Sirolimus-Eluting Stents for the Treatment of Stenoses in Small Coronary Arteries: What Have We Learned?

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Percutaneous coronary intervention (PCI) in small vessels (broadly defined as stenosis in vessel with reference diameter <2.75-2.80mm, or <3.00mm)[1,2], have been historically associated with high rates of restenosis (18-52%) and vessel revascularization (up to 27%)[1,3-5]. Prior to drug-eluting stents (DES), a strong correlation between restenosis and vessel size was recognized, with an inverse association between vessel size and angiographic restenosis; this was attributed to the disproportionately greater amount of neointimal hyperplasia (NIH) relative to the vessel caliber in smaller vessels[1,3]. This phenomenon seemed to be aggravated in diabetics who often present "small" arteries because of diffuse coronary disease and exaggerated neointimal proliferative response[4]. Several studies had attempted to demonstrate the efficacy of stenting versus balloon angioplasty in small vessels, but results were controversial. However, a recent meta-analysis of 11 randomized trials (2,971 patients) comparing bare metal stents (BMS) versus balloon angioplasty in vessels 2.22-2.60mm, demonstrated that restenosis was improved by stent implantation (p=0.003), with relative risk of 0.77 (95% confidence interval 0.65, 0.92)[1].

With the introduction of sirolimus-eluting stents (SES), many expected that the similar effectiveness of SES for preventing restenosis in uncomplicated lesions would extend to high risk subsets such as small vessels. In this issue of the *Arquivos Brasileiros de Cardiologia*, Devito et al[6] reports the outcomes of 80 patients enrolled in a prospective, non-randomized comparison between SES (Cypher® stent) versus a BMS (ML-Pixel® stent), for the treatment of *de novo* coronary lesions in vessels 2.20-2.75mm in diameter. All stents were implanted successfully and final luminal dimensions were similar in both groups. (It is important to note that in this investigation, patients were consecutively enrolled at two different time points, and even though baseline clinical demographics were comparable, the two groups were not perfectly matched according to some important criteria, including lesion complexity and stent size.) At follow-up, late lumen loss (LLL), restenosis and NIH area were significantly reduced with SES; also, a 3.5-fold decrease in target lesion revascularization (TLR) was found in SES compared to BMS, a difference that did not reach statistical significance.

The performance of SES in small vessels has been evaluated in several randomized clinical trials and registries (Table 1). LLL, a surrogate of NIH, was significantly decreased with SES compared to BMS in "small vessels" by 98.7%, 78.8%, 81%, 88.2%, and 82.2% in RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, and SES-SMART, respectively[2,5,7-10]. In Devito's study, LLL was decreased by 77.5%, p<0.001[6]. A slightly higher in-stent LLL (0.36mm) was found in SIRIUS-2.25 compared to the other studies (0.01-0.21mm) (Table 1). SIRIUS-2.25 had increased rates of diabetics (40%) and complex lesions (71% B2/C) [11]. Diabetics have been demonstrated to have higher LLL compared to non-diabetics[12,13]. In Devito's analysis, which also had 40% of diabetes but less complex lesions, LLL was 0.25mm[6]. Overall, these LLL were comparable to the LLL found in lesions in larger vessels treated with SES[7-9,14], and were considerably lower compared to BMS (0.80-1.05mm)[2,5,7,10], confirming the consistency and effectiveness of SES in preventing NIH, despite differences in diabetes rates, vessel size and lesion characteristics.

The classic inverse relationship between vessel size and restenosis was not seen with SES in RAVEL (0% restenosis in all vessel sizes)[7]. But, in a sub-analysis of the SIRIUS trial (which had longer and more complex lesions), lesions were divided into tertiles according to vessel size, and in-stent restenosis was 5%, 2.5%, and 1.9% with SES in small (2.32mm), "medium" (2.78mm), and large (3.31mm) vessels. Conversely, in-segment restenosis was increased in small vessels (17.6%), compared to "medium" (6.6%), and large (1.9%) vessels[9]. As a result, the risk reductions for in-segment restenosis with SES decreased by 93.7%, to 81.7%, to 58.8% in large,

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Table 1 - SES In "Small Vessel" Trials

	RAVEL*[7]	SIRIUS†[17]	E-SIRIUS[10]	C-SIRIUS[5]	SES-SMART[2]	RESEARCH‡[14]	SVELTE[15]	SIRIUS 2.25mm[11]	Devito et al[6]
Number of patients	42	350	175	50	129	91§	101	100	50
Diabetics, %	19	27.1	19	24	19.4	26	26.7	40	40
Lesion class B2/C (ACC/AHA), %	61.9||	59¶	-	64	30.4	92¶	-	71	32
QCA									
RD, mm	2.09	2.41	2.60	2.65	2.22	1.88	2.36	2.04	2.44
Lesion length, mm	9.5	14.6	14.9	14.5	13.0	12.3	14.5	12.2	13.8
Follow-up (6-8 months)									
Late lumen loss, mm									
In-stent#	0.01	0.17	0.20	0.12	0.16	-	0.21	0.36	0.25
In-segment**	-0.04	0.23	0.19	0.12	0.16	0.07	0.21	0.23	0.30
Binary restenosis, %									
In-stent#	0	3.9	3.9	0	4.9	10.7	3.2	11.7	0
In-segment**	0	11.6	5.9	2.3	9.8	10.7	6.3	16.9	4
IVUS									
NIH area, mm^2	0.11	0.58	-	-	-	-	0.08	0.16	0.24
Clinical outcome									
Follow-up	12-month	12-month	9-month	9-month	8-month	12-month	12-month	6-month	8-month
TLR, %	0	5.7	4	4	7	5.5	3	4.3	4
Any MACE,†† %	5.8‡‡	9.4	8	4	9.3§§	7.7	7.9	7.4	4
SAT (n)	0	1	2	1	1	1	0	1	0

*Values are expressed as mean or frequencies (% of column total). *Sub-analysis reporting the lowest tertile of vessel size. †SES sub-group from SIRIUS "matched" (and compared) with SVELTE by diabetes, RD (2.20-2.75mm) and lesion length (>15mm, estimated). ‡Sub-group with lesions treated with 2.25mm SES only. §Includes 112 lesions. ||Type B2 only. ¶Overall percentage of patients with complex lesions in the study. #In-stent – defined as within the stented segment. **In-segment – defined as spanning the stented segment plus the 5 mm proximal and distal peri-stent areas. ††Major adverse clinical events, typically defined as death, myocardial infarction and/or target lesion revascularization. ‡‡Overall percentage of patients with MACE in the SES group in RAVEL. §§Includes 1 (0.8%) CVA. ACC/AHA=American College of Cardiology/American Heart Association; CVA=cerebral-vascular accident; IVUS=intravascular ultrasound; QCA=quantitative coronary angiography; RD=reference (vessel) diameter; SAT=subacute stent thrombosis; TLR=target lesion revascularization*

"medium", and small vessels, respectively. In SIRIUS-2.25, restenosis rates were comparable to SIRIUS "small vessel" tertile, and was associated with stent length, diabetes and number of stents implanted[11]. In Devito's report, there was no in-stent restenosis and only 4% in-segment restenosis with SES compared to 33.3% in-stent and 36.7% in-segment restenosis with BMS ($p<0.001$)[6]. Similar results were found in RAVEL, E- and C-SIRIUS, and SVELTE[5,7,10,15]. In RESEARCH, vessel size was considerably smaller compared to the other studies (Table 1), and restenosis (only in-stent) occurred mostly after treatment of ostial lesions[14]. Importantly, in the SES-SMART sub-analysis in diabetics, SES was associated with significant decrease in LLL and restenosis compared to BMS; however, when considering only insulin dependents (35%), restenosis with SES rose to 40%[12]. These data convey some considerations regarding SES in small vessels, including: 1) small vessels experience higher restenosis rates compared to larger vessels; 2) restenosis appears to increase according to lesion severity and stented length; 3) diabetics may experience higher rates of restenosis. This may be related not only to the hyperproliferative and aggressive vascular response often observed, but also to suboptimal stent deployment (incomplete lesion coverage, inadequate stent expansion, see below), since diabetics frequently present with long and diffuse disease (as mentioned before); and 4) the higher "in-segment" restenosis (compared to "in-stent") observed in the majority of studies (Table 1) may be reflecting incomplete lesion coverage and/or injured segment during PCI. This situation has been recognized[8,16] and improvement in the "DES" technique – minimize peri-lesion trauma using short pre-dilatation balloons, complete lesion/injured segment coverage, short post-dilatation balloons (positioned within the stented area to prevent injury outside of the stent edges), and overlap multiple stents avoiding gaps, may be critical to optimize results in small vessels.

Previous studies with IVUS demonstrated that final luminal dimensions in vessels <2.75mm predict vessel

revascularization[17]. Similar results were found with SES. In the IVUS sub-study of the SIRIUS trial, a final minimum stent area >4.5mm^2 for vessels <2.8mm (by QCA) was found to be a threshold that predicted an "adequate" IVUS lumen at follow-up (>4.0mm^2). The positive predictive value of the IVUS stent dimensions was 90%[18]. In addition, Takebayashi et al reported a series of patients with target vessel failure post-SES implantation where the majority of failures (especially in-stent restenosis) were associated with stent *underexpansion*[19]. This is expected as once an effective drug, (in this case, sirolimus), inhibited most of the NIH (Table 1), the main cause of in-stent restenosis became stent *underexpansion*. At last, a larger reference percentage of plaque area and a larger edge stent area/reference minimum lumen area were associated with edge stenosis with SES in SIRIUS[20]. These evidences suggest that successful SES is relied upon a combination of SES' ability to prevent NIH formation and optimal stenting technique. In the context of small vessels, IVUS guided PCI for SES implantation should be especially considered and even recommended, as it: 1) allows accurate assessment of vessel size and lesion length before the procedure, helping operators to selected the proper device and technical approach to achieve full lesion coverage and proper stented segment matching; and 2) may identify inadequate stent expansion, permitting the operator to post dilate the stent to achieve optimal stent expansion.

Finally, implantation of SES in small vessels has been associated with a high procedural success rate (>95%) and sustained safety (comparable to larger vessels treaded with SES), reflected by the low incidence of stent thrombosis and MACE during the mid- and long term follow-up (Table 1)[2,5,6,8,10,11,14,15]. In addition, SES led to a 70% to 81% relative reduction of TLR compared to BMS in "small vessel" randomized trials[2,5,10]. Importantly, both TLR and MACE rates with SES (Table 1) were remarkably low in all studies (<10%), especially given the high-risk lesions treaded and the high-risk population. These results confirm the dramatic impact and overall benefits of SES compared to BMS and historical controls of PCI in small vessels. Nevertheless, despite the impressive progress obtained in the field, small vessel is still predictive of restenosis after SES implantation[8]; therefore, continued efforts, including optimize DES technique and development of novel DES technologies specifically designed for small vessels, are still needed to improve outcome.

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