Balloon angioplasty using the "GRIP™" scoring balloon for treatment of coronary in-stent restenosis

Immediate and 12-month clinical outcomes

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Summary

Objectives: We sought to determine the efficacy and safety of a scoring balloon for the treatment of in-stent restenosis (ISR).

Background: The optimal therapy for ISR is not yet properly established and subject to many discussions. The GRIP™ Balloon (Acrostak, Switzerland) might be of interest for the treatment of certain types of ISR.

Methods: Between 2003 and 2009, 157 patients who were treated for ISR (182 lesions, 164 interventions) with the GRIP™ balloon were retrieved from our database and followed clinically. The safety endpoint was the occurrence of immediate coronary complication (such as perforation or dissection). The efficacy endpoint was freedom from major adverse cardiac events (MACE: cardiac death, myocardial infarction, and target lesion revascularisation) at 12-month clinical follow-up.

Results: Mean age was 65 ± 11 years and 82% were men. A focal ISR was found in 54% (n = 93) of lesions. Additional stenting was performed in 22% of lesions after angioplasty with the GRIP™ balloon. There was no perforation as immediate coronary complication whereas localised dissection was identified in five patients (3%). Survival was 98% at 12 months. MACE occurred in 13% of patients (n = 21). Target lesion revascularisation (TLR) needed to be performed in 17 (11%). Myocardial infarction occurred in 2 (1%), and stent thrombosis occurred in 1 (1%) patient. MACE rates were higher in patients with diffuse ISR (20%) compared with focal ISR (7%) (p = 0.02).

Conclusions: Balloon angioplasty with the GRIP™ balloon for ISR can be safely and successfully performed, and leads to good clinical outcome in patients presenting with focal ISR.

Key words: in-stent restenosis; scoring balloon; percutaneous coronary intervention

Introduction

In-stent restenosis (ISR) used to be responsible for almost one million revascularisation procedures each year worldwide [1]. The successful launch of drug-eluting stent (DES) in 2002 decreased the need for revascularisation after stenting from 15–25% to currently 5–10%, and modified the restenotic pattern to more focal ISR [2–7]. Stable and troponin-negative unstable angina are the standard clinical presentations of ISR but 9–19% of patients present with myocardial infarction or death due to stent thrombosis [8–13].

Several therapeutic options have been recommended for the treatment of ISR: use of rotational atherectomy, cutting balloon, drug-eluting balloon (DEB), additional DES implantation, endobrachytherapy, or coronary artery bypass grafting (CABG) [14–18]. Yet, based on two studies [PACCOCATH-I and –II and PEPCAD-II] [15, 19], DEB has been recommended

Abbreviations	
BMS	Bare metal stent
DEB	Drug-eluting balloon
DES	Drug-eluting stent
ISR	In-stent restenosis
MACE	Major adverse cardiac events
MLD	Minimum lumen diameter
PCI	Percutaneous coronary intervention
RVD	Reference vessel diameter
ST	Stent thrombosis
TLR	Target lesion revascularisation

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Figure 1

Computer simulated image of the GRIP™ scoring balloon (Acrostak, Switzerland) with 4 lines of knobs on its surface that protect against balloon slippage (by courtesy of Acrostak, Winterthur, Switzerland).
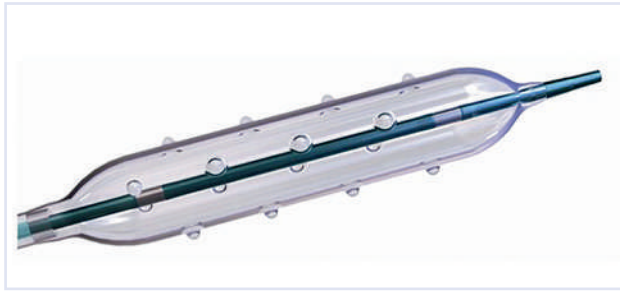
for treatment of restenosis after BMS in the 2010 ESC-guidelines on myocardial revascularisation [class IIa recommendation, level of evidence B] [20].

Because conventional balloons tend to slip out of the lesion during ISR-angioplasty, some balloons were specifically designed to address this issue and avoid potential consequences of balloon slippage, such as geographical miss, dissection, or perforation. The GRIP™ balloon (Acrostak, Switzerland, fig. 1) has 4 lines of knobs on its surface that aim to prevent balloon slippage and could even help to crush tender hyperplastic tissue.

The purpose of this retrospective study was to evaluate the immediate results and the 12-month clinical outcome after angioplasty with GRIP™ balloons for ISR.

Materials and methods

Between 2003 and 2009, 157 patients who were treated for ISR (182 lesions, 162 interventions) with the GRIP™ balloon at our institution were retrieved from the database. Included were patients at least 18 years of age that had clinical evidence of stable or unstable angina and presented a restenotic lesion in a stented coronary artery. Clinical exclusion criteria were acute myocardial infarction in the previous 48 hours, moderate to severe renal failure (defined as creatinine clearance of 30–60 ml/min and <30 ml/min respectively), a known or presumed hypersensitivity to heparin, antiplatelet drugs and hypersensitivity to contrast media that was uncontrollable with pre-medication. Patients that presented with a thrombus in the restenotic segment were equally excluded, as were those unable or unwilling to provide written, informed consent or to participate in follow-up.

Medical records including medical history, information regarding the index procedure such as implanted stent type, clinical presentation, lesion characteristics, information regarding the ISR procedure, and clinical outcome up to twelve months were reviewed. An informed written consent was obtained from every subject included in this scientific work. The revascularisation risk was estimated using the surgical logistic EuroSCORE (European system for cardiac operative risk evaluation) [21].

Quantitative angiography

Coronary angiograms were recorded before, during, and immediately after the intervention. Digital angiograms were analysed with the use of automated edge-detection system (CAAS II, Pie Medical Imaging). Quantitative measurements included the diameter of the reference vessel, minimal luminal diameter, and percent diameter of stenosis (defined as the diameter of the reference vessel [RVD] minus the minimal luminal diameter [MLD], divided by the reference diameter and multiplied by 100). Quantitative measurements were performed before and after each angioplasty device used.

Follow-up

Data collected during clinical follow-up were: death, cardiac death (CD), non-fatal acute myocardial infarction (MI), target lesion revascularisation (TLR), and stent thrombosis (ST). Data were retrieved from the hospital's electronic database. In addition to medical records, death records were carefully reviewed. Follow-up angiography was performed at operator discretion.

Definitions

The *index procedure* was defined as PCI with stent implantation that led to ISR. *ISR* was defined as any luminal narrowing >50% within the stent. ISR pattern was classified according to the Mehran classification and was considered focal if <10 mm (type I) or diffuse if >10 mm of length (type II, III and IV) [22]. All *ISR procedures* were ischaemia-driven.

The safety endpoint was the occurrence of immediate coronary complication (perforation or dissection). Dissections were categorised using the NHLBI classification [23]. The efficacy endpoint was a composite of cardiac death, myocardial infarction and target lesion revascularisation *(major adverse cardiac event, or MACE)* at 12-month follow-up. *Death* was classified as either cardiac or non-cardiac, according to the Academic Research Consortium (ARC) definition [24]. Deaths that could not be classified were considered cardiac. The diagnosis of *myocardial infarction* after the intervention was established whenever new Q-waves of at least 0.4 seconds duration in at least 2 contiguous leads appeared on the electrocardiogram with an elevated creatine kinase MB fraction level, or in the absence of pathologic Q waves, an elevation in creatine kinase levels to more than twice the upper limit of normal with an elevated creatine kinase MB or troponin I level. *Target lesion revascularisation* was defined as any repeat percutaneous or surgical intervention of the target lesion or within 5 mm of the stent edges. *Stent*

thrombosis was defined according to ARC into definite, probable, and possible, and categorised into early (<30 days), late, and very late (>1 year) [24].

Statistical analysis

Statistical analysis was performed using dedicated software (SPSS 18, SPSS Inc, Chicago, IL, USA). For continuous variables QQ plots were computed to check for a normal distribution. Normally distributed variables were analysed using parametric tests and non-normally distributed data using non-parametric tests. Continuous variables are expressed as mean ± standard deviation or median with 25–75% interquartile range and differences were compared using Student's-*t* test or Mann Whitney U test. Categorical variables are expressed as counts and percentages. Cumulative survival-free of MACE was depicted by computation of Kaplan-Meier curves. We further computed a binary logistic regression model with respect to MACE in order to show which variable would be able to predict their occurrence at 12-month follow-up.

Results

From 162 interventions included in the study, 10 were excluded from the analysis due to missing medical records. Of the remaining 152 interventions with a total of 172 lesions, 93 were classified as focal (Mehran class I) and 79 as diffuse (Mehran class II, III and IV).

Baseline data

Baseline clinical characteristics are summarised in table 1. Mean age was 65 ± 11 years and 82% were men. Dyslipidaemia, arterial hypertension, and a positive family history of coronary artery disease were frequently encountered. Diabetes mellitus was found in 38 patients (23%). No statistically significant difference in baseline characteristics was found between patients suffering from focal and patients with diffuse ISR.

Index procedure

The index procedure was performed for de novo lesions in 88% (n = 151) of the cases, ISR in 11% (n = 20), and spontaneous dissection in 1% (n = 1). Bare metal stents (BMS) were used in 33% (n = 57) and DES in 58% (n = 99) of lesions. Information regarding implanted stent type was missing in 9% of cases.

ISR procedure

Median time from index procedure to ischaemia-driven ISR procedure was 24 [9–55] months without statistically significant difference between patients treated with BMS (27 [8–74]) and DES (19 [9–46], p = 0.2), as well as between focal (29 [9–54]) and diffuse ISR (16 [8–55], p = 0.3).

The most common presentation of ISR was stable angina (59%). Focal ISR was found in 54% (n = 93) of lesions. According to Mehran and colleagues [22], type IA was found in 1% (n = 2), type IB in 14% (n = 24), type

Table 1
Baseline data.

	All (n = 172)	Focal (n = 93)	Diffuse (n = 79)	*p*-value
Male, n (%)	141 (82)	77 (83)	64 (81)	0.84
Age, years ± SD	65 ± 11	64 ± 12	65 ± 10	0.53
Risk factors				
Hypertension, n (%)	110 (64)	58 (62)	52 (66)	0.87
Smoking, n (%)	47 (27)	27 (29)	20 (25)	0.68
Dyslipidaemia, n (%)	126 (73)	64 (69)	62 (78)	0.29
Diabetes mellitus, n (%)	38 (22)	17 (18)	21 (27)	0.27
Family history, n (%)	77 (45)	47 (51)	30 (38)	0.09
Medical history				
Previous MI, n (%)	93 (54)	56 (60)	36 (46)	0.91
Previous PCI, n (%)	53 (31)	27 (29)	26 (33)	0.74
Previous CABG, n (%)	27 (16)	16 (17)	11 (14)	0.54
Presentation at index procedure				
Stable angina, n (%)	64 (37)	35 (38)	29 (37)	0.87
Unstable angina, n (%)	95 (55)	50 (54)	45 (57)	0.87
Euroscore, n ± SD	4.4 ± 3.7	4.2 ± 3.6	4.6 ± 3.8	0.29
Presentation at ISR PCI				
Stable angina, n (%)	102 (59)	54 (58)	48 (61)	0.72
Unstable angina, n (%)	70 (41)	39 (42)	31 (39)	0.72

CABG = coronary artery bypass graft surgery; ISR = in-stent restenosis; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation.

IC in 37% (n = 64), and type ID in 2% (n = 3). Diffuse ISR was found in 46% (n = 79). According to Mehran's classification, 32% (n = 56) were classified as type II, 8% (n = 13) as type III (proliferative), and 6% (n = 10) as type IV (chronic total occlusion).

Quantitative angiography data are given in table 2. Intervention with the GRIP™ balloon improved the mean degree of stenosis from 62 ± 17% to 22 ± 12% (*p* = <0.001) and was the only treatment in 66% (n = 114). An additional intervention was performed in the remaining: in 8% (n = 13) of the cases additional balloon angioplasty with noncompliant balloons was performed; in 22% (n = 38) additional stent implantation (DES 94%) was done, and in 4% (n = 7) both techniques were performed. These additional interventions led to a further reduction in mean degree of stenosis to 12 ± 9% (*p* = 0.08). After Grip intervention, MLD (2.0 ± 0.4 mm vs 1.8 ± 0.5 mm, *p* = 0.003) was higher and percent stenosis (19 ± 11% vs 24 ± 13%) lower in focal compare to diffuse lesions (*p* = 0.008). These differences did not persist at the end of the ISR procedure (*p* = 0.18 and *p* = 0.46 respectively, table 2).

Patients who underwent revascularisation for recurrent (second) ISR presented more frequently a history of revascularisation [PCI (100%, n = 20); CABG (40%, n = 8] than those with naïve (first) ISR [PCI (21%, n = 33; *p* <0.001); CABG (12%, n = 19; *p* = 0.001]. No significant difference was noticed with regard to risk factors, clinical presentation, procedural characteristics, complications or clinical outcome except for a higher preprocedural % stenosis in the recurrent-ISR group (68 ± 14% vs 61 ± 17%; *p* = 0.06) and a reduced postprocedural %stenosis (4 ± 6% vs 13 ± 9%, *p* = 0.02) compared to the naïve-ISR group.

Safety outcome

No perforation was seen as immediate coronary complication. A dissection was seen in five patients (3%) after GRIP™ balloon inflation. All dissections were classified as localised (NHLBI type A and B) and successfully covered by stent implantation.

Clinical follow up

Clinical follow-up was available in 160 patients (93%). Mean follow-up was 771 ± 565 days. Follow-up angiography was available in 73 cases (42%). The 12-month clinical outcome is summarised in table 3. Survival was 98%. MACE were achieved by 13% of patients (n = 21).

Table 2
Data on index procedure and ISR PCI.

	All (n = 172)	Focal (n = 93)	Diffuse (n = 79)	*p*-value
Index procedure				
Indication				
De novo lesion, n (%)	151 (88)	80 (86)	71 (90)	0.61
Restenosis, n (%)	20 (11)	12 (13)	8 (10)	0.61
Dissection, n (%)	1 (1)	1 (1)	0 (0)	0.61
BMS, n (%)	57 (33)	29(31)	28 (35)	0.62
DES, n (%)	99 (58)	55 (59)	44 (56)	0.62
Median time from index to ISR-PCI, months (IQR)	23.8 (8.6–55.2)	29.1 (9.1–53.9)	15.9 (8.0–55.2)	0.3
ISR-PCI				
RVD before PCI, mm ± SD	2.5 ± 0.5	2.6 ± 0.5	2.5 ± 0.6	0.36
MLD before PCI, mm ± SD	1.0 ± 0.4	0.9 ± 0.4	0.9 ± 0.4	0.12
Stenosis before PCI, mm ± SD	62 ± 17	60 ± 16	65 ± 17	0.15
RVD post Grip, mm ± SD	2.5 ± 0.5	2.6 ± 0.5	2.5 ± 0.5	0.18
MLD post Grip, mm ± SD	2.0 ± 0.5	2.0 ± 0.4	1.8 ± 0.5	<0.01
Stenosis post Grip, mm ± SD	22 ± 12	19 ± 11	24 ± 13	<0.01
RVD post additional treatment, mm ± SD	2.8 ± 0.5	2.8 ± 0.5	2.7 ± 0.4	0.34
MLD post additional treatment, mm ± SD	2.4 ± 0.5	2.5 ± 0.5	2.3 ± 0.5	0.18
Percent stenosis post additional treatment mm ± SD	12 ± 9	11 ± 8	13 ± 10	0.46
Balloon angioplasty after Grip, n (%)	13 (8)	10 (11)	3 (4)	0.06
Maximum balloon pressure for Grip balloon, atm ± SD	17 ± 4.2	17 ± 4.2	17 ± 4.2	0.41
Stenting after Grip, n (%)	38 (22)	18 (20)	20 (25)	0.21
Dissection after Grip, n (%)	5 (3)	3 (3)	2 (3)	0.79

BMS = bare metal stent; DES = drug-eluting stent; IQR = interquartile range; ISR = in-stent restenosis; MLD = minimum lumen diameter; PCI = percutaneous coronary intervention; RVD = reference vessel diameter; SD = standard deviation.

Median time to secondary endpoint was 148 days [IQR 105–225]. Cumulative survival free of MACE is depicted in figure 2. TLR was performed in 17 patients (11%): 13 (8%) were treated by re-PCI and 4 (3%) underwent CABG. Myocardial infarction occurred in 2 patients (1%) and definite stent thrombosis occurred in 1 patient (1%). Most of patients suffering from MACE had diffuse stenosis (n = 15 vs 6, p = 0.02). This trend was even more germane to patients treated solely with the GRIP™ balloon and is depicted in figure 2B.

ISR prediction
Binary logistic regression showed that diffuse restenosis was associated with occurrence of MACE at tewlve months (OR 3.4; 95%CI: 1.2–9.9, p = 0.03).

Discussion

Plain balloon angioplasty to treat ISR has been intensively investigated for over a decade and has been associated with suboptimal outcome as illustrated by recurrent restenosis rates of to 22–54% at six months [25, 26]. With the successful introduction of DES, the pattern of ISR evolved to more focal lesion. Moreover new interventional modalities have emerged like scoring balloons that decrease the risk of balloon slippage and allow greater luminal gain than conventional angioplasty balloons. Therefore, balloon dilatation with scoring balloons like the GRIP™ balloon has been considered as the first-line treatment of ISR at our institution.

In the present observational study we found that: (1) Balloon angioplasty with GRIP™ balloons is safe. (2) When post-procedural result is good, plain balloon angioplasty is effective to treat focal ISR with 12-month

Table 3
Clinical outcome of patients undergoing PCI with the GRIP™ balloon for ISR at 12-month.

	All (n = 160)	Focal (n = 83)	Diffuse (n = 77)	*p*-value
Any MACE, n (%)	21 (13)	6 (7)	15 (20)	0.02
Death, n (%)	4 (2)	2 (2)	2 (3)	0.66
Cardiac death, n (%)	4 (2)	2 (2)	2 (3)	0.94
Non-fatal MI, n (%)	2 (1)	0 (0)	2 (3)	0.14
TLR, n (%)	17(11)	4 (5)	13 (17)	0.01
Stent thrombosis, n (%)	1 (1)	0 (0)	1 (1)	0.29

ISR = in-stent restenosis; MACE = major adverse cardiac events; MI = myocardial infarction; PCI = percutaneous coronary intervention; TLR = target lesion revascularisation.

Figure 2
Survival free of MACE at 12 months according to lesion pattern in the whole population (A), and in patients treated solely with GRIP™ balloon (B). ISR = in-stent restenosis; MACE = major adverse cardiac events.
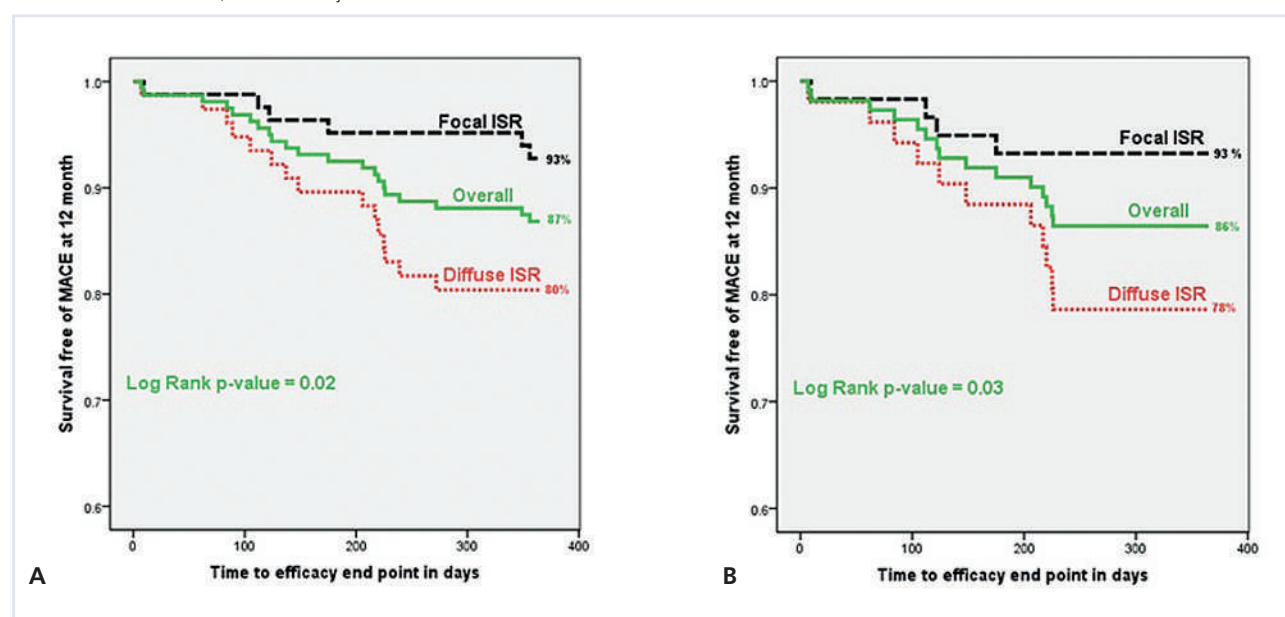
MACE of 7%. (3) When post-procedural result is insufficient, additional stent placement (sandwich technique) is justified and does not negatively influence clinical outcome. (4) Diffuse ISR is associated with worse outcome. As expected patients treated for a recurrent-ISR had more frequently a history of previous revascularisation at the index procedure. The differences observed for patients with recurrent-ISR compared to patients with naïve ISR might translate a higher tolerance to ischaemia in patients with recurrent-ISR as suggested by higher degrees of stenosis at presentation. One can speculate that the better post-procedural result in this latter group might translate the operator's intention to avoid further TLR.

A scoring balloon has elements placed outside of the balloon in order to reduce the occurrence of slippage during inflation for ISR and to increase the acute luminal gain. To date, three scoring balloons have been introduced in Europe [GRIP™ (Acrostak), Lacrosse NSE (Goodman) and AngioSculpt (Angioscore/Biotronik)], but no data are available regarding their safety and efficacy to treat ISR in humans. The main concern of the scoring balloon is that the elements on its surface could lead to higher complication rates such as dissection, perforation, or entrapment of the scoring elements [27]. In the present study, no entrapment or perforation was observed with the GRIP™ balloon. Moreover, dissections were rarely observed (five cases) and the incidence was considered within the anticipated range of 10%–13% incidence based on previous publications [25, 28].

According to the current guidelines, DEB should be considered as first-line treatment for ISR after BMS. Paclitaxel-eluting balloons have been found superior to plain old balloon angioplasty (POBA) for the treatment of restenosis after BMS in the randomised PACCO-CATH trial (5-year TLR 9% vs 39%, p <0.001) [29]. In the PEPCAD-II trial were non-inferior to paclitaxel-eluting stents with regard to clinical endpoints such as TLR (3-year follow-up: 8% vs 19%, $p_{superiority}$ = 0.07) [30] and achieved a significantly lower rate of late lumen loss. Similarly, Habara and colleagues demonstrated encouraging results in patients with ISR after sirolimus-eluting treated by DEB vs POBA (6-month TLR 4% vs 42%, p = 0.003) [31]. Rittger and colleagues reports similar results in DES-ISR with a significantly lower rate of late lumen loss, TLR and MACE at six months in patients treated by DEB (TLR 15.3% vs 36.8%, p = 0.005; MACE 16.7% vs 50.0%, p = <0.001) [32]. Clinical long-term data with DEB for restenosis are however, still scarce.

TLR was 11% in our population, clearly higher than the initial reported TLR in patients treated with DEB for BMS restenosis (5%–6%) [15, 19, 33]. Yet, when compared to TLR in patients treated with DEB for in-DES restenosis, these rates are within the expected range (4%–18%) [31, 32, 34]. Table 4 depicts TLR rates for relevant DEB trials. As noted in the introduction conventional angioplasty was always performed prior to DEB application in restenotic patients. Maybe the adjunction of a scoring balloon prior to DEB could yield to higher luminal gain and eventually even more favourable clinical outcomes.

In contrast, the anti-slip effect of GRIP™ balloons works well and is associated with effective angioplasty, especially in focal lesions. The efficacy endpoint in our sample was reached by a similar percentage of patients as previously reported [3, 8, 10, 35–38]. For instance, the figures are close to the recent publication of Tagliareni and colleagues in 213 patients undergoing PCI for ISR [39]. As expected, patients with focal lesions had a better clinical outcome than patients with diffuse ISR. This was solely due to lower TLR in the focal group. In line with this, Rathore et al. reported that a focal pattern of ISR after sirolimus-eluting stent implantation was an independent predictor of lower re-

Table 4
Rates of TLR in randomised controlled DEB-trials and registries.

	n =	Restenotic device	DEB compared with	End point at	TLR
Scheller et al. 2006, 2008	54	BMS	Orbus X, uncoated balloon	24 months	3 (6.2%)
Unverdorben et al. 2009	66	BMS	Taxus Liberté (DES)	12 months	4 (6.3%)
Silber et al. 2011	168	BMS	–	8 months	10 (5.9%)
Toelg R et al. 2012	43	BMS	–	12 months	2 (4.7%)
BMS total	**331**				**19 (5.7%)**
Rittger et al. 2012	72	DES	POBA (not specified)	6 months	11 (15.3%)
Habara et al. 2011	25	DES	POBA (not specified)	6 months	1 (4.3%)
Silber et al. 2011	87	BMS	–	8 months	9 (9.8%)
Toelg R et al. 2012	38	DES	–	12 months	7 (18.4%)
DES total	**97**				**28 (12.6%)**

BMS = bare metal stent; DEB = drug-eluting balloon; DES = drug-eluting stent; POBA = plain old balloon angioplasty; TLR = target lesion revascularisation.

current restenosis rate [40]. In addition, Cosgrave et al. reported a recurrence rate following PCI for ISR in drug-eluting stent from 18% in patients with focal lesion and 51% in patients with diffuse lesion [41]; the incidence of TLR at 14 months was close to our findings with 10% and 23%, respectively. Interestingly, TLR rates were similar in patients treated with POBA or sandwich drug-eluting stent implantation (focal lesion: 11% vs 9%, $p = 0.6$; diffuse lesion: 24% vs 23%, $p = 1.0$) [3]. Finally, Mishkel et al. reported higher rates of TLR (28.2%) and MACE (42.9%) at 12-month in 92 patients who were mostly treated by sandwich DES (84%) for ISR [42].

With the current therapeutical armamentarium including scoring, cutting, and drug-eluting balloons, as well as effective drug-eluting stents, such results underline that ISR treatment should be tailored to and based on ISR pattern (focal versus diffuse), presence or absence of stent fracture, and type of stent implanted (BMS, DES).

Limitations

The present study was designed as a retrospective analysis and therefore lacks randomisation and intention-to-treat data. Since no sample size calculations were performed, we acknowledge that our results may be affected by a type II error.

Conclusion

Balloon angioplasty with the GRIP™ balloon for ISR can be safely and successfully performed, and leads to an especially good clinical outcome in patients presenting with focal ISR.

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