Review

Interventional Cardiology

Bioengineering stents with proactive biocompatibility

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Percutaneous coronary intervention has revolutionized the treatment of coronary artery disease. Successive improvements in implantation techniques, stent materials and design, combined with dual antiplatelet therapy have improved stent safety. However, optimal biocompatibility and long-term effectiveness in the absence of pharmaceutical intervention remains elusive. Drug-eluting stents, introduced to combat in-stent restenosis was found to impair endothelial regeneration, increasing thrombotic risk. Innovations in polymer technology and new stent designs have improved, but not solved, these issues. Despite the drawbacks of drug elution it remains a key component of stent platforms, leaving the need for a truly biocompatible platform with lasting clinical efficacy and safety unmet. This review will examine current stent designs and explore proactive approaches to enhance stent biocompatibility.

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Cardiovascular disease (CVD) has had a tremendous health impact across the globe. A rise in obesity levels, sedentary lifestyle and diabetes (in particular in developing countries) has led to CVD becoming a leading cause of mortality. Coronary artery disease (CAD) is by far the single largest contributor to the burden of CVD [1]. Percutaneous treatment of CAD has been one of the most significant advancements in clinical cardiovascular medicine, offering the advantage of a minimally invasive procedure with rapid recovery time and short hospital stay. While the prognostic benefit of percutaneous coronary intervention (PCI) has been questioned in patients with stable angina, robust evidence for PCI in acute coronary syndrome exists with reductions in mortality and myocardial reinfarction [2]. After nearly four decades of use, PCI has evolved from balloon angioplasty to contemporary drug-eluting stents (DES). Driven by a desire to improve clinical efficacy and to reduce adverse outcomes related to PCI, refinements have been made in stent technology with promising novel strategies. This update will briefly review the biocompatibility shortcomings of bare metal stents (BMS) and DESs. We will explore promising new stent platforms and shine a light on nondrug-eluting strategies with proactive biocompatibility.

Concept of biocompatibility

Biocompatibility is a broad term used to describe the interaction of an implanted prosthesis with the human body. A key requirement of a biomaterial is to cause the least amount of harm to the host environment. The choice of biomaterial reflects this goal, 316L stainless steel, titanium and cobalt chromium alloys used extensively in clinical and vascular applications are highly corrosion resistant [3], thereby reducing tissue toxicity from *in vivo* deterioration following implantation.

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Our understanding of biocompatibility has evolved with more in depth knowledge of tissue and cellular responses to biomaterials. A prosthesis is not simply a passive nonreactive entity but can be an active participant in the host response to its presence. Biocompatibility has been redefined to reflect this realization, incorporating three important tenets: a biomaterial has an active functional role in local tissue, should elicit an appropriate biological response and the response to the biomaterial needs to be appropriate and will depend on the intended role [4]. This represented a shift from the simple goal of 'do no harm' to one of active modulation of the biological response, specific to the clinical application and local tissue environment. In the context of coronary stents, biocompatibility encompasses hemocompatibility (freedom from thrombosis) and modulation of intimal hyperplasia that must be reconciled with the mechanical needs of scaffolding an artery to maintain vessel patency.

Clinically available stents

Bare metal stents

The predominant material used for construction of coronary stents are metallic alloys (316L stainless steel and more recently cobalt chromium and platinum chromium), borne out of the need for mechanical strength, deformability and radio-opacity [5]. Two early landmark trials, the Benestent and STRESS studies ushered in the stent era by demonstrating high rates of procedural success, improved immediate and long-term vessel luminal diameter over balloon angioplasty [6–8]. However, the hemocompatibility of metallic stents were brought into question. Inherent thrombogenicity of metallic alloys coupled with disruption of the endothelium following stent expansion led to a high incidence of subacute (1–30 days) stent thrombosis [9]. In contemporary practice, higher pressure stent deployment combined with dual antiplatelet therapy (DAPT) have reduced early thrombosis rates to <1% [10]. Nonetheless, the price of combination antiplatelet therapy is the increase in major and gastrointestinal bleeding [11].

Inability of metal only platforms to modulate the local host response led to additional biocompatibility issues. High incidences of in stent restenosis (ISR) presenting clinically as recurrent angina to acute coronary syndrome have been reported, necessitating repeat revascularization [12]. ISR is an inflammatory fibrocellular healing reaction to arterial injury and damage, an inevitable consequence of stent implantation [13]. Vascular smooth muscle cells (VSMCs) and extracellular matrix (ECM) rich in proteoglycans contributes to the neointima [14]. An increase in neointimal thickness and degree of restenosis is seen when stent struts penetrate the lipid plaque core causing fracture of the tunica media [15], indicating the healing response is directly proportional to the extent of vascular trauma.

Drug-eluting stents

The sirolimus (rapamycin) eluting Cypher stent and the paclitaxel eluting Taxus stent were shown in pivotal trials to be markedly superior to BMS at preventing ISR [16,17]. Both drugs act nonspecifically, inhibiting the proliferation of VSMCs and endothelial cells. Use of DAPT reduces early stent thrombosis rate to less than 1% for both BMS and DES [18]. Analysis of randomized DES trials revealed an increase in very late (>1 year) stent thrombosis in both paclitaxel- and sirolimus-eluting stents, a risk which appeared to persist at a rate of 0.35–0.6% annually [19–21]. DES thrombosis is associated with a mortality of 20–40% and myocardial infarction of 50–70% [22].

One of the main differences in the biological response to BMS and DES is the rate of stent strut endothelialization, occurring significantly faster in BMS [13]. In contrast high-resolution optical coherence tomography (OCT) showed incompletely endothelialized DES struts, 2 years after implantation [23,24]. Impairment of poststenting endothelial healing leads to continued exposure of metallic struts to blood, negatively impacting hemocompatibility.

Second-generation everolimus (EES) and zotarolimus (ZES) DES have largely replaced Cypher and Taxus stents. Using cobalt chromium (CoCr) for construction strut thickness was significantly lowered, reducing stent footprint, potentially limiting vessel injury, intimal hyperplasia [25] and thrombogenicity [26]. More recently platinum–chromium has been adopted in the Element platform (Boston Scientific) with excellent radial strength and corrosion resistant [27].

Preclinical assessment of second-generation DES showed improved biocompatibility with reduced inflammation and thrombogenicity, improved endothelial adhesion and more complete strut endothelialization [28]. In a 13-month OCT study of EES and ZES, 92.6–94.2% of struts were endothelialized [29]. In recent randomized trials, the XIENCE V stent (CoCr, fluropolymer, everolimus elution) exhibited a reduction in stent thrombosis and nonfatal myocardial infarction compared with first-generation paclitaxel-eluting stents [30,31]. Despite the improvements in biocompatibility, continued requirement for prolonged DAPT highlights a need for further improvements in hemocompatibility without a decline in the modulation of intimal hyperplasia.

New stent platforms to improve biocompatibility

Drug eluting platforms

Polymer-free DES

Inflammation and hypersensitivity concerns over permanent polymer-coated DES have led to innovative stent designs aiming to develop alternate means of drug delivery. A stent only delivery system allows drug elution without concerns of polymer peeling and polymer-driven inflammatory reactions. Prominent examples of this approach are discussed below and summarized in Table 1.

The VESTA-sync™ stent is a stainless steel platform employing a microporous hydroxyapatite coating carrying oil-based sirolimus. Hydroxyapatite remains stable for 4 months with complete dissolution by 9–12 months, while elution of sirolimus is complete within 4 weeks [32]. The FIM trial, consisting of 15 patients with simple *de novo* coronary lesions, showed in-stent late loss of 0.30 mm and percent stent obstruction of 2.8% at 4 months and 0.36 mm and 4% at 9 months, respectively [32,33]. No MACE was reported at 2 years [34], one target lesion revascularization (TLR) was noted at 3 years [35]. Preliminary results from the Vestasync II trial comparing Vestasync to BMS revealed 8-month in-stent late loss of 0.39 mm for VESTA-sync stent compared with 0.74 mm with BMS [35].

The Amazonia PAX stent uses a microspray crystallization process to deposit paclitaxel onto the abluminal surface of a CoCr stent. A relatively rapid drug elution occurs within 45 days [36]. The PAX A trial randomizing 30 patients to the Amazonia stent or Taxus

Table 1. Recent advances in drug-eluting stent design.

Stent name	Design feature	Drug eluted	Drug elution time	Latest clinical trial result
Polymer-free DES				
VESTA-Sync™	Hydroxyapatite coating	Sirolimus	4 weeks	Late loss superior to BMS (8 month) [35]
Amazonia PAX	Microspray crystallization	Paclitaxel	45 days	Similar late loss to Taxus at 4 months [37]
Biofreedom™	Microabrasion texturing	Biolimus	28 days	Noninferior to Taxus at 12 months [39]
Yukon®	Microporous	Sirolimus	21 days	
DUAL-DES	Yukon analog	Sirolimus/Probucol	56 days	Superior to Cypher® at 2 years [46]
Biodegradable polymer DES				
Biomatrix	PLA coating	Biolimus	90 days	Lower MACE than Cypher at 3 years [54]
Nobori®	Parylene layering	Biolimus	6–9 months	Safety shown in 1-year registry [57]
Supralimus™	PLLA/PLGA	Siroliumus	48 days	7% MACE at 30 months, 0.6% ST [58]
Infinnium™	Supralimus analog	Paclitaxel	49 days	Reduced TLR vs BMS at 9 months [60]
Yukon® Choice	Proprietary coating	Sirolimus	4 weeks	Similar to Cypher, Xience at 3 years [62]
JACTAX	PLLA microdots	Paclitaxel	90 days	Noninferior to Taxus at 6 months [52]
Costar	Strut reservoirs	Paclitaxel	30 days	Inferior to Taxus [49]
Nevo	Costar analog	Sirolimus	90 days	Trend to superior over Taxus 1 year [50]
Synergy™	PLGA	Everolimus	90–120 days	Noninferior to Promus Element™ Plus [65]
Orsiro	Silicon carbide/PLLA	Sirolimus	100 days	Noninferior to Xience Prime [68]

BMS: Bare-metal stent; DES: Drug-eluting stent; PLA: Polylactide; PLGA: Poly(lactic-co-glycolic acid); PLLA: Poly-L-lactic acid; TLR: Target lesion revascularization.

stent reported early 4-month results showing similar in-stent late loss between the two stent groups [37]. A larger 100 patient nonrandomized PAX B trial is ongoing. Similarly, the abluminal surface of the Biofreedom stent is treated with a microabrasion method to create a textured surface [36]. Biolimus A9, a highly lipophilic rapamycin analog is then coated onto the surface [38]. 12-month angiographic follow-up from the BIOFREEDOM FIM trial found noninferiority in in-stent late loss with the standard dose (15.6 μg/mm of stent) Biofreedom stent when compared with the Taxus stent [39]. Larger trials are needed to evaluate the Biofreedom stent to establish superiority and safety.

The Yukon® DES also has a microporous surface created by mechanical treatment of a stainless steel stent [40]. Sirolimus is sprayed on in the catheterization suite, using a proprietary coating methodology. The majority of the drug is eluted in the first 6 days followed by prolonged release over 21 days [41]. The Yukon stent was found in the ISAR-TEST trial to be noninferior in late loss and TLR when compared with the Taxus stent. However, results from the ISAR-TEST 3 comparing the Yukon and Cypher® stent found inferior late loss results [42]. The short drug elution time does not provide adequate control of intimal hyperplasia. Efforts to counter the suboptimal results from the rapamycin only elution gave rise to the Dual-DES, in which a combination of 1.0% rapamycin, 1.0% probucol and 0.4% shellac resin was coated onto the stent [43]. Probucol, an antihyperlipdemic agent has potent antioxidant effects and can inhibit VSMC proliferation [44]. In the ISAR TEST-2 trial, the DUAL-DES was found to be comparable in binary restenosis and TLR to Cypher and significantly better than the Endeavor stent [45]. Results were maintained out to 2 years, importantly the 'late catch up' phenomenon noted in the Cypher stent group was absent in the DUAL DES [46]. The recently released large ISAR-TEST 5 trial demonstrated very promising results with the DUAL-DES stent shown to be noninferior to the next-generation Resolute stent in the composite primary endpoint of cardiac death, target vessel-related myocardial infarction or TLR [47].

Biodegradable polymer DES

An alternative approach to avoiding adverse polymer reactions is to use a biodegradable polymer based drug carrier which erodes over a defined time period. This potentially delivers the benefit of superior drug release kinetics but leaves no permanent source of inflammation. The compositions of these polymers are predominantly based on lactic acid/lactide analogs. Variations between the stents include the polymer coating, the drugs eluted, kinetics of elution and the degradation time for the polymers.

The Costar stent consists of struts with reservoirs filled with a biodegradable polymer polylactide-co-glycolide impregnated with paclitaxel [48]. Results from the Costar II trial [49] comparing against the Taxus stent were disappointing due to reduced efficacy from the lower dose of paclitaxel used and the short release kinetics. The Nevo stent is based on the same reservoir system but uses sirolimus with more prolonged elution. Despite promising results from the NEVO RES-ELUTION I study [50] problems identified in the balloon delivery system resulted in suspension of the reservoir platform.

The JACTAX stent utilizes a biodegradable polylactide (PLA) polymer placed in a focal microdot fashion onto the abluminal surface of the stent. Noninferiority in MACE, TLR compared with historical data from the Taxus Atlas trial was reported in the FIM JACTAX HD trial (HD = higher dose, 9.2 μg each of drug and polymer per 16 mm stent) [51]. The OCTDESI OCT based trial examined the degree of stent strut coverage at 6 months, no benefit in endothelialization was reported for the JACTAX stent over Taxus [52].

The Biomatrix Stent consists of a stainless steel platform coated with a polylactic acid and Biolimus coating. The coating is directed toward the abluminal surface [53], full degradation of the polymer occurs over 9 months. The LEADERS trial randomized patients to Biomatrix stent or Cypher stent. At 12-month follow-up the composite primary endpoint (cardiac death, myocardial infarction and target vessel revascularization) was noninferior in the Biomatrix group versus the cypher group [54]. Clinical follow-up now to 3 years show a trend toward a lower MACE rate in Biomatrix stent group (Biomatrix 15.7 vs 19% Cypher; P for superiority = 0.09) with cumulative very late ST rates remaining low at 0.2% [54].

The Nobori stent employs the same stent design and biodegradable polymer as Biomatrix, but with the addition of an ultrathin nondegradable parylene coating between the stent and the polymer to improve polymer attachment. Trials with the Nobori® stent have further reinforced the positive results of this approach. The Nobori I trial confirmed noninferiority at 9 months in in-stent late loss against the Taxus stent [55], with recently reported clinical follow-up out to 5 years showing no ST [56]. 1-year clinical data from the 3068 patient all comers registry (Nobori 2 study) reported excellent efficacy and safety result with target lesion failure of 3.6% and MACE of 4.8% [57]. The Nobori stent will be further evaluated in the SORT-OUT V trial (vs Cypher), COMPARE II (vs Xience), SECURITY (vs Resolute with 6-month DAPT arm and 2-month DAPT arm) and BASKET PROVE 2 (vs ProKinectic and Xience).

The Supralimus™ sirolimus-eluting stent utilizes two biodegradable coatings on a stainless steel stent platform. The undercoat consists of a matrix of poly L-Lactic acid, poly DL-lactide-co-glycolide and polyvinyl pyrrolidone intermixed with 1.4 mcg/mm^2 of sirolimus. A top coat of polyvinyl pyrrolidone prevents early release of the drug. The dissolution of the top coat within 2 h after implantation leads to a rapid burst release over 7 days of half of the drug. At 48 days the drug is completely eluted. Complete polymer degradation occurs over 7 months. The FIM Series I study (nonrandomized 100 patients) showed at 6 months a low in-stent late loss of 0.09 mm and binary restenosis of 0%. At 30 months MACE was 7%. 2-year data from the acute coronary syndrome all comers E-Series registry had reassuringly low ST rates of 0.6% [58]. The Series III trial currently in progress will evaluate the Supralimus against the Xience stent. The Supralimus and Supralimus Core using a thinner CoCr platform have both recently received European CE Mark. The Infinnium stent utilizes the same biodegradable polymer components and has the same release kinetics as the Supralimus. The polymers are mixed with paclitaxel in various ratios to form three layers with distinct fast, medium and slow release kinetics. A good safety and efficacy profile was shown in the nonrandomized SIMPLE II registry [59]. The PAINT study randomized patients to the Infinnium stent, Supralimus stent or a BMS. In brief, both the Infinnium and Supralimus stents showed significant reductions in angiographic in-sent late loss at 9 months, with reduced TLR at 12 months compared with the BMS. The Supralimus stent had superior angiographic but equivalent clinical results to the Infinnium stent [60].

The Yukon Choice PC stent platform is based on the microporous Yukon stent. A proprietary biodegradable matrix (degraded in 6–9 weeks) is mixed with sirolimus and a natural resin and then applied in the catheterization laboratory. In the ISAR-3 trial the efficacy of the Yukon Choice stent was noninferior to the Cypher stent [42]. ISAR-4 was a clinically driven large randomized study evaluating the Yukon Choice against Cyper and Xience stents. MACE at 1 year was comparable between the three stents. Cardiac death, myocardial infarction, TLR and ST were not significantly different [61]. Efficacy and safety remained similar between the stents in a recent report of 3-year results [62].

The Synergy™ platform elutes everolimus from a poly-lactide-co-glycolide polymer (degraded over 4 months) coated on to the abluminal surface of a platinum chromium constructed stent (strut thickness 74 μm). Evaluated in porcine models the Synergy stent was found to have equivalent vascular compatibility to Promus element and bare metal platinum chromium Element stent [63]. Moving forward, the randomized first in man Evolve trial assessed the safety and efficacy of low and standard dose everolimus eluting Synergy stent against the Promus element stent. At 6 month, both formulations of the Synergy stent were found to be noninferior in the primary angiographic endpoint of in-sent late loss (0.15 ± 0.34 mm PROMUS Element, 0.10 ± 0.25 mm Synergy and 0.13 ± 0.26 mm Synergy half-dose). Encouragingly no stent thrombosis occurred in any group at 6 months [64]. The Evolve 2 USA pivotal trial randomized over 1600 patients with stable coronary or non-ST-segment-elevation acute coronary syndrome to Synergy or Promus element plus stent. Noninferiority of the 12-month primary end point of target lesion failure was demonstrated (6.7% Synergy and 6.5% Promus Element plus, p = 0.0003 for noninferiority). Definite/probable stent thrombosis was noted in 0.4 versus 0.6% (p = 0.50), for Synergy and Promus Element plus, respectively [65]. Moving toward US FDA approval, the already CE marked Synergy stent may become the first biodegradable polymer stent permitted in USA.

Similarly, the Orsiro stent is undergoing evaluation in the currently enrolling Bioflow-V study with the goal of obtaining FDA approval. Fashioned from CoCr, the 60 μm thick stent is coated with a sealant layer of silicon carbide preventing release of ions from the metal alloy. A biodegradable poly-L-lactic acid (PLLA) polymer is used as carrier for sirolimus with complete drug elution in 100 days. Encouraging in-stent late lumen loss of 0.12 ± 0.19 mm and 0.05 ± 0.22 mm at 4 and 9 months, respectively and a low MACE rate of 10% was reported in the BIOFLOW-I first in man study [66]. BIOFLOW-II, a noninferiority study against Xience Prime stent, demonstrated comparable levels of in-stent late lumen loss at 9 months 0.1 ± 0.32 mm and 0.11 ± 0.29 mm, and target lesion failure of 6.5 and 8.0% for Orsiro and Xience Prime, respectively. No stent thrombosis was reported in both groups [67]. Building on these results the BIOSCIENCE study compared the Orsiro stent against the Xience Prime stent in a larger all comers cohort powered for clinical endpoints. Target lesion failure (cardiac death, target vessel myocardial infarction and target lesion revascularization) at 12 months was noninferior to Xience Prime [68].

Conclusive long-term safety data for biodegradable polymer stents remain incomplete. Studies have been relatively small, often based on surrogate angiographic endpoints and powered to establish noninferiority to contemporary stents. While the ISAR-TEST 3 and ISAR-TEST 4 demonstrated similar efficacy and safety to the leading first- and second-generation DES, superiority in safety have yet to be demonstrated to validate

the theoretical benefit of biodegradable polymers. In this regard a recent meta-analysis by Bryne *et al.* [69] of pooled 3-year data from the LEADERS, ISAR-TEST 3 and ISAR-TEST 4 trials encompassing 4000 patients found a significant reduction in ST in the biodegradable polymer group at 1.2% than the nonerodible polymer group at 2.1% (p = 0.013). A reduction in the composite clinical end points (cardiac death, MI, TLR) was also noted in the biodegradable polymer group (18.2 vs 20.1%, p = 0.04). This was largely due to a reduction in TLR.

Biodegradable stents

Biodegradable polymeric and metallic stent structures have been developed as an alternative to persistent metallic substrates. The aim is to deliver a temporary scaffold, which can mechanically support the vessel against recoil while negating the issue of unfavorable host response to a permanent prosthesis. Late stent thrombosis although rare can occur with BMS particularly with discontinuation of aspirin [70] highlighting the ongoing thrombotic risk of metallic alloys.

A biodegradable stent (BDS) has a number of theoretical benefits, reducing the dependence on prolonged antiplatelet therapy, removing the chronic negative effect of a rigid metallic stent on vasomotor tone and positive vessel remodeling, providing greater options for future coronary intervention, bypass surgery and safety for MRI imaging [71]. However, ongoing challenges include preventing acute vessel recoil soon after deployment and maintaining stable medium-term support as the stent starts to degrade [72], developing an appropriate time frame of degradation, ensuring adequate radio-opacity and preventing vessel inflammation to the polymer.

PLA the main polymer used in BDS undergoes hydrolysis, breaking down to carbon dioxide, lactic acid and water. [71] Animal models demonstrated robust acute radial strength was maintained out to 1 month. Degradation occurred over a 9-month period with good vascular biocompatibility and a low toxicity profile [73]. The Igaki-Tamai PLA stent evaluated in 15 patients with 6-month follow-up validated the mechanical integrity of the stent in the prevention of acute recoil, comparable restenosis rates to BMS and an adequate safety profile with no MACE or stent thrombosis [74]. A larger 50 patient trial demonstrated complete resorption of the stents, a low subacute and late stent thrombosis rate and TLR of 12.7% at 1 year. The main impediment to the wide spread adoption of the Igaki-Tamai stent has been over its method of deployment. The stent requires heating (to between 65 and 75°C) prior to implantation for expansion, leading to concerns of arterial wall necrosis and accentuating intimal hyperplasia [75].

Biodegradability may enhance hemocompatibility it does not however address the issue of restenosis caused by vessel injury. Full absorption of BDS takes more than 6 months [71] and both vessel recoil and negative remodeling occur within this time. [76] Persistence of struts beyond this time may lead to greater intimal hyperplasia without providing any additional support benefit [77]. The Abbot Vascular BDS (BVS) seeks to address the shortcomings of BDS by combining biodegradability with an antirestenotic strategy. Based on a PLLA backbone, the BVS additionally releases the antiproliferative drug everolimus. Thicker 150 μm stent struts than is commonly used for metal alloy platforms were used to maintain radial strength. At 1 year, good clinical safety and efficacy with no TLR and MACE of 3.3% (1 non-Q wave MI) was noted [78]. Safety was maintained with a steady MACE rate (3.4%) reported at 3 years [79]. The 6-month late loss (0.44 mm) [78] was higher than the metallic equivalent (Xience stent) (0.11 mm) [80] due to a reduction in the stent area from both acute recoil [81] and progressive loss of radial strength with absorption of PLLA. [78] Encouragingly at 2 years there was no further late catch up in late loss and stent strut resorption was noted [82].

A redesigned stent geometry (in-phase zig zag hoops linked by bridges) was used to provide more uniform and improved radial support. Angiographic follow-up at 6 months of 45 patients were more encouraging demonstrating a lower late loss of 0.19 mm than revision 1.0, suggesting improved radial strength. A larger 1000 patient Absorb Extended trial is currently in progress to further evaluate the BVS in patients with more complex coronary lesions.

Alternatives to drug eluting platforms

The majority of new stent platforms under clinical investigation are dependent on drug elution to control intimal hyperplasia. Eluted cytotoxic agents are indiscriminate in the inhibition of cell activity. The impact on endothelial cells can delay endothelialization of the stent struts. Below we highlight some alternative strategies either with clinical data or in preclinical stages designed to modulate smooth muscle cell activity. Ranging from coatings which accelerate endothelialization to functionalizing stent surfaces with smooth muscle cell-regulating biomolecules (Table 2).

Proendothelial surface coatings

EPC capture

Coatings designed to enhance healing have attempted to leverage the antithrombotic and antirestenosis functions of the endothelium for improved stent biocompatibility. A functional and intact endothe-

lium has important ramifications in restenosis and neoatherosclerosis. The degree of intima formation correlates with the area of endothelial denudation, with increasing thickness with more endothelium injured [83]. Moreover, endothelial regeneration over the injured vasculature appear to retard smooth muscle growth and extracellular deposition [84]. The endothelial secretion of NO maintains VSMC in a quiescent phenotype [85]. Poorly regenerated and dysfunctional endothelium has reduced NO secretion.

The Genous endothelial progenitor cell (EPC) capture stent (GS) (OrbusNeich Medical) employs murine monoclonal antihuman CD-34 antibodies coupled to a polysaccharide coating to capture EPCs. Preclinical studies showed promising results with reduced thrombogenicity, more EPC coverage and increased endothelialization on the GS when compared with BMS [86]. The HEALING-FIM trial examined this stent in 16 patients, reported no ST despite only 1 month of DAPT and a MACE rate of 6.3% with one TLR at 9 months [89]. The HEALING-II registry, with 63 patients again showed no ST with 1 month of DAPT. At 6 months in-stent late loss was 0.78 mm, however at 18 months regression and remodeling was seen with reduction of 16.9% in late loss [90]. The much larger e-HEALING registry with 4939 patients, reported at 1 year an overall and late ST rate of 1.1 and 0.2% respectively, with only 34% of patients remaining on DAPT and a low rate of TLR of 5.7%. [91]

Randomized data have raised concerns over the efficacy of this platform. Beijk *et al.* randomized 193 patients with high risk for restenosis to either the Genous stent or Taxus Liberte stent. 1-year target vessel failure driven largely by increase TLR was significantly higher at 17.3% in the Genous group versus 10.5% in the Taxus group [87]. The TRIAS-HR trial was stopped early after disappointing results from 622 randomized patients. Patients randomized to the Genous stents had at 1 year significantly higher TLR 17.4 versus 7% in DES groups [88]. In order to counter these results the prohealing qualities of the Genous R stent has been combined with sirolimus drug elution. A permanent polymer [92] and a bioabsorbable polymer variant (Combo stent) are being investigated at present [93]. Recent results from a randomized trial against the Taxus stent demonstrated noninferior angiographic restenosis, low rates of complications and no ST [94]. These findings will need to be validated in larger randomized trials.

The inability of the Genous stent to make a meaningful contribution to restenosis does not necessarily invalidate the prohealing strategy. Coated antibody to $CD34^+$ is used to capture EPCs. However, EPCs are a heterogeneous group of cells with overlapping surface markers. To date, no unique set of surface markers can definitive identify an EPC [95]. The $CD34^+$ marker is nonspecific and can be found on a variety of cells including primitive hematopoietic cells [96] and mature endothelial cells [97]. Furthermore, EPCs only represent a small fraction of the cells bearing $CD34^+$ surface markers. Taken together, the effectiveness and specificity of $CD34^+$ based EPC capture is uncertain. It is likely a rather heterogonous group of cells is captured on to the stent surface, with varying contributions to endothelialization and modulation of vascular smooth muscle cell activity.

Table 2. Alternative approaches to traditional drug-eluting stent.

Stent name/type	Design feature	Preclinical and clinical results
Biodegradable stents		
Igaki-Tamai	PLA platform, degrades over 9 months	Low subacute and late thrombosis. 12.7% TLR at 1-year [75]
Abbott BVS	PLLA backbone + everolimus elution	Low subacute and late thrombosis. 12.7% TLR at 1-year [75]
Endothelial cell promoters		
Genous	CD-34 antibodies to capture EPCs	Higher rates of TLR than Taxus [87]
Genous Combo	Genous + sirolimus elution	Noninferior to Taxus [94]
Estrogen		No restenosis reduction in clinical trials [100,101]
VEGF		No endothelialization or restenosis benefit in rabbit model [104]
RGD variants		Best porcine model results rely on everolimus elution [110]
Tropoelastin	Plasma-activated coating	Safely deployed in rabbit iliac model [116]
Gene therapy		
Plasmids		Proof of concept in rat models [134]
siRNA	Hyaluronic acid coating	Restenosis suppression in rabbit iliac model [124]

EPC: Endothelial progenitor cell; PLA: Polylactide; PLLA: Poly-L-lactic acid; siRNA: Small interfering RNA; TLR: Target lesion revascularization.

Endothelial cell stimulation & promotion

Estrogen enhances the gene expression of endothelial growth factor and increases NO production, with estrogen releasing stents showing promise in animal studies with improved endothelialization [98,99]. Disappointingly, clinical studies failed to show any advantage in restenosis reduction [100,101]. In a similar attempt to accelerate endothelialization VEGF releasing stents were conceived. VEGF is a specific endogenous signaling protein that simulates angiogenesis [102]. It has a broad range of effects on endothelial cells including proliferation, migration and actin reorganization. Small animal models demonstrated locally delivered VEGF-enhanced endothelial recovery and control of intimal hyperplasia after vessel injury [103]. On the back of these promising results, VEGF-eluting stents were designed to prolong the exposure to local tissue. However in stented rabbit iliac arteries no benefit on endothelialization or restenosis was evident [104].

Cells interact with ECM proteins via transmembrane surface integrin. These interactions give vital signaling cues to direct cellular activity including migration, differentiation, adhesion and proliferation [105]. Ligands for integrin reside within short amino acid sequences (motifs) on the extracellular protein. The RGD (Arg–Glu–Asp) tripeptide is one of the most prevalent integrin binding motifs [106] and supports adhesion to extracellular proteins for a wide range of cells [107]. Structurally altered cyclic RGD (cRGD) can preferentially promote cell adhesion of one cell type over another. cRGD functionalized stents were found in preclinical models to substantially reduce neointimal area by accelerating endothelial coverage presumably through augmenting EPC activity without stimulating VSMCs [108,109]. Dual cRGD and everolimus-coated stents have recently been investigated in porcine models finding a good balance between retardation of hyperplasia while supporting endothelialization [110]. Certainly promising, in man studies are needed to see if preclinical findings are maintained. Potentially a more selective novel biofunctional peptide, *RRETAWA* has been designed with *in vitro* data pointing to a more endothelial specific interaction without platelet stimulation [111].

Extending further the benefit of ECM-based surface functionalization, our laboratory has developed a proprietary coating technology that facilitates the covalent attachment of biomolecules to almost any substrate, while retaining bioactivity [112]. The plasma-activated coating has been used successfully to functionalize stainless steel surfaces with recombinant human tropoelastin, the soluble precursor of elastin [113]. In *in vitro* assays tropoelastin modified stainless steel surfaces showed enhanced endothelial cell attachment and proliferation in combination with very low thrombogenicity [114,115]. *In vivo* implantation in a rabbit iliac stenting model demonstrated stability of the plasma polymer coating and lack of immunogenic response to the tropoelastin functionalized coronary stents [116]. Efficacy in the control of intimal hyperplasia is undergoing further preclinical testing.

Gene therapy has also been investigated as a strategy to specifically modulate cellular protein production for biointegration of coronary stents. Plasmids, double-stranded DNA found in bacteria, have been exploited as a vehicle for intranuclear delivery of DNA. Relative ease of construction, along with lack of pro-oncogenic potential are the main advantages of plasmids [117]. Proof-of-concept animal studies have shown successful transfection of rat aortic smooth muscle cells using green fluorescent protein plasmid DNA eluted from a polymer-coated stent [118]. Phosphorylcholine polymer covered VEGF plasmid-infused stents implanted in rabbit iliac arteries augmented endothelialization, reduced restenosis and enhanced endothelial function by increasing NO production [119]. Endothelial NO synthase DNA plasmid can successfully transfect rabbit endothelial cells raising NO production and suppressing smooth muscle cell proliferation [120]. Inhibitory proteins can also be induced with plasmids. *Anti-MCP-1* gene, which inhibits mononuclear and VSMCs can be eluted from a stent. A reported reduction in neointimal formation after 6 months was found in monkeys [121]. Alternative delivery methods include viral vectors such as retrovirus and adenovirus. Highly efficient as a gene delivery vehicle [122] concerns over mutagenesis from tumor suppressor gene disruption or oncogene activation has limited its broad investigation for stent biocompatibility. Animal models show that an adenovirus-coated stents can successfully transduce *TIMP-3* into smooth muscle cells resulting in decreased neointimal formation [123].

Direct elution of small interfering RNA (siRNA) has also been used. Hyaluronic-coated stent surfaces can deliver siRNA nanoparticles against the *Akt1* gene/protein responsible for stimulating cell growth. Following balloon injury, siRNA-eluting stents deployed in the rabbit iliac segments suppressed smooth muscle growth and restenosis [124]. To date, human studies have yet to be conducted with gene therapy stents. This is an exciting area of development still some time away from actual clinical utilization.

Conclusion

The issue of stent biocompatibility remains unsolved. At present, there is no stent that can successfully biointegrate into the vasculature with low enough throm-

bogenicity as to not require prolonged DAPT. There is also no platform that can simultaneously promote a rapid reinstitution of a functional vascular endothelium while controlling the reactive smooth muscle response. The constant juggling act between the three cornerstones of stent biocompatibility healing, restenosis and thrombogenicity is complex and interconnected.

In the past two decades the field of interventional cardiology shifted from the mechanical support of vessel with the introduction of the bare metal stent to the goals of controlling of intimal hyperplasia and improving thrombogenicity. While a host of different passive and bioactive coatings improved thrombogenicity they alone failed to control restenosis. DES quite successfully emerged as the dominant strategy to address intimal hyperplasia.

The cytoinhibitory approach to restenosis comes at the cost of endothelial recovery and along with permanent polymers led to issues of late stent thrombosis and a necessity for prolonged DAPT. Despite the introduction of next generation DES and new stents under investigation, a definite and significant advancement in clinical safety and efficacy over previous platforms remains to be seen. In the short-term drug elution strategies remain the mainstay of clinical treatment but developments in alternative strategies provide hope for a more comprehensive solution in the future.

Future perspective

Improving the biocompatibility of coronary stents needs a multifaceted approach addressing three key aspects: thrombogenicity, intimal hyperplasia and endothelialization. Currently, there are promising evolutions in stent technology to improve biocompatibility but no solution encompasses all three components. A dominant platform has yet to emerge to truly replace DES in the coming few years. BDS are certainly a promising next step however lingering concerns and the need for more real world clinical data means we are still some time away from embracing this technology. Further into the future, over the next decade we predict a shift away from antiproliferative agents as focus shifts to more holistic, proactive biocompatibility. The application of biomolecules with differential and selective biological activities to stent surfaces may accelerate endothelial healing, attenuate intimal hyperplasia and cloak against clotting elements.

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Executive summary

- Coronary artery stenting has become the main procedural modality for treatment of coronary artery disease.

Clinically available stents

- Today a truly histocompatible coronary artery remains elusive.
- Stent thrombosis and restenosis while improved with contemporary drug-eluting stents remain as clinical manifestations of suboptimal biocompatibility.

New drug-eluting stent platforms

- Polymer free stents, degradable polymer stents and completely biodegradable stents are been investigated as potential replacements for current generation stents. Robust long term clinical data are lacking and as yet these new platforms have not replaced traditional drug-eluting stents in clinical practice.

Alternative strategies to drug elution

- Proactive stents functionalized with bioactive molecules offer an attractive strategy with the potential to be prohealing and/or control vascular smooth muscle cell activity.

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