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Evolutionary Perspective of Drug Eluting Stents: From Thick Polymer to Polymer-Free Approach

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Abstract

The introduction of drug-eluting stents (DES) has remarkably altered the management of coronary artery disease by efficiently reducing the risk of restenosis after percutaneous coronary intervention (PCI). Early-generation DES were thick and had durable polymer coatings to deliver anti-proliferative agents directed against neointimal hyperplasia; however, these designs were associated with serious complications of delayed endothelial healing, chronic inflammation, and increased risk of late stent thrombosis, thereby warranting further advancement in stent technology. This review will focus on the progressive evolution of DES technologies, from thick polymer systems to thinner bioresorbable or polymer-free coatings. It will attempt to examine how these innovations have tried to overcome some of the limitations of their predecessors and what implications these developments might have for improving clinical outcomes in interventional cardiology. With the advancement in DES design came thinner strut platforms, polymers with better biocompatibility or resorbability, and polymer-free drug delivery strategies. The newer designs have shown better-endothelialization rates and, thus, reduced adverse events like late-stent thrombosis. Next-generation DES have been shown to be safe and effective in clinical trials, although further research is required to better optimize release kinetics, mechanical integrity, and long-term vascular compatibility. The evolution of DES has been driven by the desire to maximize their safety and efficacy through innovations in materials and delivery systems. A bioadaptive polymer, nanotechnology, and personalized medicine approaches may be harnessed in combination in the future to further mitigate complications and truly personalize therapy. The evolving design phase will require strong direction from ongoing research and long-term clinical studies.

Keywords; Angioplasty, Bare metal stents, Cardiovascular disease, Sirolimus, Stents, Xience.

INTRODUCTION

Life-threatening diseases are fast emerging, aggravated by poor physical activity levels due to the impact of a sedentary lifestyle peculiar to the twenty-first century, affecting the general populace. These life-threatening diseases comprise diabetes, obesity, cancer, and, most importantly, ischemic heart diseases. This accumulation of fatty acids, diabetes mellitus, hypertension, smoking, and a sedentary lifestyle is what mainly causes cardiovascular diseases (CVDs), leading to the formation of atherosclerotic plaques [1]. To counter this health menace globally, percutaneous coronary intervention (PCI) and stenting techniques have been developed and widely applied.

During PCI, a stent crimped onto a deflated balloon is delivered via a catheter to the site of obstruction [2]. Upon inflation of the balloon, the stent expands and compresses the plaque against the wall of the artery restoration of blood flow. The use of metallic stents has been considered a revolutionary advance in the treatment of cardiovascular diseases and has become the standard of care in clinical practice [3].

Since the initiation of stent technology, a constant endeavor has been made to improve the outcome of PCI. This review is intended to trace the stepwise development of drug-eluting stents (DES), explaining how from one generation to another every effort was made to solve the problems caused by the previous design with bare-metal stents (BMS) and first-generation DES.

Coronary artery disease (CAD) continues to be one of the leading causes of global morbidity and mortality. PCI and DES have dramatically improved the outlook for CAD patients in recent decades. DES were introduced in order to prevent the incidence of restenosis, or re-narrowing of the arterial lumen following angioplasty. This was enabled through a controlled release of anti-proliferative agents from polymeric coatings, inhibiting smooth muscle cell proliferation and neointimal hyperplasia [1] [4].

The first generation of DES mainly used thick polymer coatings made of durable polymers for sustained drug release, including sirolimus and other drugs like paclitaxel. However, those durable polymers were also found to cause delayed endothelial healing and to set up a chronic inflammatory process with a high risk of late stent thrombosis [3] [8]. Consequently, the further evolution of DES design had involved thinner polymer coatings, biodegradable polymers, and eventually polymer-free systems to minimize these unwanted effects [2] [4].

This review strives to analyze the technological progress of DES from permanent polymer-coated platforms to the newly emerging polymer-free stent technologies and to highlight the future directions in the development of stents [5] [6] [7].

LITERATURE REVIEW

The benefit of first-generation DES over bare-metal stents (BMS) was very much apparent yet offered space for additional enhancements [1] [10]. Thinner-strut feature and lesser polymer thickness were designed into the newly engineered second-generation metallic alloy-coated stents. The drug-eluting application rationally adopted advanced active agents from paclitaxel and sirolimus to zotarolimus and everolimus, which yielded poorer comparative outcomes [8], [11].

Nevertheless, these considerations have also necessitated third-generation drug-eluting stents (DES) manufactured from bio-resorbable polymers, which are ultimately not supposed to last as long as the durable polymers, at least in terms of time to drug elution and thus long-term inflammatory responses and late thrombosis [3]. Further improvements have now created the fourth generation of DES-stent systems characterized by polymer-free coatings for the delivery of drugs. Such systems will provide controlled drug delivery without the need for permanent or bioresorbable polymers [2] [4] [5].

The transition from bare-metal stents (BMS) towards drug-eluting stents (DES) studies is highlighted in this review as well as the improvements in polymer technology, which have decreased in thickness and eventually reach polymer-free designs from thick and durable varieties [7] [13].

Drug Eluting Stents (DES)

Hence, these drug eluting stents have been designed to overcome the limitations of bare metals by incorporating into their metallic platform the anti-proliferative drug within a carrier system intended for controlled drug release. The drugs used are intended to avoid restenosis with minimum systemic effects as well as being used along with the carrier for localized and sustained delivery [14] [15]. Early DES designs followed this model and showed promising outcomes. Continuous advancements have resulted in thinner strut designs, enhanced metal alloys, and more refined drug-polymer combinations. Each DES generation has aimed to overcome the limitations of its predecessors, improving both safety and efficacy [7] [12]. In this regard, the treatment with drug-eluting stents today results in better outcomes with lower incidence of restenosis compared to older modalities such as brachytherapy.

Evolution of Drug-Eluting Stents

1. First Generation (DES): The Early Days: Thick Polymer-Based DES

The first-generation drug-eluting stents (DES) were introduced in the early 2000s. These stents were coated with durable polymers like polyethylene terephthalate (PET) or polyurethane, which constituted the carrier for anti-proliferative agents and helped in controlled drug release at the lesion site [15]. The use of these early DES was instrumental in reducing bouts of re-stenosis considerably as opposed to bare-metal stents (BMS), which themselves were plagued with almost 20% rates of re-stenosis, and target lesion revascularization (TLR) within 12 months of implantation [15] [18].

To address these limitations, pharmacological agents with anti-inflammatory and anti-restenotic properties were incorporated into stent platforms using polymer matrices, thereby enhancing therapeutic efficacy and vascular healing [16] [17]. Over time, both drug formulations and polymer technologies evolved, culminating in the development of four generations of DES, each characterized by distinct design features, including polymer type, drug selection, and platform structure [18] [19]. A comparative summary of the generational progression of DES is presented in **Table 1**.

Table 1 'Profound features of three generations of Drug Eluting Stent'

'Generations	Platform	Strut Thickness	Polymer	Polymer Type	Drugs	Commercially available DES
1st	Stainless Steel	>130	SIBS PEVA PBMA	Permanent	Sirolimus Paclitaxel	Cypher Taxus
2nd	CoCr PtCr	80 µm to 100 µm	PVDF-HFP BioLinks	Permanent	Everolimus Zotrolimus	Xience Endeavour Resolute
3rd	CoCr PtCr	55 µm to 85 µm	PLA PGLA	Biodegradable	Sirolimus Everolimus Biolimus	YukonPC Biomatrix Orsiro Ultimaster Synergy
4th	CoCr Stainless Steel PLLA Magnesium	70 µm to 90 µm 130 - 150	Polymer free PLLA PDLLA	Biodegradable	Sirolimus Probucol Sirolimus Novolimus Everolimus	YukonChrome ISAR Absorb Absorb-GTI MeRes Magmaris'

In 2002, Cordis/Johnson & Johnson released the Cypher Sirolimus Eluting Stent, the first drug eluting stent of its kind, after it gained a CE mark. Boston Scientific introduced Taxus ExpressTM, a different DES, in 2004 after receiving a CE mark for it the previous year. These two stents represent the backbone of DES technology and constitute the first generation of stents. In **Figure 1**, we can see the characteristics of this generation:

The early devices had numerous limitations, with the most important of all being the danger of thrombosis because of the delayed endothelialization. The thick polymer coatings proved useful in sustaining drug release but affected the normal healing processes of the artery, which contributed to a greater risk of stent thrombosis, especially in the first year following implantation.

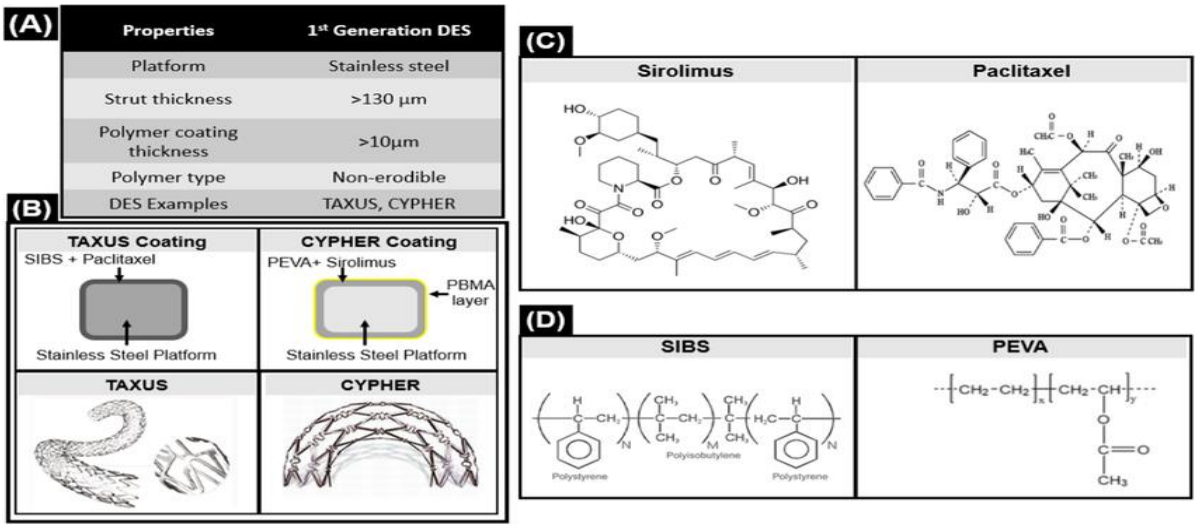

Figure 1 First generation of drug eluting Stents

Cypher vs. Taxus

First-generation drug-eluting stents (DES) were proved to significantly reduce rates of restenosis and showed better outcomes as compared with bare-metal stents (BMS) in terms of clinical outcomes. Among these drug-eluting stents, sirolimus-eluting stents (SES; Cypher) and paclitaxel-eluting stents (PES; Taxus) are most commonly studied. Despite the efficacy established for both stents, a number comparative studies claimed SES to be superior over PES [17] [18]. REALITY trial was conducted to compare SES and PES, where the results showed a similar incidence of major adverse cardiac events (MACE) in both groups;

however, the ISR late loss was significantly lower for the SES group (0.09 mm) than for the PES group (0.31 mm). Whereas, thrombosis in stents (ST) had a higher incidence in patients with PES (1.9%) than PAS (0.7%) [18]. The enhancement in performance of SES has been attributed to their optimized drug release kinetics. Under clinical conditions for DES, early restenosis and thrombus formation should be inhibited by rapid drug release and at the same time allow support for prolonged arterial healing. The drug release profile for Cypher stenting is more inline with that therapeutic requirement while Taxus stent has its supposed prolonged release kinetics due to the fact that it requires several years to clear 90% of its drug content [17].

Nevertheless, while the effectiveness improved over BMS the complications associated with first-generation DES were chronic inflammatory response and delayed endothelialization, which were mostly attributed to the durable polymer coatings. These limitations necessitated the advancement to second-generation DES [18] [19].

2. Second Generation: Refined Thin Polymer Coatings and Bioresorbable Polymer Technologies

To reduce vascular inflammatory effects while maintaining good drug delivery, these improvements were implemented [18]. Furthermore, the introduction of bioresorbable polymers allows the polymer matrix to disintegrate with time, thereby reducing foreign body reactions and improving endothelial recovery in the long term [19] [20].

These advancements were necessitated by the evils of mechanical as well as biological failures faced by the first generation. This led to stents constructed with thinner struts and better polymeric coatings, and incorporating recently approved anti-proliferative agents like everolimus, leading to overall enhancement in safety and clinical performance [20] [21]. **Figure 2** summarizes the basic features of second-generation DES.

To an end that vascular inflammation is decreased as much as possible without hindering the capability of the drug to be delivered effectively [18]. Furthermore, bioresorbable polymers were included to permit the polymer matrix to be degraded over time so that such foreign body reactions are reduced in their long-term effects and endothelial recovery enhanced [19] [20].

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So that vascular inflammation is decreased as far as it can go without altering the ability of the drug to deliver effectively [18]. In addition, bioresorbable polymers have been included to allow degradation of the polymer matrix after time; thereby the longer term effects of foreign body reactions are diminished and endothelial recovery is improved [19] [20].

Such innovations stemmed from the voluntary shortcomings of both mechanical and biological first generation. With that, thinner struts, better polymeric coatings, and lately approved anti-proliferative agents like everolimus were incorporated into stents due to safety and clinical improvement [20] [21]. The basic characteristics of second-generation DES are outlined in **Figure 2**

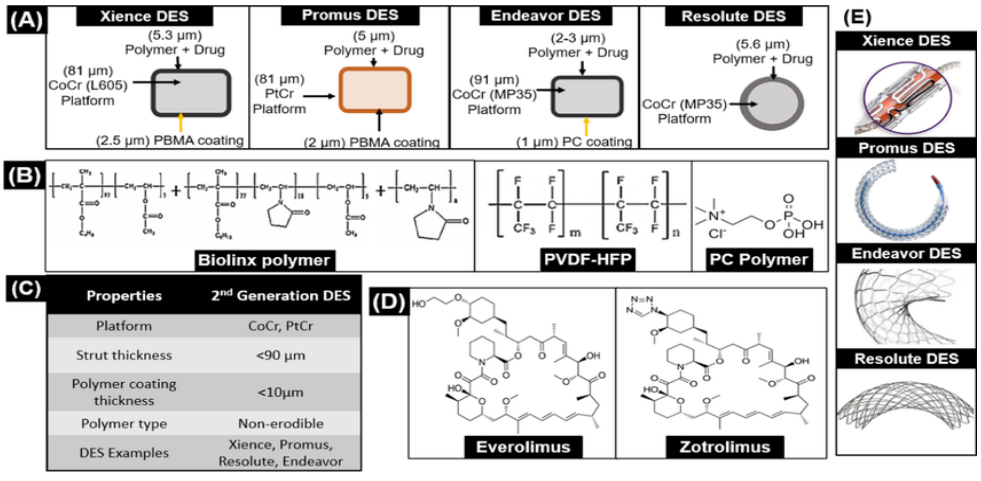

Figure 2 Second generation of drug eluting stents

Metallic platforms

The ISAR-STEREO Trial conducted in 2001 reiterated the importance of thinner stent struts. The trial sought to compare the restenosis rates of stents, which were identical in design and material but differed in strut thickness. It recruited a total of 651 patient subjects, most of them being those who received the ACS RX Multi-Link stents. These stents were available in two strut thicknesses, namely, 50 m (thin struts) and 100 µm (thick struts). According to the outcome of the trial, the group of patients receiving thin-strut stents exhibited a mortality rate of 1.5%, while the thick-strut group recorded 2.5%. The specific results presented in **Table 2**.

Table 2 'ISAR-STEREO trial outcome'

'Group	Strut Thickness (µm)	Mortality Rate (%)	MI (%)	Restenosis (%)
Thin Strut (n=325)	50	1.5	0.9	15
Thick Strut (n=325)'	140	2.5	1.2	25

A thinner strut configuration is known to facilitate better clinical outcomes by minimizing injurious vascular interaction and inflammatory reactions thereby, enhancing endothelialization and delaying neointimal formation and thrombogenicity considerations by virtue of smaller surface area. ISAR-STEREO was the initial trial to shift the prevailing notion in favor of thin strut stents for clinical and manufacturing purposes, giving evidence of their superior results compared to thick ones. In support of the above findings, ISAR-STEREO-2 was designed and published in 2003, whose results, given in **Table 3**, further endorsed and validated the benefit seen in the original ISAR-STEREO trial.

Table 3 'ISAR-STEREO trial outcome (6-month follow-up)'

'Group	Target vessel revascularization	Restenosis (%)	MI and Death
Thin Strut (n=309)	12.3	17.9	No significant difference in 1- year follow-up'
Thick Strut (n=302)	20.95	31.5	

The two trials have proved sufficiently that reduced strut thickness could improve stent performance and minimize complications. Newer metallic platforms such as Cobalt Chromium (CoCr) and Platinum Chromium (PtCr) were introduced to allow thinner strut designs while maintaining requisite mechanical properties such as radial strength and recoil resistance. CoCr is heavier than stainless steel. Its superior characteristics are preferred for stent development, as elaborated in ***Table 4***. It is, however, PtCr, the specialty alloy, that was designed specifically to further refine stent quality. This ushering in of new materials has led to a drastic reduction in strut thickness—up to approximately 70 µm, as opposed to the 130 µm generally for stainless steel stents. The comparative attributes of Stainless Steel, CoCr (MP35), CoCr (L605), and PtCr are illustrated in ***Table 4***.

Table 4 'Properties of Stent Metals'

'Properties	Stainless Steel 316L	CoCr(mp35)	CoCr(mp35)	PtCr
Elastic Modulus (GPa)	190	233	243	203
Yield Strength (MPa)	275	414	500	480
Tensile Strength (MPa)	535	930	1000	834
Density (g/cm³)'	7.9	8.4	9.1	9.9

1. Drugs

New generation des introduced new drugs from Limus family called Zotarolimus and Everolimus apart from Sirolimus. Although these two analogs have the base structure of Sirolimus, they differ in the functional groups. Zotarolimus is a semisynthetic derivative that incorporates a tetrazole ring in the 42 position instead of the hydrophilic hydroxyl group. This tetrazole modification was intended to increase the lipophilicity of the drug, making Zotarolimus the most lipophilic and non-aqueous of the Limus analogs. This, in turn, makes it deliver the active agent over time and at controlled rates without the initial burst release of some earlier formulations.

2. Polymeric Coatings

The polymer matrix responsible for drug-eluting stents plays a very important role in drug release kinetics, but this is the way through which initial success in drug-eluting stents was marred by complications such as excessive neointimal proliferation and inflammation, which had often been observed to be associated with the polymer composition.

The second generation of DES managed to solve these problems through advanced polymer formulations. Abbott Laboratories developed a fluorinated copolymer called poly(vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP) that offers excellent mechanical strength in addition to the elastic elongation properties during stent Deployment and extension.

3. Xience Stent

Considered among the topmost in stent technology across the globe, Xience is said to present the best all-round solution using optimum materials, design configuration, and drug-delivery performance. The framework is Cobalt Chromium (CoCr)-based, and Xience stent struts are only 81 µm thick. Its polymeric coating system has two layers:

- A base coat of poly (n-butyl methacrylate) (PBMA)
- The top layer of PVDF-HFP integrated with Everolimus at a concentration of 100 µg/cm².

The polymer coating, totally, measures 7.8 µm, wherein the layer containing the drug amounts to 5.3 µm of that.The stent's design includes a nonlinear link and open-cell configuration, enhancing its flexibility and vessel conformability (as illustrated in **Figure 2**).

Clinically, Xience has demonstrated exceptional safety and efficacy, with several studies reporting a 0% restenosis rate. It has been evaluated in 49 randomized clinical trials involving over 50,000 patients. The first clinical study, SPIRIT I, launched in 2003, enrolled 60 patients to assess Xience's feasibility and performance. At six months, the trial showed significantly suppressed neointimal growth compared to an identical bare-metal stent. Successive trials, SPIRIT II and III, further confirmed Xience's clinical superiority over time. Additional trial outcomes are summarized in **Table 5**.

Table 5 'Different trials of Xience DES'

'Trial Name	Stent	Duration	Stent Thrombosis Rate (%)
ABSIRB II	BVS vs. Xience (n = 501)	4 Years	2.8 vs. 0
ABSORB China	BVS vs Xience (n = 480)	2 Years	0.9 vs. 0.0
STOPDAPT	Xience (n = 1522)	1 Years	0
TWENTE	Endeavor Resolute vs Xience (n = 1391)	1 Years	1 year 0.58% and 0% (ρ = 0.12)'

Bioresorbable polymer DES has promised a reduced risk of stent thrombosis and improved long-term safety of the device. So far, these biodegradable polymers, after degradation, leave a material-free vessel, which enables the arterial wall to heal naturally. However, the challenges lie in optimizing the degradation rates and appropriate release rates of the drug.

3. Third generation stents: Drug-eluting Stents without Polymers

This recent advancement in the evolution of drug-eluting stents revolves around the idea of polymer-free drug-eluting stents. These types of stents a metal surface where drug coating is made straight onto it or an attached drug-bound layer whose slow elution of drug does not rely on a polymeric binder. The advantageous feature of polymer-free stents is that there is no foreign substance that is left intravascularly thereby making the process less susceptible to inflammation, much less to thrombosis, and delayed endothelialization.

First-generation drug-eluting stents such as Cypher and Taxus effectively reduced restenosis in interventional cardiology breakthroughs. Stent products belonging to second-generation products such as Xience and Promus became the preferred gold standard in the stent market as they overcame the disadvantages of first-generation stents, including inflammation and restenosis, with a marked reduction in mortality types.

Actually, while those devices have been successful at first, long-term clinical studies brought out newer issues with these second-generation stents, including late and very late stent thrombosis, delay in vascular healing, and inflammation along the late course post-implantation. These complications were all attributed to the permanent polymer coating remaining in the vessel after the drug had completely eluted. The remaining non-degradable polymers may incite continuous inflammation, foreign body reactions, and a further potential trigger of a restenosis event.

This led to the invention of third-generation stents, which can either have biodegradable polymer coating that will disintegrate naturally over time or may not include polymers at all and are termed polymer-free stents. The main descriptive characteristics and configurations of these third generation devices are shown in **Figure 3**.

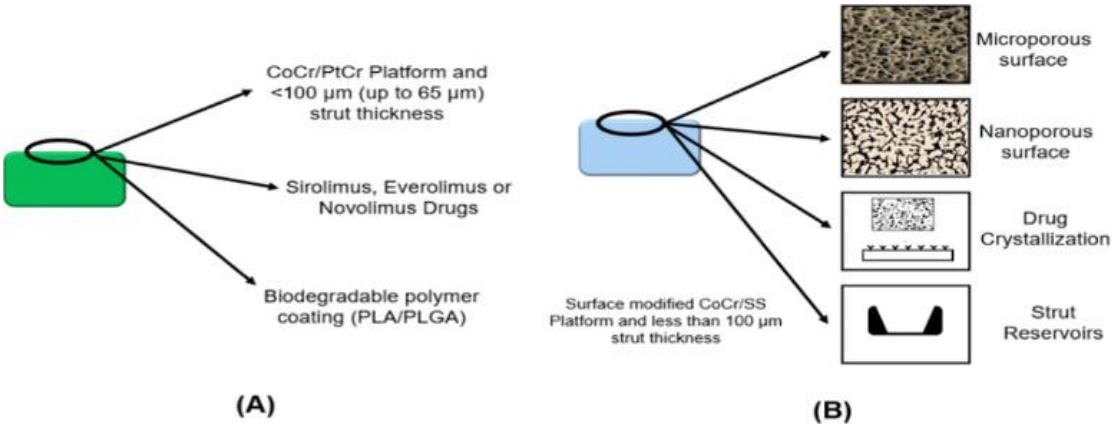

Figure 3 Third generation of drug eluting stents

Metallic platforms

In the third generation of DES, the previously mentioned metallic platforms used in the first and second generations, including stainless steel, CoCr, and PtCr-alloy material, continued to be used. Among these metals, CoCr was the mostly used platform in the second generation while stainless steel was reintroduced in the third generation. This generation shows the broadest diversity of stent systems because of the inclusion of all three metal types.

PtCr specifically was used in stents that had biodegradable polymer coatings whereas stainless steel and CoCr were used in both biodegradable polymer-coated stents as well as in polymer-free stents. The latter two metals have a better capability for surface modification, which is essential for effective drug retention in polymer-free designs of drug-eluting stents.

1. Drugs

New agents from the -limus family were introduced in the second generation of drug-eluting stents (DES) to enhance their pharmacological efficacy. Zotarolimus and everolimus, two semisynthetic derivatives of sirolimus, served as antiproliferative agents. While the structure of these two analogues is very similar to that of sirolimus, they differ in functional groups. Specifically, the chemical modification to Zotarolimus entails the insertion of a tetrazole ring in position 42 while, at the same time, replacing a hydrophilic hydroxyl group with a more lipophilic moiety. This modification thus increases the hydrophobicity of this compound, making Zotarolimus the most lipophilic of all sirolimus analogues, thereby enabling a sustained and controlled-release profile instead of a burst-release profile [19] [21].

2. Polymeric Coating Innovations

The nature and composition of the polymer matrix emerged as critical determinants of drug release kinetics in DES platforms. Although first-generation stents yielded favorable clinical outcomes, limitations such as uncontrolled neointimal proliferation and inflammation were frequently reported. These adverse responses were primarily attributed to the durable polymer coatings used in early designs [22] [23]. To address this challenges, the more second-generation DES worked with biocompatible polymeric systems. Another important milestone was the creation of fluorinated copolymer poly (vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP) at Abbott Laboratories. It had extremely good mechanical strength coupled with elastic elongation during stent deployment, a property that favors its high biostability and biocompatibility.

3. Xience Stent System

The Xience stent system marked a major advancement in the evolution of drug-eluting stent (DES) technology. Engineered with a cobalt-chromium (CoCr) platform and a strut thickness of 81 µm, the Xience stent combined mechanical excellence with advanced pharmacological and polymeric features. Its dual-layered coating comprises a base layer of poly (n-butyl methacrylate) (PBMA) and a topcoat of PVDF-HFP blended with Everolimus at a concentration of 100 µg/cm². The overall coating thickness is 7.8 µm, with the drug-loaded layer accounting for 5.3 µm.The stent's architecture—featuring a nonlinear link and open-cell design—enhances conformability to the native vessel wall, as illustrated in **Figure 2** [19] [21].

Xience drug-eluting stents have undergone an extensive clinical evaluation process, which yielded consistent results

of exceptional safety and efficacy. Clinical studies done, including those under the SPIRIT programs, have reported a 0% restenosis rate in selected populations. The SPIRIT I study initiated in 2003 and involved 60 patients to investigate the feasibility and performance of the Xience stent platform. Six-month follow-up data indicated substantial inhibition of neointimal proliferation as compared with a bare-metal stent control. Further studies, namely SPIRIT II and III, corroborated these conclusions and clinical superiority of Xience. To date, the Xience platform has been assessed in 49 randomized trials exceeding 50,000 patients [20] [21] [24].

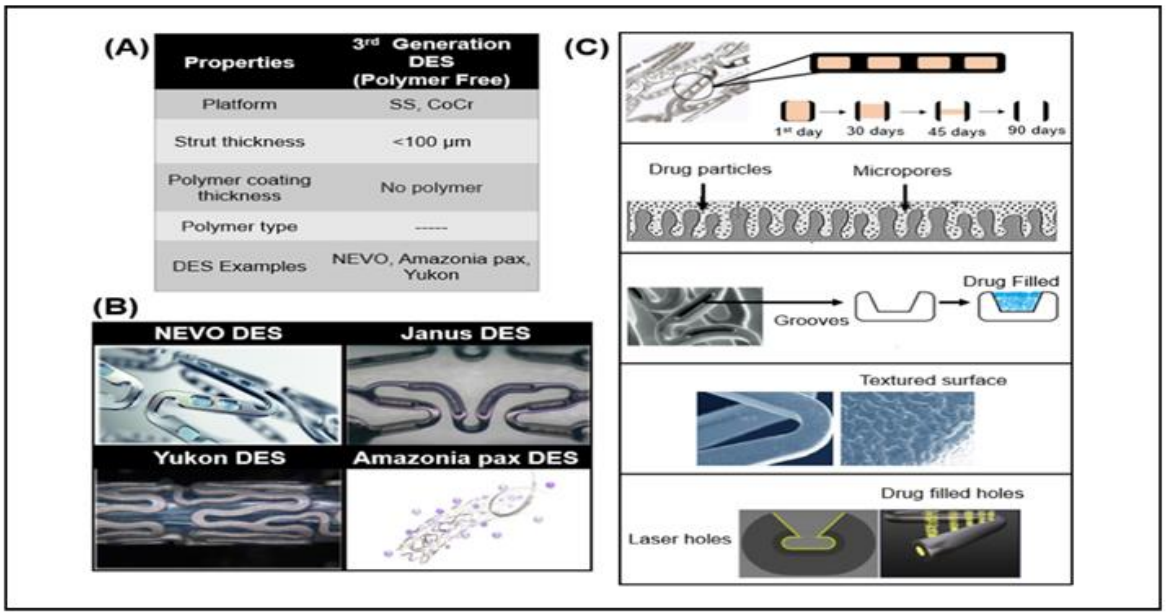

Figure 4 Polymer Free stents (3G B)

Comparison of Three generations

The onset of Cypher™ stents was a turning point in interventional cardiology, as treatment proved to substantially lessen the chances of restenosis and thrombosis. Yet with the emergence of some limitations, that is, late and very late stent thrombosis, the introduction of Cypher™ stents encouraged more profound research in drug-polymers technology development and future innovations [21] [24]. The first-generation drug-eluting stents employed durable polymer coatings together with antiproliferative agents to achieve a huge extent in the reduction of neointimal hyperplasia and in-stent restenosis. However, the drawbacks of these first-generation systems included thick-strut designs, suboptimal metallic platforms, and poor polymer biocompatibility leading to adverse outcomes, such as delayed arterial healing and chronic inflammation [21] [24].

These shortcomings were solved by the use of second-generation DES with thinner struts, improved metallic scaffolds (e.g., cobalt-chromium), more biocompatible polymers, and refined drug formulations such as everolimus and zotarolimus. These advancements resulted in superior clinical outcomes, with significant reductions in restenosis, target lesion revascularization, and early stent thrombosis [20] [21].

Over time, however, concerns regarding very late stent thrombosis (VLST) emerged, attributed primarily to the use of permanent polymeric coatings. These non-degradable polymers remained within the vascular environment indefinitely and, under mechanical stress and hemodynamic forces, were susceptible to delamination and inflammatory responses [23] [24]. In response, third-generation DES were developed with biodegradable polymer coatings that degrade after drug elution, leaving behind only the bare-metal framework. These stents demonstrated non-inferiority to second-generation stents while offering reduced long-term inflammatory risk [20] [24].

In parallel, polymer-free DES platforms were introduced to eliminate polymer-related complications entirely. These systems have been shown through randomized clinical trials and meta-analyses to be superior to first-generation DES and comparable in safety and efficacy to second-generation systems [22] [23].

The progressive evolution across DES generations has been rigorously validated through numerous clinical trials and meta-analyses, underscoring a continuous trajectory of safety, efficacy, and biocompatibility enhancement [20] [24].

Table 6 ISAR Test 4 trial

Characteristics	Time Interval	First Generation (Cypher) (%)	Second Generation (Xience V) (%)	Third Generation (Yukon PC) (%)
MACE	30 days	-	4.5	4.4
ST		-	0.4	0.4
MACE	12 months	-	14.4	13.8
Cardiac death		-	3.2	2.8
TLR		-	9.4	8.8
ST		-	1.5	1.0
MACE	2 years	-	16	18.8
ST		-	1.4	1.9
TLR		-	9.9	13.5
MACE	10 years	54.9	46	47.7
Cardiac death		37.2	30.3	31.8
MI		9.1	7.9	7.7
ST		2.4	0.8	1.1
TLR		22.5	18.2	20.3

Fourth generation (bioresorbable stent)

In an effort to overcome the limitations associated with metallic platforms, polymeric backbone-based stents were developed. These devices were engineered to gradually degrade and disappear following the complete elution of the incorporated therapeutic agent. This innovative concept introduced a novel direction in coronary stent technology, and multiple products were subsequently introduced into the clinical market. However, these polymeric stents failed to maintain market presence due to critical shortcomings, most notably insufficient mechanical integrity and suboptimal drug release kinetics [24] [25]. Despite these limitations, this class of stents remains of considerable scientific interest due to its theoretical advantages. The identification and development of an optimal polymeric backbone system that possesses adequate mechanical properties, coupled with a controlled drug delivery mechanism, would undoubtedly mark a major revolution in the field of interventional cardiology [24] [25].

Discussion

The shift from thick polymer-coated drug-eluting stents (DES) to polymer-free DES marks a new mile stone in the field of interventional cardiology. While first-generation DESs reduced the rate of restenosis substantially compared to bare-metal stents (BMS) [1], they were accompanied by inflammatory complications and late stent thrombosis due to durable polymers, which led to the use of thinner and biodegradable coatings [2] [3]. Second-generation DES provided a better improvement in clinical outcomes with regard to thinner struts and more biocompatible polymers [10] [12]. Nevertheless, the fact that the durability of polymers was still of concern with this generation propelled the development of third-generation DES with biodegradable polymers, similar to performance but with fewer late adverse effects [3] [15] [17]. Polymer-free DES aim to remove polymers entirely, offering comparable safety and effectiveness while reducing thrombogenic risks [[2] [4] [5]. Yet, challenges persist regarding controlled drug release and endothelial healing without a polymer matrix [4] [6]. Additionally, bioresorbable stents with polymeric backbones were developed to disappear post-drug delivery. Despite initial promise, most failed due to poor mechanical strength and inadequate drug release [24] [25].

CONCLUSION

The progress of drug-eluting stent technology evolution from thick, durable polymer-based coatings to polymer-free platforms is a testament to the rapid advancement in cardiovascular device engineering and vascular pathophysiology. Each generation of DES almost invariably applied learned lessons to the preceding generation's limitations resulting in small gains in safety, efficacy, and clinical benefits for the patients concerned [1] [3] [4]. Although the treatment of choice in coronary artery disease was bare-metal stents, DESs have ultimately replaced them in terms of effectiveness at limiting the incidence of

restenosis-including improved long-term clinical endpoints [6] [7].

Third-generation DESs with biodegradable polymers have become a very promising alternative in striking a good balance between drug delivery and biocompatibility. Moreover, polymer-free DES offer further potential by eliminating the source of long-term inflammation and thrombogenicity [5] [19]. Despite these advances, challenges such as controlled drug elution and adequate endothelial healing without polymer support continue to limit the widespread adoption of polymer-free systems [5] [6].

The vision of a fully bioresorbable stent that vanishes after drug delivery remains an ambitious yet appealing goal. While so far, attempts have been limited, research on new bioabsorbable materials and scaffold designs may eventually lead to their actualization in an effective solution [24] [25].

Drugs-eluting stents have proven to change the course of interventional cardiology through their evolution over time through the components making up methyl, structural and pharmacological innovations. As a result of different ongoing clinical trials and serious material science research being done, future generations of DES, especially without permanent polymer components, will bring enhanced vascular healing, reduced late-stage complications, and new paradigms of care into coronary artery disease.

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