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Review

Novel bioabsorbable polymer and polymer-free metallic drug-eluting stents

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ABSTRACT

The introduction of drug-eluting stents (DES) significantly reduced angiographic restenosis and the clinical need for revascularization following percutaneous coronary intervention. However, concerns remain regarding the long-term safety and efficacy of DES. The use of durable polymers for drug elution that have limited biocompatibility is thought to contribute toward DES failure, by promoting an adverse local inflammatory response and vascular toxicity. Biodegradable polymer and polymer-free metallic stents represent two novel technological solutions to this challenging clinical problem. This review summarizes the available clinical evidence supporting the use of either biodegradable polymer or polymer-free DES platforms.

Contents

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Introduction

Coronary stents were introduced >25 years ago in an effort to mitigate the risk of acute vessel closure and reduce recoil/early restenosis associated with 'plain old balloon angioplasty' (POBA) [1]. Although short-term procedural outcomes were improved, bare-metal stents (BMS) were prone to development of in-stent restenosis (ISR), a new entity resulting from diffuse proliferation of neointimal tissue within the stented segment [2]. Early angiographic studies of BMS found ISR rates around 25% [3], fueling the need for therapies that inhibit neointimal growth. The addition of anti-proliferative drug coatings to the metallic stent frame, carried in a permanent 'durable' polymer (DP) layer, heralded the arrival of the drug-eluting stent (DES). Anti-proliferative agents, including sirolimus and paclitaxel, were the most successful of initial attempts to prevent neointimal cellular replication by cytostatic and cytotoxic actions [4]. Early randomized trials confirmed significant reduction in rates of ISR with use of DES, principally due to significant reductions in neointimal tissue volume [5,6]. These results led to widespread adoption and use of DES, resulting in percutaneous coronary intervention (PCI) becoming the most commonly performed invasive medical procedure worldwide.

Concerns with drug-eluting stent use

Despite clear reductions in ISR rates following DES implantation, pooled data from randomized trials suggested that rates of death and myocardial infarction (MI) at long-term follow-up were not reduced, when compared with BMS [7]. The long-term safety of DES was then questioned when registry data and meta-analyses [8,9] began demonstrating increased incidence of MI and very-late (>1 year after implantation) stent thrombosis (VLST) [10,11] with estimated annual risk of VLST approximately 0.2–0.6% and importantly not diminishing with time [12]. Although VLST remains infrequent, it is associated with very poor outcomes [13]. Furthermore, despite widespread use of DES, patients continue to experience high rates of target lesion revascularization (TLR), with studies showing that around 1 in 10 patients receiving early-generation devices required repeat procedure within 5 years [14,15]. Lack of long-term efficacy and device safety concerns, coupled with increasing urgent/emergent presentations and uncertainty of the efficacy of PCI compared with optimal guideline-driven medical therapy [16], have led to a net downturn in elective PCI procedure volume.

Drug-eluting stent failure

DES failure is a multi-factorial process involving patient-specific, pharmacological, procedural, and mechanical/biological factors [17]. Although many of these factors cannot be modulated, precise DES implantation and optimization during implantation is crucial. Studies have consistently found that DES under-expansion is not only common, but may be associated with increased risk of ISR [18] and stent thrombosis (ST) [19]. Geographical miss, where deployed stents fail to cover the entire target plaque longitudinally, also appears to be important with such lesions often exhibiting higher rates of adverse events [20,21]. Mechanical factors, related to the stent itself, also appear to play a role; stent fracture is associated with restenosis in ~60% of cases [22], and there are reports that microscopic disruption (e.g. peeling or cracking) of the polymer/drug coating may result in failure to inhibit neointimal growth and lead to restenosis [23]. Increased stent strut thickness also increases restenosis in BMS [24,25], as thick struts induce subtle alterations to coronary blood flow, resulting in low or oscillatory wall shear stress regions downstream of the strut that act to promote platelet accumulation, cytokine release, and neointimal growth [26]. Late DES failure may also be precipitated by the development of in-stent neoatherosclerosis, which can be identified through use of invasive imaging modalities including optical coherence tomography [27]. Although neoatherosclerosis appears more common following BMS [28], macrophage infiltration and necrotic core formation has been observed as early as 4 months after DES implantation [29]. As such, neoatherosclerosis remains an ongoing safety concern and further research into its mechanism and strategies to mitigate risk are required.

Delayed arterial healing, following PCI with DES, is also thought to be an important driver for adverse clinical events [30,31]. A combination of clinical, pathological, and animal studies have demonstrated that poor arterial healing, often characterized by delayed re-endothelialization, hypersensitivity, eosinophilic infiltration, and chronic inflammation, is associated with VLST [32,33]. Although the exact pathological processes underlying hypersensitivity reactions and delayed arterial healing remain obscure, one potential etiological agent implicated in this phenomenon may be the durable polymer left coating the stents when drug-elution has completed [32].

In the hope of improving clinical outcomes, considerable effort and resources have been committed into designing technologies that might negate the requirement for durable polymers in metallic DES manufacture. In effect, leaving a BMS after the time required for the drug-elution to be completed. This review will detail those platforms that are currently, or soon to be, commercially available and explore the existing clinical data supporting their use.

Biodegradable polymer drug-eluting stents

As DP-DES have been implicated in delayed arterial healing, developing a polymer that would disappear after drug elution may be advantageous. This was highlighted by data from the SCAAR registry, where the annual risk of VLST was lower in BMS compared with DES after 1 year [34] with several manufacturers having developed biodegradable polymer (BP)-DES over recent years. A list of existing commercially available systems can be found in Table 1, together with their material construct, drug delivered, strut thickness, and biodegradable polymer utilized where known.

Biomatrix

The Biomatrix DES (Biosensors Europe, Morges, Switzerland) is a thick-strut (150 μm) 316L stainless steel stent with a coating composed of 50:50 poly-l-lactic acid (PLLA) and biolimus-A9 mix. Biolimus is approximately ten times more lipophilic than sirolimus, thereby easily crossing the cell membrane to achieve

Table 1
Biodegradable polymer stent characteristics.

Stent name	Manufacturer	Material	Drug	Polymer	Strut thickness	Polymer degradation (months)	Drug release (months)
Biomatrix	Biosensors	316L	Biolimus A9	PLLA	120 μm	6–9	6
Biomime	Meril	CoCr	Sirolimus	PLLA and PLGA	65 μm	2	1
Cordimax	Rientech	316L	Sirolimus	PLGA	NA	NA	NA
DESyne BD	Elixir	CoCr	Novolimus	PLLA	81 μm	6–9	3
Infinnium	Sahajanand Medical Tech.	316L	Paclitaxel	Polymer blend	80 μm	NA	NA
MiStent	Micell Tech.	CoCr	Sirolimus	PLGA	64 μm	3	9
Nobori	Terumo	316L	Biolimus A9	PLLA	120 μm	6–9	6
Orsiro	Biotronik	CoCr	Sirolimus	PLLA	60 μm or 80 μm[a]	14	12
Supraflex	Sahajanand Medical Tech.	CoCr	Sirolimus	PLLA/PLGA	60 μm	9–12	1.5
Supralimus	Sahajanand Medical Tech.	316L	Sirolimus	Polymer blend	80 μm	2–6	1.5
Synergy	Boston Scientific	PtCr	Everolimus	PLGA	74 μm	4	3
Ultimaster	Terumo	CoCr	Sirolimus	PLGA	80 μm	4	4

316L, stainless steel; CoCr, cobalt chromium; PLLA, poly-L-lactic acid; PLGA, poly(lactic-co-glycolic) acid; PtCr, platinum chromium; NA, not available.
[a] 60 μm for the 2.25–3.00 mm platform and 80 μm for the 3.50–4.00 mm platform.

therapeutic effects with low systemic exposure [35]. The platform has extensive published data confirming long-term safety and efficacy; the 1707 patient, randomized LEADERS trial [36], demonstrated that the Biomatrix stent was non-inferior to the DP-DES sirolimus-eluting platform (Cypher, Cordis, Fremont, CA, USA) at 4 years, with a target vessel failure rate of 9%. The study also hinted at longer-term benefits, with an 80% relative risk reduction for VLST in the BP-DES group, between 1 and 4 years [37]. At 5 years, the Biomatrix BP-DES stent was statistically non-inferior to the DP-DES stent for the primary endpoint, a composite of cardiac death, MI, and clinically indicated TVR, with rates of 22.3% and 26.1%, respectively [38]. Within the LEADERS trial, a pre-specified subgroup of patients also underwent optical coherence tomography (OCT) evaluation of strut re-endothelialization, finding that strut coverage was improved in the Biomatrix group (1.8% vs. 6.3%) [39].

Nobori

The second BP-DES with broad clinical data is the Nobori DES (Terumo Corporation, Tokyo, Japan), which again utilizes a PLLA polymer combined with biolimus-A9. The Nobori-1 study randomized patients, 2:1 to receive the Nobori device or paclitaxel-eluting DP-DES. The study met its primary angiographic outcome of late lumen loss (LLL), with the device exhibiting superior performance (0.15 ± 0.27 mm vs. 0.32 ± 0.33 mm; $p = 0.006$) [40]. The Nobori-2 study, an observational prospective registry of 3067 patients extended this work, attempting to ascertain the safety and clinical outcomes for use in 'real-world' complex lesion and patient subsets, including, among others, multi-vessel disease, left-main intervention, ISR, bifurcations, and primary PCI. With long-term data available in 89.3% patients, the recently published 5-year data reported cumulative TLR and definite/probable ST rates of 5.3% and 1.1%, respectively. Between years 1 and 5 the TLR and VLST rates were 3.5% and 0.6%, respectively [41]. More recently, the COMPARE II [42] and NEXT [43] trials also showed non-inferiority of the Nobori stent at 5 years and 3 years in regard to safety and efficacy when compared to the Xience-V (Abbott Vascular, Redwood City, CA, USA) and Xience/Promus (Abbott Vascular) stents, respectively.

Orsiro

The Orsiro DES (Biotronik Inc., Berlin, Germany), a sirolimus-eluting cobalt chromium BP-DES with strut thickness of either 60 or 80 μm, originally succeeded in demonstrating safety in BIOFLOW-1 [44]. Following this success, BIOFLOW-II randomized 452 patients, in a 2:1 fashion in comparison with the Xience Prime (Abbott Vascular) DP-DES. Provisional results demonstrated similar in-stent LLL and target lesion failure (TLF) [45]. In the OCT subgroup, 98.3% of stent struts were re-endothelialized at 9 months compared with 97.5% in the Xience Prime group. Non-inferiority was confirmed in the 2119 patient BIOSCIENCE trial [46] with results extending to 2 years demonstrating similar rates of TLF and ST between groups [47]. Interestingly, the BP-DES platform appeared to outperform Xience when utilized for ST-segment elevation MI, a predefined subgroup analysis. Although the mechanisms for this remain unclear, patients presenting with an acute coronary syndrome may exhibit impaired strut endothelialization [48] and thus a more biocompatible polymer may better facilitate arterial healing. Real-world experience with the Orsiro platform is now also available from a 1356 patient registry, showing a TLF rate of 5.1% at 1 year [49]. More recently, the large-scale BIO-RESORT study, an all-comers, real world randomized trial of 3514 patients, compared Orsiro with either Synergy (Boston Scientific, Natick, MA, USA) or Resolute Integrity (Medtronic Inc., Santa Rosa, CA, USA) DP-DES. The primary finding at 1 year was that the BP-DES were non-inferior to the DP-DES with regard to the primary endpoint of cardiac death, target vessel MI, and TVR with a risk difference of −0.7% (95%CI −2.4–1.1) [50]. Finally, the PRISON IV trial assessed Orsiro in patients with chronic total occlusions, a more complex lesion cohort; in this setting, the Orsiro BP-DES was associated with greater in-segment LLL and more frequent restenosis (8.0% vs. 2.1%, $p = 0.028$) [51].

Synergy

The SYNERGY BP-DES (Boston Scientific) utilizes an ultra-thin stent strut design, cut from a platinum chromium alloy. The manufacturing process ensures the polymer/drug coating is only applied to the abluminal strut edge, thereby minimizing unnecessary drug load. The first-in-human clinical study, EVOLVE, recruited 291 patients in a 1:1 fashion to assess clinical and angiographic results using both the full- and half-dose everolimus formulations, when compared with the PROMUS Element DP-DES (Boston Scientific) [52]. Clinical events at 30 days and the 6-month in-stent LLL measurements were similar between groups, with similar 2-year outcomes [53]. The single-blinded EVOLVE II randomized trial demonstrated non-inferiority of the SYNERGY stent compared with PROMUS Element DP-DES at 1 year [54]; the primary endpoint of TLF was assessed in 1684 patients, and occurred in 6.7% of SYNERGY and 6.5% of PROMUS Element patients ($p = 0.0005$ for non-inferiority). Rates of target-vessel MI, symptom- or ischemia-driven TLR, and ST at 1 year were also equivalent. Indeed, the recently published results from the SCAAR registry of which 7886 received SYNERGY stents, again showed non-inferiority compared with DP-DES [55].

BioMime

The BioMime BP-DES (Meril Life Sciences Pvt. Ltd., Gujarat, India) is an ultra-thin strut design, utilizing a cobalt chromium alloy, sirolimus-eluting stent and demonstrated safety in the MeriT-1 first-in-human study [56]. Angiography at 8 months demonstrated a LLL of 0.15 mm [Q1–Q3, 0.09–0.33 mm], consistent with expectations. The larger non-randomized MeritT-2 study reported a TLR rate of 5.2% at 1 year. More recently, the MeriT-3 study including 1161 patients reported 12-month major adverse cardiovascular event (MACE) rates of 2.4%, and ST rates of 0.1%, comparable with other DP-DES platforms [57].

DESyne BD

The DESyne BD (Elixir Medical Corp., Sunnyvale, CA, USA) stent is a thin strut, low profile, novolimus cobalt chromium platform with a BP coating. The EXCELLA-II multicenter study assessed the DESyne BD platform compared with the Endeavor zotarolimus DP-DES (Medtronic) [58]. Patients ($n = 210$) were enrolled in a 2:1 design, with 139 receiving the novolimus platform. The primary endpoint at 9 months, LLL as quantified by intravascular ultrasound (IVUS), was significantly reduced in those with the BP-DES. Clinical event rates were also similar between groups, although these findings require confirmation in a larger and more complex patient cohort. At 5-year follow-up, the DESyne BD group had significantly lower incidence of patient-oriented (HR 0.52, 95% CI: 0.32–0.87, $p = 0.013$) and device-oriented (HR 0.38, 95%CI: 0.17–0.83, $p = 0.011$) composite endpoints, but there was no difference in cardiac death and ST between groups [59].

Supralimus/Infinnium

The Supralimus BP-DES and Infinnium BP-DES (Sahajanand Medical Tech., Surat, India) both utilize biodegradable polymer blends combined with sirolimus (Supralimus) or paclitaxel (Infinnium). The Supralimus BP-DES was assessed in the SERIES I study of 100 patients treated with 126 stents [60]. The primary endpoint of binary ISR in this low-risk cohort was 0% (in-stent) and 1.7% (in-segment). LLL was 0.09 ± 0.37 mm with 7% MACE at 30 months. Although no cases of definite ST were seen, there was one probable and one possible case according to ARC definitions. Subsequent to this, the PAINT study randomized 274 patients to Supralimus, Infinnium or BMS in a 2:2:1 design [61]. At 9 months, in-stent LLL was reduced in both BP-DES, with a resulting reduction in TVR at 1 year. Finally, the recently published multicenter CORE registry assessed the Supralimus stent in a real world population. In 376 patients, MACE rates were found to be 1.1% with a TLR rate of 0.3% at 6 months [62].

MiStent

The DESSOLVE I and II trials assessed the MiStent (MiCell, Durham, NC, USA) sirolimus-eluting BP-DES and encouraging 2-year follow-up data were published [63]. DESSOLVE II compared the MiStent BP-DES with the Endeavor (Medtronic) zotarolimus-eluting DP-DES and demonstrated superiority in the primary endpoint of 9-month LLL and comparable 2-year MACE, TLF, and TVR rates [64].

Other BP-DES platforms

The Cordimax BP-DES (Rientech Medical, Shandong, China) is a 316L stainless steel, abluminal-coated sirolimus-eluting platform. A trial of 402 patients randomized in a 1:1 fashion compared the Cordimax BP-DES and Cypher DP-DES [65]. At 9 months, the primary endpoint of angiographic LLL was shown to be non-inferior and at 5-year follow-up, clinical results compared favorably with other studies showing trend toward decrease in MACE, TVR, and ST rates.

The Supraflex BP-DES is a sirolimus-eluting device with ultra-thin struts (60 μm) constructed from cobalt chromium alloy. It was studied in the MANIPAL-FLEX non-randomized study of 189 patients with 9-month angiographic and 12-month clinical follow-up. The primary endpoint of TLF occurred in 5.3%, with cardiac death, MI, and TLR occurring in, 1.6%, 1.6%, and 2.1% respectively. Secondary endpoints of in-stent and in-segment LLL at 9 months were 0.18 ± 0.23 mm and 0.11 ± 0.33 mm, making the Supraflex potentially one of the most effective BP-DES reported to date [66]. Finally, the Ultimaster BP-DES (Terumo Corporation) the next iteration of the Nobori technology, using a cobalt chromium stent with improved design and sirolimus (not biolimus A9) coating, was assessed in the CENTURY II randomized trial with safety and efficacy endpoints of TLF and device-oriented events at 9 months [67]. A total of 1123 patients were randomized in a 1:1 fashion with the Xience DP-DES. TLF rates were 4.4% for Ultimaster and 4.9% for Xience, with composite of cardiac death and MI occurring in 2.9% and 3.8% ($p = 0.40$), respectively. Subsequent publication of longer-term follow-up and subgroup analyses based on lesion-length, diameter, and location have shown similar non-inferior results [68–71].

Effectiveness of biodegradable polymer drug-eluting stents

Although early clinical trial results have been broadly favorable, the theoretical advantage offered by biodegradable polymers relates to a reduction in the risk of VLST observed with early-generation DES. Conflicting data have now emerged, based on analyses from clinical trials and registries, as to whether this goal will be realized; firstly, a pooled analysis of 4062 patients from the ISAR-Test 3, ISAR-Test 4, and LEADERS study assessed clinical outcomes after 4 years. The investigators found that the risk of ST was lower with BP-DES when compared with DP-DES controls, predominantly driven by a significantly lower risk of VLST (HR 0.22, 95%CI 0.08–0.61; $p = 0.004$) (Fig. 1A) [72]. Similar results were reported from a large meta-analysis, showing that BP-DES outperformed early-generation devices [73]. However, these benefits were less apparent when BP-DES were compared to newer generation devices (e.g. everolimus-eluting cobalt chromium DES). Furthermore, in the landmark analysis performed after 1 year, BP-DES were associated with an increased risk of death, compared with cobalt chromium everolimus-eluting stents. Subsequent meta-analyses have again shown conflicting results. In a study of 19,886 patients treated with either BP- or newer-generation DP-DES with mean follow-up of 26 months, the use of BP-DES showed no additional benefit nor harm, with a 1-year landmark analysis showing no reduction in VLST. Similar results were found regardless of strut thickness, stent platform, polymer, or drug-release kinetics (Fig. 1B). Note must be made however of the reasonably short mean duration follow-up and that VLST data were available in only 6 of the 12 included studies [74]. These disappointing findings replicated results of an earlier network meta-analysis of 63,242 patients undergoing DES implantation with a combination of early-, newer-generation or biodegradable polymer biolimus devices [75]. Despite widespread published non-inferiority data of BP-DES, it remains a matter of debate as to whether superiority will be shown or if clinical outcomes will improve, as the technology is further developed and follow-up extended.

Polymer-free drug-eluting stents

It may be argued that the best polymer for DES is in fact no polymer at all; consequently there has been a growing interest in

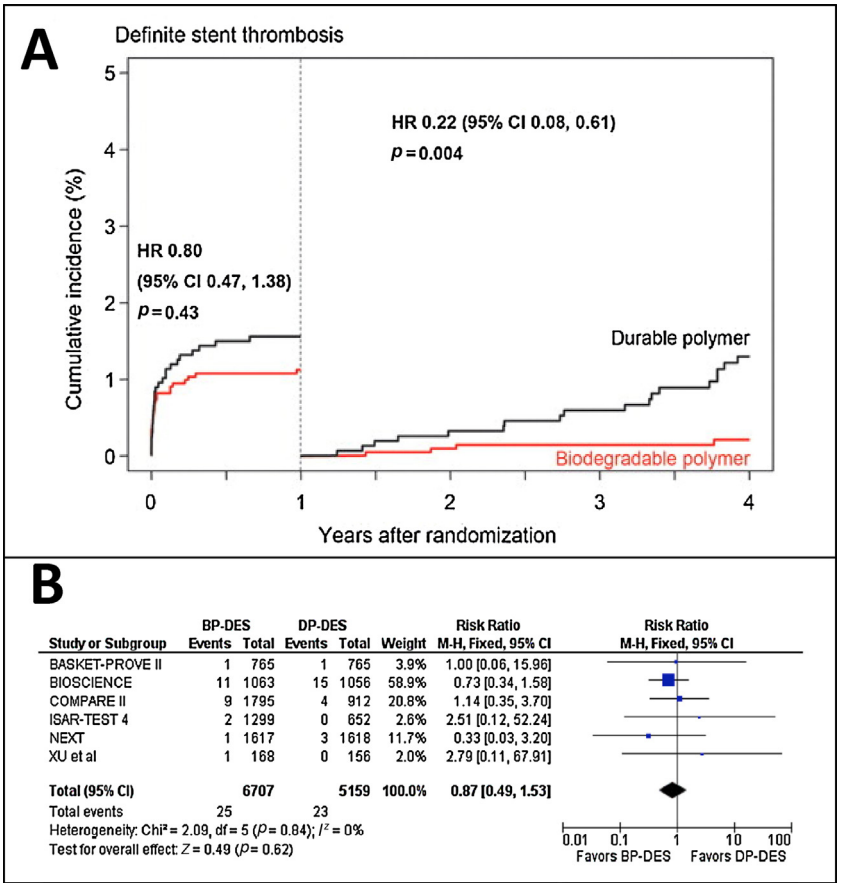

Fig. 1. Clinical outcomes following biodegradable drug-eluting stent implantation. (A) Kaplan–Meier curves illustrating the cumulative incidence of definite stent thrombosis in a pooled population receiving either durable or biodegradable polymer stents, with landmark analysis at 1 year [72]. (B) Forest plot illustrating the risk of VLST for biodegradable polymer in comparison with newer-generation durable polymer stents in a landmark analysis beyond 1 year [74]. BP, biodegradable polymer; DES, drug-eluting stent; DP, 'durable' polymer.

Table 2
Polymer-free stent characteristics.

Stent name	Manufacturer	Material	Drug	Strut thickness	Mechanism of drug delivery
Yukon	Translumina	316L	Sirolimus	87 μm	Microporous stent surface
BioFreedom	Biosensors	316L	Biolimus A9	199 μm	Microstructured abluminal stent surface
Dual-DES	NA	316L	Sirolimus and probucol	87 μm	Micropores with shellac resin
VESTAsync	MIV Therapeutics	316L	Sirolimus	65 μm	Microporous hydroxyapatite coating
Drug Filled Stent (DFS)	Medtronic	CoCr	Sirolimus	NA	Diffusion from stent core

316L, stainless steel; CoCr, cobalt chromium; NA, not available.

the possibility of 'polymer-free' stents, focusing on novel approaches for coating stents with anti-restenotic agents. However, there remain significant manufacturing and engineering challenges to the development of polymer-free drug-eluting stents (PF-DES), principally relating to maintenance of drug concentration/elution over a protracted period when no polymer for carriage is present. Manufacturers have turned to innovative engineering solutions, including textured or nonporous metallic surfaces, crystallization, or even drug reservoirs [76]. Examples of platforms undergoing clinical evaluation are included in Table 2. More novel concepts are still under development and first-in-human studies of these devices are currently underway.

Yukon

The Yukon (Translumina, Hechingen, Germany) is a PF-DES with two components: a pre-mounted micro-structured stainless steel microporous stent and coating device. The architecture of the microporous stent surface increases the drug reservoir capacity and permits a retarded drug release without obligatory polymer application. The cartridge holding the stent system is placed into the coating device and sirolimus is then delivered evenly to the microporous stent via a uniform jet system. Drug coating of the stent is performed at the hospital, with this technique permitting varied drug dosing according to physicians' wishes and needs. Pharmacokinetic assays have demonstrated that sirolimus is continuously eluted for >3 weeks, with more than two-thirds released in the first week. This methodology has been shown to be feasible and safe, demonstrating a dose-dependent efficacy and restenosis benefit at 1 year (25.9% with BMS to 18.9%, 17.2%, 14.7% with 0.5%, 1.0%, and 2.0% concentration sirolimus solution, respectively; $p = 0.024$) The need for TLR at 1-year follow-up was similarly significantly reduced (21.5% BMS vs. 8.8% for 2.0% sirolimus concentration, $p = 0.006$) [77]. Furthermore, a

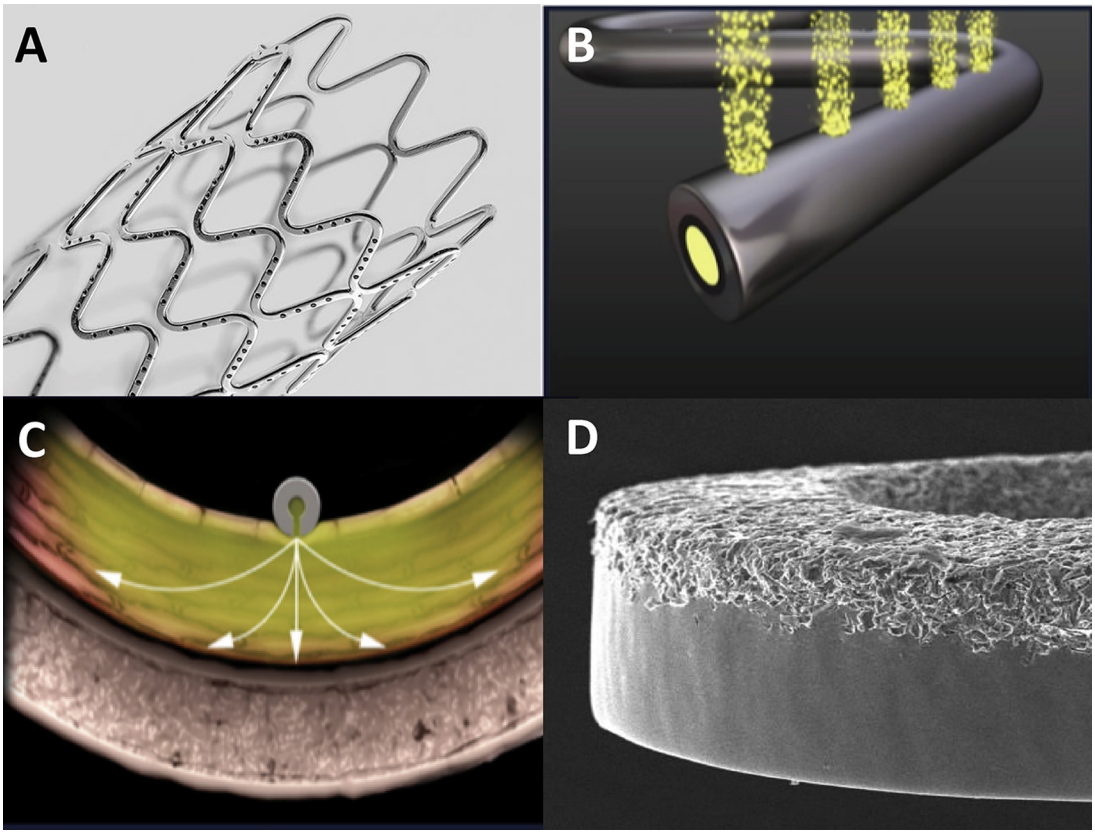

Fig. 2. Next generation polymer-free stents. (A) The Drug Filled Stent (DFS, Medtronic, Santa Rosa, CA, USA) [93] (B) exhibits a hollow design with sustained drug elution through diffusion via (C) direct interaction with the vessel wall. (D) The BioFreedom drug-eluting stent platform (Biosensors Europe, Morges, Switzerland) as seen with electron microscopy, illustrating the highly texturized abluminal surface [85].

450 patient randomized trial found that the sirolimus-eluting Yukon PF-DES had similar effect to the paclitaxel-eluting DP-DES in their capacity to reduce ISR (14.2% vs. 15.5%, p = 0.73) and TLR (9.3% vs. 9.3%, p = NS) [78]. Extended follow-up to 5 years has supported the efficacy and safety of this stent platform [79].

Using the same stent platform and utilizing the capability to vary drug type and dosing, the ISAR-TEST-2 study randomized 1007 patients to receive the microporous stent backbone incorporating probucol and sirolimus (Dual DES) and compared against the DP-sirolimus- (Cypher) and zotarolimus-eluting (Endeavour) DES [80]. Probucol, a potent liposoluble antioxidant, has proven efficacy in both animal and clinical trials in reducing neointimal hyperplasia [81]. ISAR-TEST 2 found that binary restenosis was significantly lower in the Dual DES group compared with the Endeavour ZES (11.0% vs. 19.3%, p = 0.002), but comparable with Cypher SES (12.0%, p = 0.83) [80,82]. These trends were mirrored in the extent of LLL and TVR at 1-year across groups without difference in death, MI, or ST. At 2 years there were no significant differences in the safety profile between the three platforms; however, the Dual DES maintained an advantage with respect to binary restenosis and TLR compared with Cypher and Endeavor (p = 0.009 for both) [82]. More recently, the ISAR TEST-5 group randomized 3002 patients to treatment with the Dual DES, and found that it was non-inferior with respect to cardiac death, target-vessel MI, or TVR at 12 months (p for non-inferiority = 0.006) [83] and 5 years [84] when compared with zotarolimus-eluting device.

BioFreedom

Building on the early success of the Biomatrix stent and its biodegradable polymer, the key feature of the BioFreedom PF-DES (Biosensors Europe) is that it has a selectively micro-structured surface that holds biolimus-A9 in the abluminal surface of its stainless steel structure (Fig. 2) [85]. A micro-abrasion process is used to texturize the surface, providing an effective means for anchoring the drug to the stent surface without polymer requirement [86]. The BioFreedom first-in-human randomized trial recruited 182 patients to receive the BioFreedom stent at either the standard (15.6 μg/mm) or low dose (7.8 μg/mm) of biolimus, comparing both iterations with the DP paclitaxel-eluting Taxus Liberte (Boston Scientific) [87]. In-stent LLL was non-inferior in the BioFreedom standard-dose group (p for inferiority = 0.001) with a trend toward superiority compared with Taxus at 12 months [medians 0.17 mm (0.09–0.39) vs. 0.35 mm (0.22–0.57), p for superiority = 0.11]. Safety and efficacy of the BioFreedom stent has been shown to 5 years with no significant difference in MACE between the groups and no ST occurring across all groups [88]. The platform was subsequently examined in 2466 patients at high-bleeding risk recruited to the LEADERS FREE trial [89]. In this pivotal study, patients were randomized to either BioFreedom or BMS (Gazelle), followed by 1 month only of dual anti-platelet therapy. The PF-DES outperformed BMS both in the primary safety endpoint (composite of death, MI, and ST) and efficacy endpoint (clinically driven TLR). Results of the real world e-Biomatrix all comers registry of 2365 patients enrolled from 42 centers replicated the results of the LEADERS FREE trial, showing similar results of MACE and ST at 1 and 2 years [90]. These results suggest a potential expanding indication for PF-DES to patient cohorts where premature discontinuation of dual anti-platelet therapy may be required or uncertain.

VESTAsync

The VESTAsync (MIV Therapeutics, Atlanta, GA, USA) is a hydroxyapatite, sirolimus-eluting PF-DES. It comprises a stainless

steel platform coated with microporous hydroxyapatite, serving as a drug carrier for the biocompatible sirolimus formulation. A potential advantage of hydroxyapatite is that it normally constitutes 70% natural bone, and therefore has intrinsic biocompatibility, with in vivo studies suggesting complete absorption at 1 year [86]. First-in-human evaluation of the VESTAsync stent involved treatment of 15 patients with follow-up at 4, 9, and 12 months [91]. LLL was assessed angiographically and with IVUS (% stent obstruction). At 4 months there was no significant increase in neointimal hyperplasia, with 0.30 ± 0.25 mm LLL and $2.6 \pm 2.2\%$ volume obstruction. VESTAsync II, a proof-of-concept trial including 75 patients randomized in a 2:1 fashion again demonstrated the sustained efficacy of this PF-DES, however larger trials with more complex lesions are needed to confirm these results [92].

Drug Filled Stent (DFS)

The Drug Filled Stent (DFS) (Medtronic) has a unique design concept that incorporates a sinusoidal wire design with a helical wrap system, similar to Medtronic's trademark Resolute Integrity platform. The DFS utilizes a tri-layered continuous wire with an outer cobalt chromium layer, middle tantalum layer which increases radio-opacity, and inner continuous lumen. In contrast to the Integrity platform, the architecture is hollow, with laser drilled elution holes on the abluminal surface, and the core of the device contains a reservoir of sirolimus, delivered to the arterial wall by way of diffusion (Fig. 2). The first-in-human ReVolution trial studied 101 patients treated with DFS in two cohorts and has recently reported 9-month results demonstrating in-stent LLL of 0.26 ± 0.28 mm compared with 0.36 ± 0.52 mm for Resolute-treated historical controls [93]. Larger-scale clinical trials with longer follow-up are required however to determine whether these results translate into more favorable clinical outcomes.

Conclusions

Although early- and newer-generation metallic DES systems exhibit early favorable clinical outcomes, their long-term performance beyond 1 year is somewhat questionable and improvements in device safety and efficacy are undoubtedly required. The development of biodegradable and polymer-free metallic stent platforms represents novel solutions to this clinical problem. Early randomized trials using these technologies have shown equivalent short-term rates of restenosis and clinical outcomes, when compared with several existing DES platforms. Despite these encouraging results, concerns remain over device safety and there remains a lack of convincing data suggesting that these devices have clear advantages over existing DP-DES platforms. Long-term follow-up in larger and more diverse patient populations is now required to fully assess whether these technologies fulfill their potential to reduce the long-term risk of VLST and late DES failure.

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Conflicts of interest

NEJW has acted as a consultant to Abbott Vascular.
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