Drug-eluting stent restenosis: Effect of drug type, release kinetics, hemodynamics and coating strategy

Michail I. Papafaklis a,b,⁎, Yiannis S. Chatzizisis c, Katerina K. Nakab, Katerina K. Nakab, d, George D. Giannoglou c, Lampros K. Michalis b,d

a Cardiovascular Division, Brigham and Women’s Hospital, Harvard Medical School, Boston, USA
b Michailideion Cardiac Center, University of Ioannina, Ioannina, Greece
c 1st Cardiology Department, AHEPA University Hospital, Aristotle University Medical School, Thessaloniki, Greece
d Department of Cardiology, Medical School, University of Ioannina, Ioannina, Greece

Abstract

Restenosis following stent implantation diminishes the procedure’s efficacy influencing long-term clinical outcomes. Stent-based drug delivery emerged a decade ago as an effective means of reducing neointimal hyperplasia by providing localized pharmacotherapy during the acute phase of the stent-induced injury and the ensuing pathobiological mechanisms. However, drug-eluting stent (DES) restenosis may still occur especially when stents are used in complex anatomical and clinical scenarios. A DES consists of an intravascular metallic frame and carriers which allow controlled release of active pharmaceutical agents; all these components are critical in determining drug distribution locally and thus anti-restenotic efficacy. Furthermore, dynamic flow phenomena characterizing the vascular environment, and shear stress distribution, are greatly influenced by stent implantation and play a significant role in drug deposition and bioavailability within local vascular tissue. In this review, we discuss the performance of DES and the interaction of the different DES components with the hemodynamic milieu emphasizing on the inhibition of clinical restenosis.

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1. Introduction

A new era in the percutaneous treatment of coronary artery disease commenced when stent-based drug delivery systems were firstly introduced in clinical practice. Although mechanical treatment of coronary lesions using plain balloon inflations was certainly a breakthrough in 1977, it rapidly became obvious that this technique could only provide a temporary solution in a large number of cases (Gruentzig et al., 1987). Restenosis rates following balloon angioplasty were very high (40–60%) due to a “rebound effect” of vessel recoil and constrictive remodeling. The percutaneous insertion of metallic scaffolds, namely, stents, during angioplasty had a dramatic impact on obliterating any acute and chronic recoil phenomena, but the unavoidable vessel injury initiated a pathobiological cascade leading to neointimal hyperplasia. Late luminal loss

Abbreviations: DES, drug-eluting stent(s); PES, paclitaxel-eluting stent(s); SES, sirolimus-eluting stent(s); SS, shear stress.

⁎ Corresponding author at: Brigham and Women’s Hospital, Harvard Medical School, 1620 Tremont Street, 3 East, Boston, MA 02120, USA. Tel.: +1 617 525 7745. E-mail address: m.papafaklis@yahoo.com (M.I. Papafaklis).
reduced the long-term efficacy of bare metal stent implantation with restenosis rates ranging between 20 and 40% depending on clinical characteristics, such as diabetes (Abizaid et al., 1998), and procedural and lesion-related parameters including residual stenosis, number of stents, stent length and plaque burden (Hibi et al., 2002; Kasaoka et al., 1998), all of which were associated with higher failure rates.

Drug-eluting stents (DES) provide mechanical restoration of blood flow at sites of stenoses complemented by localized pharmacotherapy for inhibiting the in-stent restenotic vessel response. Almost a decade after the approval of the first generation DES (sirolimus-eluting Cypher stent [SES] and paclitaxel-eluting TAXUS stent [PES]), clinical evidence has been overwhelming in supporting a clear benefit over bare metal stents attributed mainly to a dramatic decrease in repeat revascularization procedures for the target lesion failure (James et al., 2009; Moreno et al., 2007). However, in-stent restenosis may still occur especially when DES are used in the complex clinical and anatomic setting of real-world practice (Alfonso, 2010; Lotan et al., 2009), while the undisputable concerns about poor re-endothelialization (Jimenez-Valero et al., 2009), delayed healing (Farb et al., 2001), incomplete stent apposition and tissue regression behind the strut struts (Hong et al., 2006), demonstrate that DES performance is still not optimized. DES are comprised of a metallic platform loaded with a pharmacologic agent in the presence of either a bioabsorbable or biodegradable polymeric carrier, all of which may have various biologic effects on both the luminal and abluminal milieu; this combination creates a therapeutic device with many critical parameters that need to be harmonically orchestrated for achieving optimal outcomes.

DES implantation, as any stenting procedure, affects the regional arterial geometry, and consequently alters the local flow conditions. The in vivo local vascular environment is a dynamic state with flow properties which produce physical phenomena, such as boundary layer at the lumen–wall interface. Drug deposition is determined by a complex interplay between strut–wall contact, amount and duration of drug release, and flow-driven transport forces which contribute to the local anti-restenotic drug effect (Hwang et al., 2001). Hemodynamic factors, except for influencing drug deposition, may also directly trigger molecular processes, thereby having an impact on the local neointima distribution. Shear stress (SS), the tangential stress derived from the friction of blood on the vessel wall, is known for its role in atherosclerosis (Chatzizisis et al., 2007), and has also been recently implicated in the pathobiology of in-stent restenosis and stent thrombosis (Papafaklis & Michalis, 2005; Wentzel et al., 2008).

The purpose of this review is to summarize recent information about the effect of critical DES features (i.e., pharmacologic agent, drug dosage and release kinetics, strut frame, coating strategy) on the device’s efficacy emphasizing on differences observed in the clinical setting, and to highlight the interaction between flow dynamics and the pharmacotherapeutic device describing the possible implications for the inhibition of the restenotic process.

2. Pathology of neointimal hyperplasia

The pathophysiology of in-stent restenosis involves accumulation of new tissue within the subendothelial space of the arterial wall. Implantation of stents on the vascular bed by applying high pressure through an expandable balloon causes endothelial denudation which may also be followed by medial injury, plaque disruption and necrotic core penetration in cases of large atheromata (Nakazawa et al., 2008b). Neointima formation is caused by a cascade mechanism initiated by platelet activation–aggregation and expression of adhesion molecules and chemokines, which recruit monocytes and facilitate inflammatory cell infiltration. Growth factors (e.g., platelet-derived and vascular endothelial growth factors) released in response to vessel injury (Carter et al., 1994; Sherr & Roberts, 1999; Tanner et al., 2000), as well as hemodynamic SS (Akimoto et al., 2000; Kraiss et al., 2001), influence intracellular positive and negative regulators of the cell cycle (Cyclin-Dependent Kinases and Inhibitors; Fig. 1) controlling vascular smooth muscle cell proliferation and transmigration to the intima. During this process smooth muscle cells undergo a phenotypic switch from a contractile (differentiated) phenotype to a synthetic (de-differentiated) one (Komatsu et al., 1998), which leads to increased proteoglycan and extracellular matrix production and deposition.

3. Drug type effect

Several immunosuppressive and antiproliferative molecules, such as dexamethasone, actinomycin D, cytochalasin D, 17-beta-estradiol, mycophenolic acid, and angiopeptin, have been tested during the last decade for their effect on inhibiting the pathway of neointimal hyperplasia, but the drugs that have been demonstrated to have superior performance in a consistent and reproducible fashion both in preclinical investigations and clinical trials are the Limus family compounds and paclitaxel (Table 1).

3.1. Limus family

Limus family compounds used in DES are immunomodulators that include mammalian target of rapamycin inhibitors (e.g., rapamycin [=sirolimus], everolimus, zotarolimus and biolimus A9) and calcineurin inhibitors (e.g., tacrolimus and pimecrolimus).

The inhibitors of the mammalian target of rapamycin share an almost identical lipophilic chemical structure and bind to their major cytosolic receptor (FKBP12) forming a complex which subsequently binds to their cellular target (Fig. 1). The major cellular effects include a decrease of the positive (blockage of the p70S6 kinase pathway of the Cyclin-Dependent Kinases) and an increase of the negative (through inhibition of the growth factor-induced downregulation of Cyclin Kinase Inhibitor p27KIP1) regulators of the cell cycle (Braun-Dullaeus et al., 2001); the net effect is the arrest of the cell cycle at the G0/G1 phase inhibiting both cell (mainly smooth muscle cells) proliferation and migration (Poon et al., 1996). Since the cells remain viable, the mechanism of action is cytostatic rather than cytotoxic.

Tacrolimus and pimecrolimus are not analogs of the archetypal rapamycin; after they bind intracellularly to FKBP12, the complex in turn binds to and blocks a calcium-dependent phosphatase, calcineurin (Fig. 1). This results in the blockage of signal transduction pathways in T cells and the inhibition of the synthesis of pro-inflammatory cytokines, which are essential for macrophage activation and amplification of the immune response (Thomson et al., 1995).

3.2. Paclitaxel

Paclitaxel is a lipophilic molecule with potent antiproliferative and antimigratory activity. The drug is a microtubule-stabilizing agent which enhances formation of microtubular polymerized structures and thus, decreases the concentration of tubulin required for new microtubule formation (Liuzzo et al., 2005). Microtubules are components of the cytoskeleton and mitotic spindle, which are essential for cell division (Abal et al., 2003), and as a result, paclitaxel impacts primarily the M phase of the cell cycle inhibiting growth factor-induced DNA synthesis and cell proliferation (Fig. 1), and leads to apoptosis or cell death (Wang et al., 2000). In contrast to the limus family, the mode of action of paclitaxel is primarily cytotoxic.

3.3. Clinical anti-restenotic efficacy and drug type

Although all above-mentioned pharmacologic agents ultimately aim to reduce the proliferation and migration of smooth muscle cells, which are predominantly responsible for neointima formation, large clinical trials have demonstrated that significant differences in the anti-restenotic efficacy exist among different DES types (Stettler et al., 2007) (Table 1; Fig. 2). Furthermore, variations in histopathologic
characteristics of human restenotic tissue according to DES type have been reported. Smooth muscle cells were found to be less de-differentiated maintaining in part their contractile characteristics in stents eluting sirolimus or tacrolimus compared with paclitaxel, which was associated with a more synthetic phenotype resembling the findings in bare metal stents (Chieffo et al., 2009). Therefore, variations in the restenotic process may contribute to the differences in DES clinical performance.

Head-to-head comparisons of 1st generation DES (Table 1; Fig. 2), i.e., sirolimus (CYPHER, Cordis, Johnson & Johnson, Miami Lakes, FL, USA) vs. paclitaxel (TAXUS, Boston Scientific Corp, Natick, MA, USA), as that performed in the REALITY randomized trial (Morice et al., 2006), have demonstrated a superior inhibition of neointimal hyperplasia by SES (8-month in-stent late loss: 0.09±0.43 vs. 0.31±0.44 mm, p<0.001). Furthermore, a meta-analysis of 16 randomized trials (8695 patients) comparing these 2 DES types showed a reduced rate of target lesion revascularization in SES (hazard ratio: 0.59 [95% CI: 0.47–0.74], p<0.0001) and myocardial infarction (hazard ratio: 0.54 [95% CI: 0.41–0.71]; p<0.0001) (Kereiakes et al., 2011). Similar overall 9-month clinical safety and effectiveness have been demonstrated for a biolimus-eluting stent with biodegradable polymer (BioMatrix; Biosensors Inc, Newport Beach, CA, USA) compared to durable-polymer-based CYPHER SES in a non-inferiority randomized trial which included patients with stable angina or acute coronary syndromes (Windecker et al., 2008)( Table 1; Fig. 2). In contrast, the zotarolimus-eluting ENDEAVOR stent (Medtronic Vascular, Santa Rosa, CA, USA) was associated with an increased re-intervention rate (odds ratio: 1.62, 95% CI: 1.31 to 2.00, p<0.001) when compared to 1st generation SES and PES according to a meta-analysis summarizing data from 7954 patients with up to 2 years follow-up (Dibra et al., 2010).

4. Drug dosage

Drug efficacy is inherently linked to the pharmacokinetic profile. Although the specific biological mechanism of a pharmacologic agent is critical for inhibiting the pathophysiological pathway of restenosis, the dosage for achieving the desirable local effect without any adverse events, as well as drug release kinetics, influence vascular injury and effectiveness in the clinical setting.
High or extreme drug doses have been associated with toxic effects such as augmented fibrin deposition, intra-intimal hemorrhages, medial necrosis, mural thrombus and excessive arterial expansion, and may lead to stent thrombosis and exacerbation of neointimal tissue (Lyssias et al., 2007; Nakazawa et al., 2008b). Furthermore, a narrow therapeutic range is disadvantageous, since it may result in increased cytotoxicity; actinomycin D, a powerful inhibitor of cell proliferation, was observed to have toxic effects at dosages close to the therapeutic ones in pre-clinical investigations (Wessely et al., 2006), while the randomized trial testing the safety and efficacy of actinomycin-eluting stents demonstrated a significantly lower 1-year survival free of target-territory revascularization compared to bare metal stents proving that this compound could not prevent stent restenosis in humans (Serruys et al., 2004). Conversely, insufficient dosage may result in minimal anti-restenotic benefit as demonstrated in the ELUTES and ASCOT dose-finding trials (Gershlick et al., 2004; Kaluza et al., 2004). Paclitaxel (doses: 0.2, 0.7, 1.3, 1.4, 2.7 and 3.1 μg/mm² stent surface area) was delivered from non-polymer-based stents in these two trials, and significantly reduced 6-month diameter stenosis only at the highest applied dose versus bare metal controls, while, overall, there was a reduction of all angiographic parameters of restenosis (% diameter stenosis ranged from 33% for the lowest dose to 14% for the highest one) in a dose-dependent fashion.

5. Drug release kinetics

Drug release kinetics directly impact drug retention in the wall and can influence vascular healing and the therapeutic effect. A balance between the rates of drug release and arterial drug uptake, i.e., neither too rapid release exceeding the tissue absorption rate nor too slowly limiting the amount of drug presented to the artery (Balakrishnan et al., 2007), is essential for optimizing the device’s efficacy. The absolute duration of drug release also plays a fundamental role in the dynamics of the restenotic process, since molecular biology studies demonstrate pro-restenotic gene activation for periods up to 3 weeks implying the necessity for presence of drug-induced inhibition for at least a minimum time period (Tanner et al., 1998). In vitro experiments with novel polymer films permitting adjustable paclitaxel release profiles, i.e., fast (30-day) to moderate (45-day) and slow (80-day) release (Fig. 4), showed a differential behavior regarding toxicity and inhibitory effect on smooth muscle cell proliferation. The fast release kinetics resulted in perfect inhibition immediately but could lead to local toxicity; the moderate releasing film appeared to be the best choice to obtain full inhibitory effect at reduced risk; and the slow releasing film had a brief loss of inhibitory action in early days but could be beneficial in the later days since it provided sustainable release of up to 3 months (Lao & Venkatraman, 2008). Moreover, impaired endothelialization associated with stent thrombosis following DES implantation is attributed to the cytotoxic drug effect and animal studies have shown that extended-release sirolimus formulations providing a slow release over several weeks may be beneficial by leading to a higher percentage of stent strut coverage similar to what is observed in bare metal stents (Frey et al., 2008).

The first human study to demonstrate the significance of elution kinetics in reducing angiographic restenosis was the PISCES trial which tested 6 paclitaxel release formulations differing in dose, duration and direction of release. Elution duration was found to have the most prominent effect on the inhibition of neointimal growth since the extended release (30 days) stent with 10 μg of paclitaxel was more effective than the 10-day release formulation with identical concentration in the new ENDEAVOR RESOLUTE stent compared with the extended release (30 days) stent with 10 μg of paclitaxel. Furthermore, differences in drug release kinetics between the commercially available TAXUS and CYPHER stents may account in part for the aforementioned superior efficacy of the latter which has a longer release profile. The TAXUS stent (loading: 1 μg/mm² paclitaxel) is characterized by ~10–30% release of the drug within 10–15 days, while the rest remains in the polymer indefinitely. In contrast, almost all the sirolimus has eluted from the CYPHER stent (loading: 1.4 μg/mm²) by 4–6 weeks, leaving a polymer-coated bare metal stent.

A more delayed release (50% and 85% of drug released at 7 and 60 days, respectively, after stent implantation) of the same zotarolimus concentration in the new ENDEAVOR RESOLUTE stent compared with the original ENDEAVOR stent (75% of drug released in 2 days) seems to have been the major reason for a dramatically improved efficacy in clinical trials (Daemen & Serruys, 2007; Raber & Windecker, 2011).

Table 1

<table>
<thead>
<tr>
<th>DES category</th>
<th>Drug</th>
<th>Trial</th>
<th>Follow-up</th>
<th>In-segment binary restenosiça</th>
<th>In-stent late lossb (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First generation durable polymer</td>
<td>Sirolimus</td>
<td>SRTAX (Windecker et al., 2005)</td>
<td>9 months</td>
<td>6.6%</td>
<td>0.12 ± 0.36</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>SRTAX (Windecker et al., 2005)</td>
<td>9 months</td>
<td>4.9%</td>
<td>0.09 ± 0.43</td>
</tr>
<tr>
<td>Second generation durable polymer</td>
<td>Everolimus</td>
<td>SPIRIT II (Serruys et al., 2006)</td>
<td>6 months</td>
<td>3.4%</td>
<td>0.11 ± 0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SPIRIT III (Stone et al., 2009)</td>
<td>8 months</td>
<td>4.7%</td>
<td>0.16 ± 0.41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resolute all comers (Serruys et al., 2010)</td>
<td>13 months</td>
<td>6.5%</td>
<td>0.19 ± 0.40</td>
</tr>
<tr>
<td></td>
<td>Zotarolimus</td>
<td>ENDEAVOR II (Fajadet et al., 2006)</td>
<td>8 months</td>
<td>13.2%</td>
<td>0.61 ± 0.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ENDEAVOR IV (Leon et al., 2010)</td>
<td>8 months</td>
<td>15.3%</td>
<td>0.67 ± 0.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resolute all comers (Serruys et al., 2010)</td>
<td>13 months</td>
<td>5.2%</td>
<td>0.27 ± 0.43</td>
</tr>
<tr>
<td>Biodegradable polymer</td>
<td>Biolimus A9</td>
<td>LEADERS (Windecker et al., 2008)</td>
<td>9 months</td>
<td>6.7%</td>
<td>0.13 ± 0.46</td>
</tr>
<tr>
<td></td>
<td>Sirolimus</td>
<td>ISAR-TEST-3 (Mehilli et al., 2008)</td>
<td>6–8 months</td>
<td>9.0%</td>
<td>0.17 ± 0.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ISAR-TEST-4 (Byrne et al., 2009a)</td>
<td>6–8 months</td>
<td>11.6%</td>
<td>0.24 ± 0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NEVO ResElution-I (Ormiston et al., 2010)</td>
<td>6 months</td>
<td>3.2%</td>
<td>0.13 ± 0.31</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>JACTAX HD (Grube et al., 2010)</td>
<td>9 months</td>
<td>6.2%</td>
<td>0.33 ± 0.45</td>
</tr>
<tr>
<td>Polymer-free</td>
<td>Sirolimus</td>
<td>ISAR-TEST-3 (Mehilli et al., 2008)</td>
<td>6–8 months</td>
<td>16.9%</td>
<td>0.47 ± 0.56</td>
</tr>
<tr>
<td></td>
<td>Biolimus A9</td>
<td>BioFreedom FIM (Grube, 2010)</td>
<td>12 months</td>
<td>–</td>
<td>0.17 (0.09–0.39)c</td>
</tr>
<tr>
<td>Fully bioabsorbable</td>
<td>Everolimus</td>
<td>ABSORB Cohort B2 (BVS Rev. 1.1) (Serruys et al., 2011)</td>
<td>12 months</td>
<td>3.5%</td>
<td>0.22 (0.06–0.41)c</td>
</tr>
</tbody>
</table>

a In-segment binary restenosis is defined as diameter stenosis ≥50% at the stented area and 5 mm margins proximal and distal to each stent edge.
b Unless otherwise specified, values are mean ± standard deviation.
c Values are median (interquartile range).
Both late luminal loss (Table 1) and revascularization rates were lower for the stent with delayed release compared to the original one, which was recently shown to be non-inferior to the everolimus-eluting XIENCE stent regarding major adverse clinical events including repeat revascularization rates (Serruys et al., 2010).

6. In-stent flow dynamics and efficacy of local drug delivery

Stents have not only an abluminal surface which is in direct contact with the arterial wall, but also a luminal side characterized by dynamically changing blood flow. Both solvent-driven flow in the vessel lumen and diffusion due to drug concentration gradients dictate mass transport and drug distribution in stent-based drug delivery (O’Connell et al., 2010). Simulations using coupled computational fluid dynamics and mass transfer models have demonstrated that direct strut contact accounts for only 38% of peak and 11% of arterial drug, whereas non-contacting strut surfaces can contribute up to 90% of arterial drug deposition (Fig. 5) (Balakrishnan et al., 2005). Flow patterns around the stent struts determine the quantity of blood-solubilized drug, which is washed away by the free flow stream or trapped in flow stagnation zones and deposited not only under or adjacent to struts but also in distal tissue segments or in inter-strut zones (Kolachalama et al., 2009b). These zones create substantial levels of drug concentration at the mural surface that serve as secondary sources of tissue uptake. The degree of drug deposition and penetration into the tissue not only ultimately

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**Fig. 2.** Forest plot of head-to-head comparisons of various drug-eluting stents regarding target lesion revascularization (TLR) rates. In most studies hazard ratios (derived from time-to-event analysis) were used as risk ratio (RR) estimates. Analysis confined to 11 trials with available individual data. In this collaborative network meta-analysis with 37 trials contributing to the analysis of TLR, the error bar represents the credibility interval. Analysis confined to 4 trials (SORT OUT IV, EXCELLENT, ISAR-TEST-4 Substudy and ESSENCE-DIABETES) providing data for TLR. SES, sirolimus-eluting stent(s) with biodegradable polymer; BP, biodegradable-polymer sirolimus-eluting stent(s); CI, confidence intervals; DP, durable-polymer sirolimus- or everolimus-eluting stent(s); EES, everolimus-eluting stent(s) with durable polymer; ZES, zotarolimus-eluting stent(s) with durable polymer; PES, paclitaxel-eluting stent(s) with durable polymer; SES, sirolimus-eluting stent(s) with durable polymer.

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**Fig. 3.** Meta-analysis of 16 randomized trials for head-to-head comparison of sirolimus-eluting stents (SES) against paclitaxel-eluting stents. Kaplan–Meier curves of reintervention in each of the drug-eluting stent groups for the pooled population (analysis confined to 11 trials with available individual data). Hazard ratio indicates the HR associated with SES. Reprinted from Schomig et al. (2007), with permission from Elsevier.

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**Fig. 4.** Adjustable paclitaxel release profiles from biodegradable polymer films of different compositions. PCL, polycaprolactone; PLGA, Poly (dl-lactide-co-glycolide); PLGAPEG, PLGA with addition of 10 wt.% PEG (polyethylene glycol); PTX, paclitaxel. Reprinted from Lao and Venkatraman (2008), with permission from Elsevier.
determines drug efficacy, but also may contribute to the side-effects of DES implantation.

Flow-generated SS, which has been increasingly appreciated during the last 40 years as a critical factor explaining the localized distribution of atherosclerotic lesions (Caro, 2009; Chatzizisis et al., 2007), induces cell proliferation in the absence of exogenous mitogens through signaling pathways akin to the ones activated during restenosis and targeted by stent-based pharmacotherapy (Kraiss et al., 2000). In addition, recent in vivo investigations indicate that low SS, e.g., in regions with slow or recirculating flow, may augment the neointimal hyperplastic response (Wentzel et al., 2008).

Stent design impacts flow and in this way design plays a critical role in the effectiveness of the therapeutic device. Flow-induced variations in drug deposition and in-stent SS distribution, as well as their interaction, may explain in part the broad spectrum of restenosis patterns across patients after DES implantation (Corbett et al., 2006).

6.1. Impact of stent characteristics on hemodynamics and drug deposition

Stent implantation alters coronary artery hemodynamics due to the immediate effects of the scaffolding on local arterial geometry, and may lead to large alterations in spatial SS distribution especially at the stent edges (Wentzel et al., 2000). Stents characterized by increased mechanical compatibility to their host environment conforming to native vessel curvature cause minimal changes in SS distribution and may be beneficial from a hemodynamic perspective (LaDisa et al., 2006). Furthermore, stent struts have a profound influence on near-wall velocity and wall SS; minimum wall SS is decreased by approximately 80% within the stent and at the outlet of the stent in stented compared to non-stented vessels, while regions of low SS are localized around stent struts and are associated with stagnation flow and boundary layer separation immediately upstream and downstream of the struts (LaDisa et al., 2003).

Stent architecture (e.g., strut number and thickness) influences the detailed characteristics of post-stent implantation blood flow patterns because of disturbance effects (Balossino et al., 2008). Increasing the number of struts from four to eight has been shown to produce a 2.75-fold increase in exposure to low SS, whereas a reduction in strut thickness from 96 to 56 μm is associated with a decrease in regions subjected to low SS by approximately 87% (LaDisa et al., 2004). Of note, larger stent struts have been associated with bigger vessel injury and less endothelial coverage, underscoring the importance of stent characteristics on both flow dynamics and the response of the arterial wall (Charonko et al., 2009). Furthermore, 2nd generation DES (e.g., everolimus) are made of cobalt chromium alloy which allows a more flexible stent frame with thinner struts (>80 μm) instead of the more bulky stent structure (130–140 μm) made of stainless steel in the earlier DES, and may be one reason for the improved results in clinical trials (Lange & Hillis, 2010).

Stent strut profile has a significant impact on flow dynamics and drug diffusivity in the arterial wall. Streamlined profiles (e.g., elliptical and tear-drop) exhibit better hemodynamic performance compared to the standard square or circular profiles since the streamlined ones have smaller recirculation zones and a lower percentage of inter-strut area where the SS level is decreased (Jimenez & Davies, 2009; Mejia et al., 2009). Multidomain analyses incorporating structural wall characteristics have further showed that circular struts enable to obtain a greater in-the-tissue penetration degree resulting in greater drug concentration values (about 20%) when compared to square ones (Vairo et al., 2010).

Stent-related parameters driven by the angioplasty procedure perse, such as stent-to-artery expansion ratio, strut embedment and overlapping stents, can also affect substantially SS and drug distribution. An increase in the deployment ratio (1.1:1 vs. 1.2:1) has been demonstrated to increase the exposure to low SS by 12-fold (LaDisa et al., 2004). Over-expanding the stent with a second balloon affects the alignment of the stent geometry leading to higher SS at the inlet and lower values in mid-stent regions. However, overexpansion – at the expense of potentially greater tissue injury – may help secure strut positioning at the wall surface and may also result in increasing the depth of strut embedment which has been associated with improved drug distribution in the arterial wall (Fig. 6) (Mongrain et al., 2005).

The use of overlapping stents in place of a single longer stent appears to disrupt the flow within the stented region and create a SS deficit region downstream of the overlapping region (Charonko et al., 2010). In addition, overlapping DES dramatically affect drug distribution not only by adding to the amount of local drug and area of contact with the arterial wall, but also by influencing the degree of strut protrusion into the lumen, and consequently, flow disruption (Balakrishnan et al., 2005). In cases of bifurcational stenting, drug deposition is determined not only by stent strut configuration, but also by flow disturbances imposed by the flow divider (Nakazawa et al., 2010). The presence of the side branch affects drug distribution in the stented main vessel, thereby creating zones of excessive drug deposition and areas of drug depletion, which could ultimately lead to vascular toxicity and restenosis, respectively (Kolachalama et al., 2009a).

Fig. 5. (A) Single DES strut. Visual representation of drug concentration distribution (in color) and blood flow profiles (black curves). Inset, High magnification of area outlined by white dashed line demonstrating 2 distinct recirculation regions proximal and distal to the strut; the latter is larger than the former. These zones create pockets of stagnant drug-laden blood that allow drug accumulation at the luminal–arterial wall interface and subsequent entry into the arterial wall. (B) Arterial wall drug concentration profiles as function of axial distance along artery at depth of 1.5 strut heights into arterial wall. Each curve represents case in which 0, 1, or >1 surfaces of single strut were simulated as noneluting (black). Boxes in legend represent various strut configurations. Drug coating is designated by colored strut sides. Color of concentration profiles corresponds to strut surface coloring. When only the contacting strut surface is drug coated, drug concentration peaks directly beneath the strut; when only the contacting surface is drug free, the peak drug concentration occurs distal to the strut and is of greater magnitude.

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6.2. Shear stress, neointima distribution and drug interaction

Animal experiments have shown that neointimal hyperplasia predominantly occurs in stented arterial regions of low SS and elevated spatial SS gradients (LaDisa et al., 2005). Stenting of the main branch in bifurcations of large peripheral porcine arteries was reported to lead to highly eccentric restenotic lesions located at the lateral wall where an area of boundary layer separation, flow stagnation and thus, decreased SS magnitude was observed (Richter et al., 2004). Conversely, an artificial 2-fold increase of SS after placing a prototype flow divider in stented segments of rabbit iliac arteries was demonstrated to result in significantly lower (>50%) mean late luminal loss, reduction (>40%) in neointimal thickness and a reduced inflammation and injury score, as assessed by macrophage infiltration and internal elastic lamina disruption (Carlier et al., 2003).

In humans, a significant negative correlation between SS and neointimal thickness 6 months after implantation of both balloon- and self-expandable stents has been reported (Sammartin et al., 2006; Wentzel et al., 2001). Although the locations of intimal hyperplasia are not steadily predicted by SS in all cases (Stone et al., 2003), it seems that in-stent regions with low SS have a higher probability for neointimal hyperplasia to occur and be more profound. Intra-coronary radiation therapy, a therapeutic modality developed for reducing restenosis, has been shown to diminish the inverse relationship between in-stent neointimal thickness and SS probably due to the deleterious effect of radiation on the proliferation of the cells which sense and are affected by SS (Papafaklis et al., 2009).

Neointima distribution following DES implantation may include both neointimal hyperplasia and tissue regression reflecting localized failure of the drug to prevent restenosis and an excessive drug effect leading to lumen dilation in some cases, respectively. The role of SS in these processes, as well as the potential drug effect on the pro-restenotic activity of low SS, has lately emerged. An initial study of 6 patients by Gijsen et al. (2003) showed that neointimal thickness 6 months following sirolimus-eluting stent (SES) implantation was inversely related to SS in the majority of the patients; inter-strut shallow pits were observed and attributed to tissue regression induced by high SS. Both neointimal growth and tissue regression were present in a patient presenting with lumen enlargement and incomplete stent apposition a few weeks after paclitaxel-eluting stent (PES) implantation; only neointimal hyperplasia thickness was found to be inversely correlated to SS, whereas there was no association between tissue regression depth and SS (Papafaklis et al., 2007). Histopathological analyses in human autopsy specimens have further showed augmented neointimal thickness and a lower percentage of uncovered stent struts at the lateral wall (low SS) compared with flow divider sites (high SS) of bifurcations treated with DES (Nakazawa et al., 2010). In contrast to the previous reports, a study investigating the correlation between neointimal hyperplasia volume and SS in a diabetic population at 9-month follow-up after SES implantation found no association between the two parameters (Suzuki et al., 2008). The limited role of SS in neointima distribution under sirolimus elution is also supported by a latest study in thirty patients at 6-month follow-up after sirolimus- or paclitaxel-eluting stent implantation compared with bare metal stents. A significant negative correlation of neointimal thickness to SS – similar to the observations in bare metal stents – was found only in PES patients, whereas sirolimus elution was demonstrated to attenuate the SS effect, and overall, resulted in superior inhibition of neointimal growth compared to PES (Papafaklis et al., 2010). The distinct biologic mechanisms of the two drugs, and specifically the exclusive effect of sirolimus on the same molecular pathway (p70S6 kinase pathway of the Cyclin-Dependent Kinases; Fig. 1) through which SS exerts its cellular effects (Kraiss et al., 2001), seem to account for the differential neointimal response to SS observed in this study, and may also contribute to the superior anti-restenotic efficacy of SES against PES in large randomized trials.

7. Coating strategy

Loading of drugs on stent platforms can be performed either directly onto the stent struts (e.g., via solvent evaporation, impregnation onto microporous stent surfaces) (Wessely et al., 2005), or on a carrier vehicle matrix which is added to the device surface (Puskas et al., 2009). These carriers are usually polymeric and increase the effective surface area, thereby enabling sufficient loading and drug release in a more controlled manner. Durable polymers have been exclusively used in first generation DES, and in the everolimus- and zotarolimus-eluting stents of newer DES tested in large clinical trials.

7.1. Durable polymers

Since the magnitude and duration of the inflammatory response following stent-induced vascular injury critically influences the extent of neointimal growth and healing processes, biocompatibility of the polymeric carrier is of utmost importance, so that the carrier does not elicit any adverse biological reactions. An increase in the degree of the hyperplastic response up to two times has been observed

![Graphical representation of drug concentration distribution for different strut configurations: Not-Embedded, Half-Embedded, and Full-Embedded struts, showing increased drug distribution and better spatial drug concentration uniformity.](https://example.com/graph.png)

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when certain non-compatible polymers are used compared with control substances (Granada et al., 2003). Polymers are not inert materials and have been associated with potentially negative effects after DES implantation such as ongoing vascular inflammation involving granulomatous inflammation and para-strut fibrin deposition persisting up to 2 years (Nakazawa et al., 2008a), impaired arterial healing and endothelialization (John et al., 2008), hypersensitivity/toxic reactions and thrombotic events (Nebeke et al., 2006). Polymer-drug coatings do not seem to inherently increase acute clotting, but, on the contrary, they may improve material properties of metallic struts (Gutensohn et al., 2000), and according to latest findings from ex vivo flow studies polymer/drug-coated stents uniformly reduce thrombogenicity relative to bare metal counterparts by ≈30% (Kolandaivelu et al., 2011). However, the acute and long-term biore sponsiveness of the peri-stent environment to the polymer is the factor that ultimately determines the risk for adverse events.

Endurance for witholding the mechanical stresses during the angioplasty procedure and maintaining their integrity, as well as durability for the lifetime of the stent implant are required for ideal polymeric matrices. Polymer disruption, peeling and cracking, especially when DES are used in complex lesions (e.g., tortuous calcified segments) and demanding interventional procedures (e.g., kissing balloon dilation with stent overstretching), have been revealed with scanning electron microscopy and may lead to early drug losses and erratic local drug distribution potentially affecting DES anti-restenotic efficacy (Farooq et al., 2011).

7.2. Biodegradable polymer approach

In contrast to bioabsorbable polymers, which remain on the stent after elution of the drug and therefore, may perpetuate biologic sequelae for a long period, biodegradable (or absorbable) polymers have been developed in order to perform their “task” as drug carriers for as long as they are actually needed. Bioerodible polymer coatings (e.g., polyglycolic acid, poly-L-lactic acid) are degraded by hydrolysis and enzymatic activity, and are eventually metabolized to water and carbon dioxide. The efficacy and safety of the biodegradable polymer technology has been lately supported by favorable results showing promise in the clinical setting. The ISAR-TEST-4 trial compared a custom-made biodegradable-polymer stent platform (a microporous stainless steel stent coated with sirolimus, a biodegradable polymer and a biocompatible resin) with the commercially available CYPHER (sirolimus) and XIENCE (everolimus) stents in a large, randomized clinical trial designed to assess non-inferiority of the biodegradable polymer platform versus the two permanent-polymer platforms (Byrne et al., 2009a). A total of 2603 real-world patients were included and the primary endpoint was a composite of cardiac death, myocardial infarction related to the target vessel, or target lesion revascularization at 1-year of clinical follow-up. Biodegradable polymer DES was non-inferior to permanent polymer DES concerning the primary endpoint (13.8 vs. 14.4%, respectively, p = 0.005 for non-inferiority; relative risk = 0.95 [95% confidence interval, 0.78–1.17]), and showed similar rates of cardiac death or myocardial infarction related to the target vessel (6.3 vs. 6.2%, respectively, p = 0.94), target lesion revascularization (8.8 vs. 9.4%, respectively, p = 0.58; Fig. 2), and stent thrombosis (1.0 vs. 1.5%, respectively, p = 0.29). An angiographic substudy from the same trial further proved that the biodegradable-polymer platform had similar anti-restenotic efficacy as the permanent-polymer one (6–8-month in-stent late loss: 0.24 vs. 0.26 mm, respectively, p = 0.49), while both stent types demonstrated a focial pattern of restenosis (Kufner et al., 2011).

Novel stent technologies also aim to reduce the thickness of the biodegradable polymer or the overall contact of the polymer with the arterial wall. The JACTAX DES system (Boston Scientific Corp, Natick, Mass, USA) is coated with a mixture of an ultrathin biodegradable poly lactide polymer and paclitaxel applied as microdots (Fig. 7). A first-human-use study of this platform showed that 9-month major adverse cardiac event rate, in-stent late loss, restenosis (Table 1), and net volume obstruction were comparable to those observed with the durable-polymer PES using identical stent frame (Grube et al., 2010), without, however, any improvement in strut coverage assessed by optical coherence tomography at 6 months (Gugliumi et al., 2010).

A stent specifically designed for drug delivery incorporating hundreds of small reservoirs filled with sirolimus–polymer compositions is NEVO SES (Cordis Corporation, Johnson & Johnson, Warren, NJ), which has a surface that is 75% bare metal upon insertion, thereby minimizing tissue–polymer contact. Six-month results from a randomized trial comparing NEVO SES with the surface-coated TAXUS PES demonstrated similar rates in clinical events (Ormiston et al., 2010), but superior anti-restenotic (neointimal obstruction: 5.5 vs. 11.5%, p = 0.02) performance (Otake et al., 2011).

A step further to exploiting the complete potential of the biodegradable polymer technology was the development of fully bioabsorbable DES providing the undisputable theoretical advantage of using a temporary scaffold that serves its purpose when needed and then disappears. The bioabsorbable everolimus-eluting stent system (bioabsorbable vascular scaffold [BVS]; Abbott Vascular, Santa Clara, CA, USA) is made from a polymer backbone of Poly-L lactic acid which is coated with a thin layer of a 1:1 mixture of a more rapidly absorbed Poly-β-lactide polymer and the anti-proliferative drug everolimus. Preclinical studies employing optical coherence tomography and histology have demonstrated that by 3–4 years the struts of the scaffold are completely integrated into the wall resulting in foci of low-cellular-density connective tissue (Onuma et al., 2010). The results from the first clinical application proved the device’s procedural success (100%) and clinical safety with no ischemia-driven target revascularization and stent thrombosis in a small patient cohort (n = 30) at 2 years post-implantation (Serruys et al., 2009). However, substantial stent resorption was documented at 6 months (Ormiston et al., 2008), and the signs of stent shrinkage (late recoil) accounting for significant luminal loss at 6 months subsequently led to the development of the “second-generation” BVS which has a modified platform design and different manufacturing process of the polymer enhancing its mechanical integrity and ensuring its longer endurance. One-year clinical and imaging outcomes after implantation of this newest version showed that the scaffold area remained unaltered, neo intima inhibition was well-controlled (Table 1), and changes in minimal and mean lumen area by intravascular ultrasound were non-significant, while the stented segment had pharmacologically induced vasomotion restored (Serruys et al., 2011). The device’s performance is expected to be tested against current best standards in a large randomized clinical trial for drawing more definite conclusions.

7.3. Polymer-free platforms

Attempts to address the undetermined short- or long-term effect of polymers on arterial healing have led to the development of polymer-free DES, which have been associated with decreased fibrin deposition and inflammation in animal experiments (Tada et al., 2010). An early clinical study comparing polymer-based with nonpolymer-based first-generation PES demonstrated a benefit in angiographic (in-stent late lumen loss: 0.22 vs. 0.74 mm, p < 0.001) and intravascular ultrasound (neointima area: 0.62 vs. 2.36 mm², p = 0.003) measures of neointimal hyperplasia in favor of the polymer-coated stents (Lofina et al., 2006).

More recently, the ISAR-TEST-3 randomized non-inferiority trial of rapamycin-eluting stents with 3 different coating strategies (polymer-free vs. biodegradable vs. permanent polymer) showed that polymer-free stents had inferior mid-term efficacy (6–8-month angiographic late loss: 0.23 vs. 0.47 mm, p = 0.94 for non-inferiority) in reducing angiographic restenosis compared to the permanent-polymer stent (Mehill et al., 2008). However, extended 2-year follow-up with paired angiographic data showed a similar clinical safety profile among the 3 stents.
(Byrne et al., 2009b); of note, ongoing delayed late lumen loss (between 6–8 months and 2 years) was observed only for the 2 polymer-based stents (Fig. 8).

In addition, latest 1-year results from the BioFreedom FIM study (Table 1) in a small patient population showed that a novel polymer-free biolimus-eluting stent was non-inferior to the 1st generation PES with a trend towards superiority in terms of in-stent late lumen loss (Grube, 2010).

8. Conclusions

A DES is a highly sophisticated device enabling localized drug delivery for preventing neointimal growth following percutaneous coronary intervention. Although the actions of the pharmacologic agents used in DES are primarily responsible for drug biologic potency, customization of dosage and elution kinetics is essential for enhancing the therapeutic effect and minimizing the side-effects. The implantation of the scaffold on the endothelial surface has a dramatic impact on the local hemodynamic milieu, which in turn interacts with the prosthesis determining drug deposition, distribution and retention in the arterial wall, while flow-generated SS influences the vessel’s restenotic response. Additionally, coating strategy plays an integral role in DES performance affecting both biocompatibility and drug release. Optimization of DES efficacy necessitates a multi-aspect approach including each component of the device and integrating the interaction of DES features with the vascular environment.

References


