Symptomatic failure after sirolimus-eluting stent implantation: A rare but challenging condition

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BACKGROUND: Limited information is available regarding restenosis after implantation of a sirolimus-eluting stent (SES).

OBJECTIVE: To report on angiographic characteristics, clinical presentation and treatment of this particularly complex type of coronary lesion.

METHODS AND RESULTS: A total of 1424 SES were implanted in 1159 patients (average 1.2 per patient) for chronic or acute coronary syndromes in the University Hospital of Siena (Siena, Italy), which is a tertiary centre. Symptomatic in-SES restenosis was observed in 26 patients (2.2%) at 10±5 months (median eight months, range four to 23 months) following the initial intervention. In-SES restenosis was associated with stable angina in 16 patients, acute myocardial infarction in three patients and unstable angina in seven patients. Two patients had restenosis in two separate SES. Conditions often associated with in-SES restenosis included treatment of chronic total occlusion, geographic miss or in-stent restenosis during the index procedure. Among the first 20 patients, those with focal, in-body SES (type Ic) restenosis received balloon-only angioplasty, and patients with other patterns received repeat SES implantation. Clinical and angiographic follow-up (average 16±7 months) recorded one death (noncardiac) in the balloon-only group and four cases of unstable angina (three due to relapsing in-SES restenosis in the balloon-only group and the fourth due to a *de novo* lesion). Follow-up quantitative angiography showed a higher incidence of binary restenosis after balloon-only treatment (57% versus 17%; $P<0.05$), as well as higher lumen loss and loss index ($P<0.05$).

CONCLUSIONS: Restenosis after SES implantation occurs more commonly in a focal pattern in-body or at the proximal edge of the stent. Repeat SES implantation appears to be a safer and more effective therapeutic choice than balloon-only angioplasty.

Key Words: Percutaneous coronary intervention; Restenosis; Sirolimus; Stents

In-stent restenosis is generally considered to be a chronic and relatively benign condition that is due to progressive intimal hyperplasia, and whose most common presentation is stable angina. However, this condition represents a quantitatively relevant problem because it may affect as many as 8% to 40% of patients treated with percutaneous revascularization (1). Although the introduction of sirolimus-eluting stents (SES) has dramatically reduced this figure, 2% to 9% of patients still present with symptomatic restenosis following therapy with SES and require repeat therapy (2,3). It is thought that in the future, this percentage may increase due to a generalized trend

Une insuffisance symptomatique après l'implantation d'une endoprothèse par élution de sirolimus : Un trouble rare et complexe

HISTORIQUE : On possède peu d'information au sujet de la resténose après l'implantation d'une endoprothèse par élution de sirolimus (EÉS).

OBJECTIF : Rendre compte des caractéristiques angiographiques, de la présentation clinique et du traitement de ce type de lésion coronaire particulièrement complexe.

MÉTHODOLOGIE ET RÉSULTATS : Au total, 1 424 EÉS ont été implantées chez 1 159 patients (moyenne de 1,2 par patient) en raison de syndromes coronariens chroniques ou aigus à l'hôpital universitaire de Sienne, en Italie, un centre de soins tertiaires. On a observé une resténose sur EÉS symptomatique chez 26 patients (2,2 %) à 10±5 mois (durée médiane de huit mois, fourchette de quatre à 23 mois) après l'intervention initiale. La resténose sur EÉS s'associait à une angine stable chez 16 patients, à un infarctus aigu du myocarde chez trois patients et à une angine instable chez sept patients. Deux patients ont souffert d'une resténose dans deux EÉS distincts. Les états souvent associés à une resténose sur EÉS étaient le traitement d'une occlusion totale chronique, la non-atteinte du foyer ou une resténose sur endoprothèse pendant l'intervention de référence. Chez les 20 premiers patients ceux qui souffraient d'une resténose corporelle sur endoprothèse focale (type Ic) ont subi seulement une angioplastie par ballonnet, et les patients présentant d'autres types de resténose ont subi des implantations répétées d'EÉS. Le suivi clinique et angiographique (moyenne de 16±7 mois) ont enregistré un décès (non cardiaque) dans le groupe ayant subi seulement l'angioplastie par ballonnet et quatre cas d'angine instable (trois causés par une rechute de la sténose sur EÉS dans le ballonnet après l'angioplastie par ballonnet seulement, et le quatrième imputable à une lésion *de novo*). Le suivi de l'angioplastie quantitative a révélé une incidence plus élevée de resténose binaire après l'angioplastie par ballonnet seulement (57 % par rapport à 17 %; $p < 0,05$), ainsi qu'une perte plus élevée de la lumière et de l'indice de perte ($p < 0,05$).

CONCLUSIONS : Une resténose sur EÉS se produit surtout selon un profil focal dans l'organisme ou sur la bordure proximale de l'endoprothèse. L'implantation répétée d'EÉS semble un choix thérapeutique plus sécuritaire et plus efficace que l'angioplastie par ballonnet seulement.

toward more aggressive percutaneous treatment of coronary artery disease.

Although data from single-centre experiences have reported that this type of lesion tends to be focal and most often located within the stent or at one of its edges (more frequently the proximal one) (4), to date, little information is available regarding the angiographic characteristics and clinical presentation of in-SES restenosis (5). As well, there are no reports suggesting the superiority of one particular treatment strategy over another, and a recent publication showed a very high (43%) incidence of recurrent restenosis after

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TABLE 1
Clinical and procedural characteristics during the index procedure (26 patients, 28 lesions)

Age, years (mean $\pm$ SD)	63 $\pm$ 12
Male sex, n (%)	21 (81)
Diabetes, n (%)	7 (27)
Acute myocardial infarction, n (%)	3 (12)
Unstable angina, n (%)	12 (46)*
Sirolimus-eluting stent used, n (number per patient)	29 (1.1)
Mean total stent length, mm (range)	32 (8–66)
Mean stent diameter, mm (range)	2.9 (2.5–3.5)
Lesion type, n (%)	
Total occlusion	6 (23)
In-stent restenosis	3 (12)
Stented vessel, n (%)	
Left anterior descending artery	13 (46)
Circumflex coronary artery	2 (7)
Right coronary artery	5 (11)
Venous graft	2 (7)
Diagonal branch	1 (4)
Obtuse marginal artery	4 (14)
Left main coronary artery	1 (4)

*Clinical presentation of these patients was not different from the overall patient cohort. *Includes recent-onset angina (within one month)*

percutaneous treatment (6). Given this background, we present data from single-centre, real-world experience regarding this issue.

PATIENTS AND METHODS

SES implantation

Between May 2002 and December 2004, 1424 SES were implanted in 1159 patients (average 1.2 per patient) for chronic (stable angina or asymptomatic evidence of ischemia by a provocative test, 40%) or acute (unstable angina, including recent-onset angina, and myocardial infarction, 60%) coronary syndromes in the University Hospital of Siena (Siena, Italy), which is a tertiary centre. All stents were implanted using high-pressure balloon dilation. Double antiplatelet therapy (acetylsalicylic acid continued indefinitely and clopidogrel or ticlopidine for at least six months) was started in all patients immediately after the procedure. After discharge, all patients were referred to their treating physicians and underwent a provocative test at six to 12 months after SES implantation. Treating physicians were recommended to refer patients to the University Hospital (the only one performing angioplasty in the area) in case of symptoms and/or instrumental evidence of cardiac ischemia. Repeat coronary angiography was performed as clinically indicated by symptoms or documentation of myocardial ischemia in 202 patients. In-SES restenosis (greater than 50% diameter stenosis located in the stent or in the adjacent proximal and distal 5 mm, as evidenced by an angiogram performed more than three months after index procedure) was found in 26 patients (2.2% of 1159). Cases of in-SES restenosis were collected in a prospective, observational registry.

Treatment of in-SES restenosis

Studies have shown that focal in-body restenosis (type Ic [7]) constitutes a more benign pattern of in-stent restenosis, which can be

effectively treated using conventional angioplasty (7-9). Conversely, other types of restenosis that are more frequently associated with procedural issues (eg, geographic miss, in the case of type Ib restenosis) or with aggressive neointimal proliferation may benefit from repeat SES implantation. According to this hypothesis, the first 20 consecutive patients presenting with symptomatic in-SES restenosis were treated with balloon-only angioplasty for type Ic restenosis, and repeat SES implantation was used for all other patterns. Double antiplatelet therapy was continued (or restarted) in all patients for the following 12 months. Clinical follow-up was continued for at least another nine months to determine the incidence of major cardiac adverse events (all-cause death, nonfatal myocardial infarction or repeated target lesion revascularization). Angiographic follow-up was performed in all 20 patients at the end of clinical follow-up, or earlier in cases suggestive of myocardial ischemia.

Analysis

Angiographic follow-up (for methods see reference 10) was performed in all patients treated for in-SES restenosis at the end of clinical follow-up or earlier in cases suggestive of myocardial ischemia. A modified version of Image J (National Health Institute, USA) and custom-designed software were used. Quantitative analysis was performed using the worst and least foreshortened image of the stenosis. All continuous data are presented as mean $\pm$ SD. For statistical analysis, a paired or unpaired *t* test, or a corresponding nonparametric test was used as appropriate.

RESULTS

Characteristics of in-SES restenosis

During follow-up, symptomatic in-SES restenosis was found in 26 patients (2.2% of 1159) at 10 $\pm$ 5 months (median eight months, range four to 23 months) from the index procedure. A total of 28 lesions (2% of 1424) were found at angiography (two patients presented with lesions in two separate SES). Patient characteristics and procedural data are shown in Table 1. In-SES restenosis was associated with symptoms of stable angina (n=16), acute myocardial infarction (n=3) and unstable angina (n=7). Longitudinal geographic miss (nine cases) and suboptimal result at the index procedure (stent underexpansion mostly due to highly calcific lesions, as defined by 20% or more residual stenosis – six cases) were identified as likely procedure-related causes of restenosis. Two patients developed simultaneous restenosis in a bare metal stent placed in a separate vessel during the index procedure. The angiographic pattern of in-SES restenosis is presented in Figure 1. In terms of clinical presentation, while type Ic in-SES restenosis presented in all cases as stable angina, other patterns presented more commonly (10 patients [56%]) as acute coronary syndromes. Symptom relapse was not associated with interruption of antiaggregant therapy in any cases.

Treatment of in-SES restenosis

Twenty consecutive patients presenting with in-SES restenosis received treatment according to the strategy described above: type Ic in-SES restenosis was treated with balloon-only angioplasty (balloon-only group, eight lesions, seven patients; all presenting with stable angina due to in-SES restenosis), while other patterns of restenosis received repeat drug-eluting stent implantation (SES group, 13 lesions, 12 patients; one presenting with myocardial infarction, six with unstable angina, five with stable angina). In one case of type IV restenosis (SES

Type of restenosis	Presentation	Number of cases
Ia (focal, gap between two SES)		1
Ib (focal, proximal edge)		7
Ib (focal, distal edge)		3
Ic (focal, body of SES)		9
II (diffuse)		1
III (proliferative)		1
IV (totally occlusive)		6

Figure 1 Angiographic presentation of in-sirolimus-eluting stent (SES) restenosis (see also reference 7). Restenosis is represented in black

group), reintervention failed, and the patient was treated medically. Angiographic success was obtained in the other 19 cases. In the patients who received a new SES, the stented length was significantly shorter than that of the index procedure (treatment of in-SES restenosis: 22 ± 8 mm, range 18 mm to 36 mm; index procedure: 32 ± 17 mm, range 8 mm to 66 mm, $P < 0.05$). Those in the balloon-only group received repeated (average 2 ± 1 inflations, range two to five inflations), high-pressure (12.5 ± 2 atm, range 10 atm to 15 atm) angioplasty with 16 ± 4 mm long balloons. In both cases, the diameter of the device used (SES or balloon) exceeded that of the SES implanted at the index procedure (SES group: index procedure 2.9 ± 0.2 mm, retreatment 3.1 ± 0.3 mm; balloon-only group: index procedure 2.7 ± 0.2 mm, retreatment 3.1 ± 0.3 mm). Clinical follow-up data were obtained at an average follow-up of 16 ± 7 months (range nine to 27 months) from the time of treatment of in-SES restenosis. During this period, one noncardiac death occurred in the balloon-only group. Four patients developed recurrent symptoms of unstable angina, three of whom had been treated with balloon-only angioplasty and presented with recurrent in-SES restenosis requiring retreatment (type IV in one case, type Ib in the second and type Id in the third). The fourth patient (in the SES group) required treatment of a de novo lesion. All four patients received a new SES.

Quantitative angiography

Follow-up angiography was performed in the 19 patients included in the prospective registry at 15 ± 8 months (range four to 27 months). Overall, the incidence of binary restenosis was 32% (six patients). In those who had been treated with SES ($n=12$), binary restenosis was present in two patients (17%, both asymptomatic). In one case, it was a type II, 60% diameter stenosis in which treatment was deemed unnecessary; in the other, it was a type Id (multifocal), 70% diameter stenosis, which was treated with implantation of a third SES. In contrast, binary in-SES restenosis was present in four patients (57%, only one asymptomatic) in the balloon-only group ($n=7$). Quantitative angiography data are reported in Table 2, showing significantly less late lumen loss in the subjects treated with SES.

DISCUSSION

In-SES restenosis is a relatively rare condition that affects 2% to 9% of patients. Our data confirm the findings of previous reports, suggesting that this type of lesion occurs more

TABLE 2
Quantitative coronary angiography data

	Balloon-only group (8 lesions, 7 patients)	SES group (13 lesions, 12 patients)	P
After treatment of SES restenosis			
RD, mm	3.0 ± 0.1	3.1 ± 0.4	NS
MLD, mm	2.5 ± 0.5	2.3 ± 0.4	NS
Follow-up			
RD, mm	3.0 ± 0.2	3.1 ± 0.4	NS
MLD, mm	$1.5 \pm 1.0^*$	2.2 ± 0.7	< 0.1
LLL, mm	1.0 ± 0.9	0.2 ± 0.6	< 0.05
Loss index	0.4 ± 0.3	0.1 ± 0.2	< 0.05
Binary restenosis	4 (57%)	2 (17%)	

Binary restenosis is expressed as absolute number (% incidence). * $P < 0.05$ compared with after treatment of sirolimus-eluting stent (SES) restenosis. LLL Late lumen loss; MLD Minimum lumen diameter; NS Not significant; RD Reference diameter

commonly in a focal pattern, and in the majority of the cases, involves the body (5) or the proximal edge of the stent (11,12). The most common explanation for the occurrence of restenosis in our patient population was a procedure-related issue, emphasizing the need for careful evaluation after SES implantation. In particular, because a likely mechanism of in-SES restenosis in our population was negative-edge remodelling due to geographic miss, our data support the concept that SES length should be accurately chosen to completely cover (and possibly slightly exceed) the margins of the lesion. In terms of clinical presentation, while type Ic in-SES restenosis presented as stable angina, other patterns were more commonly associated with acute coronary syndromes (38% of the total). In these patients, late in-stent thrombosis may have led to the angiographic appearance of in-SES restenosis. Of note, there are reports of delayed in-SES thrombosis that may account for this possibility. Finally, in-SES restenosis was observed after a mean follow-up period of 10 months (ie, later than the typical six months for bare metal stents [1]), which emphasizes the need for a longer follow-up.

The present report is the first to compare the outcomes of two different treatments for in-SES restenosis. Our treatment strategy was based on the pattern of restenosis (simple balloon angioplasty for focal in-body SES restenosis and restenting for all other patterns). In this strategy, SES reimplantation was reserved for those patterns of in-SES restenosis that are thought to be more complex and at higher risk of recurrent restenosis. Despite this deliberate bias, target lesion revascularization at follow-up was recorded in three of seven patients (43%) in the balloon-only group and one of 12 patients (8%) in the SES group. Similarly, the incidence of binary restenosis, as well as angiographic indexes of neointimal proliferation, were markedly lower in the SES group. Therefore, although successful in terms of immediate angiographic outcome, balloon-only angioplasty seemed to be associated with a worse clinical and angiographic outcome. These data reflect the findings observed in the setting of bare metal stent restenosis, in which SES implantation is associated with a lower incidence of recurrent restenosis (13,14).

A small sample size, a nonrandomized design and a lack of strict entry criteria have to be acknowledged as limitations to our report, and a large, randomized trial is warranted. In particular, the small number of subjects who received balloon-only

angioplasty limits our capacity to draw final conclusions on the outcome of this treatment. While these limitations need to be recognized, our data suggest that, in the setting of in-SES restenosis, implantation of a new SES is a safe and effective therapeutic choice, while balloon-only angioplasty may not be. To date, this is the largest database available regarding this rare and challenging condition. Overall, the data presented here have led us to use a new SES (or of a different drug-eluting stent) to treat SES restenosis independently of its pattern.

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