The Perfect Drug-Eluting Stent

Goals for stent, polymer, and drug development.

BY TIM A. FISCHELL, MD, FACC, FSCAI; DWIGHT DISHMON, MD; ADAM ELHADDI, MD; SHADWAN ALSAFWAH, MD; AND SANTHOSH R. MANNEM, MD

Drug-eluting stents (DES) have revolutionized our ability to perform simple to complex coronary interventions with extremely low rates of target lesion failure.[1-5] Even the first-generation DES have performed well, demonstrating significant advantages over bare-metal stents (BMS) in virtually every category and subcategory of coronary lesion and patient type.[1-3]

The long-term safety of DES is another key issue that has been controversial.[6-15] Studies and editorials from 2 to 3 years ago stirred controversy and generated tremendous publicity in the lay press in relation to the safety of DES for the treatment of coronary artery disease.[6-9] More recent studies with longer follow-up have discredited this concern, with the preponderance of scientific evidence now showing that -olimus-eluting stents with durable polymer are at least as safe as, if not safer than, BMS and have sustained improvement in efficacy versus BMS at 3- to 5-year follow-up.[10-17] As with BMS, a large majority of DES thrombosis is related to operator error and stent underexpansion.[18-20]

This article will review and critique the shortcomings of today's DES and will propose future directions for development that would achieve the elusive goal of creating the ideal or perfect DES. We will briefly review issues related to stent design, strut thickness, stent delivery systems, metals, the use of polymers (biostable vs bioabsorbable, or none), the kinetics of drug release, and the choice of drugs.

STENT DESIGNS AND DELIVERY SYSTEMS

Modern stent designs have evolved during the last 10 years so that most contemporary stents are reasonably flexible, deliverable, and provide adequate scaffolding and radial hoop strength. Most current stents have achieved flexibility by either creating an open-cell structure (eg, Xience/Vision [Abbott Vascular, Santa Clara, CA], Endeavor/Driver [Medtronic, Inc., Minneapolis, MN], etc.) or by using undulating longitudinal connectors (eg, Cypher [Cordis Corporation, Warren, NJ], Xience/Vision, etc.) to connect the expandable "Palmaz" circumferential slotted structures. Ultimately, a great deal of the deliverability or flexibility of the stent system is also determined by the stent delivery balloon and catheter. In many cases, this can be more important than the stent structure itself. Although there are data suggesting improved drug-delivery distribution[21,22] and less plaque prolapse with closed-cell stent designs (eg, Cypher),[23] the translation of these observations to clinical events is less well defined.

As stent designs continue to evolve, the perfect stent will achieve even greater flexibility by using thin struts, open cells with undulating connectors, and potentially the use of a hybrid-type design, such that the nonconnected struts are shorter than the connected struts. This type of design will allow optimal flexibility and create less flaring and fish scaling of the nonconnected struts as the predeployed stent structure is advanced around bends.

Further improvements in balloon and catheter technology, including the potential use of systems such as Stent-On-A-Wire (Svelte Medical Systems, Inc., New Providence, NJ), may allow extraordinary flexibility with extremely low profiles (≤ 0.028 inch) and ease of deliverability (Figure 1A and B).[24] Similarly, the very low-profile Sparrow nitinol-based self-expanding DES (CardioMind, Inc., Sunnyvale, CA) will be another highly deliverable DES concept for smaller vessels (Figure 1C and D).[25] Although there is some appeal in a fully biodegradable polymeric DES (discussed later), these devices will likely suffer, to some extent, in their deliverability characteristics and radial hoop strength compared to the upcoming, state-of-the-art, metallic stent structures and delivery systems.

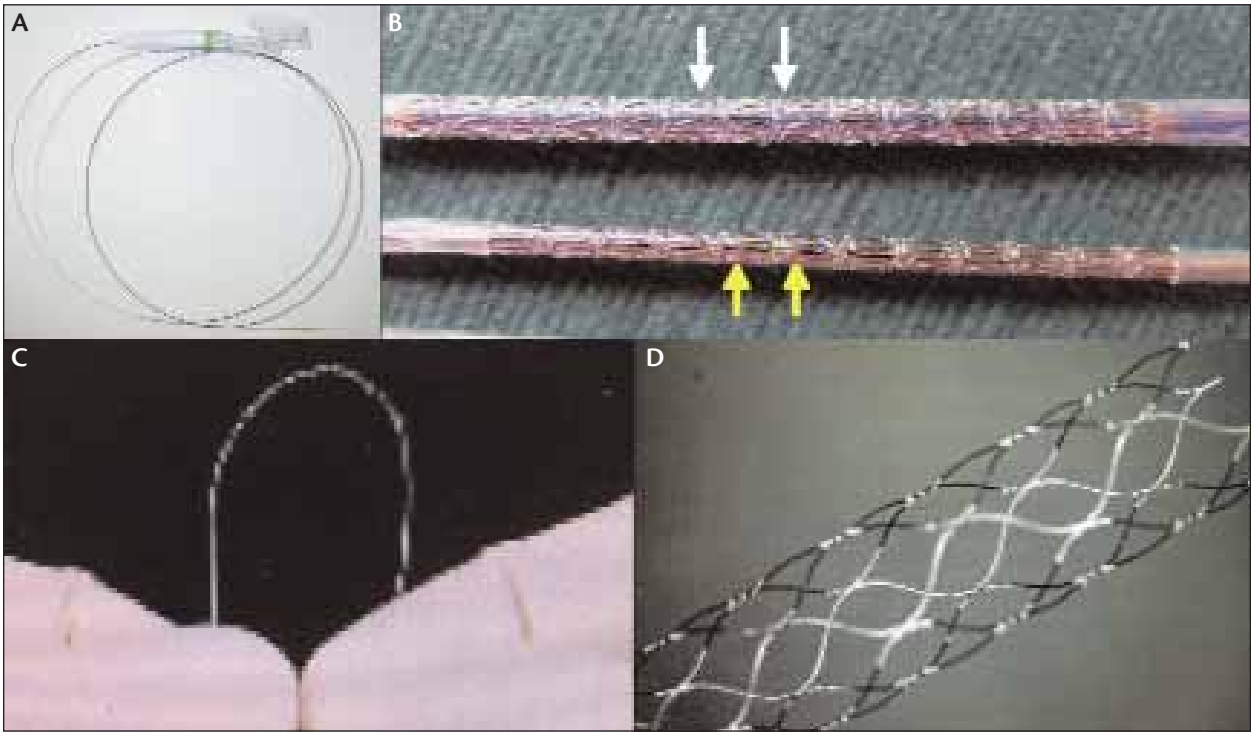

Figure 1. The Stent-On-A-Wire balloon-expandable stent system (A). The Xience stent (white arrows) and the Stent-On-A-Wire (yellow arrows) delivery system profiles (B). The predeployment (C) and postdeployment (D) of a Sparrow nitinol stent.

STRUT THICKNESS

Historically, there have been data generated with BMS suggesting that thinner struts may be associated with lessened neointimal hyperplasia and restenosis.[26] However, this widely held belief is based predominantly on a lone single-center trial without an independent core laboratory.[26] These results have not been supported by numerous large studies with independent angiographic core laboratories, and therefore they fail to demonstrate any consistent relationship of strut thickness with late luminal loss, target lesion revascularization (TLR), or restenosis, even with BMS.[27,28]

With DES, it becomes even clearer that strut thickness is not predictive of late loss, restenosis, major adverse cardiac events (MACE), or stent thrombosis.[11,29,30] In the recently reported ZEST trial, the thicker-strutted Cypher stent had a TLR rate of 1.4% compared to 4.8% with the thin-strutted Driver/Endeavor stent. Similarly, the MACE and stent thrombosis rates were as low or lower for Cypher than for Endeavor (stent thrombosis was 0.5% for the thin-strutted Endeavor and 0% for the thick-strutted Cypher).[29] Similar results were reported in the Endeavor III study, in which the thicker-strutted Cypher with sirolimus substantially outperformed the thinner-strutted Endeavor stent in a randomized clinical trial.

Thus, in the current DES era, strut thickness appears to play no role in clinical outcomes such as TLR or MACE rates. Nonetheless, as discussed later, thinner struts may provide significant advantages with regard to acute stent performance. Thinner-strutted stents will provide greater flexibility, deliverability, vessel conformity, and will reduce the stent system delivery profile. However, there are no randomized data to suggest that thinner struts affect side branch access. The ideal newer DES platforms will utilize thinner struts to enhance these acute stent performance characteristics. However, it should be recognized that there are some trade-offs when the struts are thinned (ie, a loss of radial hoop strength and radiopacity), regardless of which metal substrate is used.

BIOSTABLE VERSUS BIODEGRADABLE VERSUS POLYMER-FREE DES

One of the more exciting and controversial areas in DES design is related to the use of biostable versus biodegradable polymer systems to control drug elution. The first two major DES systems (Cypher and Taxus Express, [Boston Scientific Corporation, Natick, MA]) have used different biostable polymers. The Cypher DES contains sirolimus, which elutes from a polyethylene-co-vinyl acetate/poly N-butyl methacrylate polymer, and the Taxus DES elutes paclitaxel from a styrene-isobutylene-styrene (SIBS) polymer.

The SIBS polymer used on the Taxus stent is a form of rubber and an adhesive compound with elastomeric prop-

erties. SIBS is a biologically inactive and biostable compound that allows the ability to retain the drug (paclitaxel) on the stent, provides relatively uniform drug delivery, prevents mechanical disruption during processing and deployment, and has a relatively long shelf life. Although the SIBS polymer has properties that make it a suitable drug-delivery polymer, it also has unfavorable physical properties related to its adhesive behavior, with high forces required for the deflated balloon withdrawal when the stent is deployed in curved segments.[30] Other biostable polymers, such as those used with Cypher, and more recently with Endeavor and Xience stents, do not appear to have this characteristic of polymer stickiness.

Safety issues have been raised by some investigators, suggesting that biostable polymers can incite chronic inflammation, resulting in late adverse events such as late restenosis or very late stent thrombosis.[6,7] As previously cited, these concerns appear to be overstated based on numerous peer-reviewed studies published more recently, suggesting that DES with biostable polymers appear at least as safe as BMS, particularly when the studies or registries are controlled for the greater complexity of patients treated with DES compared to BMS (ie, longer lesions, more stents, smaller vessels, etc.).[10-15]

The one exception may be Taxus stents, which seem to have an increasing slope of adverse events beginning after 1 to 2 years.[16,17] This may be related more to the pharmacokinetics of Taxus rather than to the polymer itself. Unlike Endeavor (very short drug release) or Cypher and Xience stents (intermediate but complete drug elution by 90 days), the Taxus system retains at least 90% of the drug on the polymer after the initial 10% of the paclitaxel is eluted during the first few months. This large reservoir of paclitaxel contained in the biostable polymer may allow a low level of ongoing drug elution that may last for years. Although speculative, it may be the lack of healing from intermittent and ongoing paclitaxel release from the SIBS polymer that may best explain the divergence of safety curves seen in recent analyses.[16,17]

Although there appears to be excellent long-term efficacy and safety with certain biostable DES systems, there is an emerging interest and trend to use a very thin layer or, in the case of the Nevo stent (Cordis Corporation), pores filled with biodegradable polymer as the means to elute the drug or drugs. There is some appeal to this technique of delivering the drug along with the bioabsorption of the polymer drug carrier because, after the drug elution is completed, only a BMS is left behind. This approach, if successful, will likely overtake and replace biostable polymers due to the perception of a potential for inflammation with biostable polymers.

The Nevo stent,[31] Sparrow stent, and others,[32,33] have now presented preliminary safety and efficacy data to suggest that -olimus-eluting drugs delivered with a biocompatible degradable polymer, such as polylactic-co-glycolic acid (or others), can create late loss data that appear comparable to -olimus-eluting DES with biostable polymers.

In a study that was recently presented at EuroPCR 2009, the Nevo sirolimus-eluting coronary stent had significantly lower in-stent late lumen loss than the Taxus Liberté in a prospective randomized clinical trial.[31] Late lumen loss was reduced by 64% in the Nevo arm as compared to the Taxus Liberté arm (0.13 mm vs 0.36 mm; $P < .001$). In addition, Nevo also showed superior angiographic results (binary restenosis of 1.1% in the Nevo arm vs 8% in the Taxus Liberté arm; $P < .002$).[31] It is likely that this approach (ie, a biodegradable polymer with -olimus) will eventually be favored over biostable polymeric drug release during the next 3 to 6 years. There are a large number of new polymers and DES using both biostable and bioabsorbable polymers that are in various stages of development.[34,35] A summary of the ongoing proliferation of DES in development is detailed in Table 1.

The next major step forward may be the use of metallic stent structures with porous surfaces, allowing for appropriate drug-elution kinetics without the use of a polymer. A number of newer stent designs are trying to test this approach by incorporating drugs into a nanoporous surface of the stent and mimicking Cypher drug kinetics. The Vestasync stent (MIV Therapeutics Inc., Vancouver, British Columbia, Canada) with hydroxyapatite releasing sirolimus, and the Biolimus A9 stent (Biosensors International Group, Ltd., Singapore) with biolimus represent two early devices using a "no-polymer" approach. This approach may ultimately prove to be optimal if appropriate dosing and pharmacokinetics can be achieved. Some of these nanoporous surfaces may also promote early re-endothelialization and/or have antithrombogenic properties after the drug is eluted, further enhancing early healing and a reduction in the need for dual-antiplatelet therapy and/or late stent thrombosis.

FULLY BIOABSORBABLE DES

More than a decade ago, the concept of a fully bioabsorble polymeric stent was tested extensively with the premise that the long-term placement of a BMS in the vessel wall would be inflammatory and lead to inevitable restenosis. When this turned out to be incorrect (ie, long-term BMS very rarely incite any late events), the interest in fully bioabsorbable BMS waned.

Interest in a fully bioabsorbable DES has now regained momentum due to the appeal of leaving nothing behind after the drug has been fully eluted. Recent data for the BVS

TABLE 1. DRUG-ELUTING STENT POLYMER-BASED COMPARISON

Stent Design	Manufacturer	Drug (Dose)	Polymer
AMS	Biotronik, Inc.	None	None
Axxess	Devax, Inc.	Biolimus A-9 (15.6 µg/mm)	PLA
Axxion	Biosensors International, Ltd.	Paclitaxel	None
BioMatrix	Biosensors International, Ltd.	Biolimus-A9	PLA
BVS	Abbott Vascular	Everolimus (8–8.5 µg/mm)	PLLA + PDLLA
Cardiomind	CardioMind, Inc.	Sirolimus	PLA+PGLA
Champion	Boston Scientific Corporation	Everolimus	PLA
Corio	Cordis Corporation	Pimecrolimus	N/A
CoStar	Cordis Corporation	Paclitaxel	PLGA
Cura	OrbusNeich	Sirolimus (1.7 µg/mm^2)	PLA + PLGA
Cypher	Cordis Corporation	Sirolimus (1.4 µg/mm^2)	PEVA + PBMA
Cypher Select	Cordis Corporation	Sirolimus	PEVA + PBMA
Dreams	Biotronik	Pimecrolimus	N/A
Elixir Myolimus	Elixir Medical	Myolimus (40 µg)	Methacrylate
Endeavor	Medtronic, Inc.	Zotarolimus (10 µg/mm)	Phosphorylcholine
Endeavor Resolute	Medtronic, Inc.	Zotarolimus	BioLinx
Excel	JW Medical Systems Ltd.	Sirolimus (195–376 µg)	PLA
Excella	Elixir Medical Corporation	Novolimus (0.85 µg/mm^2)	Methacrylate
Genous	OrbusNeich	Anti-CD34	None
Igaki-Tamai	Kyoto Medical Planning Co. Ltd.	None	PLLA
Infinnium	Sahajanand Medical Technologies Pvt. Ltd.	Paclitaxel	PLLA + PLGA + PVP
Janus Flex	Sorin Group	Tacrolimus	None
Nevo	Cordis Corporation	Sirolimus (166 µg)	PLGA
Nobori	Terumo Medical Corporation	Biolimus A-9	PLA
Promus	Boston Scientific Corporation	Everolimus (1 µg/mm^2)	Fluoropolymer
REVA	REVA Medical Inc.	Paclitaxel	Polycarbonate
Stellium	DISA Vascular (Pty) Ltd.	Paclitaxel	PLGA
Supralimus	Sahajanand Medical Technologies Pvt. Ltd.	Sirolimus (1.4 µg/mm^2)	PLLA + PLGA + PVP
Symbio	Cordis Corporation	Pimecrolimus + paclitaxel	PLGA
Synchronnium	Sahajanand Medical Technologies Pvt. Ltd.	Sirolimus + heparin	N/A
Taxus Express	Boston Scientific Corporation	Paclitaxel (1 µg/mm^2)	SIBS (Translute)
Taxus Liberté	Boston Scientific Corporation	Paclitaxel (1 µg/mm^2)	SIBS (Translute)
Taxus Petal	Boston Scientific Corporation	Paclitaxel	SIBS (Translute)
Titan2 BAS	Hexacath	Titanium-NO	None
Vestasync	MIV Therapeutics Inc.	Sirolimus	None (Hap + lipid)
Xience V	Abbott Vascular	Everolimus (1 µg/mm^2)	Fluoropolymer
Xtent	Xtent, Inc.	Biolimus A-9	PLA
Yukon	Translumina GmbH	Sirolimus	None
ZoMaxx	Abbott Vascular	Zotarolimus (10 µg/mm)	Phosphorylcholine

Abbreviations: BioLinx, hydrophilic C19 + polyvinyl pyrrolidone (PVP) + hydrophobic C10; Hap, hydroxyapatite; N/A, not available; NO, nitric oxide; PBMA, poly-n-butyl methacrylate; PDLLA, poly-DL-lactic acid; PEVA, polyethylene-co-vinyl acetate; PLA, polylactic acid; PLGA, poly (lactide-co-glycolide); PLLA, poly-L-lactic acid; SIBS, poly (styrene-b-isobutylene-b-styrene).

Biocompatibility	Polymer Thickness (µm)	Stent Platform	Strut Thickness (µm)
Bioabsorbable	None	Magnesium alloy	N/A
Bioabsorbable	N/A	Stainless steel	112
None	None	Stainless steel	119
Bioabsorbable	10	Stainless steel	112
Bioabsorbable	N/A	PLLA	150
Bioabsorbable	N/A	Nitinol	67
Bioabsorbable	N/A	Stainless steel	N/A
Bioabsorbable	N/A	Cobalt chromium	89
Bioabsorbable	N/A	Cobalt chromium	89
Bioabsorbable	5–10	Stainless steel	100
Durable	12.6	Stainless steel	140
Durable	N/A	Stainless steel	100
Bioabsorbable	N/A	Magnesium alloy	N/A
Durable	< 3	Cobalt chromium	N/A
Durable	5.3	Cobalt chromium	91
Biocompatible	N/A	Cobalt chromium	81
Bioabsorbable	N/A	Stainless steel	150
Durable	3	Cobalt chromium	81
Durable (proendothelial)	None	Stainless steel	N/A
Bioabsorbable	N/A	PLLA	170
Bioabsorbable	N/A	Stainless steel	84
N/A	N/A	Stainless steel	110
Bioabsorbable	N/A	Cobalt chromium	99
Bioabsorbable	N/A	Stainless steel	120–149
Durable	7.6	Cobalt chromium	81
Bioabsorbable	N/A	Polycarbonate	N/A
Bioabsorbable	N/A	Cobalt chromium	N/A
Bioabsorbable	N/A	Stainless steel	80
Bioabsorbable	N/A	Cobalt chromium	89
Bioabsorbable	5–6	Stainless steel	60
Durable	16	Stainless steel	132
Durable	16	Stainless steel	97
Durable	N/A	Platinum chromium	N/A
Bioactive (proendothelial)	None	Stainless steel	70–140
N/A	0.6	Stainless steel	65
Durable	7.6	Cobalt chromium	81
Bioabsorbable	N/A	Cobalt chromium	N/A
N/A	None	Stainless steel	87
Durable	5	Stainless steel/tantalum	74

stent system (Abbott Vascular) are encouraging and suggest that this approach may be feasible.[36-38] However, some of the remaining issues with this approach include early stent absorption leading to the loss of scaffolding and allowing late loss from the type of negative remodeling seen after balloon angioplasty without stenting; the degradation of a much larger mass of polymer compared to a metallic structure with a very thin layer of biodegradable polymer, potentially leading to long-term adverse effects due to inflammation; and issues related to the profile, flexibility/deliverability, and radial hoop strength, which may not be competitive with thin-strutted, state-of-the-art, metallic stents with thin-layered biodegradable (or no) polymer. These and many other questions remain regarding what application this type of DES will have. It is likely that this type of device will find a niche in bifurcation disease and/or distal disease, which might compromise bypass grafting at some later date.

METALS FOR DES

Current DES use either stainless steel 312 alloy or cobalt-chromium alloys. These metals have reasonably good behavioral profiles with regard to biocompatibility, fatigue testing and fracture, and radiopacity. The cobalt-chromium alloys appear to have some advantages over stainless steel by providing a somewhat denser metal and allowing thinner struts to enhance acute stent performance while retaining adequate radiopacity. Newer metals that incorporate a tri-layer with either platinum or tantalum as a central layer to enhance radiopacity, as well as some other novel new alloys including alloys of tantalum, nitinol, titanium oxide, etc., may further enhance the usual trade-off between thinning struts to enhance flexibility and profile, and losing radiopacity and hoop strength.

As previously discussed, the advantages of thinner struts on DES performance relate to the impact on flexibility and the stent delivery system profile. Thus, the use of metallic stents with strut thicknesses in the 0.0028- to 0.0034-inch range may prove to be nearly optimal in reaching a compromise for the best flexibility profile (± endothelial cell coverage) while providing acceptable radial hoop strength and radiopacity. Thinning the metallic structure of a DES to < 0.0028 inch will likely result in worse performance and unacceptable hoop strength and/or radiopacity, even with the newest alloys.

DRUGS AND PHARMACOKINETICS

Many drugs have been proposed and/or tested to reduce neointimal hyperplasia and/or inflammation with DES. It is very important to recognize that not all drugs are equally safe and effective for use on a DES.[16,17,39-49] Actinomycin, for instance, yielded results that were substantially inferior to BMS. The use of paclitaxel failed with the Achieve coronary stent (Guidant Corporation, Indianapolis, IN) and the V-Flex Plus stent (Cook Medical, Bloomington, IN). Most recently, there was an unfavorable outcome using a biodegradable polymer (with paclitaxel) with the Nevo stent. In contrast, paclitaxel has been reasonably effective in the SIBS polymer on the Taxus stent system. Given the complete failure of paclitaxel with the Cook, Guidant, and CoStar stents (Cordis Corporation) using a limited duration of paclitaxel elution, the more favorable antirestenosis effect with Taxus is likely related to the large reservoir of paclitaxel left on the stent, likely resulting in a long-term and slow elution of the drug over many years.

Overall, the -olimus-eluting family of drugs appears to be the current drug(s) of choice for DES.[16,17,29-41] The prototype drug, sirolimus, has shown very potent antiproliferative and anti-inflammatory properties with durable results and safety now reported out to 5-year follow-up from the pivotal United States study.[5] The majority of DES going forward also use sirolimus or other -olimus-eluting drugs, including everolimus (Xience, Promus [Boston Scientific Corporation], and BVS), zotarolimus (Endeavor, Resolute), biolimus A9 (Axxess [Devax, Inc., Irvine, CA] and others), myolimus (Elixir Medical Corporation, Sunnyvale, CA), etc.

TABLE 2. CHARACTERISTICS OF THE PERFECT DES

- Very flexible, conformable (hybrid open-cell)
- Very low-profile stent delivery system (< 0.030 inch)
- High-pressure balloon, suited for direct stenting with minimal balloon lengthening at a high pressure
- Adequate radiopacity and radial hoop strength (metallic ± better than bioabsorbable)
- Delivers -olimus drug (or future better drug)
- Drug delivery for approximately 60 to 90 days, then complete absence of the drug
- Very thin (homogeneous) surface of bioabsorbable (noninflammatory) polymer
- Elution from a microporous, nonpolymeric surface with Cypher-like elution kinetics
- Thrombus-resistant luminal surface
- Promotion of early re-endothelialization
- Very low late loss (≤ 0.2 mm)
- Features allow antiplatelet treatment for ≤ 3 months

Although most, if not all, of these agents appear to be potent and with similar efficacy, the efficacy of these -olimus-eluting drugs is also closely related to an adequate dosing and pharmacokinetic profile. When the drug is delivered for only a short duration of < 1 month, the results appear less favorable and predictable than when the drug is given for at least 2 to 3 months. This is evident in the relatively poor results comparing Endeavor (short duration of release) and Cypher (Endeavor III and ZEST trials). Recent data with the same -olimus drug (zotarolimus) with a longer release kinetic on the Resolute stent appear to be more similar to the results observed with Cypher and Xience. Although the -olimus-eluting drugs appear to be a superior class of drugs for DES, other drugs, such as bevacizumab (a monoclonal antibody directed against vascular endothelial growth factor), are still being evaluated and may prove to be safe and effective.

CONCLUSION

There are numerous new and exciting trends leading to a variety of improved DES platforms that are in development, clinical trials, and early release in commercialization. The ideal DES has not been determined, but will most likely incorporate a number of newer and improved materials and delivery systems to further enhance safety, efficacy, and cost efficiency. Table 2 outlines some characteristics of the ideal, or perfect DES system. This process typically proceeds in an iterative fashion with slow but continuous improvements for this revolutionary class of medical devices. ■

Tim A. Fischell, MD, FACC, FSCAI, is Director of the Heart Institute at Borgess Medical Center in Kalamazoo, Michigan. He has disclosed that he receives grant/research funding from Medtronic, Inc., Abbott Vascular, Cordis Corporation, and Boston Scientific Corporation. He has also disclosed that he is a paid consultant to Abbott Vascular and Svelte Medical Systems, Inc.; he holds patent ownership or part ownership with Svelte Medical Systems, Inc.; he has royalty agreements with Abbott Vascular, Cordis Corporation, and Svelte Medical Systems, Inc.; and he is an owner of or shareholder in Svelte Medical Systems, Inc. Dr. Fischell may be reached at (269) 226-8374; tafisc@gmail.com.

Dwight Dishmon, MD, is with the Borgess Heart Institute in Kalamazoo, Michigan. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein.

Adam Elhaddi, MD, is with the Borgess Heart Institute in Kalamazoo, Michigan. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein.

Shadwan Alsafwah, MD, is with the Borgess Heart Institute in Kalamazoo, Michigan. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein.

Santhosh R. Mannem, MD, is with the Borgess Heart Institute in Kalamazoo, Michigan. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein.

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