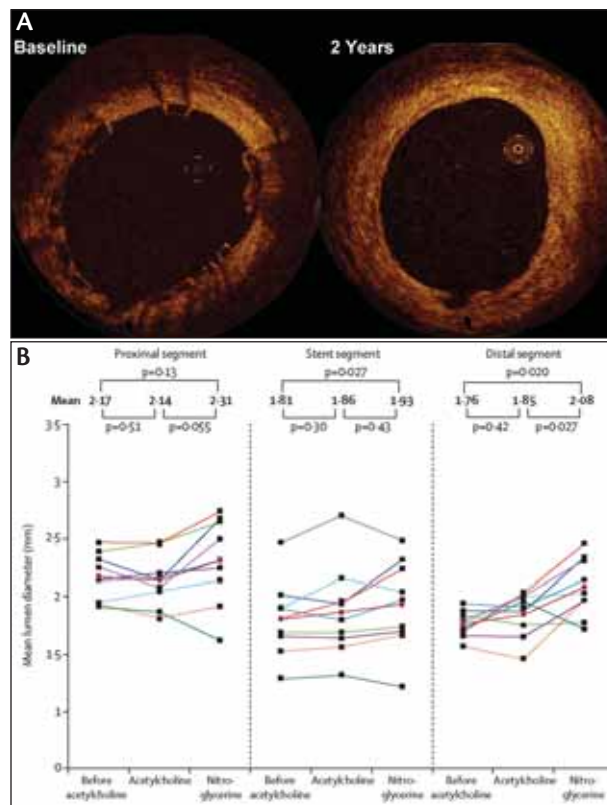


Figure 6. Optical coherence tomography of the Abbott Vascular BVS fully bioabsorbable stent at baseline and 2 years after implantation from the ABSORB clinical trial (A) (Image courtesy of Abbott Vascular. ©2010 Abbott Laboratories. All Rights Reserved). Restoration of vasomotor function in the stented segment of the BVS stent (B) (Reprinted from *The Lancet*, © 2009 with permission from Elsevier).⁴⁴

ABSORB Clinical Program at Abbott Vascular have shown that within 2 years, the scaffold of the stent is almost entirely invisible with optical coherence tomography (Figure 6A). Furthermore, when the vessel is challenged by acetylcholine or methergin, the vessel vasoreactivity and physiological response can be restored (Figure 6B).⁴⁴

Stent strut fracture (which increases the risk of restenosis) is a continuing challenge, particularly in areas such as the adductor hiatus in the legs, vessel tortuosity, and in stent strut overlap regions. If biodegradable stents can optimize vascular results in these challenging anatomical areas, then biodegradable nonmetallic stents may have a larger market than many physicians currently suggest.

THE FUTURE OF DES

Considerable advances have been made in platform, drug, and polymer technology since the advent of the first-generation DES. Future stents will focus on further

optimizing the design to incorporate thinner struts, the reduced use of durable polymers, and combination therapies to inhibit restenosis while promoting endothelialization and reducing dependence on dual-antiplatelet therapy. In addition, drugs and platforms customized to treat specific patient profiles (eg, small vessels, bifurcation, and diabetes) will likely be explored further. ■

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