Classification and Current Treatment Options of In-Stent Restenosis

Present Status and Future Perspectives

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Abstract

Coronary stent implantation is currently performed in > 80% of percutaneous coronary interventions. Its main late complication is the development of in-stent restenosis (ISR), occurring in 10–80% of lesions treated in daily practice. The classification by Mehran et al. is most commonly used. Current therapeutic options to treat ISR include repeat balloon angioplasty, repeat stenting, cutting balloon angioplasty, directional coronary atherectomy, rotational coronary atherectomy, brachytherapy, and drug-eluting stents (DES).

DES have been effective in reducing binary restenosis in de novo lesions in randomized controlled trials. The novel use of DES to treat ISR has been shown to be safe and effective in multiple studies involving sirolimus- and paclitaxel-eluting stents. As DES implantation becomes more widespread, ISR in DES is emerging as a new problem. The use of debulking techniques to treat ISR in DES is to be cautioned against. In this new era, the optimal treatment of this new problem is currently unknown. We await further data to see whether repeat DES implantation may help solve this vexing clinical problem.

Key Words: Drug-eluting stents · In-stent restenosis · Stents · Restenosis · Sirolimus · Paclitaxel

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Klassifikation und gegenwärtige Behandlungsmöglichkeiten der In-Stent-Restenose: Gegenwärtiger Stand und zukünftige Entwicklungen

Zusammenfassung

Bei Koronarinterventionen wird heute in über 80% eine Stentimplantation vorgenommen. Unter Alltagsbedingungen ist ihre häufigste Spätkomplikation die Entwicklung einer In-Stent-Restenose (ISR) in 10–80%. Die Klassifikation der ISR erfolgt meist nach Mehran et al. Die gegenwärtigen Behandlungsmöglichkeiten der ISR umfassen die erneute Ballonangioplastie, erneutes Stenting, den Cutting balloon, die direkte Atherektomie, die Rotablation, die Brachytherapie und die Medikamente freisetzenden Stents (DES). In randomisierten Studien haben DES ihre Wirksamkeit in der Reduktion der binären Restenoserate bei De-novo-Stenosen bewiesen. In multiplen (nicht randomisierten) Studen hat der Einsatz von Sirolimus- und Paclitaxel-DES seine Sicherheit und Wirksamkeit auch bei der Behandlung der ISR gezeigt. Die Verwendung von DES in ISR führen zu einem neuen Problem: Der Einsatz von ablativen Verfahren zur Behandlung der ISR nach DES sollte mit Bedacht geschehen. Die optimale Behandlung der ISR nach DES ist unklar. Mehr Daten zum Einsatz einer erneuten Implantation von DES bei ISR nach DES werden zeigen, ob dieses lästige Problem gelöst werden kann.

Schlüsselwörter: Medikamente freisetzende Stents · In-Stent-Restenose · Stents · Restenose · Sirolimus · Paclitaxel

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Introduction

Coronary stent implantation reduces clinical and angiographic restenosis compared to balloon angioplasty alone and is currently performed in > 80% of percutaneous coronary interventions [1–3]. In-stent restenosis (ISR), the most frequent late complication of stent implantation, occurs in 10–80% of lesions treated in everyday practice [4]. In 2001, it was estimated that 150,000 cases of ISR occurred in the USA alone [5]. On a worldwide scale, the burden is much greater. The recent development of drug-eluting stents (DES) has reduced the incidence of stent-related restenosis to < 10% [6, 7], but has not eliminated it completely.

Pathophysiology

Coronary stent implantation is inherently traumatic and this trauma leads to a significant vessel wall "response to injury" reaction that includes platelet activation and adhesion to the vessel surface. Smooth muscle cells are then activated, proliferate and migrate to the intima. Excessive extracellular matrix is produced and accumulates. Neointimal formation is principally composed of smooth muscle cells and extracellular matrix. This exaggerated neointimal formation can lead to ISR.

Certain factors are known to increase the risk of ISR. Lesion-related factors include vessel diameter [8] and prior restenosis [9]; procedure-related specific factors include the presence of residual dissection [10] and length of stented vessel [11]; patient-related factors include diabetes mellitus [12, 13]. In addition, multiple genetic factors have been implicated in the development of ISR.

Classification

Currently, the most widely used classification for ISR in bare metal stents is that proposed by Mehran et al. [4]. The classification in based on the length and pattern of the restenotic lesion in relation to the stented portion of the vessel. Four types of ISR have been defined: (I) focal (≤ 10 mm length); (II) diffuse (ISR > 10 mm within the stent); (III) proliferative (ISR > 10 mm extending outside the stent); and (IV) occlusive ISR. Type I is further subdivided into types IA–ID based on the site of focal ISR in relation to the stent. This classification has prognostic implications, as the incidence of target vessel revascularization (TVR) is related to the type of ISR (Figure 1). Interestingly, with the introduction of DES, the pattern of restenosis has changed into a predominantly focal one [14, 15].

Current Treatment Options

A variety of percutaneous techniques are currently available to treat ISR. These include balloon angioplasty (POBA), cutting balloon angioplasty, rotational coronary atherectomy, directional coronary atherectomy (DCA), repeat bare stent implantation, brachytherapy, and, more recently, DES. These various techniques may be used either individually or in combination.

	Incidence of ISR in bare stents (n = 293 lesions)	TVR for ISR in bare stents at 1 year
Focal	42%	19.1%
Diffuse	21%	34.5%
Proliferative	30%	50.0%
Total occlusion	7%	83.4%

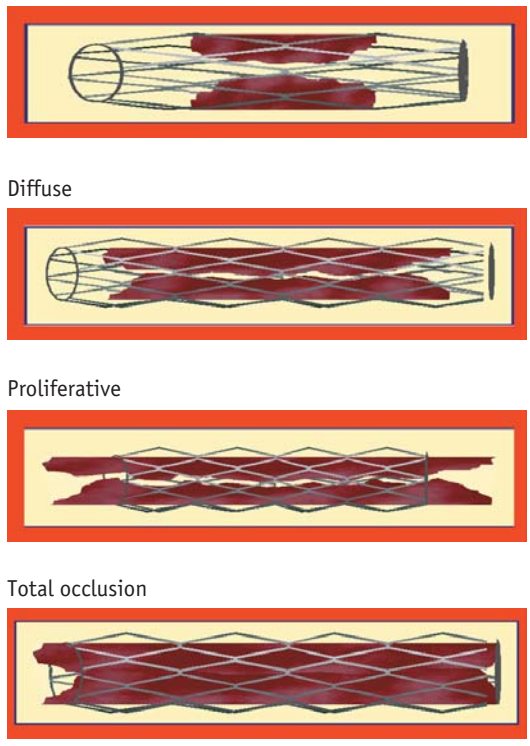

Figure 1. Classification and incidence of in-stent restenosis (ISR) in bare stents according to Mehran et al. [4]. TVR: target vessel revascularization.

Abbildung 1. Klassifikation und Häufigkeit der In-Stent-Restenose unbeschichteter Edelstahlstents (nach Mehran et al. [4]).

Balloon Angioplasty

POBA to treat ISR is the most appealing technique as it is simple, cheap, universally available and requires no new training. In the landmark angiographic study which included 29% diffuse lesions, the angiographic re-restenosis rate following POBA was only 22% [16]. The authors noted that although the overall results in their study were good, repeat intervention for diffuse and severe ISR was associated with a high rate of recurrent restenosis.

New Stent Implantation

New stent implantation for ISR was evaluated in a clinical trial of 450 patients who were randomized to either new stent implantation or POBA [17]. 60% of ISR were diffuse lesions. Restenosis rates were similar (33% vs. 38%), as were rates of TVR (19.6% vs. 24.3%; p = 0.25), indicating that systematic stenting was no better than POBA in this setting.

Cutting Balloon Angioplasty

Cutting balloon angioplasty is a modality that relies on microblades embedded on the surface of an angioplasty balloon to incise the atherosclerotic plaque on balloon inflation. In a retrospective study of matched lesion subsets (30% diffuse lesions) comparing rotational coronary atherectomy, POBA, stenting and cutting balloon for the treatment of ISR, cutting balloon emerged as a negative predictor of target lesion revascularization (TLR; odds ratio 0.34 [0.16–0.73]; p = 0.001) [18]. The angiographic re-restenosis rate amounted to 20%. TLR at 9 months in this study was 15.8%, suggesting that cutting balloon may be advantageous in this setting.

Rotational Coronary Atherectomy

The ARTIST study was a multicenter, randomized, prospective European trial comparing usual-practice POBA to rotablation followed by adjunctive low-pressure (≤ 6 atm) POBA in 298 patients with diffuse ISR. The results showed that in the long term, POBA was better than rotablation. 6-month event-free survival in the POBA group was 91.3% compared with 79.6% in the rotablation group (p = 0.0052) [19]. However, a subsequent trial known as the Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-Stent Restenosis (ROSTER) trial which was a single-center, randomized trial comparing rotablation to POBA (both with intravascular ultrasound [IVUS] guidance) in the treatment of diffuse ISR in 200 patient, showed conflicting results [20]. In the rotablation group (n = 100), rotablation was followed by adjunctive balloon dilatation at low pressure (4–6 atm). In the POBA group (n = 100), high-pressure (> 12 atm) balloon dilatation was performed using an optimal-size balloon. The incidence of TLR was 32% in the rotablation group and 45% in the POBA group (p = 0.042), with a similar trend noted in the angiographic substudy. The authors concluded that rotablation resulted in less residual intimal hyperplasia, lower repeat stent use, and decreased TLR. Further studies may clarify the role of rotational atherectomy in this setting.

Directional Coronary Atherectomy

In a nonrandomized study of 119 patients with ISR of native coronary arteries, 58 underwent DCA and 61 underwent rotablation for symptomatic coronary ISR [21]. Adjunctive balloon angioplasty at relatively high pressures was performed in both groups. In both groups, 79% of patients had a diffuse pattern of ISR. Long-term (12 month) results in the DCA group were superior as reflected by a lower TLR (21% vs. 39%; p = 0.02) and better event-free survival (72% vs. 56%; p = 0.03). Although nonrandomized, this suggests a beneficial effect of DCA over rotablation.

Other Techniques

Other debulking techniques such as excimer laser cathether ablation (ELCA) have been studied [22, 23]. ELCA plus POBA was compared to POBA alone in a study with 40% of diffuse ISR [22]. The results showed no significant difference although there was a trend toward a lower TVR in the ELCA group (21% vs. 38%; p = 0.0823). A small angiographic study of exclusively diffuse lesions treated with ELCA and POBA reported a reocclusion rate of 46% [23].

Brachytherapy

Brachytherapy is, so far, the only proven therapy for ISR. Randomized studies comparing brachytherapy to placebo for the treatment of ISR have demonstrated significant reductions in restenosis rates and in major adverse cardiac event (MACE) rates (Table 1). However, brachytherapy has limited availability, is costly, requires training and additional personnel, and may call for renovation of the catheterization laboratory in the case of γ-radiation. Furthermore, potential side effects of brachytherapy include late thrombosis [24], delayed healing [25], the "black hole" phenomenon [26], and ge-

Table 1. Randomized brachytherapy trials for in-stent restenosis. MACE: major adverse cardiac events.

Tabelle 1. Randomisierte Brachytherapie-Studien zur In-Stent-Restenose: In allen Studien zeigte sich eine signifikante Reduktion der In-Stent-Re-Restenose nach Brachytherapie.

Radiation source	Trial name	Patients (n)	Lesion length (mm)	Restenosis rate (%)		p-value	MACE (%)		p-value
				Treated	Placebo		Treated	Placebo	
β-radiation									
$^{90}Sr/^{90}Y$	START [54]	476	< 20	29	45	0.001	19	29	0.024
^{32}P wire	INHIBIT [55]	332	< 22	26	52	0.0001	15	31	0.006
^{90}Y	BETA WRIST [56]	50	< 47	34	71	0.001	34	76	0.001
γ-radiation									
^{132}Ir wire	GAMMA-I [5]	252	< 45	32	55	0.01	28	44	0.02
	GAMMA WRIST [57]	130	< 47	22	60	0.0001	35	68	< 0.001
	SCRIPPS [58]	55	< 30	17	54	0.01	15	48	0.01
	SCRIPPS 3 years [59]	55	< 30	33	64	< 0.05	23	55	0.01
	Long WRIST [62]	120	36–80	45	73	< 0.05	42	63	< 0.05

ographic miss [27] limiting the applicability of the technique.

A combination strategy of pretreatment with cutting balloon angioplasty followed by g-brachytherapy was investigated as a substudy of the SCRIPPS III Trial. In their retrospective report, 76 patients received cutting balloon angioplasty while 407 patients received conventional percutaneous transluminal coronary angioplasty (PTCA) before γ-brachytherapy. The groups were reasonably matched for baseline characteristics. TVR was similar in both groups (35.1% vs. 29.8%; p = 0.4) but was associated with less requirement for new stents (11% vs. 22%; p = 0.02) [28].

Drug-Eluting Stent Implantation for In-Stent Restenosis

Following on from the encouraging results obtained in de novo lesions, there has been interest in the extension of this application to ISR lesions. The use of DES to treat ISR is immensely attractive. As mentioned above, stent implantation is simple, requires no further training, and, most importantly, does not call for the complex logistics of a brachytherapy unit. To date, however, clinical experience has been limited to small groups of patients [29–34].

Sirolimus-Eluting Stents

Sirolimus or rapamycin, a natural macrocyclic lactone, is a potent immunosuppressive agent. Sirolimus binds to its cytosolic receptor, FK506-binding protein 12, and this complex then inhibits a kinase called the mammalian target of rapamycin (mTOR) [35], which is a component in a pathway that regulates cell cycle progression which ultimately induces cell cycle arrest in the late G1 phase. It inhibits the proliferation of both rat and human smooth muscle cells in vitro [36, 37] and reduces intimal thickening in models of vascular injury [38]. Evidence that sirolimus may have an active role to play in the treatment of ISR is further supported by a study which demonstrated a robust upregulation of FK506-binding protein 12 in atherectomy specimens of ISR from human coronary arteries compared to control specimens [39].

The efficacy of the sirolimus-coated Bx Velocity stent (Cypher™, Cordis a Johnson and Johnson Company) in preventing neointimal hyperplasia in stented de novo lesions was first demonstrated in the First in Man (FIM) Trial [40, 41]. These findings have now been confirmed in two further landmark trials, the RAVEL [42], and SIRIUS [6] trials. More recently, the RESEARCH Registry comprising 508 consecutive de novo patients treated in the real world with sirolimus-eluting stents (SES) reported similar excellent results [43].

Rotterdam FIM. In the Rotterdam FIM Registry, 16 consecutive patients with severe recurrent ISR in a native coronary artery with objective evidence of ischemia were included [32]. They were treated with at least one 18-mm SES. At 4-month angiographic follow-up, one patient had suffered sudden death, while among the remaining 15 patients, three had recurrent ISR (20%).

São Paulo FIM. In the São Paulo FIM Registry, 25 consecutive patients with ISR in a native coronary

Table 2. Summary of published studies with drug-eluting stents (DES) for the treatment of bare metal stent in-stent restenosis (ISR). MACE: major adverse cardiac events; N/A: not available; TLR: target lesion revascularization.

Tabelle 2. Zusammenfassung der bisher publizierten Daten für Medikamente freisetzende Stents zur Behandlung einer In-Stent-Restenose nach Implantation eines unbeschichteten Edelstahlstents.

DES	Rotterdam FIM [32] Sirolimus	São Paulo FIM [31] Sirolimus	RESEARCH-ISR [44] Sirolimus	SES for failed brachytherapy [33] Sirolimus	TAXUS III [34] Paclitaxel
Patients (n)	16	25	44	12	28
Diffuse disease (%)	81	68	58	75	64
Follow-up duration (months)	9	12	9	8.5	12
Re-restenosis rate [n (%)]	3/15 (20)	1/25 (4)	N/A	4/10 (40)	4/25 (16)
TLR (%)	8.3	N/A	16.3	25.0	21.4
MACE (%)	18.7	N/A	18.5	41.6	29.0

artery were treated with at least one 18-mm SES [31]. At 12-month angiographic follow-up, one patient had ISR (4%).

SES versus Brachytherapy. To date, only one study has been published comparing the results of SES implantation versus vascular brachytherapy (VBT) for the treatment of ISR [44]. This nonrandomized study compared 43 patients treated with VBT against 44 patients treated with SES. Baseline characteristics were similar in both groups. During follow-up, three patients (7%) died in the VBT group and none in the SES group. The incidence of myocardial infarction was 2.3% in both groups. TLR was performed in 11.6% of the VBT patients and 16.3% of the SES patients (p = NS). The 9-month MACE-free survival was similar in both groups (79.1% VBT vs. 81.5% SES; p = 0.8 by log rank). The authors concluded that SES implantation was at least as effective as VBT for the treatment of ISR.

SES for Post-Brachytherapy Failures. Post-brachytherapy failures, defined as the recurrence of ISR following intracoronary brachytherapy to treat ISR, have a high rate of recurrence and make up a small but significant proportion of patients. In a small study of twelve patients who received SES for the above indication, ten returned for angiographic follow-up between 4–7 months post procedure and ISR was found in four patients (40%) [33]. In addition, they were followed up clinically for 8.5 ± 4.5 months during which time seven of twelve remained event-free (58%). Another study looked at the clinical follow-up of 51 patients following repeated VBT for failed VBT and reported that 71% of their patients were event-free at 9 months [45]. To date, there have been no head-to-head comparisons of SES versus VBT in failed VBT patients, although the results from the two studies cited appear to suggest that they are similar.

Paclitaxel-Eluting Stents

Paclitaxel, an antitumor agent used in the treatment of ovarian and breast cancer, acts by binding to microtubules and stabilizes their structure, thus enhancing microtubule assembly, resulting in inhibition of cellular replication [46]. Cells remain viable; however, cell processes dependent on microtubule turnover such as mitosis, migration, endocytosis and secretion are inhibited. Thus, paclitaxel acts at two sites in the cell cycle: the G2/M junction and the M/G0 junction. In vitro studies have demonstrated that paclitaxel inhibits the proliferation and migration of vascular smooth muscle cells [47–50].

The efficacy of paclitaxel-eluting stents (TAXUS NIRx™, Boston Scientific Corporation) for the treatment of de novo lesions was demonstrated in the TAXUS I and II Trials [51, 52]. These findings have now been confirmed in the landmark trial, TAXUS IV [7].

TAXUS III. The TAXUS III Trial was a single-arm, two-center study of 28 patients with ISR of mean lesion length 13.6 mm treated with TAXUS NIRx™ stents (Boston Scientific Corporation) [34]. 25 patients completed angiographic follow-up at 6 months, with a binary re-restenosis rate of 16%. TVR at 6 and 12 months was unchanged at 21.4%; similarly, MACE was also unchanged between 6 and 12 months at 29%.

QuaDS-QP2 ISR. A negative study that deserves mention is the first experience with the QuaDS-QP2 stent (Quanum Medical Corporation) of 15 consecutive patients with ISR treated at two centers [53]. Although 6-month angiographic follow-up demonstrated a restenosis rate of 13.3%, by 12 months this had deteriorated markedly to 61.5%. TLR at 12 months was 60%.

Future Perspectives

In-Stent Restenosis in Drug-Eluting Stents

To date, DES trials have demonstrated that the restenosis rate in DES ranges from 0 to 9% [6, 7] (Table 3). While this number is a great improvement over the results seen with bare stents, it is certainly not negligible, and as the use of DES increases worldwide, the optimum treatment of this new problem will need to be defined. Currently, there is no data on the best way to treat ISR in DES. Possible options are:

(1) repeat DES implantation with the same DES;
(2) repeat DES implantation with a different DES – this may prove beneficial if localized drug resistance to the initial DES is suspected;
(3) another previously described method – possibly brachytherapy;
(4) coronary artery bypass grafting, should the above strategies fail.

The current practice at our institution is that 85% of these lesions have been treated with repeat DES implantation.

Debulking Techniques and DES. A note of caution is warranted in relation to the application of debulking techniques (rotablation, DCA, cutting balloon angioplasty) for the treatment of restenosis in DES. Most of the stents have a polymer coating the stent struts. Disruption of the polymer may have unforeseen consequences. First, this polymer layer may contain significant drug reservoir that was not released during the initial eluting phase. Second, disruption of the polymer may expose elements of the polymer to the systemic circulation.

Of note, the type of ISR in DES has changed to a predominantly focal pattern. Between 84–100% of ISR have been reported as predominantly focal (≤ 10 mm) [14, 15]. Whether the classification of Mehran et al. [4] remains pertinent with regards to TLR remains to be seen.

Other Drug-Eluting Stents

Other DES are currently in various phases of development. Their utility in the treatment of simple de novo lesions must first be proven before any attempt is made to extend their application to the treatment of ISR. Drugs that appear promising currently include everolimus (Guidant Corporation), ABT-578 (Abbott Vascular and Medtronic), and biolimus (Terumo and Biosensors). This list is by no means exhaustive, and many more drugs will be tested in the future to determine their ability to reduce the incidence of ISR.

Conclusion

ISR in bare stents remains a major therapeutic hurdle as long as bare stents are implanted. Brachytherapy is the only proven tool, but its application is a logistic nightmare. Preliminary results available so far indicate that DES, in particular Cypher™ and TAXUS™, are safe and feasible alternatives to treat ISR. The increasing use of DES to treat de novo lesions has introduced a new therapeutic challenge with the development of ISR in DES albeit with a much lower incidence than seen with bare stents. In this new era, the optimal treatment of this new problem is currently unknown. We await further data to see whether repeat DES implantation may help solve this vexing clinical problem.

Table 3. Incidence of restenoses in major drug-eluting stent (DES) trials. MACE: major adverse cardiac events; N/A: not available; TLR: target lesion revascularization.

Tabelle 3. Häufigkeit einer Restenose in den größeren Studien mit Medikamente freisetzenden Stents.

Study	SIRIUS [6]	TAXUS IV [7]	E-SIRIUS [60]	ASPECT [61]	RESEARCH [43]
Drug	Sirolimus	Paclitaxel	Sirolimus	Paclitaxel	Sirolimus
Study design	Randomized, single de novo lesion	Randomized, single de novo lesion	Randomized, single de novo lesion	Randomized, dose-finding, single de novo lesion, high dose	Consecutive registry, all comers de novo lesions
Patients in DES group (n)	533	662	175	60	508
Follow-up duration (months)	9	9	9	6	12
Follow-up type	Angiographic and clinical	Angiographic and clinical	Angiographic and clinical	Angiographic and clinical	Clinical
Restenosis rate (%)	8.9	7.9	5.9	4.0	N/A
TLR (%)	4.1	3.0	4.0	1.7	~ 3.5
MACE (%)	8.6	7.6	8.0	4.0	9.7

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