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Evolution of Drug-Eluting Stents: A Biomedical Engineering Breakthrough in Cardiovascular Intervention

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Abstract
When compared to bare-metal stents, drug-eluting stents (DES) dramatically lower restenosis rates, revolutionizing interventional cardiology. With an emphasis on stent design, medication selection, and polymer coatings, this paper examines the developments in DES technology. The creation of biodegradable polymers, the optimization of medication release kinetics, and the switch from first- to second- and third-generation stents are some of the major trends identified by a systematic review of research published between 2010 and 2023. Even with these developments, problems like biocompatibility and late stent thrombosis still exist. This study emphasizes the necessity for novel materials and customized strategies to further improve the effectiveness and safety of DES.

1. Introduction

Stents are hollow cylinders, usually fabricated from metal meshes that are inserted in a collapsed state across a site of arterial blockage and stretched open by inflating an angioplasty balloon. Although stenting has become the principal treatment for atherosclerosis or coronary artery disease, many patients develop an aggressive inflammatory response to stent placement that results in neointimal hyperplasia tissue overgrowing the stent and causing restenosis. Drug-Eluting Stents (DES) were introduced to address these limitations by delivering antiproliferative agents locally at the stent site.

Stent technology was a breakthrough in the field of surgery, there are some drawbacks are associated with it i.e., in-stent restenosis and increased risk of thrombosis aroused due to injury caused to the endothelium during the procedure. The neointimal hyperplasia and repeated revascularization due to BMS implantation lead to the introduction of a pharmaceutically active agent that is applied onto the BMS in coatings with a polymer as drug carrier called DES to lower the risks posed by BMS.(1)

The development of “drug-eluting stents (DES)” to control in-stent restenosis has been pioneered through a combination of understanding the biology of restenosis, the selection of drugs that would target one or more pathways in the restenosis process, controlled release drug delivery strategies and the use of the stent as a delivery platform. Drug-eluting stents may be defined as implantable blood vessel scaffolding devices that release single or multiple bioactive agents in a controlled manner into blood vessels after implantation

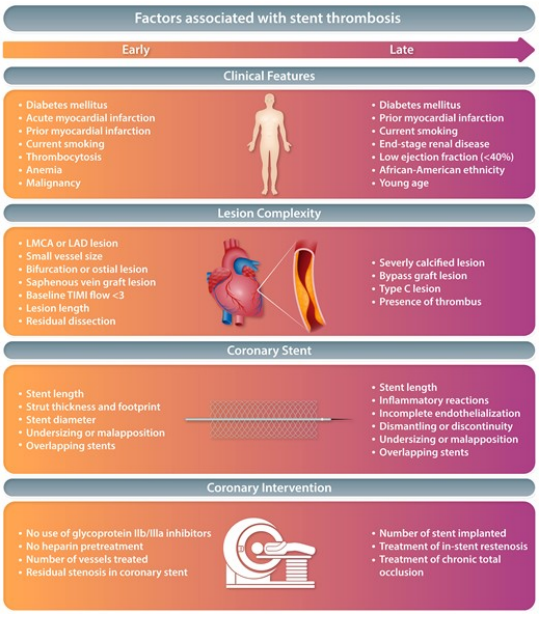
2. First-Generation Drug-Eluting StentsAlthough the development and testing of the first-generation DESs focused to a considerable degree on efficacy parameters, including restenosis, recent concerns over late clinical events have prompted a refinement of the design criteria for succeeding generations of these devices. The primary objective in the design of first-generation DESs was to decrease the neointimal formation seen with BMSs while maintaining an effective luminal dimension. Were it the case that stent dimensions remained static after deployment, the efficacy of the DES could be measured by the degree of inhibition of neointimal growth. The

efficacy of the next-generation DES systems—biodegradable Stent deliverability is one of the most under-recognized requirements for intracoronary stent technology4 and as such represents one of the key properties necessary for the ideal DES. Stents can perform their function only after deployment in target lesions. The first-generation DESs, with insufficient deliverability and lesion accessibility of their balloon-expandable delivery systems, may occasionally be limited in providing optimal clinical benefit. The serious procedural complications associated with failures of stent deployment in target lesions include vessel injury, dissection, and thrombosisThe platform material used in current DES designs is cobalt chromium, which can provide superior radial force and better radiopacity, with thinner strut formulations. The self expanding (as opposed to balloon-expandable) stent platform may offer better deliverability by means of a lower crossing profile. A self-expanding bare nitinol stent, based on a 0.35-mm (0.014-in) guidewire, is currently under investigation in humans (CardioMind, Inc., Sunnyvale, CA).In DES systems, stent thickness may have more effect on deliverability than on efficacy

DESs are designed to reduce in-stent neointimal growth through the elution of agents that arrest the cycle of cell proliferation. To ensure the restoration of proper endothelium and endothelial function, the ideal DES drug should inhibit proliferation of vascular smooth muscle cells Molecular mechanisms of vascular endothelial functional impairment after DES implantation remain incompletely defined, but recent work has provided profound insight into the potential etiologies of this complex phenomenon. Multiple factors may be involved, including direct toxic effect from the entrapped drug and/or an acute or delayed hypersensitivity reaction from the polymer and/or drug.

Late Stent Thrombosis

Although RCTs initially did not raise any safety issues with first-generation DES , a subsequent report of 4 cases of angiographically confirmed ST late after elective implantation of SES or PES raised concerns of a possible very late ST risk with DES



The controversy regarding the safety of DES was fueled by additional real-world studies that showed an increased risk of late ST and MI in patients treated with first-generation DES after discontinuation of dual antiplatelet therapy The absence of a significant difference in mortality or MI between firstgeneration DES and BMS despite the increased risk of very late ST with DES may be explained by the fact that in-stent restenosis is not always a benign phenomenon, presenting as acute MI in 3.5% to 19.4% of patients.

Before the introduction of DES, ST was perceived as a complication occurring early after stent implantation. In 2004, McFadden et al. described 4 cases of late and very late ST in first-generation DES (sirolimus-eluting stent, Cypher, Cordis, Warren, New Jersey, and paclitaxel-eluting stent, Taxus, Boston Scientific, Natick, Massachusetts).

Stent malapposition is defined as lack of contact between stent struts and the underlying arterial wall intima (despite full stent expansion at its nominal diameter). Late stent

malapposition is typically the result of positive vessel wall remodeling (i.e., outward arterial wall expansion "away" from the stent struts that were well apposed at the time of implantation), appears more commonly in DES compared with BMS, and has been associated with (very) late ST.
Other Limitations In October 2003, an FDA advisory described 50 hypersensitivity cases after CYPHER stent implantation . Symptoms included rash, dyspnea, hives, itching, and fevers. In November 2003, a follow-up advisory indicated that almost all of the hypersensitivity reactions were caused by standard drug therapy associated with stent implantation . Nevertheless, components of DES and closely related compounds have caused hypersensitivity reactions in other settings, suggesting that components of the stent itself may be causative factors in some cases . Moreover, there has been no public verification of the FDA case-based findings through epidemiologic analysis of clinical trial data; hypersensitivity data is not presented in the package insert or in publications of the clinical trials.

Case reports of nickel allergies have been published since 1980, with estimates of a 10% overall incidence in the general population. Because it is thought that piercing sensitization is the cause in the majority of cases, incidence in women is higher, between 14% and 20% Most of the reported cases of nickel allergy manifest as a common contact dermatitis, but patients with nickel-containing medical implants who develop nickel allergy typically have a more pronounced systemic response, which frequently include diffuse eczematous rash with no or poor response to corticosteroids.Hypersensitive skin reactions are more often described to nickel, but allergic signs or symptoms can also occur in other metals such as cobalt, chromium, molybdenum, and gold
3. Mechanisms of DES Functionality
Drug-eluting stents (DES) are advanced vascular implants that function as both mechanical scaffolds and drug delivery platforms. Their primary role is to restore and maintain arterial patency after percutaneous coronary intervention (PCI) while simultaneously preventing restenosis through localized pharmacological intervention.
3.1. Dual Functionality: Structural Support and Drug Delivery
DES perform two critical functions:
Mechanical Scaffolding: Similar to bare-metal stents (BMS), DES provide immediate structural support to the arterial wall post-balloon angioplasty, preventing elastic recoil and vessel closure.
Controlled Drug Elution: Unlike BMS, DES incorporate a pharmacologically active agent embedded in a polymer matrix that elutes over time to inhibit smooth muscle cell (SMC) proliferation and neointimal hyperplasia.
This dual-action mechanism significantly reduces the need for repeat revascularization procedures and improves long-term vessel patency.

3.2. Pharmacodynamics and Drug Mechanism
The therapeutic agents used in DES are primarily antiproliferative or immunosuppressive drugs that target key biological processes involved in restenosis. Most commonly, these include:
Sirolimus (Rapamycin): An mTOR inhibitor that arrests the cell cycle in the G1 phase, inhibiting vascular smooth muscle cell proliferation without promoting thrombosis.
Paclitaxel: A microtubule-stabilizing agent that disrupts mitosis and induces apoptosis in proliferative cells.

Everolimus and Zotarolimus: Second-generation drugs derived from sirolimus, offering improved tissue penetration and reduced toxicity.
These agents are selectively cytostatic to SMCs while sparing endothelial cells, promoting favorable re-endothelialization under ideal conditions.

3.3. Role of Polymer Coatings
The drug in DES is incorporated into a polymeric matrix, which serves as a reservoir and controls the rate and duration of drug release. These polymers may be:

- Durable Polymers: Used in first-generation DES; often associated with delayed healing and hypersensitivity.
- Biocompatible/Biodegradable Polymers: Employed in later-generation stents to reduce inflammation and promote healing.
- Polymer-Free Designs: Utilize microporous or nanoporous surfaces to control elution without the need for polymers.

The choice of polymer directly influences drug release kinetics, tissue reaction, and the overall biocompatibility of the stent system.

3.4. Drug Release Kinetics
The kinetics of drug elution is a crucial determinant of stent performance. Ideal drug release follows a biphasic model:

- Initial burst release: Ensures adequate drug levels at the time of maximum injury and inflammation.
- Sustained release phase: Maintains therapeutic levels over several weeks to inhibit the delayed proliferative response.

Overly rapid elution can result in subtherapeutic exposure, while excessively prolonged release may impair endothelialization and promote late thrombosis.

3.5. Endothelial Healing and Re-Endothelialization
One of the key challenges in DES functionality is balancing antiproliferative effects on smooth muscle cells with the need for rapid re-endothelialization. Delayed healing can expose thrombogenic surfaces, increasing the risk of late or very late stent thrombosis (LST/VLST).

- First-generation DES were associated with delayed endothelial coverage and increased late thrombotic events.
- Second- and third-generation DES aim to optimize endothelial healing by refining drug specificity and minimizing chronic inflammation through polymer improvements.

3.6. Molecular and Cellular Pathways
Recent studies have identified several molecular mechanisms involved in DES functionality:

- Inhibition of mTOR pathway: Disrupts cell cycle progression and protein synthesis in SMCs.
- Suppression of VEGF expression: Can delay angiogenesis and endothelial repair.
- Activation of pro-inflammatory cytokines: Particularly with non-biocompatible polymers, leading to chronic inflammation.

5. Advancements in Stent Design
Current stent designs are based on a sequential-ring construction method consisting of a series of expandable Z-shaped structural elements (known as struts) joined by connecting elements (known as bridges, hinges or nodes). In closed cell designs, the adjacent ring segments are connected at every possible junction. This provides greater radial force and scaffolding uniformity but reduces flexibility and conformability – even with flexible bridge connectors – compared to an open-cell

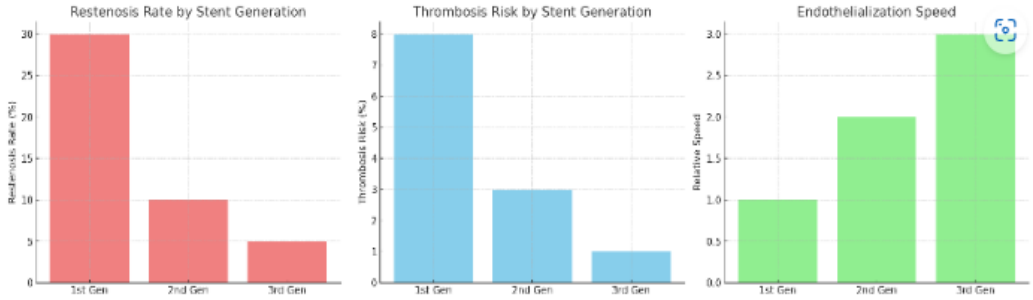
design where some of the internal inflection points are joined by bridging connectors. An open-cell configuration provides greater flexibility, adaptability and access to side-branches and has a higher resistance to fracture.

All of the currently available stents are made by laser-cutting metallic tubes. Continuous sinusoid technology is a manufacturing method that folds a single strand of cobalt alloy wire into a sinusoidal wave, enabling greater deliverability and conformability to the vessel wall. It remains to be seen whether nanotechnology will make the design of stents with ultrathin struts feasible in future.

Great advances have been made in the field of coating and polymers. Drug release and availability are determined not only by the properties of the drug but also by the characteristics and architecture of the polymer that contains it. Depending on its composition, the polymer can cause undesirable inflammatory phenomena

Stent manufacturers have adopted different approaches to decrease the elution rate. These approaches can be roughly separated into five categories: smooth surface, macroporous, microporous, nanoporous and drug-filled stents.[26] Perhaps the simplest polymer-free design is where the drug is coated directly onto the relatively unmodified smooth surface of the metal stent. With no polymer or pores to control drug release, the release rate is determined solely by the solubility and diffusion coefficient of the drug in the release medium and by the thickness of the coating.

In-stent restenosis secondary to low-grade inflammatory response to the polymer or device is mitigated. The risk of late or very late thrombosis is eliminated as the foreign material (platform plus coating) is replaced by connective tissue and the scaffolded segment healed with matured endothelium. The use of BRS could shorten the DAPT administration period and due to secondary bleeding.



Here is a comparative statistical visualization showing:

1. **Restenosis Rate** dramatically dropping from 1st to 3rd generation stents.
2. **Thrombosis Risk** also declining significantly.
3. **Endothelialization Speed** improving across generations (higher = faster healing).
4.

Latest Innovations and Applications

Widespread use of first-generation DES has drawn attention to several unresolved, clinically relevant issues such as late stent thrombosis (ST) and late restenosis (2). Histopathological studies of first-generation DES have revealed that a chronic reaction to components of the permanent polymer reaction may lead to the delayed arterial healing, which is associated with increased risks of late DES failure (3,4). In addition, neoatherosclerosis is suggested as another cause of very late ST and late TLR (5). To overcome these limitations, biocompatible and biodegradable polymers have been developed and equipped with second-generation DES.

thinner strut improves the stent quality and reduces the issues associated with it. The new metallic platforms for stent, Cobalt Chromium (CoCr) and Platinum Chromium (PtCr), were introduced for thinner struts to keep the other properties of the stent intact such as radial strength, recoil, etc. CoCr is a denser metal compared to Stainless steel with enhanced properties that are best suited for developing stent.

New drugs from the Limus family were introduced in the second-generation stents. The new drugs Zotarolimus and Everolimus are derivatives of Sirolimus. Both derivatives have the same structure as Sirolimus; however, they differ in the type of functional group.
Zotarolimus is a semisynthetic derivative of Sirolimus. Its mechanism of action is similar to Sirolimus, but chemical composition is different by the insertion of tetrazole ring at position 42 (substitution of the hydrophilic hydroxyl group) of the native structure. Though the outcomes of the first generation of drug eluting stents were very encouraging, some issues like uncontrolled neointimal proliferation and inflammation were seen in first generation stents, and one of the main causes for eliciting these responses was the nature of the polymer. For better results, new and different types of polymers were introduced in the second generation of stents
The second Generation of DES houses a large number of commercially available stents. The first Second Generation DES was Medtronic's Endeavour which received FDA approval in 2004. Abbott's Xience and Boston Scientific's Promus were approved by the FDA in 2008 and 2012, respectively. The characteristics and clinical results of the best candidates of Second-Generation DES. To avoid these undesirable and potentially devastating side-effects, biocompatible and bioabsorbable polymers, as well as polymer-free DES have been developed. Bioabsorbable stents, both polymeric and metallic, have also been designed to decrease potential late complications.
7. Case Studies and Market Trends
In 2005, two-and-a-half million drug eluting stents were expected to be implanted in patients around the world. In the U.S., which accounted for nearly three-quarters of the total DES market, only two companies had regulatory approval to sell the small devices: Johnson & Johnson and Boston Scientific. In combination, these two organizations expected 2005 DES sales of approximately $5.5 billion - an increase of 36 percent from 2004.
Product recalls and program failures were common as companies sought to bring new DES technologies to market. And, against this backdrop, the segment was characterized by dramatic swings in market share as interventional cardiologists shifted their loyalties in response to new product releases, incremental device innovation, and negative publicity generated by the many challenges encountered by DES manufacturers. Despite these challenges, the future for drug eluting stents looked promising. This paper explores the medical device industry and examines the unusual story of drug eluting stents as one of the sectors most dynamic and complex segments.
In October 2002, approximately 6 months prior to their general release in the United States, the Interventional Committee of the SCAI surveyed its membership, asking them about their expected utilization pattern . Respondents were queried as to how they thought DES would find utility in their practices. In many cases, the expected application was not based on clinical trial data but rather on the areas where improved outcomes would be most welcomed (Table I). A number of clinical and morphologic subgroups not formally tested at that time were believed to be the most likely to receive DES, once released. The majority of the membership thought that their catheterization labs would develop guidelines governing their use,

although many expressed concern that an overly conservative position would lead to a competitive disadvantage with other institutions and/or practices in the local region.

Only 9% of the respondents indicated that DES were used on all PCI cases. Of those respondents who indicated selective use, the only patient or lesion subgroups which approached an 80% penetration were diabetics and vessels in the 2.6 to 3.0 mm diameter range. Although the reasons are not clear from this data, the complex reimbursement formula, self-imposed limits on use per case, limited supply in some sizes at many hospitals, concern about late thrombotic occlusions and a staggered release strategy to some hospitals and not others in the same region can be cited as potential explanations. Surprisingly, few hospitals developed the guidelines expected by the physicians to guide their usage (44%), again leaving physicians to determine their own strategy.

8. Future Directions

8.1. Fully Bioresorbable Scaffolds (BRS)

One of the most promising innovations in stent development is the shift from permanent implants to bioresorbable vascular scaffolds (BVS). These devices provide temporary mechanical support and drug delivery, followed by complete degradation into inert by-products (e.g., lactic acid) over time.

Clinical Promise: BRS allow restoration of natural vasomotion, reduce late stent thrombosis, and eliminate long-term foreign body reactions.

Challenges: Issues remain with radial strength, deployment precision, and increased rates of scaffold thrombosis in early trials.

Example: The ABSORB trial evaluated a polylactic acid-based scaffold but highlighted concerns with thicker struts and scaffold recoil, indicating the need for material innovation and improved design.

8.2. Polymer-Free and Nanoengineered Drug Delivery Systems

Polymers, although critical for drug release, can provoke chronic inflammation and delayed healing. Future DES platforms are moving towards:

Polymer-free stents with microporous, nanoporous, or drug-filled reservoirs.

Nano-coatings and nanocarriers (liposomes, dendrimers) that enable precise, sustained release.

Targeted delivery mechanisms that respond to pH, temperature, or biochemical cues at the lesion site.

These technologies aim to fine-tune the release kinetics while eliminating the inflammatory burden of polymers.

8.3. Ultra-Thin Struts and Novel Materials

Strut thickness is directly correlated with vessel injury, thrombogenicity, and deliverability. Ultra-thin strut platforms (<70 μm) using novel alloys like platinum-chromium (PtCr) or magnesium-based bioresorbable metals are being developed.

Thinner struts enhance flexibility and endothelialization.

Advanced materials maintain radial strength while minimizing trauma.

Innovation Spotlight: Continuous sinusoid technology and shape-memory materials offer greater adaptability to complex vessel geometries.

8.4. Customized and AI-Guided Stenting

A personalized medicine approach is gaining traction in interventional cardiology. Artificial intelligence (AI) and machine learning (ML) can:

Predict restenosis or thrombosis risk based on clinical, anatomical, and genetic data.
Assist in stent selection, optimal sizing, and placement strategies.
Develop patient-specific elution profiles for individualized drug dosing.
Such intelligent DES systems may also incorporate biosensors to monitor local hemodynamics or biochemical markers post-implantation.

8.5. Reduction of Dual Antiplatelet Therapy (DAPT) Duration
A major goal of next-generation DES is to shorten the required duration of DAPT, thereby minimizing bleeding risks in high-risk patients (e.g., elderly, those on anticoagulants).
Trials such as LEADERS FREE and STOPDAPT-2 have demonstrated the feasibility of ultra-short DAPT with certain DES platforms.
Stents with pro-healing surface modifications (e.g., endothelial progenitor cell-capturing coatings) may enable safe re-reendothelialization in under 30 days.
8.6. Hybrid Scaffolds and Dual-Drug Stents
Innovative designs are exploring combinations of materials and dual-drug elution to simultaneously target:

- Early thrombosis (anti-platelet agents)
- Late restenosis (antiproliferative agents)

These stents may include layers or reservoirs that release different drugs at distinct phases of the healing response, offering phased therapeutic action.

8.7. Integration with Regenerative Medicine
There is a growing interest in integrating tissue engineering and regenerative medicine with DES technology. Strategies include:

- Stents seeded with endothelial cells or coated with extracellular matrix proteins.
- Biomimetic coatings that promote faster vascular repair.
- Use of growth factor-loaded nanoparticles to accelerate arterial remodeling.

These approaches seek not only to prevent complications but also to actively promote vascular regeneration.

9. Comparative Summary

Comparative Overview

Feature	First-Generation	Second-Generation	Third-Generation
Platform Material	Stainless Steel	Cobalt/Platinum Chromium	Advanced Cobalt Chromium
Polymer Type	Durable	Durable (biocompatible)	Bioresorbable or none
Drug	Sirolimus, Paclitaxel	Everolimus, Zotarolimus	Everolimus, Biolimus
Strut Thickness	Thick	Thinner	Ultra-Thin
Thrombosis Risk	Higher	Lower	Minimal
Endothelialization	Delayed	Faster	Optimized

10. conclusion

The development of drug-eluting stents from first- to third-generation devices exemplifies the profound impact of translational research and biomedical engineering in clinical medicine. While first-generation DES dramatically reduced restenosis rates compared to BMS, safety concerns necessitated further innovation.

Second-generation DES improved safety without compromising efficacy, while third-generation DES push the frontier toward complete vascular healing and individualized therapy.

Future directions may focus on fully bioresorbable scaffolds, intelligent drug-delivery systems, and stents tailored to patient-specific needs, ultimately aiming for the ideal balance between efficacy, safety, and vascular restoration.

11. References

1. https://www.sciencedirect.com/science/article/pii/S0169409X0600024X
2. https://www.ahajournals.org/doi/abs/10.1161/01.cir.0000078025.19258.28
3. https://wires.onlinelibrary.wiley.com/doi/abs/10.1002/wnan.38
4. https://www.sciencedirect.com/science/article/abs/pii/S0002914907016542
5. https://www.sciencedirect.com/science/article/pii/S1936879809006724
6. https://www.sciencedirect.com/science/article/pii/S0735109713041235
7.
8. https://www.sciencedirect.com/science/article/pii/S0735109705027191
9. https://pmc.ncbi.nlm.nih.gov/articles/PMC8364397/
10. https://www.sciencedirect.com/science/article/pii/S1936879814011674
11. Image https://academic.oup.com/cardiovascres/article/119/3/631/66313
12. https://pmc.ncbi.nlm.nih.gov/articles/PMC6159420/
13. https://www.gsb.stanford.edu/faculty-research/case-studies/drug-eluting-stents-paradigm-shift-medical-device-industry
14. https://www.gsb.stanford.edu/faculty-research/case-studies/drug-eluting-stents-paradigm-shift-medical-device-industry
15. The First-Generation Drug-Eluting Stents and Coronary Endothelial Dysfunction | JACC: Cardiovascular Interventions
16. https://link.springer.com/article/10.1186/s13019-022-01812-y?
17. https://www.reuters.com/business/healthcare-pharmaceuticals/health-rounds-adaptable-implant-may-be-improvement-over-heart-stents-2024-10-30/?
18. https://jtd.amegroups.org/article/view/5989
19. Cardiothoracic Surgery
20. Nature
21. Oxford Academic
22. ACVP Online
23. www.bostonscientific.com
24. Reuters
25. Health Rounds: Adaptable implant may be improvement over heart stents