

Treatment of Drug-Eluting Stent Restenosis With Another Drug-Eluting Stent: Do Not Fail the Second Time!

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Drug-eluting stents (DES) have dramatically diminished but not eradicated in-stent restenosis (ISR) and even though they have resulted in single digit rates in simple lesions, it is not unusual to see double figure rates of ISR in more complex lesions and real world studies.

Despite this problem little attention has been given to evaluate the pathogenesis of DES restenosis and the optimal treatment of this condition. Thus, the study by Byrne et al¹ published in this issue of *Revista Española de Cardiología* is welcomed and provides a foundation for the discussion of DES restenosis. First we would like to briefly highlight what we have learnt over the last few years about DES failure.

We have seen a developing consensus regarding the predictors of DES restenosis which include: diabetes, treatment of ISR, ostial lesions, lesion length, stent length, reference vessel diameter, post-intervention minimal lumen diameter, final diameter stenosis, non-left anterior descending coronary artery lesions, and complex lesions.²⁻⁴ While the treatment of bifurcation lesions and chronic total occlusions were not shown to be predictors of restenosis in some studies, there is no doubt that both are associated with increased risk. In bifurcations the ostium of the side branch is the major offender while the increased risk with long stents frequently utilized in chronic total occlusions is the corresponding risk factor.

Byrne et al¹ found that in 43 restenotic lesions, the predominant pattern of paclitaxel-eluting stent (PES) restenosis was focal (77%) with a non-focal pattern in the remainder (Table 1).⁵⁻¹¹ Recent data from our centre examining the largest cohort of restenotic lesions found a similar spread of restenosis patterns.¹² In a cohort of

150 restenotic sirolimus-eluting stent (SES) lesions, 71% were focal, 16.7% diffuse, 0.7% proliferative and 11.3% occlusive. While the predominant pattern in the PES cohort of 149 lesions was also focal (51.7%), there was a significantly higher incidence of diffuse (26.2%) and occlusive restenosis (21.5%). Similar to SES, proliferative restenosis was extremely rare (0.6%). We also studied the prognostic implications of the pattern of restenosis following both SES and PES implantation.¹³ We identified 250 restenotic lesions (66.4% SES and 33.6% PES) with a focal pattern in 65.2% and non-focal in 34.8%. The rate of recurrent restenosis was 17.8% in the focal group and 51.1% in the non-focal group ($p = 0.0001$). The incidence of target lesion revascularisation (TLR) also increased with the type of restenosis treated (9.8% and 23% respectively, $p = 0.007$). Thus unlike BMS restenosis the predominant pattern of restenosis with DES is focal, which appears to be associated with a better prognosis.

The aetiology of DES restenosis appears to be multifactorial and the potential mechanisms include several mechanical factors such as underexpansion or overexpansion of the stent, strut fracture, nonuniform strut distribution, or stent malapposition. There are also important drug-specific factors like nonuniform drug deposition, polymer disruption due to difficult stent delivery, localized hypersensitivity, and drug resistance.^{10,14,15} Although not definitively proven, it is widely speculated that non-focal restenosis is associated with drug resistance or drug failure, whereas focal restenosis is more likely related to mechanical, technical or specific local factors such as stent underexpansion, stent fracture, geographic miss, or at a gap between stents.^{14,15} In the present study¹, Byrne and associates hypothesised that drug resistance may be the predominant mechanism and thus elected to treat PES restenosis with a different or hetero-DES, in this case a SES. This strategy was associated with a re-restenosis rate of 16.7% and a TLR rate of 16.3% at 2 years. However, are these results better than if the same DES was used; i.e. a PES to treat PES restenosis? There are 3 studies (Table 1) that retrospectively analysed the outcomes of DES restenosis treated with implantation of a different DES or the same DES.⁹⁻¹¹ None of these studies found a significant difference in major adverse cardiac event (MACE) or

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Summary of the Published Studies Examining the Treatment of Drug-Eluting Stent Restenosis

Study	Patients/ Lesions	Follow-up (months)	Angiographic Follow-up	Reste notic stent	Pattern of ISR	Treatment	MACE	TLR	ISR
Lemos et al ⁵	24/27	16.3	78%	SES	Focal/Diffuse-14%; proliferative-43%; occlusive-43%	BMS (1), BA (3), SES (12), PES (11)	N/A	N/A	42.9% overall; DES: 18.2%
Kim et al ⁶	55/58	12	83%	SES (27), PES (31)	Focal-47%; diffuse-22%; proliferative-24%; occlusive-7%	SES (33) vs CB (11) or ICB (14)	N/A	3.2% vs 8.3%	3.6% vs 35% ^a
Torguson et al ⁷	111/112	8	N/A	SES (78%); PES (22%) ^b	Focal-63%; diffuse-26%; proliferative-11%	DES (50) vs ICB (52)	10% vs 24% ^a	10% vs 8%	N/A
Lee et al ⁸	125/140	7.2 ± 1.8	30%	SES	N/A	PES	17.2%	14%	N/A
Cosgrave et al ⁹	174/201	25.7 ± 7.6	70%	SES, PES	Focal-62%; diffuse-26%; proliferative-3%; occlusive-9%	Same DES (107) vs different DES (94)	26% vs 17.9%	15.9% vs 16%	26.4% vs 25.8%
Garg et al ¹⁰	116	12	N/A	SES, PES	Focal-44%; Nonfocal-56%	Same DES (54) vs different DES (62)	22.5% ^c vs 21.4%	17.9% vs 15%	N/A
Mishkel et al ¹¹	92/108 ^c	12	N/A	SES, PES	Focal-41%; diffuse-18%; proliferative-1%; occlusive-8%; Edge-32%	Same DES (64) vs different DES (22) vs BA (19), BMS (2), ICB (1)	43% ^c vs 25.1% vs 76.3%	28.5% vs 19.0% vs 36.5%	30.6% overall
Byrne et al ¹	43	24	84%	PES	Focal-77%; Diffuse-19%; proliferative-2%; occlusive-2%	SES	25.8% ^c	16.3%	16.7%

BA: balloon angioplasty; BMS: bare-metal stent; CB: cutting balloon; DES: drug-eluting stent; ICB: intracoronary brachytherapy; ISR: in-stent restenosis; MACE: major adverse cardiac events; N/A: not available from manuscript; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; TLR: target lesion revascularisation; TVR: target vessel revascularisation.

^aSignifies where comparison is significant; i.e. $p < 0.05$. All other comparisons are non-significant

^bIncludes 7 patients treated with a paclitaxel nonpolymeric stent

^cMACE includes TLR whereas elsewhere includes TVR

^dIncludes 8 patients treated for stent thrombosis but results are not reported separately.

TLR rates. The present study together with the previous reports summarised in Table 1, provides valuable clinical data and reassurance on the efficacy of repeated DES using either the same or as in this report a different platform in patients who failed initial DES therapy. However, it should be pointed out that none of these studies are randomised, and like the present report majority are limited by a small sample size and/or lack of a control group. It is also evident from Table 1, that DES restenosis identifies a high risk cohort that have a significant recurrence and MACE rate with repeat percutaneous intervention especially in the subset with non-focal restenosis. As a result coronary artery bypass surgery should be considered as a viable treatment alternative for complex DES restenosis.¹¹ Furthermore, we currently only have information on the treatment of DES restenosis with the first commercially available PES and SES platforms and none of the newer generation DES.

Important questions still remain unanswered: Is implanting a different DES superior to the same DES?

Will individualizing therapy based on the possible mechanism of ISR (i.e. mechanical vs. drug-related) improve outcomes? If it becomes possible to identify patients with drug resistance, will they benefit from the use of a different DES?⁷ The first of these questions will hopefully be answered by the GISE-CROSS study. This study will randomly assign 2 separate groups of patients with ISR after PES or SES to repeat intervention using the same DES (No-CROSS groups) or a different DES (CROSS groups).¹⁴ Thus given the lack of clear guidelines and absence of randomized data, what is the ideal way to treat a DES restenosis? Our approach is somewhat pragmatic and is based on the response to 2 critical questions: 1) Is the restenosis focal or diffuse? 2) Is there a relative contra-indication to DES implantation (e.g. high risk of bleeding, compliance with dual antiplatelet therapy, anticipated surgery, etc.)? In cases of focal DES restenosis, we either implant another DES (same or different drug) or treat with balloon angioplasty, cutting balloon or medical therapy. In cases of diffuse ISR we

prefer utilizing a DES with a different antiproliferative agent. Finally, we recommend the liberal use of intravascular ultrasound (IVUS) in cases of DES failure which may often elucidate a possible mechanical cause. Usually IVUS tells us that the vessel is larger than what we expected angiographically. The possibility of obtaining a larger final in-stent minimal diameter, sometimes 0.5 mm larger compared to an angiographic evaluation, further decreases the risk for a second restenosis. In treating DES restenosis we make every attempt to optimise the result and not fail the second time.

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