

VIEWPOINT

Sirolimus and Paclitaxel on Polymer-Based Drug-Eluting Stents

Similar But Different

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Recent clinical studies that investigated the efficacy of the two U.S. Food and Drug Administration-approved drug-eluting stent (DES) platforms Cypher (Cordis, Johnson and Johnson, Miami Lakes, Florida) and Taxus (Boston Scientific, Boston, Massachusetts) suggest that there are differences between both DES concerning neointimal growth. Both DES elute compounds that inhibit the cell cycle, but at different stages: Cypher stents elute sirolimus, which induces G₁ cell cycle inhibition, and Taxus stents release paclitaxel, which predominantly leads to M-phase arrest. In an attempt to explain the differences observed in human studies, the properties of these stent-based compounds on critical molecular and cellular events associated with the pathophysiology of in-stent restenosis are discussed in detail with the conclusion that both sirolimus and paclitaxel are different in their pleiotropic anti-restenotic effects. This may be in part responsible for the differences observed in recent clinical studies. (J Am Coll Cardiol 2006;47:708–14) © 2006 by the American College of Cardiology Foundation

The introduction of drug-eluting stents (DES) into clinical cardiology at the beginning of the new millennium can be considered a success story opening the gates for a new era in interventional cardiology. Comprehensive understanding of the molecular and cellular basis of neointimal hyperplasia, which ultimately accounts for in-stent restenosis (1), has enabled the identification of compounds that efficiently inhibit mitogen-induced smooth muscle cell proliferation (2,3), the leading cause of in-stent neointimal hyperplasia and consequently restenosis. Currently, two U.S. Food and Drug Administration-approved DES platforms are commercially available: Taxus (Boston Scientific, Boston, Massachusetts) and Cypher (Cordis, Johnson and Johnson, Miami Lakes, Florida). Various studies have shown that both DES efficiently prevent angiographic and clinical restenosis rates compared with bare-metal stents (4,5). The compounds applied on these particular DES platforms are different: Cypher elutes sirolimus (SRL), Taxus releases paclitaxel (PTX).

CLINICAL STUDIES DIRECTLY COMPARING THE EFFICACY OF THE SRL-ELUTING CYPHER STENT WITH THE PTX-ELUTING TAXUS STENT ON THE PREVENTION OF RESTENOSIS

As expected, randomized, prospective multicenter trials were conducted to address the question of whether one of these stents is superior to the other, primarily concerning efficacy but also safety. Efficacy is generally measured by

both angiographic and clinical parameters. Angiographically, the late loss in in-stent lumen diameter at least six months after stent placement is a common parameter for directly assessing neointimal growth because of its greater statistical power compared with clinical restenosis rates (6). Importantly, there is a close relationship between late in-stent lumen loss and the incidence of binary restenosis (6) as well as target vessel revascularization (7), therefore, assessment of late lumen loss can be regarded as an appropriate marker for assessing the efficacy of a DES platform. The Prospective Randomized Multi-Center Head-to-Head Comparison of the Sirolimus-Eluting Stent (Cypher) and the Paclitaxel-Eluting Stent (Taxus) (REALITY) trial is not yet published, but the findings of this study were presented at the 2005 annual meeting of the American College of Cardiology (8). This trial compared the angiographic and clinical outcome of Taxus and Cypher stents in patients with de novo lesions between 2.25 and 3 mm in diameter. A total of 1,353 patients were included in this trial. Cypher stents did reveal significantly less in-stent late lumen loss (Cypher, 0.09 ± 0.43 mm; Taxus, 0.31 ± 0.44 mm; $p < 0.001$) and an increased in-stent minimal lumen diameter at eight months of angiographic follow-up (Cypher, 2.00 ± 0.54 mm; Taxus, 1.85 ± 0.52 mm; $p < 0.001$). However, in this particular study, this did not translate into a significant reduction of the binary restenosis rate by the Cypher stent (Cypher, 7.0%; Taxus, 8.3%; $p = 0.32$) as was reported in the recently published Sirolimus-Eluting and Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) (9) trial. In the latter study, which included 1,012 patients, Cypher stents yielded again significantly less late in-stent lumen loss compared with Taxus

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Abbreviations and Acronyms

- CKI = cyclin-dependent kinase inhibitor
- DES = drug-eluting stent
- mTOR = mammalian target of rapamycin
- PTX = paclitaxel
- SRL = sirolimus
- TLR = target lesion revascularization
- VSMC = vascular smooth muscle cell

stents (0.13 ± 0.37 mm vs. 0.25 ± 0.49 mm, respectively; $p < 0.001$) as well as a lower incidence of clinical restenosis, as reflected in the target lesion revascularization (TLR) rate (4.8% vs. 8.3%, respectively; $p = 0.025$).

Additionally, in selected high-risk subsets for restenosis, such as patients treated for recurrent in-stent restenosis, Cypher stents prevented late in-stent lumen loss more efficiently compared with Taxus stents in the Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) study (10). Further, despite the relatively small patient number included in this trial that was powered to show differences between PTCA alone and DES for the prevention of recurrent in-stent restenosis, the significantly better late lumen loss in the Cypher group did translate into a significantly lower TLR rate after one year compared with Taxus (Cypher, 8.0%; Taxus, 19.0%; $p = 0.02$). Similar results are reported for patients receiving stent-based percutaneous coronary intervention for the treatment of de novo diabetic lesions (11) with a decreased late lumen loss in Cypher compared with Taxus stents, but the trend toward lower clinical restenosis rates in patients treated with Cypher did not reach statistical significance (6.4% vs. 12.0% for Taxus; $p = 0.13$) because the trial was not powered to address this issue. A recent meta-analysis that included all presently available major studies that directly compared outcomes between Cypher and Taxus (4) showed a significantly better angiographic and clinical restenosis rate in patients who received a Cypher stent (Fig. 1).

Hence, there is emerging evidence showing that Cypher stents are more efficient for the inhibition of in-stent restenosis. This certainly leads to the question of what accounts for the difference between the two DES platforms. In the pre-DES era, stent design was considered an important predictor for the rate of restenosis (12); however, this factor might be less important for DES, and there are no studies available yet that compare different stent designs with identical coatings. Additionally, release kinetics may be important for both efficacy and safety of a DES platform. Importantly, the presence and type of polymeric coating may also influence the rate of in-stent restenosis (13,14) and stent thrombosis (15) because polymers can be associated with ongoing vascular inflammation and delayed vascular healing (16-18). However, little information is available concerning the detailed role of the polymers used on Cypher and Taxus, respectively, on vascular healing processes and thus restenosis and late adverse events. However, data from animal stent models suggest that both stents have an increased rate of ongoing vascular inflammation compared with bare-metal stents (19,20).

As implied in the term “drug-eluting stent,” the compound and its pharmacologic properties hold a major key for the safety and efficacy of a DES. In contrast to release kinetics and polymer issues, there is considerable information available on how these drugs are different in terms of their anti-restenotic properties. To address these differential effects of SRL and PTX in the cardiovascular context, the impact of these substances on fundamental molecular and cellular mechanisms associated with in-stent restenosis and vascular healing must be revisited. These include smooth muscle cell proliferation and migration, impact on endothelial regrowth and function, immunosuppressive properties, diffusion capacity of the compound and drug accumulation in distinct layers of the vascular wall, the impact of release kinetics and dosage, as well as therapeutic range and cytotoxicity, including impact on apoptosis and necrosis.

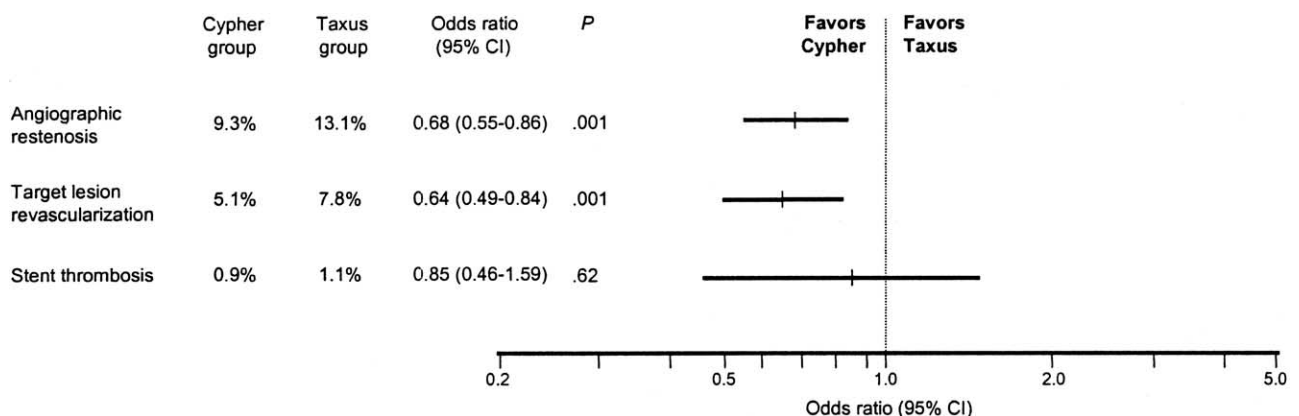


Figure 1. Odds ratio of angiographic restenosis, target vessel revascularization, and stent thrombosis associated with Cypher and Taxus stents according to a meta-analysis of studies that directly compared the performance of the two drug-eluting stent platforms in clinical trials (4). This meta-analysis suggested a superior performance of the sirolimus-eluting Cypher stent regarding angiographic restenosis and target lesion revascularization; no difference in the rate of stent thrombosis could be detected between the two DES platforms.

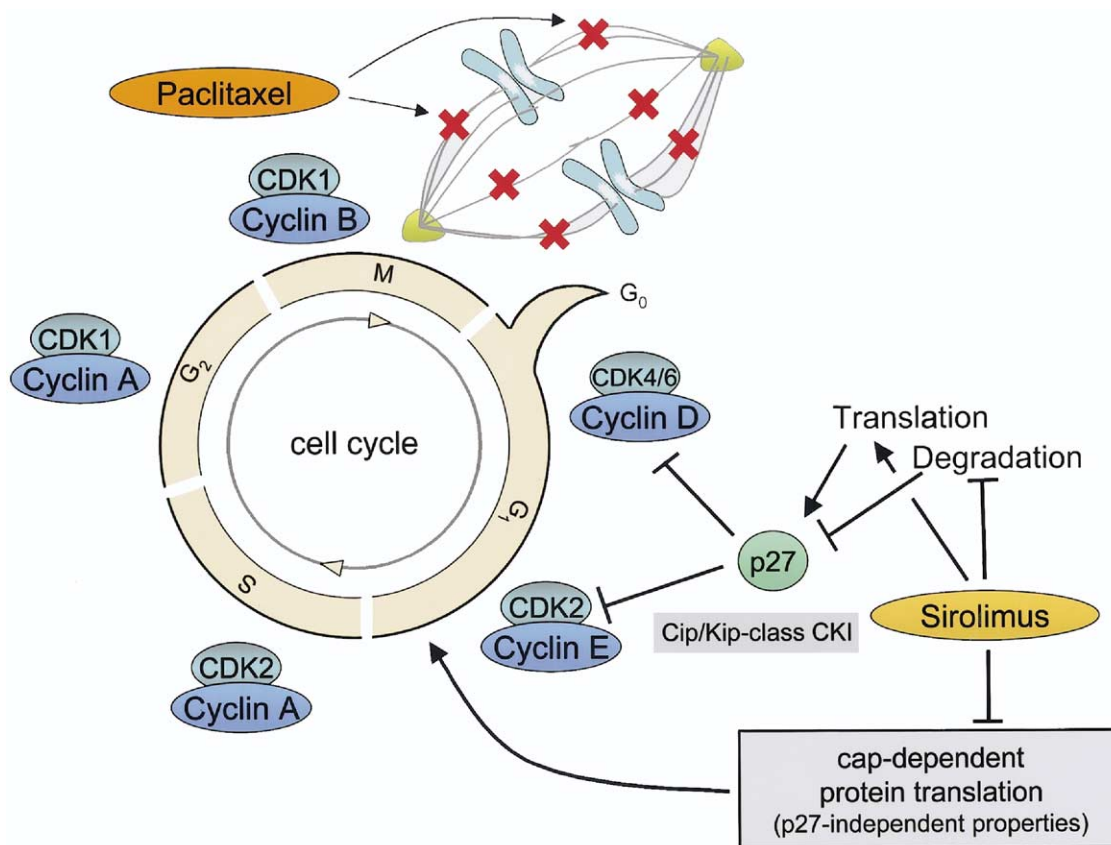


Figure 2. Schematic illustration of the cell cycle and its regulatory mechanisms that are relevant for the inhibitory effect imposed by sirolimus (SRL) and paclitaxel (PTX). The cell cycle is regulated by the oscillating activities of cyclin/cyclin-dependent kinase (CDK) complexes. Cyclin-dependent kinase inhibitors (CKIs) negatively control the activity of distinct cyclin/CDK complexes. The CKIs of the Cip/Kip class are major regulators of the cell cycle in its initial stage, the G₁/S phase. Cip/Kip CKI include p21^{Cip1} and p27^{Kip1}, among others. Both are critical cell cycle regulators in smooth muscle cells. p27^{Kip1} activity is regulated at the post-transcriptional level via protein stability and translation. Subsequent to binding its intracellular receptor FKBP12 (FK506 binding protein), SRL inhibits the activity of mammalian target of rapamycin (mTOR). mTOR is a pivotal protein kinase that mediates mitogen-induced cell proliferation. The inhibition of mTOR by SRL attenuates p27^{Kip1} degradation, thus increasing p27^{Kip1} protein stability. Additionally, p27^{Kip1} protein translation may also be enhanced. Non p27^{Kip1}-dependent mechanisms of mTOR that lead to stimulation of cap-dependent protein synthesis and are inhibited by SRL include p70^{S6K} and eIF4E activation, the latter via induction of eIF4E binding protein-1 (4EBP1). Paclitaxel impacts predominantly during cell division in the mitosis (M) phase of the cell cycle through centrosomal impairment, induction of abnormal spindles and suppression of spindle microtubule dynamics.

IMPACT ON SMOOTH MUSCLE CELL PROLIFERATION AND MIGRATION

Percutaneous coronary intervention imposes vascular injury that leads to the initiation of vascular healing processes. Mitogen-mediated proliferation of vascular smooth muscle cells (VSMC) represents a crucial event for the formation of neointimal hyperplasia (1). Complex activation of various partially redundant signaling pathways converge in a final common pathway, activation of the cell cycle (21). Both compounds show inhibition of the cell cycle but have different modes of action (Fig. 2). Subsequent to binding to its major intracellular receptor FKBP12, SRL inhibits mammalian target of rapamycin (mTOR) and ultimately restrains the degradation of p27^{Kip1}, a cyclin-dependent kinase inhibitor (CKI) that plays a crucial role for VSMC cycle regulation (22,23). Elevated levels of p27^{Kip1} inhibit cell cycle in the G₁ phase (24), which represents the initial phase of cell cycle progression. Loss of the ability to upregulate p27^{Kip1} may result in SRL resistance (25).

In contrast to SRL, PTX impacts predominantly during the mitosis (M) phase of the cell cycle through centrosomal impairment, induction of abnormal spindles, and suppression of spindle microtubule dynamics (26). As a downstream event, consecutive up-regulation of p53 may occur that may lead to further cell cycle arrest in G₁, possibly through the induction of p21^{Cip1} (27). Because PTX arrests cells at a stage at which they are supposed to divide, pro-apoptotic mechanisms, in part mediated by p53, are likely to occur, thus eventually leading to apoptotic cell death (27).

Migration of smooth muscle cells from the media to the intimal region resembles an important step in the pathophysiology of restenosis. It has been well established that SRL inhibits migration of VSMC (28). Mechanistically, this effect is again predominantly mediated by p27^{Kip1} because this CKI inhibits migratory cell capacity (29). Likewise, it has also been shown that PTX may inhibit VSMC migration (3), most likely triggered by interactions with the cytoskeleton.

THERAPEUTIC RANGE, CYTOTOXICITY, AND APOPTOSIS

Every one of these partially redundant factors is important for the evaluation of compounds targeted for application on DES because exaggerated vascular injury and necrosis as well as delayed vascular healing may impose a substantial risk for adverse cardiac events. This was evident in several clinical trials. The QuaDDS DES-eluting (Quanam Medical Corp., Santa Clara, California/Boston Scientific Corp., Natick, Massachusetts) that elutes 7-hexanoyl-taxol delivered cytotoxic drug dosages into the vascular wall, which translated into an unacceptably high clinical event rate due to a stent thrombosis of more than 10% (30), in the majority of cases resulting in myocardial infarction. Another example is the use of actinomycin D on DES. In pre-clinical *in vivo* models, actinomycin D-eluting stents showed a narrow therapeutic range with cytotoxic dosages only exceeding two- to three-fold the dosage necessary to yield a therapeutic effect (31). Toxic effects included vessel remodeling, mural thrombus, and toxic changes in the vessel wall. The Actinomycin-Eluting Stent Improves Outcomes by Reducing Neointimal Hyperplasia (ACTION) trial disclosed no significant benefit toward the inhibition of neointima formation (32). Whereas actinomycin D is considered cytotoxic, SRL is a cytostatic compound with a large therapeutic range (33). In the dose range used for clinical applications, there is no appreciable pro-apoptotic effect in VSMC. This is likely not the case for PTX, which is expected to facilitate apoptotic processes even in the dose range that is considered to be therapeutic for the prevention of restenosis (27). Additionally, PTX must be considered to induce cytotoxicity either by apoptosis or, as has been shown in transformed cell lines, necrosis, at least at higher dosages (34), therefore, the therapeutic range can be considered smaller compared with SRL.

DIFFUSION CAPACITY AND DISTRIBUTION IN THE VASCULAR WALL

Therapeutic efficacy of a specific compound on a DES platform is not solely dependent on its cellular and molecular impact on various mechanisms of neointimal hyperplasia, but also on its physicochemical properties. It has been shown that hydrophobic drugs such as PTX and SRL accumulate most efficiently in the vascular wall in comparison with hydrophilic substances (35). In a very elegant study, Levin et al. (36) showed several important dissimilarities between the accumulation of SRL and PTX in distinct areas of the vascular wall. Because the cellular component of in-stent restenosis primarily originates from the medial and intimal layer (37), drug concentrations should peak in these segments of the vascular wall. Whereas SRL distributes equally within the vascular layers, PTX accumulates in the adventitia (36), which is believed to play an inferior role in the pathophysiology of in-stent restenosis.

Additionally, the transmural diffusion coefficient of SRL is more than twice as high as the respective value of PTX (36). As shown recently, penetration of the stent-based compound into the vascular wall is also dependent on the presence of thrombotic material. The PTX diffusivity is severely impaired in the presence of thrombus with a direct dependency on its red blood cell count (38). Corresponding data for SRL are presently not available.

IMPACT ON ENDOTHELIUM AND STENT THROMBOSIS

The endothelium plays a protective role in the process of neointima formation (39), and clearly, promotion of endothelial recovery is regarded as the next target for restenosis prevention (40). There are limited data regarding the effect of SRL and PTX on endothelial (re-)growth. It seems that both compounds retard endothelial regeneration, thus negatively affecting the restoration of its morphologic and functional integrity. This may facilitate, in some cases, the development of late stent thrombosis (41). Interestingly, recent findings from a human study suggest that endothelial dysfunction is frequently apparent after implantation of a Cypher stent (42,43). At this point, data available from large DES trials suggest no significant increase of stent thrombosis for the two established DES platforms (44,45) compared with bare-metal stents; however, these trials were not powered to show that difference. Yet, a recent case report raised the concern that late-stent thrombosis may occur in a subgroup of patients, especially when anti-platelet therapy was completely stopped (41). Further, a recently published study suggested that patients who are discontinuing clopidogrel while maintaining low-dose aspirin therapy also are potentially at increased risk of late stent thrombosis, whereas it seems that patients left on dual antiplatelet therapy with clopidogrel and aspirin remain on the level of stent thrombosis that is known for uncoated, bare-metal stents (46). So far, exclusively in the REALITY trial, which compared both DES platforms directly, a significant increase in the rate of stent thrombosis was reported for patients who actually received a Taxus stent (1.8% vs. 0.4% for Cypher; $p = 0.0196$), yet statistical significance was not reached in the intention-to-treat analysis (Cypher, 0.6%; Taxus, 1.6%; $p = 0.0723$) (8). This important topic is the subject of further investigations, and so far, no definite conclusions can be drawn. However, there is evidence showing that the rate of stent thrombosis may be higher in real-world patients than in controlled studies. Stent thrombosis might be dependent on vascular factors such as bifurcation stenting as well as on extravascular factors such as decreased left ventricular function and renal failure (47). As long as clear evidence is fostered, patients are now often advised to stay on prolonged anti-thrombotic therapy, especially when they are considered at elevated risk for late stent thrombosis.

IMMUNOSUPPRESSIVE PROPERTIES

Both DES platforms, Taxus and Cypher, use non-erodable polymers for retardation of drug delivery. It is well known that polymers may induce acute and chronic inflammatory responses *in vivo* (48) that can consequently lead to late adverse cardiac events in humans such as late stent thrombosis (15) or late in-stent restenosis (49). Therefore, immunosuppressive properties are regarded as beneficial for the suppression of local inflammatory responses that are predominantly precipitated by the polymer. Sirolimus was developed as an immunosuppressive agent and is clinically applied in transplantation patients to prevent graft rejection and, concomitantly, the progression of cardiac allograft vasculopathy (50). In contrast, PTX primarily is not considered to be a classical immunosuppressive agent and is not used clinically as an immunosuppressant drug. Being primarily an anti-cancer drug, this may not even be desirable in this particular background. Inferior immunosuppressive properties of PTX may explain at least in part the findings in pre-clinical animal models in which Taxus-stented vascular segments showed an increased presence of inflammatory cells compared with Cypher stents (13).

PATTERNS OF IN-STENT RESTENOSIS IN SRL VERSUS PTX-ELUTING STENTS

Both the magnitude of neointimal hyperplasia as reflected by assessment of late lumen loss via intravascular ultrasound and/or quantitative angiography as well as the pattern of in-stent restenosis give valuable insight into the potency of the compound to suppress restenotic processes in humans. The pattern of restenosis within the Cypher stent is in the large majority of cases focal (51). However, the pattern of neointima formation in Taxus stents seems to differ from what is observed with Cypher stents. In a recently published study by Iakovou *et al.* (52), 50% of restenotic Taxus stents showed a diffuse pattern of restenosis, and 21% of all restenotic lesions even showed complete occlusion. Together with the consistent finding that late in-stent lumen loss is significantly less in Cypher stents (8-11), these observations implicate a better performance of the Cypher stent platform compared with Taxus regarding the prevention of neointimal hyperplasia and thus in-stent restenosis.

RELEASE KINETICS AND DRUG DOSAGE

The effectiveness of both SRL- and PTX-coated stents is dependent not only on the totally delivered drug concentration but also on release kinetics. For polymer-coated SRL-eluting stents, the results of four-year follow-up show that the slow-release SRL-coated stent, which is available as Cypher and maintains drug release for up to 60 days, has a more favorable outcome than a similar SRL-eluting stent that releases its total dose within 7 days (53). A polymer-free rapamycin-eluting stent that liberates most of the compound within 21 days (20) showed a dose-dependent

Table 1. Comparison of Critical Parameters Associated With Restenosis and Adverse Vascular Events for Sirolimus and Paclitaxel as They Are Currently Used on FDA-Approved Drug-Eluting Stents

	Sirolimus	Paclitaxel
Inhibition of SMC proliferation	++	++
Inhibition of SMC migration	++	+
Inhibition of EC proliferation	++	++
Immunosuppressive properties	++	(+)/-
Pro-apoptotic effects	(+)	++
Therapeutic range	Wide	Narrow
Vascular wall distribution	↔	↑ Adventitia
Pattern of restenosis	Focal	≈ 50% Proliferative
Impact on late in-stent lumen loss*	++	+

*Prospective multicenter studies directly comparing Cypher and Taxus stents (8-11).
EC = endothelial cell; FDA = U.S. Food and Drug Administration; SMC = smooth muscle cell; ↔ = equal distribution. ↑ = accumulation.

reduction in angiographic and clinical restenosis rate (54). For the Taxus stent, no significant difference was found between slow- and medium-release PTX-eluting stents in a prospective human trial (55). In contrast, the polymer-free Supra-G stent (Cook, Bloomington, Indiana) showed a more favorable result in terms of restenosis for patients that received higher stent-based PTX dosages (3.1 $\mu\text{g}/\text{mm}^2$ vs. 1.3 $\mu\text{g}/\text{mm}^2$). In the recently published PISCES trial (56), a first-in-humans study that assessed the effectiveness of PTX-loaded Conor stents (Conor Medsystems, Menlo Park, California), the better outcome of stents eluting PTX for 30 days was not dependent on the absolute PTX dosage because both concentrations that were studied, 10 μg and 30 μg per stent, had similar clinical restenosis rates. Interestingly, the same dosages seemed to be less effective when they were eluted by the otherwise-identical stent platform within 10 days after percutaneous coronary intervention. Taken together, recent findings from human trials suggest that the effectiveness of both PTX and SRL may depend on total drug dosage as well as release kinetics. However, the optimal release kinetic may depend on lesion and patient characteristics, the stent platform, and the compound itself, as well as the presence of a polymer.

CONCLUSIONS

There is compelling evidence, both experimentally and clinically, showing that SRL and PTX are different concerning important features of vascular healing and the prevention of neointima formation (Table 1). These apparent differences may account for a considerable part of the disparities in angiographic and clinical outcomes now observed in several prospective randomized trials. However, a protracted follow-up period is required to confirm the differences observed with both DES platforms. Evidently, further studies investigating the effect of release kinetics and polymeric coating on critical mechanisms of neointima formation and vascular healing are warranted. For future developments in the DES era, lessons learned from pre-clinical studies in conjunction with results of clinical evalu-

ations are indispensable for overcoming the remaining problems of current DES platforms.

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