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Novel Technologies and Future Perspectives of Drug-Eluting Stent

Kohei Wakabayashi[1]*, Rajbabu Pakala[2], Michael Mahmoudi[3], Takuya Watanabe[4], Hiroyoshi Mori[1], Yoshitaka Iso[1] and Hiroshi Suzuki[1]

[1]*Division of Cardiology, Department of Internal Medicine, Showa University Fujigaoka Hospital, Yokohama, Japan*
[2]*Division of Cardiology, Washington Hospital Center, Washington, DC, USA*
[3]*Papworth Hospital NHS Trust, UK*
[4]*Laboratory of Cardiovascular Medicine, Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan*

Abstract

As compared with bare metal stents (BMS), Drug-eluting stents (DES) have dramatically reduced the incidence of target lesion revascularization and neointimal formation. There are, however, potential toxic effects of DES upon arterial tissue. Previous pathological studies have indicated that durable polymers and the drug itself play critical role in delayed endothelialization, persistent inflammation, hypersensitivity, apoptosis, necrosis, and positive remodeling leading to adverse cardiovascular events. To address these issues, new generation DES, biodegradable polymers, polymer-free and fully bioabsorbable scaffolds are currently in evolution. This review summarized the clinical trials that have assessed the feasibility and efficacy of new generation DES. A number of pivotal trials have also demonstrated the non-inferiority of biodegradable polymer or polymer-free DES to durable polymer DES in terms of clinical outcomes and angiographic in-stent late loss, although long-term follow-up data remain sparse. Fully absorbable DES has also provided promising results in selected populations and requires sufficiently powered randomized studies to assess their safety and efficacy.

Keywords: Drug-eluting stent; Polymer; Trials

History of Drug-Eluting Stent

As compared with balloon angioplasty, coronary stent implantation has dramatically improved the procedural safety of percutaneous coronary intervention (PCI) as well as long-term outcomes. This has been particularly important in reducing re-stenosis rates from approximately 30-40% with balloon angioplasty to 20-30% with bare metal stenting (BMS) [1-11]. Scaffolding by BMS overcame the negative recoiling that accompanied revascularization but neointimal hyperplasia remained problematic. This in turn led to a concerted attempt at local or systemic delivery of pharmacological agents with anti-inflammatory, anti-proliferative and anti-migratory properties for decades [12-15]. The most promising agents that were identified included sirolimus and its analogs biolimus, tacrolimus, everolimus, zotarolimas, micophenolic acid, and taxol which attenuated neointimal hyperplasia following stent implantation. Drug-eluting stents (DES) were initially made with drug delivery systems using a durable polymer to control drug elution from the stent into the arterial wall. These so called "first generation" DES included the sirolimus-eluting stent (Cypher, Cordis Corp., Johnson & Johnson, Miami, FL) and the paclitaxel-eluting stent (Taxus Express, Boston Scientific, Natick, MA) and dramatically reduced the incidence of in-stent restenosis after PCI as compared to their BMS counterparts [16,17].

The Issues of First-Generation DES

Although the first-generation DES demonstrated superior clinical efficacy with lower incidence of target lesion revascularization, a number of concerning drawbacks subsequently emerged with this technology. These included very late stent thrombosis (VLST), requirement for prolonged dual antiplatelet therapy (DAPT), late catch-up restenosis after 9 months, endothelial dysfunction, tissue injury due to the stent platform, flexibility to deliver to target lesions and geographical miss.

Sirolimus is a natural macrocyclic lactone and a potent immunosuppressive agent. Sirolimus elevates p27 levels through binding to an intracellular receptor protein, which can inhibit cyclin/cyclin-dependent kinase complexes resulting in cell-cycle arrest in the late G1 phase [18]. Paclitaxel, a lipophilic molecule derived from the Pacific yew tree Taxus brevifolia, is capable of inhibiting cellular division, motility, activation, secretory processes, and signal transduction [19]. A stent coated with such cell-cycle inhibitors suppresses neointimal hyperplasia due to VSMC proliferation and extracellular matrix production. However, high concentration of the drug by local delivery may be toxic to the arterial tissue. DES implantation has been shown to lead to delayed endothelialization, persistent inflammation, hypersensitivity, apoptosis, necrosis, thrombotic reactions and positive remodeling in local segments leading to the progression of atherothrombosis [20-26]. In addition to the anti-proliferative drug, it soon became apparent that the polymer itself was associated with delayed healing [21]. Such toxic effects are now believed to be associated with such adverse events as stent thrombosis [27]. Our understanding of neointimal hyperplasia has been further enhanced by recent studies suggesting that the composition of neointimal hyperplasia in DES and BMS are different [28-30]. These studies appear to indicate that in DES, the main cause of restenosis may be atherosclerotic in aetiology whilst in BMS; neointimal hyperplasia consists of VSMC proliferation and increased extracellular matrix deposition. Such "neoatherosclerosis" within DES may partially explain the cause of late catch-up restenosis whilst ruptured plaques in these areas may lead to vary late stent thrombosis [31].

There is considerable evidence that patients who receive DES have endothelial dysfunction at stent edge segments probably due to the toxicity of DES [32-42]. Although the impact of such endothelial dysfunction on clinical outcomes is unknown, it is possible that peri-stent segments may enhance the atherosclerotic process.

Geographical miss is an important issue of first-generation DES.

***Corresponding author:** Kohei Wakabayashi, MD, PhD, Division of Cardiology, Department of Internal Medicine, Showa University Fujigaoka Hospital, 1-30 Fujigaoka, Aoba-ku, Yokohama-City, Kanagawa 227-8501, Japan, Tel: 81-45-971-1151; Fax: 81-45-973-1019; E-mail: kwaka@live.jp

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Although longitudinal miss may result in restenosis at the stent edge, axial miss may result in in-stent restenosis. Thus to improve the efficacy of DES, every effort should be taken to avoid geographical miss.

Second-Generation DES

Second-generation DES has attempted to address some of the limitations of the first-generation DES by using more biocompatible polymer coatings, thinner stent struts and larger cell area. Everolimus-eluting stent (Xience V, Abbott Vascular, Santa Clara, CA and Promus, Boston Scientific, Natick, MA) has a thin biocompatible durable polymer , the fluoropolymer, poly (vinylidene fluoride-co-hexafluoropropylene), with lower drug load, very thin struts and large cell area [43-45]. Zotarolimus-eluting stent (Endeavor Resolute, Medtronic, Minneapolis, MN) has a novel polymer, BioLinx polymer (Medtronic Inc., Santa Rosa, CA, USA), that consists of three different polymers; the hydrophobic C_{10} acts as a drug reservoir for proper release, the hydrophilic polyvinyl-pyrrolidinone for biocompatibility, and C_{19} contains both hydrophobic and hydrophilic polyvinyl-pyrrolidinone for control of drug release and biocompatibility [45]. This hydrophilic polymer does not induce activated monocyte adhesion. Polymers of second-generation DES were found to be more biocompatible and resulted in less inflammation when tested in animal models [43]. In pivotal clinical trials, although second-generation DES has achieved satisfactory clinical outcomes, concerns regarding durable polymers persist [46-48]. This has, in part, led to the development and assessment of biodegradable polymer DES and fully biodegradable DES.

Biodegradable Polymers DES

DES consists of metal scaffolding, the drug as well as a polymer. Neointimal hyperplasia within BMS is nearly complete by 3–6 months. Slow regression of neointimal hyperplasia within the stent occurs from 6 months to 3 years post BMS implantation, indicating that perhaps the polymer and drug are not necessary beyond 6 months. Given that many of the adverse associated with DES are linked to either the polymer and/or the drug, a biodegradable polymer ought to resolve such issues whilst maintaining its beneficial effects, and indeed this hypothesis has been examined in a number of studies (Table 1).

The Limus Eluted from a Durable Versus ERodable Stent Coating (LEADERS) trial [49-52] compared the safety and efficacy of a biolimus-eluting stent with a biodegradable polymer, polylactic acid (PLA) with the sirolimus-eluting stent (Cypher; durable polymer) in routine clinical practice. The results demonstrated non-inferiority in overall cardiac events rate and in-stent late loss in the angiographic cohort. Although the biodegradable polymer did not show any clinical benefit up to 2 years of clinical follow-up, the 4-year results indicate a lower incidence of VLST from 1–4 years [52]. Given that the main purpose of a biodegradable polymer stent is to avoid VLST, the results may have a strong impact upon clinical practice in the future.

Rapamycin-Eluting Stents With Different Polymer Coating to Reduce Restenosis (Intracoronary Stenting and Angiographic Results: ISAR-TEST 3) aimed to assess the non-inferiority of a sirolimus-eluting stent with both a biodegradable-polymer (PLA) and a polymer-free stent with the Cypher stent [53,54]. The results showed non-inferiority of the biodegradable-polymer stent but no benefits were found with the durable polymer DES in terms of clinical outcomes for 2 years. Test Efficacy of 3 Limus-Eluting Stents-4 (ISAR-TEST 4) was a randomized clinical trial of 2,603 patients with broad inclusion criteria [55,56]. The clinical outcomes were compared patients treated with sirolimus-eluting stent with biodegradable polymer (PLA) versus durable polymer DES. The clinical outcomes including stent thrombosis were not different between the two groups. On the other hands, the outcomes were compared patients treated with the second generation DES, Xience V with durable polymer versus the first generation DES, Cypher with durable polymer. There was no difference in clinical outcomes between the two groups.

The NEVO Res-Elution I study, the first clinical trial of the NEVO sirolimus-eluting stent, was conducted to compare the in-stent late loss between the NEVO sirolimus-eluting stent with a biodegradable polymer, polylactide-co-glycolic acid (PLGA), (Cordis Corporation,

	Drug type	Polymer type	Patients number	Follow-up (month)	Death (%)	MI (%)	ST (%)	TLR (%)	Late loss (mm)
LEADERS[49-52]	Biolimus A9	PLA	857	9	2.6	5.7	2.6	5.4	0.13
				24	4.7	6.3	2.9	7.9	…..
				48	9.2	8.3	3.4	10.3	…..
CUSTOM I[59]	Biolimus A9	PLA	30	24 / 8*	3.3	6.6	0	3.3	0.26
CUSTOM II[60]	Biolimus A9	PLA	100	12 / 6*	1.0	4.0	1.0	4.0	0.31
ISAR-TEST-3[53,54]	Sirolimus	PLA	202	12 / 6-8*	2.0	1.5#	0.5	5.9	0.17
				24	3.5	2.5#	0.5	8.4	…..
ISAR-TEST-4[55,56]	Sirolimus	PLA	1299	12	4.7	4.3	1.0	8.8	…..
				36	9.3	4.6##	1.2	13.9	…..
NEVO RES- I[57]	Sirolimus	PLGA	198	6	0.5	2.0	0	3.6	0.13
SERIES I[61]	Sirolimus	Mixed++	100	30 / 6*	3.0	1.0	1.0	4.0 (TVR)	0.09
FUTURE I[62]	Everolimus	PLA	27	12 / 6*	3.8	0	0	3.8	0.11
MAHOROBA[63]	Tacrolimus	PLGA	47	6	0	4.3	2.1+	23.4	0.99
COSTAR I[64]	Paclitaxel	PLGA	87	12	2.3	8.0	3.4	5.7	0.55-0.90
COSTAR II[58]	Paclitaxel	PLGA	989	8 / 9*	0.5	3.4	0.6	8.1 (TVR)	0.64
EUROSTAR[65]	Paclitaxel	PLGA	282	12 / 6*	2.1	3.9	1.1	3.1	0.28-0.40
EUROSTAR II[66]	Paclitaxel	PLGA	152	8	0	3.3	0	15.1	0.41
STELLIUM[67]	Paclitaxel	PLGA	37	6	0	0	0	2.7	0.19
JACTAX[68]	Paclitaxel	PLA	103	9	0	1.9	0	1.9	0.33

MI: Myocardial Infarction; ST: Definite or probable stent thrombosis defined in Academic Research Consortium; TLR: Target Lesion Revascularization; TVR: Target Vessel Revascularization; PLA: Polylactic Acid; PLGA: Polylactide-co-glycolic Acid; ++ Mixed polymer with PLLA (Poly L-Lactic acid), PLGA (50/50 Poly DL-Lactide-co-Glycolide) and PVP (Polyvinyl Pyrrolidone); * Clinical/angiographic follow-up; # Q wave MI only; ## Target vessel MI only; + Definite stent thrombosis only.

Table 1: Clinical outcomes of patients treated with biodegradable polymer DES.

Bridgewater, NJ) and the Taxus Liberte stent (Boston Scientific Corporation, Natick, MA; durable polymer) [57]. The primary end point of in-stent late loss at 6 months showed superiority with the NEVO sirolimus-eluting stent (0.13±0.31 vs. 0.36±0.48 mm, p<0.001). It should be noted that until the NEVO sirolimus-eluting stent is compared with the Cypher stent, its superiority with regards to late loss remains to be determined, although we accept that this may not be achievable given the market withdrawal of Cypher. Although the study was not powered for clinical end points, no stent thrombosis was observed with the NEVO sirolimus-eluting stent whereas 2 cases occurred in the TAXUS Liberte cohort during 6-month follow-up.

The Cobalt Chromium Stent With Antiproliferative for Restenosis (COSTAR) II study compared the clinical outcomes and in-stent late loss between CoStar (Conor MedSystems, Menlo Park, California), paclitaxel eluting stent with biodegradable polymer (PLGA) and Taxus with durable polymer [58]. CoStar was not non-inferior to Taxus in 8 months clinically-driven target vessel revascularization [8.1 vs. 4.3%, p=0.002] and in 9 months in-stent late loss [0.64 vs. 0.26 mm, p<0.0001]. Follow-up to 9 months showed no apparent difference in stent thrombosis rates, suggesting that the advantage of biodegradable polymer DES may not be apparent in the short and medium terms. The results of COSTAR II appear to indicate that the combination of paclitaxel and PLGA is inferior to paclitaxel with durable polymer without any difference in incidence of stent thrombosis whilst the combination of biolimus A9 or sirolimus and PLA have shown promising results in in-stent late loss and clinical outcomes in other pivotal trials [49-57].

The efficacy and safety of the biodegradable polymer DES have been examined in a number of smaller studies (Table 1). Some of these studies have shown that patients treated with biodegradable polymer stents have smaller in-stent late loss and lower cardiac events whilst other studies have failed to replicate such findings [59-68]. A closer examination of the published studies tends to indicate that sirolimus and other limus analogues may be superior to paclitaxel in terms of in-stent late loss. Such observations support the results of the previous trials comparing in-stent late loss between sirolimus and paclitaxel with the same type of biodegradable polymer [69,70].

A critical question is whether biodegradable polymer DES reduces VLST as compared to durable polymer DES. The 4-year results of the LEADERS trial has demonstrated that the biodegradable polymer DES decreases VLST compared with the durable polymer DES [52] whilst the 3-year results of ISARTEST-4 showed no signs of a safety advantage with the biodegradable polymer over the durable polymer DES system [56]. This may be partly related to differences in stent choice in the control arm of the two studies with LEADERS using Cypher whereas ISARTEST-4 used both Cypher and Xience V. Another potential explanation may be the very low rates of VLST in patients undergoing PCI given the incredible advances in adjunctive pharmacotherapy and therefore the need for very large number of patients in such studies before any significant differences can be identified [47].

The safety and efficacy of this technology also requires assessment in a variety of clinical scenarios such as acute myocardial infarction, saphenous vein intervention, and complex lesions. The improvement of the dependency on prolonged dual antiplatelet therapy should be also addressed in biodegradable polymer DES and compared with the second generation DES.

Polymer-Free DES

The influence of the polymer upon such adverse events as persistent inflammation and delayed healing is being increasingly recognized [21]. This concept has been one of the driving forces in the development of biodegradable polymer and polymer-free DES (Table 2). The Intracoronary Stenting and Angiographic Restenosis-Test (ISAR-TEST) investigators were one of the first groups reporting that polymer-free microporous stents coated with sirolimus were not inferior to the durable polymer-based, paclitaxel-eluting stents in their anti-restenotic effects in patients with de novo lesions in native coronary arteries [71]. The group also developed a novel dual drug, sirolimus- and probucol-eluting, stent (Dual-DES). Probucol has a potent lipid-soluble anti-oxidant property, which reduces neointimal hyperplasia within stents [72-74]. ISAR-TEST-2 demonstrated that the polymer-free Dual-DES had high anti-restenotic efficacy without recourse to carrier polymer when compared to Cypher or Endeavor [75,76].

In ISAR-TEST-3, polymer-free stent use was associated with higher incidence of target lesion revascularization at 1 year compared with biodegradable polymer or durable polymer stent [53]. However the incidence became similar at 2 years between the 3 groups [54], indicating

	Drug type	Polymer type	Patients number	Follow-up (month)	Death (%)	MI (%)	ST (%)	TLR (%)	Late loss (mm)
ISAR-TEST [71]	Sirolimus	Free	225	9 / 6-8*	0.9	N/A	0	9.3	0.48
ISAR-TEST 2 [75,76]	Sirolimus Probucol	Free	333	12 / 6-8*	2.4	4.2	0.9	6.8+	0.23
				24	4.2	4.5	0.9	7.7+	0.30
ISAR-TEST- 3[53,54]	Sirolimus	Free	201	12 / 6-8*	2.0	2.5	1.0	12.9	0.30
				24	4.0	3.5	1.0	13.4	.....
ISAR-TEST - 5[77]	Sirolimus Probucol	Free	2002	12/6-8*	3.6	3.9	1.1	10.3	0.31
LIPSIA Yukon[78]	Sirolimus	Free	118#	9	5.1	3.4	0	10.2	0.63
ELUTES [79]	Paclitaxel 0.2 [a]	Free	37	12 / 6*	0	0	0	5.4	0.71
	Paclitaxel 0.7 [a]	Free	39	12 / 6*	0	2.6	0	5.1	0.47
	Paclitaxel 1.4 [a]	Free	39	12 / 6*	0	0	0	10.3	0.47
	Paclitaxel 2.7 [a]	Free	37	12 / 6*	2.7	2.7	2.7	5.4	0.11

MI: Myocardial Infarction; ST: Definite or probable stent thrombosis defined in Academic Research Consortium; TLR: Target Lesion Revascularization; *Clinical/angiographic follow-up; **+** Per lesion analysis; #Patients with diabetes mellitus only; [a] Paclitaxel dose density, μg/mm^2.

Table 2: Clinical outcomes of patients treated with polymer free DES.

very late outcomes may be better in the patients treated with polymer-free DES than in patients treated with the other DES. Furthermore, delayed in-stent late loss, defined as the difference between the minimal luminal diameter at 6–8-month and 2-year surveillance angiography, was significantly lower in polymer-free stent group than the other 2 groups ($p<0.001$). Thus polymer-free DES might be able to avoid late-catch up restenosis caused by the atherosclerotic process.

The ISAR-TEST 5 trial compared the clinical outcomes and angiographic efficacy between the polymer-free dual-drug sirolimus- and probucol-eluting stent using a commercially available microporous metal stent backbone (Translumina, Hechingen, Germany) and zotarolimus-eluting stent, Resolute, with durable polymer. One-year results were similar in terms of clinical outcomes and in-stent late loss between the 2 groups [77]. Because previous ISAR-TEST trials indicated that polymer-free DES have lower delayed in-stent late loss and delayed target lesion revascularization, the patients treated with polymer-free dual DES should have the advantage of longer term outcomes beyond 1 year.

The LIPSIA Yukon trial assessed 9-month in-stent late loss of the polymer-free sirolimus-eluting Yukon Choice stent (Translumina, Hechingen, Germany) compared with the durable polymer Taxus Liberte stent (Boston Scientific, Natick, Massachusetts) in patients with diabetes mellitus [78]. Although both stents showed comparable clinical safety and efficacy, the polymer-free sirolimus-eluting Yukon Choice stent failed to show non-inferiority with regard to 9-month in-stent late lumen loss (0.63±0.62 vs. 0.45±0.60 mm, p=0.04).

The European evaLUation of the pacliTaxel Eluting Stent (ELUTES) pilot clinical trial aimed to assess the safety and efficacy of the V-Flex Plus coronary stents (Cook Inc) coated with escalating doses of paclitaxel (0.2, 0.7, 1.4, and 2.7 μg/mm^2 stent surface area) applied directly to the abluminal surface of the stent in de novo lesions [79]. In this trial, polymer-free paclitaxel-eluting stent with a dose density of 2.7 μg/mm^2 reduced angiographic indicators of in-stent restenosis without short- or medium-term side effects.

Fully Bioabsorbable DES

Fully bioabsorbable DES have been developed with the principle aim of dissolution of the scaffold once vessel recoiling has been averted. Potential advantages include:

1. Lower incidence of VLST
2. Lower incidence of late-catch up restenosis after 9 months
3. Shortened DAPT
4. Little concern of stent fracture
5. Restoration of vasoreactivity by degradation
6. Avoidance of endotherial dysfunction
7. Estimation without the artifact by computed tomography or magnetic resonance imaging
8. Without any restrictions for future percutaneous or surgical revascularization

The essence of stenting has been to maintain vessel patency through radial force. Since it is difficult to maintain radial force at the same time biodegradation, there has been a need to strictly estimate stent recoiling in the clinical studies.

Fully bioabsorbale DES consists of polymeric and metallic alloys [43]. Iron and magnesium have been tested as metallic alloys of fully bioabsorbable stent. The bioabsorbable stent with iron pre-clinically failed because of too slow a degradation [43]. Clinical Performance and Angiographic Results of Coronary Stenting with Absorbable Metal Stents (PROGRESS-AMS), a non-randomised multicentre trial, was conducted to assess the feasibility and efficacy of bioabsorbable magnesium stents in 63 patients [80]. The results of this trial showed that in-stent late loss of 1.08±0.49 mm, ischemia-driven target lesion revascularization rate of 23.8% after 4 months and overall target lesion revascularization rate of 45% after 1 year without myocardial infarction, stent thrombosis, or death. Only small remnants of the original struts were visible in 4-month follow-up intravascular ultrasound. Further development in this technology is awaited.

Bioabsorbable polymeric stents have crystallinity. The degree of crystallinity is associated with the radial force to prevent stent recoiling. The Igaki-Tamai® stent (Igaki Medical Planning, Kyoto, Japan), poly-L-lactic acid (PLLA), was the first bioabsorbable stent without drug elution [81]. The percentage of acute stent recoil was high, 22±7% by quantitative coronary angiography. The main limitation of this study was that safety and efficacy were compared with a BMS. The bioabsorbable everolimus-eluting stent system (BVS; Abbott Vascular, Santa Clara, CA) is made from a bioabsorbable backbone which consists of PLA. A more rapidly absorbed PLA is coated and allows 80% of the drug to be released within 30 days, a release profile very similar to that of the Xience V or Cypher stent [43]. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB) study was conducted to assess the feasibility and safety of the BVS stent [82]. This study was a single-arm, prospective, open-label study with 30 patients. The acute recoil by quantitative coronary angiography was nearly 7%. At 1 year, only 1 patient had major adverse cardiac event, non-Q wave myocardial infarction without target lesion revascularization. Six-month follow-up angiographic in-stent late loss was 0.44 mm mainly due to a mild reduction of the stented area. Stent struts were not detected and the tendency of the vessel to return to its normal dimensions and preservation of the vasomotion capabilities were observed in 2 years follow-up intravascular ultrasound study [83]. Thus the ABSORB study showed promising findings in feasibility and efficacy with certain degradation. Second generation ABSORB BVS has been developed already. The study with 56 patients indicated small angiographic late loss (0.27±0.32 mm) and a relatively low incidence of major adverse cardiac events (7.1%) [84]. The authors concluded the 12-month performance justifies the conduct of a randomized trial against current best standards.

The Best DES for the Future

Previous clinical trials have demonstrated that some biodegradable polymer DES or polymer-free DES are not inferior to first generation or second generation DES. Fully absorbable DES has also been developed with promising results in selected populations although larger clinical studies with wider inclusion criterion are currently underway. Longer term outcomes, beyond 1 year, for such novel DES will be attractive because of their theoretical safety advantages. The first and second generation DES reduced the incidence of the target lesion revascularization compared with bare metal stent [16,17]. Restenosis at the stent edges, however, is not appreciably reduced by DES. Previous intravascular ultrasound studies suggested the edge effects of DES are different among different types of DES [85]. The improvement of edge effects, therefore, is vital in terms of efficacy. The serial assessment of the vascular response using reliable tool such as intravascular ultrasound or optical coherence tomography continues to be necessary for development of this technology.

Second generation DES such as Xience V or Endeavor Resolute have provided excellent results in practice defining randomized studies [46-48]. The Xience V stent has excellent stent design with thin strut and polymer, large cell area and better flexibility for delivery, resulting in less myocardial necrosis after stent implantation [44]. There is considerable evidence that the amount of myocardial injury after stent implantation is strongly related to long-term outcomes [86-90]. Thus newer DES should surpass not only the excellent designs of currently available DES but also provide additional benefits that may be derived from polymer-free, biodegradable polymer or fully absorbable scaffoldings. Thus the well-balanced DES incorporating such advances is likely to be the winner of the best DES in the future.

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