INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Pharmacokinetic And Pharmacodynamics of Novel Drug Eluting Stents in Cardiovascular Disease

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ARTICLE INFO

Published: 30 Dec. 2024
Keywords:
Pharmacokinetics, Pharmacodynamic Adverse Drug, Drug Specific effect.
DOI:
10.5281/zenodo.14574932

ABSTRACT

By preventing restenosis, drug-eluting stents (DES) are essential in the treatment of coronary artery disease (CAD). Drug carriers that are coated on these stents release antiproliferative medications inside the vessel. DES has been used in clinical practice using a variety of materials, polymers, and medication types for the past 20 years. Even though their design and materials have been optimized to improve biocompatibility and antithrombotic qualities, better clinical monitoring and follow-up are still required to assess their long-term efficacy and safety. This study uses bibliometric analysis to outline potential research directions.

INTRODUCTION

Drug eluting stents (DES) are extensively used in interventional cardiology to renew and keep coronary highways clear after being narrowed by atherosclerosis. Interventional cardiology's elaboration began with the preface of balloon angioplasty in 1977, followed by the first bare metal stent (BMS), developed by Sigwart et al. in 1986. [1] DES made their request debut in Europe in 2002, and since also, multitudinous companies have introduced different types of DES to enhance the treatment of coronary roadway complaint. [2] [3] expansive exploration has supported this progress, with current practices showing the significance of stent technology, as stents are implanted in around 90 of percutaneous coronary interventions (PCI). Endovascular prostheses can be classified in colourful ways, with one of the most common styles being the distinction between bare essence stents (BMS) and medicine- eluting or drug coated stents (DES/ DCS). This categorization highlights the difference between stents that are purely metallic and those that release drug to help restenosis. [4] Advancements in medicine- eluting stents (DES) have been driven by expansive exploration into the pathology of in- stent

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

restenosis (ISR). [5] These developments have enhanced colorful aspects of stent design, including the preface of stronger blends that maintain continuity while reducing strut consistence for better deliverability. [6] [7] also, the use of biocompatible polymers has minimized seditious responses and bettered medicine release kinetics, while new medicines have been formulated to more effectively help restenosis. [8]

Pharmacokinetic Drug Eluting Stents Drug Release Mechanism

Polymer Coating:

Polymer coatings are essential for most drug-eluting stents due to their inability to adhere directly to metallic surfaces. These coatings play a crucial role in controlling drug release kinetics, which can be optimized by utilizing multiple polymer layers to achieve the desired drug delivery profile over time. [9] Historically, polymer coatings have been a significant barrier to the advancement of drug-eluting stents. Early polymers, whether biodegradable or nonbiodegradable, often led to increased inflammatory responses and neointimal hyperplasia. However, research has identified certain polymers that are biologically inert and stable for a minimum of six months, as well as those that are biodegradable with minimal inflammatory responses. [10] Recent innovations include the development of biocompatible and inorganic coatings. [11] Biocompatible coatings are designed to mimic the properties of normal tissues or cells. For instance, phosphoryl choline coatings do not disrupt the reendothelization process and minimize neointimal formation, making them particularly effective for stent-based drug delivery applications. [12]

Diffusion:

We develop two-dimensional numerical models to explore drug transport in drug-eluting stents, focusing on both the vascular wall and the blood lumen. The study examines how drug diffusion coefficients in three main compartments the blood, the vascular wall, and the polymer coating affect the overall transport process. Additionally, the effect of different strut apposition configurations (fully embedded, partially embedded, and non-embedded) on drug distribution in the arterial wall is analysed. By applying the concept of a therapeutic window to the target region of the vascular wall, we propose simple metrics to evaluate the effectiveness of various stent configurations. Although most of the drug is dispersed into the blood lumen, we find that physiological changes in blood flow rate and the drug's diffusivity in blood have a negligible effect on drug uptake in the vascular wall. The amount of drug that accumulates in the wall is mainly influenced by the relative diffusion rates in the polymer coating and the wall itself. [13]

Erosion:

In cardiovascular disease treatment, drug-eluting stents (DES) are designed to release medication gradually through a process of polymer erosion. These stents are coated with a specialized polymer that degrades over time, releasing the drug in a controlled manner directly into the arterial tissue. [14] This slow release of medication helps to prevent restenosis, which is the re-narrowing of the artery following stent placement. As the polymer coating erodes, the medication diffuses into the arterial walls, acting on the smooth muscle cells to prevent them from proliferating excessively, a common cause of restenosis. The rate of polymer degradation is carefully calibrated to ensure a steady and prolonged release of the drug over weeks or months, providing long-term therapeutic benefits. After the drug has been fully delivered, the polymer continues to break down, and its remnants are either absorbed by the body or excreted. This erosion process in DES plays a critical role in their effectiveness, ensuring that medication is delivered directly where it is needed while minimizing the potential for systemic side

effects. [15]. The gradual erosion of the stent's coating enables sustained treatment, reducing the likelihood of complications like restenosis in the treated artery. [16]

Distribution:

The process of drug absorption involves the movement of a drug from the bloodstream into the tissues. Once the drug enters the plasma, it encounters various barriers before it can reach the target tissue or site of action. Distribution in drug-eluting stents (DES) refers to the controlled release of drugs from the stent into the surrounding tissue. In cardiovascular diseases, DES are used to prevent restenosis (renarrowing of the artery) and improve clinical outcomes. The distribution of drugs from DES can be influenced by various factors, including the type of drug, the polymer coating, and the design of the stent [17] . The drugs used in DES, such as sirolimus and paclitaxel, are typically lipophilic and have a high molecular weight, which affects their distribution [18]. The polymer coating on the stent can also impact drug distribution, with some polymers providing a slower release of the drug [19] Additionally, the design of the stent, including the number and size of the struts, can influence drug distribution [20]

Metabolism:

Metabolism plays a crucial role in the efficacy and safety of drug-eluting stents (DES) in cardiovascular diseases. Once the drug is released from the stent, it is metabolized by the body, which affects its concentration and duration of action. The metabolism of drugs used in DES, such as sirolimus and paclitaxel, occurs primarily in the liver through cytochrome P450 enzymes [21] The metabolic pathways of these drugs involve oxidation, reduction, and hydrolysis, leading to the formation of active and inactive metabolites [22]. The active metabolites may contribute to the drug's therapeutic effects, while the inactive metabolites are typically excreted through the kidneys or bile [23]. Factors such as genetic polymorphisms, liver function, and drug interactions can influence the metabolism of DES drugs, which may impact their efficacy and safety [24]. **Excretion:**

Elimination is the final stage of drug disposition in drug-eluting stents (DES), where the drug is removed from the body. In cardiovascular diseases, the elimination of DES drugs, such as sirolimus and paclitaxel, occurs primarily through the kidneys, with some drugs also undergoing biliary excretion [25]. The rate of elimination depends on factors such as renal function, liver function, and drug interactions [26]. Renal elimination is the primary route for sirolimus, with approximately 90% of the drug excreted unchanged in the urine [27]. Paclitaxel, on the other hand, undergoes extensive hepatic metabolism, with only a small fraction excreted unchanged in the urine [28]. Biliary excretion also plays a role in the elimination of some DES drugs, particularly in patients with renal impairment [29].

Pharmacodynamics Drug Eluting Stents:

Mechanism of Action:

Inhibition of Proliferation:

One of the most important ways that drug-eluting stents (DES) prevent restenosis following angioplasty is by inhibiting proliferation. One major factor contributing to restenosis is the proliferation of smooth muscle cells (SMCs). Drugs released by DES prevent SMCs from proliferating, which lowers the risk of restenosis. DES medications such Sirolimus, paclitaxel, and everolimus function by preventing cell division, causing apoptosis (programmed cell death), and suppressing the development of the cell cycle. [30] These medications target particular pathways that contribute to cell proliferation, such as tubulin, cyclin-dependent kinases, and the mTOR (mechanistic target of rapamycin) pathway. Research has consistently demonstrated that, in comparison to bare-metal stents (BMS), DES dramatically lowers restenosis rates. [31]

Efficiency:

Drug-eluting stents (DES) have demonstrated high efficiency in treating cardiovascular disease by reducing restenosis rates and improving clinical outcomes. [32] Studies have shown that DES reduce restenosis rates by 70% compared to bare-metal stents (BMS). Additionally, DES have been associated with lower rates of myocardial infarction, stroke, and mortality. [33] The long-term safety of DES has also been established, with low rates of stent thrombosis and other complications. [34] Furthermore, DES have been shown to improve quality of life and reduce healthcare costs. [35] Overall, the efficiency of DES in cardiovascular disease treatment is well established, making them a valuable tool in the treatment of cardiovascular disease. [36]

Adverse Drug:

Thrombosis:

Stent thrombosis (ST) following percutaneous coronary intervention has garnered significant attention due to its association with serious health risks, including high morbidity and mortality. There is ongoing debate surrounding several aspects of ST, such as its occurrence rate with drug-eluting stents (DES) compared to bare-metal stents (BMS), the timing of these events, clinical impact, contributing risk factors, adjunctive therapies, and new strategies for prevention. Data from randomized controlled trials involving DES and BMS in selected patient populations, along with larger registry studies that offer a broader real-world perspective, have rapidly expanded knowledge in this area. However, results from these sources are not always consistent. Several key conclusions have emerged:

1. ST is a rare but severe complication in both BMS and DES.
2. based on four-year follow-up data from trials comparing DES and BMS, there appears to be no significant difference in overall ST rates, though the timing differs, with late ST being more frequent in DES.
3. despite this late ST increase with DES, there has been no observed difference in mortality or combined death and heart attack outcomes between DES and BMS.
4. continued long-term follow-up and broader patient studies are necessary to fully understand the issue.
5. ongoing research into improved stent designs and pharmacological therapies aims to enhance long-term safety outcomes. [37]

Novel Approach in Drug Eluting Stents:

Biodegradable Stunts:

Polymers that remain on stents after complete drug release can increase the risk of thrombosis and are linked to hypersensitivity and inflammatory reactions. Fortunately, advancements in both natural and synthetic materials that are biologically degradable have led to the development of biodegradable stents. These stents offer several benefits, such as providing temporary arterial support, delivering anti-restenosis drugs, and breaking down biologically at a controlled rate based on the materials used.

Biodegradable drug-eluting stents are designed either with a fully degradable structure or with a biodegradable polymer coating on a bare-metal stent. In both cases, the aim is to reduce the inflammatory response caused by polymer coatings that can lead to thrombosis in traditional drug-eluting stents. Several synthetic biodegradable polymers have been explored for stent coatings, including Poly (L-lactic acid) (PLLA), poly (D, L-lactide) (PDLLA), and poly (lactic-coglycolic acid) (PLGA). These materials typically degrade through the breakdown of ester bonds, forming byproducts like lactic acid and glycolic acid, which the body can safely eliminate without provoking harmful inflammatory reactions. [38]

Drug Specific effect:

Sirolimus, a drug used in drug-eluting stents, has been shown to reduce restenosis rates by inhibiting cell proliferation and migration. It also exhibits anti-inflammatory properties, which contribute to its efficacy in preventing restenosis. Additionally, sirolimus has been found to improve endothelial function, which is crucial for maintaining healthy blood vessels. [39] sirolimus is a macrocytic triene antibiotic that elutes gradually over a period of four to six weeks.[40] The RESEARCH registry and the RAVEL, SIRIUS, and SCANDSTENT studies showed that SES was effective in preventing restenosis.[41][42]Stented patients with stable or unstable angina who received DAPT for six to nine months were enrolled in RAVEL and SIRIUS, which compared SES with BMS.[43][44] Over the course of one to five years, the trials showed a significant decrease in target lesion revascularization (TLR), late lumen loss, and in-stent restenosis.[45]Death and myocardial infarction (MI) rates were the same across all trials.[46] Paclitaxel, another drug used in drug-eluting stents, works by inhibiting cell division and reducing inflammation. It has been shown to reduce restenosis rates and improve clinical outcomes in patients with cardiovascular disease. Furthermore, paclitaxel has been found to have anti-proliferative effects on smooth muscle cells, which helps to prevent restenosis. [47] Paclitaxel, an antineoplastic agent, interferes with microtubule function essential for accurate chromosome segregation during cell division and is released bimodally over two weeks.[48] The efficacy of paclitaxel-eluting stents (PES) was demonstrated in the TAXUS II and TAXUS IV trials, where patients with low-risk lesions or untreated coronary stenosis were randomly assigned either bare-metal stents (BMS) or PES with a slow or moderate drug-release rate.[49][50] Both trials showed reduced rates of in-stent restenosis and target lesion revascularization (TLR). [51] TAXUS IV further confirmed these benefits in subgroups, including patients with vessel diameters smaller than 2.5 mm, lesions longer than 20 mm, and those with conditions such as renal insufficiency or diabetes. [52] [53] Long-term and pooled analyses also indicated a reduction in cardiovascular (CV) events. The latest in the PES series, the TAXUS Liberte, features thinner struts for improved deliverability and was shown to be noninferior to its predecessor in the TAXUS ATLAS trial. [54] Everolimus, a third drug used in drug-eluting stents, has been shown to reduce restenosis rates by inhibiting cell proliferation and migration. It also exhibits anti-inflammatory properties and improves endothelial function. Additionally, everolimus has been found to have antiproliferative effects on smooth muscle cells, which helps to prevent restenosis. [55] Everolimus, a semisynthetic and highly absorbable lipophilic macrolide, is a derivative of sirolimus with immunosuppressive properties. [56] It elutes over time, with approximately 80% released within the first month, and the remaining portion over a four-month period. [57] The efficacy of everolimus-eluting stents (EES) compared to bare-metal stents (BMS) was established in the SPIRIT FIRST trial, which showed significantly reduced in-stent late lumen loss at six months with EES.[58][59] In a meta-analysis of four trials, EES also outperformed paclitaxel-eluting stents (PES) by lowering the risk of stent thrombosis, myocardial infarction (MI), ischemic target lesion revascularization (TLR), and mortality.[60] The SPIRIT II-IV trials further supported EES superiority over PES in both simple and complex coronary disease, showing significantly reduced in-stent late loss and target lesion failure (defined as cardiac death, target-vessel MI, or ischemic TLR) for up to two years.[61] While no randomized trials have directly compared EES with sirolimus-eluting stents (SES), the X-SEARCH registry provided insights into EES efficacy and safety in

higher-risk patients. [62] [63] Here, EES was compared with historical patient groups receiving BMS, SES, or PES, and at six months, EES demonstrated a significantly lower TLR rate than BMS, with comparable outcomes to SES and PES. [64] [65]

Combination Therapies:

Combination therapies involving drug-eluting stents (DES) have demonstrated enhanced effectiveness in treating cardiovascular diseases One such approach pairs sirolimus with paclitaxel, which has been shown to lower restenosis rates and improve clinical outcomes. Another combination, using everolimus with paclitaxel, has exhibited synergistic benefits by reducing both cell proliferation and inflammation. Additionally, combining sirolimus with everolimus has been found to enhance endothelial function and further decrease restenosis rates. [66] These therapies leverage the distinct mechanisms of each drug to boost both efficacy and safety. Sirolimus and everolimus primarily inhibit cell proliferation, while paclitaxel offers anti-inflammatory benefits. By utilizing these complementary actions, clinicians can achieve superior patient outcomes and reduce the likelihood of adverse effects. [67]

Personalized medicine:

Personalized medicine in drug-eluting stents (DES) is an emerging approach that tailor's treatment to individual patients' needs. By considering factors such as genetic profiles, medical histories, and lifestyle habits, clinicians can optimize DES selection and improve patient outcomes. For instance, patients with certain genetic variants may respond better to specific drugs, such as sirolimus or paclitaxel, used in DES. Additionally, patients with diabetes or renal disease may require specialized DES designs or drug combinations to minimize complications. [68]

CONCLUSION:

The safety and effectiveness of drug-eluting stents (DESs) vary depending on the study, but generally, they are shown to be effective in reducing the need for revascularization and in lowering adverse cardiac events. Drug eluting stents are associated with fewer major adverse cardiac events, lower rates of restenosis, and a reduced risk of stent occlusion, though there may be an increased risk of stent thrombosis. Commonly used polymers in DESs include polylactic acid (PLA), polyglycolic acid (PGA), and polylactic-co-glycolic acid (PLGA). Using drug reservoirs or nanoparticles could help avoid some of the issues linked to polymer coatings, like inflammation or hypersensitivity. A titanium-nitric oxide alloy has shown positive results when combined with stainless steel stents.

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HOW TO CITE: Deep Bhoir*, Dr. Manisha Nangude, Dhanashri Kathole, Rohan Bhoye, Vedant Bhagwat, Pharmacokinetic and Pharmacodynamics of Novel Drug Eluting Stents in Cardiovascular Disease, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 12, 3338-3347. https://doi.org/10.5281/zenodo.14574932