



## Treatment of coronary in-stent restenosis: a systematic review

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### Abstract

Coronary stent implantation has significantly improved percutaneous coronary intervention and enabled the management of early complications of plain balloon angioplasty. However, a new complication has accompanied these improvements: in-stent restenosis (ISR) arising from neointimal hyperplasia. ISR after coronary angioplasty is currently one of the main limitations of this method, leading to the recurrence of exertional angina pectoris or acute coronary syndromes. The clinical incidence of ISR after bare-metal stent (BMS) implantation is approximately 20%–35%. The use of drug-eluting stents (DES) has led to a further decrease in the occurrence of ISR to 5%–10%. Evidence resulting from controlled clinical studies suggests that DES and drug-eluting balloon catheters (DEB) provide the best clinical and angiographic results in the treatment of ISR. We undertook a systematic review of the pathophysiology, diagnostics and treatment options for BMS- and DES-ISR. We discuss recent randomised studies, comparing different DES or DEB used for BMS or DES-ISR treatment, as well as the use of new biovascular scaffolds and the topic of scaffold restenosis.

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## 1 Introduction

Coronary stent implantation has significantly improved percutaneous coronary intervention (PCI) and enabled the management of early complications of plain balloon angioplasty (POBA). By preventing elastic recoil and constrictive remodeling, coronary stent implantation decreases the frequency of restenosis after PCI. However, a new complication has accompanied these improvements: in-stent restenosis (ISR) arising from neointimal hyperplasia. The clinical incidence of ISR after bare-metal stent (BMS) implantation is approximately 20%–35%. The use of drug-eluting stents (DES) has led to a further decrease in the occurrence of ISR to 5%–10%.<sup>[1,2]</sup> ISR after coronary angioplasty is currently one of the main limitations of this method, leading to the recurrence of exertional angina pectoris or acute coronary syndromes.<sup>[1,2]</sup> In this manuscript, we undertook a systematic review of the pathophysiology, diagnostics and treatment options for BMS- and DES-ISR.

Restenosis is defined as the repeated narrowing of the dilated segment of a coronary artery. Angiographic restenosis is defined as the  $\geq 50\%$  narrowing of the artery's diameter during a subsequent coronary angiography. Restenosis resulting in the recurrence of clinical manifestations of ischemia is called “clinical restenosis”, which is usually associated with the necessity to repeat target lesion or vessel revascularisation (TLR/TVR). In-stent restenosis is a restenosis in an implanted coronary stent; if we evaluate not only the area of the stent, but the whole affected segment of the vessel, we refer to it as in-segment restenosis (+5 mm from the proximal and distal edges of the stent).<sup>[3]</sup>

The generally used Mehran's angiographic classification divides ISR into four types: I-focal; II-diffuse; III-proliferative and IV-occlusive (Table 1).<sup>[3,4]</sup>

## 2 Drug-eluting stents restenosis

DES enable the local release of antiproliferative agents [paclitaxel or “limes” drug group (sirolimus, everolimus, zotarolimus, biolimus, etc)], which prevent excessive neointimal hyperplasia after stent implantation and lead to a reduction in the occurrence of ISR.<sup>[5]</sup>

While initial DES clinical trials reported near undetectable rates of ISR following DES implantation in short-term

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**Table 1. Mehran's angiographic classification of ISR.**

Type of ISR	Characteristics	Occurrence
I-focal	Length < 10 mm	42%
IA	The articulation or gap between stents	
IB	The proximal or distal margin	
IC	The body of the stent	
ID	Multifocal	
II-diffuse	Length >10 mm, not exceeding the edges of the stent	21%
III-proliferative	Exceeding the edges of the stent	30%
IV-occlusive	Total occlusion with TIMI 0	7%

ISR: in-stent restenosis; TIMI: thrombolysis in myocardial infarction.

follow-up, both long-term follow-up as well as “real-world” applications of DES in complex lesions have determined that the incidence of DES-ISR (‘DES failure’) is about 5%–10% (Table 2).<sup>[6–15]</sup>

### 3 Pathophysiology

Vascular injury sustained during PCI and stent implantation results in a complex inflammatory and reparative proc-

ess. The acute vascular reaction is characterized by early deposition of platelets and fibrin and adhesion of circulating neutrophils and monocytes to the injured vessel surface. Over weeks, acute inflammatory cells are replaced by chronic inflammatory cells (macrophages and giant cells). In addition to this inflammatory response, platelet- and leukocyte-related growth factors drive further vascular smooth muscle cells (VSMCs) proliferation and migration from the media to the nascent neointima and subsequent extracellular matrix formation. Two weeks following stent implantation, a complete neointimal layer, composed of VSMCs and a proteoglycan-rich extracellular matrix, can be observed above stent struts. The extracellular matrix is then covered from the luminal side by endothelial cells.<sup>[1–3]</sup> In BMS-ISR, the neointimal layer consists predominantly of VMSC surrounded by smaller amounts of extracellular matrix and a diffuse pattern of ISR is typical.<sup>[2,3,16]</sup> Peak BMS-ISR is observed at 3–6 months and remains relatively stable beyond one year.<sup>[1,2]</sup>

DES implantation results in delayed vessel wall healing, characterised by the presence of chronic fibrin deposits,

**Table 2. Comparisons of BMS vs. DES trials in de novo lesions.**

Trial	No. of patients	Treatment	Follow-up	The most important results
RAVEL <sup>[6,7]</sup>	238	SES vs. BMS	6 month angio 12 month clinical	Binary restenosis: 0 vs. 26.6%; TLR: 0 vs. 23.7%; $P < 0.05$ MACE: 5.8% vs. 28.8%; $P < 0.001$
			5 year clinical	TLR: 10.3% vs. 26%; $P < 0.001$ MACE: 25.8% vs. 35.2%; $P < 0.05$
SIRIUS <sup>[8,9]</sup>	322	SES vs. BMS	8 month angio 12 month clinical	Binary restenosis: 3.2% vs. 35.4%; $P < 0.001$ TLR: 4.9% vs. 20.2%; $P < 0.001$ MACE: 8.3% vs. 32.2%; $P < 0.001$
			5 year clinical	TLR: 9.4% vs. 24.2%; $P < 0.001$ MACE: 20.3% vs. 33.5%; $P < 0.001$
TAXUS IV <sup>[10,11]</sup>	1274	PES vs. BMS	9 month angio and clinical	Binary restenosis: 5.5% vs. 24.4%; $P < 0.001$ TLR: 9.1% vs. 20.5%; $P < 0.001$ MACE: 8.5% vs. 15%; $P < 0.001$
			5 year clinical	TLR: 9.1% vs. 20.5%; $P < 0.001$ MACE: 24% vs. 32%; $P < 0.001$
SPIRIT I <sup>[12,13]</sup>	56	EES vs. BMS	6 month angio and clinical	Binary restenosis: 0 vs. 25.9%; $P < 0.05$ TLR: 3.8% vs. 21.4% MACE: 7.7% vs. 21.4%;
			5 year clinical	TLR: 8.3% vs. 28%; MACE: 16.7% vs. 28%
ENDEAVOR II <sup>[14,15]</sup>	1197	ZES vs. BMS	12 month angio and clinical	Binary restenosis: 9.4% vs. 33.5%; $P < 0.001$ TLR: 4.6% vs. 11.8%; $P < 0.001$ MACE: 7.9% vs. 15.1%; $P < 0.001$
			5 year clinical	TLR: 7.5% vs. 16.3%; $P < 0.001$ MACE: 15.4% vs. 24.4%; $P < 0.001$

BMS: bare-metal stent; DES: drug-eluting stent; EES: everolimus-eluting stent; MACE: major adverse cardiac events; SES: sirolimus-eluting stent; TLR: target lesion revascularisation; PES: paclitaxel-eluting stent; ZES: zotarolimus-eluting stent.

incomplete neoendothelization and long inflammatory changes.<sup>[5]</sup> While fibrin deposits are replaced early on by neointimal tissue after BMS implantation, resulting in complete neoendothelisation within 3–6 months, DES implantation is associated with persistent fibrin deposits, a chronic inflammatory process and incomplete neoendothelisation for up to 48 months, accompanied by an associated risk of late stent thrombosis. Late vascular response after DES implantation is influenced further by the biocompatibility of the individual components of the stent, particularly the polymeric coating, which serves as a carrier and permits the controlled release of the active substance. This coating may cause persistent chronic inflammatory response in the vascular wall, leading to delayed healing and neointimal formation. In some cases, a non-specific acute inflammatory response may switch into a specific hypersensitivity reaction to polymer through the activation of eosinophils and T-lymphocytes.<sup>[5]</sup>

The stent polymer facilitates controlled elution of anti-proliferative agents over a variable period of time. Importantly, the durable polymer (DP) serves no function once drug elution has been completed and, consequently, it may be associated with inflammation, delayed healing, incomplete endothelialization or accelerating neoatherosclerosis which may contribute to the risk of late device failure compared with BMS. Contrary, biodegradable polymers (BP) may facilitate stent healing, thus enhancing clinical safety. The common BPs with therapeutic uses include polylactic acid, poly (lactic-co-glycolic acid) and poly (D,L-lactide). However, according to a recently published meta-analysis the safety and efficacy of BP-DES was similar as that of second-generation DP-DES [cardiovascular (CV) death, myocardial infarction (MI), TVR or late stent thrombosis;  $P = \text{NS}$  for both].<sup>[17]</sup>

Compared to BMS-ISR, DES-ISR appears later; its presence can be felt from 6–9 months with a further increase up to the second year after implantation. The neointimal tissue consists mainly of an extracellular matrix with a minimum of VSMCs and the focal character of ISR lesions is typical, especially for sirolimus eluting stents restenosis (SES-ISR).<sup>[3,5,16]</sup>

#### 4 Neoatherosclerosis

The neointimal layer on implanted stents may suffer from recurrent atherosclerotic changes, i.e., neoatherosclerosis. It appears that one of the predominant mechanisms involved in this process might be an incomplete regeneration of the endothelium leading to excessive uptake of circulating lipids and accelerated development of atheroscle-

rotic plaques in the nascent neointima. Intimal thickening, intracellular lipid deposition with thin fibro-atheroma cap or the presence of necrotic tissue have been detected using histopathological or optical coherence tomography (OCT) evaluations.<sup>[18]</sup>

Nakazawa, *et al.*<sup>[18]</sup> found in their histopathological autopsy study that neoatherosclerosis as a result of persistent endothelial dysfunction and incomplete neoendothelisation occurs more frequently (31% vs. 16%;  $P < 0.001$ ) and earlier (median: 420 vs. 2160 days;  $P < 0.001$ ) following DES than BMS implantation. Moreover, neoatherosclerosis in DES shows unstable characteristics (Thin-Cap Fibroatheromas or plaque rupture) earlier (about two years) after implantation, whereas similar features in BMS occur relatively later (about six years). Independent predictors of neoatherosclerosis included younger age, longer implant durations, sirolimus-eluting stent (SES) or paclitaxel-eluting stent (PES) implantation and underlying unstable plaques.<sup>[18]</sup> It is believed that neoatherosclerosis, along with the rupturing of the thin fibro-atheroma plaque, are among the predominant causes of late stent failure (i.e., delayed ISR and late or very late stent thrombosis) which could manifest as acute coronary syndromes.<sup>[18]</sup>

#### 5 ISR risk factors

BMS-ISR risk factors can be divided into patient-, lesion- or peri-procedural risk factors (Table 3).<sup>[1,3,19]</sup> Kastrati, *et al.*<sup>[20]</sup> found lesion and periprocedural characteristics as predictive factors for ISR. Complex lesions (B2/C), restenosis, vessel size  $< 3$  mm, stented segment  $> 15$  mm and particular types of BMS are associated with an occurrence of ISR. The strongest risk factor seems to be a small vessel size, with a 79% increase in the risk for a vessel of 2.7 mm versus a vessel of 3.4 mm in diameter. Differences in the incidence of ISR between different types of BMS may vary between 20% and 50%,<sup>[3,20]</sup> with significantly higher incidence in stents with thick struts compared to the newer stents with a thinner strut.<sup>[21,22]</sup>

**Table 3. ISR risk factors.**

Patient's factors	Lesion's factors	Peri-procedural risk factors
Diabetes mellitus	Complex B2/C lesions	Sub-optimal apposition
Renal insufficiency	Long lesions $> 20$ mm	Under-expansion of the stent
	Artery diameter $< 3$ mm	Post-PCI MLD $< 3$ mm
Acute coronary syndromes	Chronic closures	Implantation of multiple stents
	Ostial lesions	Stent fractures
	Bifurcation lesions	Stent fractures
	Lesions in venous bypass	Type of stent
	recurrent restenosis	

ISR: in-stent restenosis; MLD: minimal lumen diameter; PCI: percutaneous coronary angioplasty.

The most important ISR risk factors seem to be diabetes mellitus, the length of the lesion and small vessel diameter. In a multivariate regression analysis, the main BMS-ISR risk factors are diabetes mellitus (OR: 1.86), implantation of multiple stents (OR: 1.81) and a post-procedural minimum lumen diameter < 3 mm (OR: 1.81).<sup>[7]</sup> Diabetes itself increases the risk of BMS-ISR by 30%–50%.<sup>[23–25]</sup> Similarly, the risk of DES-ISR is increased in diabetic patients when compared to those without diabetes.<sup>[1,26]</sup> The length of the lesion and vessel diameter pose other ISR risk factors independent of the presence of diabetes,<sup>[1,23,26]</sup> i.e., an implanted stent length > 35 mm is associated with almost double the ISR risk compared to < 20 mm stents.<sup>[1,27]</sup>

The major risk factors for recurrent ISR are diabetes mellitus, previous ISR and type according to Mehran's classification (with an increase from I to IV).<sup>[3,4]</sup>

## 6 Biochemical and genetic risk factors

In addition to these known ISR risk factors, more biochemical or genetic factors are searched for that might contribute to the development of ISR. Mainly higher plasma levels of matrix metalloproteinases (MMPs), the proteolytic enzymes that degrade the extracellular matrix (ECM) and facilitate the proliferation and migration of endothelial and VSMCs, seem to be associated with a higher risk of in-stent restenosis.<sup>[28–30]</sup>

Many genome-wide association studies have observed single-nucleotide polymorphisms (SNPs) in individual genes, which could affect the occurrence of ISR, albeit with only a limited reach to clinical practice. One relatively large study was the GENetic DEterminants of Restenosis (GENDER) project, which examined 3100 patients with over 300 ISR cases after BMS implantation.<sup>[31]</sup> The association between some SNPs in *AGTR*, *GPXI*, *KAT2B*, *MMP12*, *FGF* and *VDR* genes and an increased risk of ISR was found.<sup>[32]</sup>

## 7 Diagnostics

### 7.1 Selective coronarography (SCG)

SCG is the standard diagnostic tool for the assessment of restenosis. Restenosis is arbitrarily defined as the repeated narrowing of the vessel lumen diameter with a cut-off value of  $\geq 50\%$ , known as “binary restenosis”.<sup>[3]</sup> However, neointimal hyperplasia, leading to re-narrowing of the lumen, represents a continuous process. Therefore, continuous variables are used to evaluate restenosis: the minimal lumen diameter (MLD), the percentage of diameter stenosis (DS%) and/or late lumen loss (LLL), representing the difference between post-procedural MLD and MLD at control coro-

nary angiography. The use of these so-called “angiographic surrogate end-points” helps, reduce the required cohort size while maintaining adequate statistical force.<sup>[33,34]</sup> A correlation, especially between LLL and DS%, and the incidence of angiographic and clinical restenosis, is proven.<sup>[3,33]</sup> Mauri, *et al.*<sup>[35]</sup> found a correlation between the LLL and the incidence of binary restenosis; LLL from 0.2 to 0.4 mm was associated with a 3.1% incidence of binary restenosis, as opposed to LLL of 0.4 to 0.6 mm, where the occurrence of ISRs increased to 6.4%. Similarly, Pocock, *et al.*<sup>[33]</sup> showed that LLL and DS% are able to predict with high accuracy the subsequent (TLR) after BMS/DES implantation (correlation coefficient about 0.90), wherein the predictive value of DS% does not depend on the artery's diameter.

### 7.2 Intravascular ultrasound (IVUS)

IVUS allows for a detailed display of the stented segment during an assessment of the cross-section of individual vessel wall layers. It is able to exclude possible mechanical causes of ISR (under-expansion, stent fracture, etc.) and provide detailed information on the extent of neointimal hyperplasia.<sup>[36]</sup> Although stent implantation under IVUS control is not routinely recommended, one of the IVUS risk factors of angiographic and clinical restenosis is the resulting minimal lumen area of the stented segment (minimal stent area, MSA). MSA increases by 1 mm<sup>2</sup> are associated with a 20% decrease in BMS-ISR.<sup>[3,37]</sup> Post-procedural MSA > 5 mm<sup>2</sup> with SES and > 6.5 mm<sup>2</sup> with BMS is a predictor of a satisfactory minimal lumen area (> 4 mm<sup>2</sup>) in the follow-up.<sup>[5,37,38]</sup>

### 7.3 Optical coherence tomography

OCT uses beam deflection with a frequency near to infrared light. This way, it achieves a significantly higher resolution compared to IVUS and allows for a more detailed assessment of stented segment.<sup>[3,5]</sup> Gonzalo, *et al.*<sup>[39]</sup> differentiate restenotic tissues according to their OCT images into the following subgroups: homogeneous, heterogeneous and stratified (layered) as well as low and high backscatter, whilst they also assess micro-vascularisation, lumen shape and the presence of intraluminal tissue. Diffuse ISR is characterised by a layered structure of neointimal tissue with high scattering, while focal lesions contain heterogeneous, low-scatter tissue.

### 7.4 Multi-slice CT (MS-CT) coronarography

64- and more-slice MS-CT have been shown to permit the detection of coronary artery stenoses in the native coronary arteries with sensitivities and specificities up to 99%, but the visualization of the lumen within coronary artery

stents by MS-CT is more challenging.<sup>[40]</sup> A major issue with assessment of metallic stents involves “metal-blooming” artifact (blooming of stent struts) such that stents appear larger than they actually are or “beam-hardening” artifacts resulting in artificial luminal narrowing and decreased intraluminal attenuation values.<sup>[41,42]</sup> These artifacts are more significant in stents < 3.0 mm in diameter.<sup>[41,42]</sup> A method to determine coronary in-stent restenosis was based mainly on contrast attenuation inside the stent lumen. In-stent restenosis was considered if the vessel distal to the stent was not visualized (occlusion) or massive low-density area (or filling defects) inside the stent lumen was detected visually when compared with the reference vessel.<sup>[43]</sup> In meta-analyses, the sensitivity and specificity of MS-CT in detection of ISR achieved 90% and 91%, with positive and negative predictive value of 68% and 98%, respectively.<sup>[44,45]</sup>

## 8 Clinical presentation of ISR

Since ISR is based on gradually increasing neointimal hyperplasia, in-stent restenosis used to be considered a relatively benign process leading to recurrent exertional angina. However, there is evidence that 30%–60% of ISR can manifest as acute coronary syndromes, mostly as unstable angina pectoris or non-ST elevation acute myocardial infarction (UAP/NSTEMI).<sup>[3,5]</sup>

In the clinical database APPROACH, ISR manifested in 52.2% of cases as UAP/NSTEMI, in 18.5% as STEMI and only in 25.3% as stable AP.<sup>[46]</sup> It is believed that ISR manifestation as an acute coronary syndrome could be caused by neoatherosclerosis and thin fibro-atheroma plaque rupture; this condition as well as delayed neoendothelialisation may cause late and very late DES stent thrombosis. The cause of stent occlusions may not be completely clear in the angiographic image. The behaviour of the lesion during the procedure (thromboaspiration, residual restenosis, etc) and imaging using IVUS or OCT may be helpful in differentiation between occluding neointimal hyperplasia and thrombotic occlusions due to neo-atherosclerotic changes or incomplete stent struts endothelialisation.<sup>[3,5]</sup>

The Mehran’s morphological character of ISR is a predictor of clinical events, with the necessity of repeated TVR between groups I-IV in 19%, 35%, 50% and 83% of cases, respectively ( $P < 0.001$ ).<sup>[3,4]</sup>

## 9 Treatment of ISR

### 9.1 Bare-metal stent restenosis (BMS)

Repeated POBA or BMS implantation was associated

with a high (nearly 40%) recurrence of binary restenosis,<sup>[47]</sup> cutting balloon dilatation did not reveal any significant benefit<sup>[48]</sup> and rotational atherectomy even led to outcomes inferior to POBA.<sup>[49]</sup> Brachytherapy has also been abandoned.

Current treatment for in-stent restenosis is based on DES. A drug released locally from the stent prevents new neointimal hyperplasia.<sup>[1,19]</sup> This treatment was established in the SISR and TAXUS V ISR trials, which compared the implantation of DES to relatively complicated brachytherapy.

In the SISR trial, the use of SES led to a significantly better angiographic outcomes and a trend to lower occurrence of repeated binary restenosis.<sup>[50]</sup>

The TAXUS V ISR trial found a significant decrease in TVR, repeated binary restenosis rate and also better clinical outcomes [major adverse cardiac events (MACE): CV death, MI or TVR] with the use of PES.<sup>[51]</sup>

The ISAR-DESIRE and RIBS II trials compared BMS-ISR treatment with DES implantation versus POBA. In the ISAR-DESIRE trial, implantation of SES or PES led to a significant decrease in repeated binary restenosis and TVR compared to POBA, whereas the direct comparison of both types of DES revealed a trend toward better outcomes in favor of SES.<sup>[52]</sup> Similarly, the RIBS II study revealed a significant decrease in restenosis and TVR after SES implantation.<sup>[53]</sup>

In contrast to DES, DEB catheters allow short-term passage of the active substance into the vascular wall, preventing hyperproliferation of VSMCs. Due to the short duration of the effect, DEB do not affect endothelial progenitor cells and stent neoendothelialization so much.<sup>[54–56]</sup>

Paclitaxel is used in the clinical practice as an effective antiproliferative agent in the case of DEB. Clinical data on the use of zotarolimus are also available.<sup>[57]</sup> Paclitaxel is highly lipophilic and rapidly penetrates into the tissues. Its concentrations used have stabilized at 3  $\mu\text{g}/\text{mm}^2$ .<sup>[55,56]</sup>

The main factor influencing the efficacy of paclitaxel-eluting balloon catheters (PEB) is the method of paclitaxel binding on the surface of the balloon catheter. Paclitaxel can be freely applied directly to the roughened surface of the balloon catheter (first generation DIOR<sup>®</sup>; Eurocor, Bonn, Germany) or is bound through the carrier, which affects its solubility and penetration through the vessel wall. In the original concept of Scheller, *et al.*,<sup>[55]</sup> paclitaxel was bound via iopromide, a hydrophilic contrast agent, which increased its solubility and penetration of the vascular wall (Paccocath). This method of preparation is used in modified form in PEB Sequent<sup>®</sup> Please (B.Braun, Melsulgen, Germany). In preclinical studies, iopromide-coated PEB showed

a significantly better angiographic outcomes than PEB without coating. In contrast, uncoated PEB failed to demonstrate any benefit compared to POBA.<sup>[58]</sup>

Many other PEBs are currently used in clinical practice: DIOR<sup>®</sup> II (shellac-coated; Eurocor, Bonn, Germany), IN.PACT<sup>™</sup> Falcon [urea-coated; Medtronic, Minneapolis, USA), Pantera<sup>™</sup> Lux (BTHC-coated (butyryl-tri-hexyl citrate); Biotronik, Berlin, Germany) and others.

The use of PEB in the treatment of ISR brings some benefits: compared to DES, PEBs allow homogeneous distribution of anti-proliferative treatment into the vessel wall with rapid achievement of an effective concentration; absence of polymers reduces chronic inflammatory response and the risk of subsequent late thrombosis; faster neoendothelialization allows shorter dual antiplatelet therapy and there is no risk of the occlusion of side branches with another layer of metallic struts.<sup>[59]</sup>

The efficacy of treatment with BMS-ISR using iopromide-coated PEB was demonstrated in comparison with PES. The Paccocath I and II trials demonstrated significantly better angiographic (lower LLL and repeated binary restenosis) and clinical outcomes (MACE) in the PEB groups compared to POBA.<sup>[60,61]</sup> Similarly, the PEPCAD II trial compared the treatment effect of PEB versus PES, showing significantly less 6-month LLL in the PEB group with a trend toward reducing the incidence of binary restenosis and 12-month MACE.<sup>[62]</sup>

The second generation DES releasing derivatives of sirolimus (everolimus, etc.) has higher efficacy and safety in the treatment of de novo lesions.<sup>[63]</sup> However, the Xience V US registry revealed significantly more target vessel failure (TVF; CV death, MI or TVR) after everolimus-eluting stent (EES) implantation in patients with ISR compared to those with non-ISR lesions.<sup>[64]</sup>

In several registries and observational trials, EES have been demonstrated to have at least the same angiographic and clinical outcomes in the treatment of BMS ISR as the first generation DES (PES/SES).<sup>[65,66]</sup>

In the recently published RIBS V trial, patients with BMS ISR were treated with PEB or EES (cobalt-chrome metallic platform). EES group had significantly higher 9-month MLD and lower DS%, however, there were not found any significant difference in LLL, repeated binary restenosis or TVR.<sup>[67]</sup>

Contrary to RIBS V, our TIS trial comparing iopromide-coated PEB and EES with a platinum-chromium metallic platform in the treatment of BMS-ISR demonstrated significantly lower 12-month LLL in the PEB group. The between-group differences in the incidence of repeated bi-

nary restenosis and 12-month MACE were also not significant.<sup>[68]</sup>

## 9.2 Restenosis in DES

In comparison with BMS-ISR, the treatment of DES-ISR is associated with worse long-term outcomes.<sup>[19,69]</sup> There is no clear consensus on whether the use of a different DES (hetero-DES) or a DES with a similar active substance (homo-DES) would be more beneficial.<sup>[19]</sup> The ISAR-DESIRE 2 trial found no angiographic or clinical differences in the treatment of SES-ISR using another SES or switching to PES.<sup>[70]</sup>

The prospective RIBS III registry compared the recommended strategy (hetero-DES, 75% of patients) to the control group (homo-DES, POBA, BMS). The hetero-DES group achieved a significantly better angiographic (higher MLD and fewer repeated binary restenosis) and clinical outcomes (MACE) compared to the disparate control group; whereas the direct comparison of hetero-DES and homo-DES subgroups revealed better outcomes in favor of hetero-DES.<sup>[71]</sup>

Similarly, the usage of PEB in the DES-ISR treatment was studied. The PEPCAD-DES trial compared the treatment of SES/PES-ISR using iopromide-coated PEB with POBA, and the use of PEB was associated with significantly better angiographic (lower LLL and repeated binary restenosis) and clinical end-points (MACE + stent thrombosis).<sup>[72]</sup>

In the PEPCAD ISR China trial, iopromide-coated PEB proved to be at least as effective as PES in the treatment of DES-ISR.<sup>[73]</sup> Habara, *et al.*<sup>[74]</sup> demonstrated better angiographic (lower LLL and repeated binary restenosis) and clinical outcomes (TVF) in patients with BMS/DES-ISR treated with iopromide-coated PEB compared to POBA. In the PEB group, significantly better results were achieved in the case of BMS-ISR compared to DES-ISR.

In the ISAR-DESIRE III study, the use of PEB was non-inferior to PES and either PEB or PES were superior to POBA alone in the treatment of SES-ISR, regarding to the primary angiographic end-point (follow-up residual %DS).<sup>[75]</sup> In the SeQuent Please World Wide Registry, PEB has been used predominantly for the treatment of ISR. Better 9-month clinical outcomes (TLR and MACE) were reported in patients with BMS- than DES-ISR.<sup>[76]</sup>

In the Valentine prospective study, patients with BMS/DES-ISR were treated with shellac-coated PEB; after 6 to 9 months, the overall incidence of TVR and MACE achieved 8.6% and 11.1%. In a sub-analysis of patients treated for DES-ISR, a significantly better clinical outcomes (MACE

and TVR) was recorded in patients with PES-ISR compared to patients with SES-ISR.<sup>[77,78]</sup>

Naganuma, *et al.*<sup>[79]</sup> did not find any significant clinical difference (TVR and MACE) between urea-coated PEB and EES groups in the treatment of bifurcation BMS/DES-ISR.

### 9.3 New DES and different PEBs

New DES composed of biodegradable polymers, polymer free or containing novel antiproliferative drugs (e.g., zotarolimus, biolimus) promise better biocompatibility. They have been tested mostly in the treatment of de-novo lesions.<sup>[17,80]</sup> However, the randomised comparisons of biodegradable and durable polymer DES in the treatment of ISR are not available.

A recently published RESTENT-ISR study, comparing EES and zotarolimus-eluting stents (ZES) used for DES-ISR treatment, did not find any significant difference between both groups.<sup>[81]</sup>

The efficacy of individual PEBs is not identical, as it is markedly influenced by the applied coating. Nijhoff, *et al.*<sup>[82]</sup> found a significantly better angiographic, fractional flow reserve and OCT outcomes in the urea-coated PEB compared to shellac-coated PEB used for treatment of BMS/DES-ISR; however, only a trend towards lower TLR was observed.

In our registry, comparing different PEBs in the treatment of BMS-ISR, a seal-wing PEB was associated with significantly worse angiographic (higher MLD, lower LLL and repeated binary restenosis) and clinical outcomes (TVR and MACE) compared to iopromide-coated PEB.<sup>[83]</sup>

Only in the Düsseldorf DCB registry, patients threatened for ISR, using BTHC-coated PEB, showed significantly better clinical outcomes compared to iopromide-coated PEB.<sup>[84]</sup>

In summary, both DES and DEB represent effective treatment of ISR. In comparison with BMS-ISR, DES-ISR treatment is associated with worse long-term outcomes. Among different PEBs, the best results are achieved with iopromide-coated ones. Results of the most important ISR trials are listed in Table 4.

### 9.4 Bioresorbable vascular scaffold restenosis (ScR)

One of the options employed to avoid the implantation of multiple metallic layers of stents into ISR (so called “onion skin”) could be the use of bioresorbable vascular scaffolds (BVS), which, compared with DEB, are able to achieve greater acute gain, prevent restenotic tissue prolapse and cover any edge dissection.

Jamshidi, *et al.*<sup>[85]</sup> proved the 100% peri-procedural success rate of everolimus-eluting BVS implantation in ISR

lesions (96% in DES-ISR), which was associated with 12.2% repeated TVR at the 12-month follow-up.

In an Italian registry involving 127 patients with BMS/DES-ISR treated with BVS, 12-month target lesion failure (TLF) was 9.1% (6.4% in BMS-ISR and 10.9% in DES-ISR). Repeated TLR due to recurrence of restenosis in BVS (scaffold restenosis; ScR) was necessary in 6.3% of cases.<sup>[86]</sup>

In most studies with everolimus-BVS used in the treatment of de-novo lesions, the primary endpoint was TLF and the incidence of scaffold restenosis was not specified; however, the main issue of BVS seems to be a late scaffold thrombosis.<sup>[87]</sup> In the GHOST-EU registry, 6-month TLF was 4.4%, 82% of which (3.6% of cases in total) arising due to ScR.<sup>[88]</sup> The optimal treatment of ScR is unknown. In this registry, ScR was treated using PEB (in 43% of cases), DES (36%), POBA with NC post-dilatation (14%), and on one occasion a further BVS was implanted (7%).<sup>[88]</sup>

## 10 Clinical implications

Despite the risk of ISR, revascularization may reduce the absolute and relative risk of cardiac death more than medical therapy in patients with moderate-large amounts of stress induced myocardial ischemia. The degree of stress-induced ischemia and left ventricle ejection fraction (LVEF) predict the effect of revascularization on outcomes in patients with coronary artery disease. In patients with post-stress LVEF  $\leq 45\%$ , the survival benefit of revascularization was seen even in the absence of stress-induced ischemia. Contrary, in patients with post-stress LVEF  $> 45\%$ , the survival benefit was depended on the presence of stress-induced ischemia.<sup>[89]</sup>

Despite the higher initial costs, the cost-effectiveness of the second generation DES implantations have been proved in recent meta analyses. The cost-reduction in the long term was primarily due to avoidance of secondary revascularisations and absence of myocardial infarction.<sup>[90]</sup>

## 11 Conclusions

Although the widespread usage of DES has reduced the incidence of ISR, this issue remains currently one of the main limitations of coronary interventions. Evidence resulting from controlled clinical trials suggests that DES and DEB provide the best angiographic and clinical outcomes in the treatment of ISR. However, new eluting balloons or stents (new antiproliferative drugs, biodegradable polymers or polymer-free etc) are rapidly evolving. Further studies are required to identify their potential benefit in the treatment of ISR.

**Table 4. Summary of the most important trials of DES/DEB treatment for BMS/DES-ISR.**

Trial (year)	N	Treatment	ISR type	Follow-up	The most important results
RIBS (2003) <sup>[47]</sup>	450	POBA vs. BMS	BMS-ISR	6-month angio 12-month clinical	Binary restenosis: 39% vs. 38%; <i>P</i> = NS MLD: 2.25 ± 0.5 vs. 2.77 ± 0.4 mm; <i>P</i> < 0.001
RESCUT (2004) <sup>[48]</sup>	428	Cutting balloon vs. POBA	BMS-ISR	7-month angio and clinical	Binary restenosis: 29.8% vs. 31.4%; <i>P</i> = 0.82 MACE: 16.4% vs. 15.4%; <i>P</i> = 0.79
ARTIST (2002) <sup>[49]</sup>	298	Rotablation vs. POBA	BMS-ISR	6-month angio and clinical	LLL: 0.91 ± 0.57 vs. 0.67 ± 0.53 mm; <i>P</i> = 0.0015 Binary restenosis: 64.8% vs. 51.2%; <i>P</i> = 0.039
SISR (2006) <sup>[50]</sup>	384	SES vs. Brachytherapy (β+γ radiation)	BMS-ISR	6-month angio 6 and 9-month clinical	TVF: 12.4% vs. 21.4%; <i>P</i> = 0.02 TVR: 8.5% vs. 19.2%; <i>P</i> = 0.004 MLD: 1.80 mm vs. 1.52 mm; <i>P</i> = 0.001 Binary restenosis: 19.8% vs. 29.5%; <i>P</i> = 0.07
TAXUS V ISR (2006) <sup>[51]</sup>	396	PES vs. Brachytherapy (β radiation)	BMS-ISR	9-month angio and clinical	Ischemia-driven TVR: 10.5% vs. 17.5%; <i>P</i> = 0.046 MACE: 11.5% vs. 20.1%; <i>P</i> = 0.02 Binary restenosis: 14.5% vs. 31.2%; <i>P</i> < 0.001
ISAR-DESIRE (2005) <sup>[52]</sup>	300	DES (SES + PES) vs. POBA	BMS-ISR	6-month angio 9-month clinical	Binary restenosis: 14.3% (SES) and 21.7% (PES) vs. 44.6% (POBA); <i>P</i> for both < 0.001 TVR: 8.0% (SES) and 19.0% (PES) vs. 33.0% (POBA); <i>P</i> < 0.001 and <i>P</i> = 0.02 SES vs. PES: binary restenosis: <i>P</i> = 0.19; TVR: <i>P</i> = 0.02
RIBS II (2006) <sup>[53]</sup>	150	SES vs. POBA	BMS-ISR	9-month angio 12-month clinical	Binary restenosis: 11% vs. 39%; <i>P</i> < 0.001 TVR: 11% vs. 30%; <i>P</i> < 0.003
Paccocath I and II (2008) <sup>[60,61]</sup>	108	Iopromide-coated PEB vs. POBA	BMS-ISR	6-month angio 1 and 2-year clinical	LLL: 0.11 ± 0.45 mm vs. 0.81 ± 0.79 mm; <i>P</i> < 0.001 Binary restenosis: 6% vs. 51%; <i>P</i> < 0.001 MACE: 11% vs. 46%; <i>P</i> = 0.001
PEPCAD II (2009) <sup>[62]</sup>	131	Iopromide-coated PEB vs. PES	BMS-ISR	6-month angio 12-month clinical	LLL: 0.17 ± 0.42 mm vs. 0.38 ± 0.61 mm; <i>P</i> = 0.03 Binary restenosis: 7% vs. 20%; <i>P</i> = 0.06 MACE: 9% vs. 22%; <i>P</i> = 0.08
RIBS V (2014) <sup>[67]</sup>	189	Iopromide-coated PEB vs. EES (Co/Cr)	BMS-ISR	9-month angio 12-month clinical	MLD: 2.01 ± 0.6 mm vs. 2.36 ± 0.6 mm; <i>P</i> < 0.001 %DS: 25 ± 20% vs. 13 ± 17%; <i>P</i> < 0.001 LLL: 0.14 ± 0.5 mm vs. 0.04 ± 0.5 mm; <i>P</i> = 0.14 Binary restenosis: 9.5% vs. 4.7%; <i>P</i> = 0.22 MACE: 8% vs. 6%; <i>P</i> = 0.6; TVR: 6% vs. 2%; <i>P</i> = 0.22
TIS (2016) <sup>[68]</sup>	136	Iopromide-coated PEB vs. EES (Pt/Cr)	BMS-ISR	12-month angio and clinical	LLL: 0.09 ± 0.44 mm vs. 0.44 ± 0.73 mm; <i>P</i> = 0.0004 Binary restenosis: 8.7% vs. 19.12%; <i>P</i> = 0.078 MACE: 10.29% vs. 19.12%; <i>P</i> = 0.213
ISAR-DESIRE II (2010) <sup>[70]</sup>	450	SES vs. Iopromide-coated PES	SES-ISR	6-month angio 12-month clinical	LLL: 0.40 ± 0.65 mm vs. 0.38 ± 0.59 mm; <i>P</i> = 0.85 Binary restenosis: 19.6% vs. 20.6%; <i>P</i> = 0.69 TLR: 16.6% vs. 14.6%; <i>P</i> = 0.52
RIBS III (2012) registry <sup>[71]</sup>	363	Hetero-DES vs. Control (homo-DES, POBA, BMS)	DES-ISR	9-month angio 12-month clinical	MLD: 1.86 ± 0.7 mm vs. 1.40 ± 0.8 mm; <i>P</i> = 0.003 Binary restenosis: 22% vs. 40%; <i>P</i> = 0.008 MACE: 23% vs. 35%; <i>P</i> = 0.039 Hetero-DES vs. homo-DES: fewer restenosis (HR: 0.41; 95%CI: 0.21-0.80; <i>P</i> = 0.01)
PEPCAD-DES (2012) <sup>[72]</sup>	110	Iopromide-coated PEB vs. POBA	DES-ISR	6-month angio and clinical	LLL: 0.43 ± 0.61 vs. 1.03 ± 0.77 mm; <i>P</i> < 0.001 Binary restenosis: 58.1% vs. 17.2%; <i>P</i> < 0.001 MACE + stent thrombosis: 50.0% vs. 16.7%; <i>P</i> < 0.001
PEPCAD ISR <sup>[73]</sup>	220	Iopromide-coated PEB vs. PES	DES-ISR	9-month angio 12-month clinical	LLL: 0.46 ± 0.51 vs. 0.55 ± 0.61 mm; <i>P</i> non-inferiority = 0.0005 TLF: CV death, MI + TLR: 15.5% vs. 17.5%; <i>P</i> = 0.69
Habara <i>et al.</i> (2013) <sup>[74]</sup>	208	Iopromide-coated PEB vs. POBA	BMS/DES-ISR	6-month angio and clinical	LLL 0.11 ± 0.33 vs. 0.49 ± 0.50 mm; <i>P</i> < 0.001 Binary restenosis: 4.3% vs. 31.9%; <i>P</i> < 0.001 TVF: 6.6% vs. 31%; <i>P</i> < 0.001 PEB for BMS- vs. DES-ISR: LLL: 0.05 ± 0.28 mm vs. 0.18 ± 0.38 mm; <i>P</i> = 0.03 binary restenosis: 1.1% vs. 9.1%; <i>P</i> = 0.04
ISAR-DESIRE III (2013) <sup>[75]</sup>	402	PES vs. Iopromide-coated PEB vs. POBA	SES-ISR	6-month angio 12-month clinical	%DS: PEB vs. PES: 38 ± 21.5% vs. 37.4 ± 21.8%; <i>P</i> non-inferiority = 0.007 PEB or PES vs. POBA (54.1 ± 25%); <i>P</i> superiority < 0.0001 for both



Table 4. Cont.

Trial (year)	N	Treatment	ISR type	Follow-up	The most important results
SeQuent Please World Wide Registry (2012) <sup>[76]</sup>	1523	Iopromide-coated PEB	BMS vs. DES-ISR	9-month clinical	TLR: 3.8% vs. 9.6%; $P < 0.001$ MACE: 11.3 vs. 5.6%; $P < 0.001$
Valentine prospective registry (2011) <sup>[77,78]</sup>	250	Shellac-coated PEB	BMS/DES-ISR	6 to 9-month clinical	overall MACE 11.1% and TVR 8.6% PES- vs. SES-ISR: MACE: 0% vs. 23.8%; $P = 0.002$ TVR: 0% vs. 16.7%; $P = 0.015$
Naganuma et al. (2014) registry <sup>[79]</sup>	158	Urea-coated PEB vs. EES	Bifurcation BMS/DES-ISR	2-year clinical	MACE: 32.1% vs. 27.6%; $P = 0.593$ TVR: 23.7% vs. 21.8%; $P = 0.884$ Independent predictors of MACE: repeated previous stent implantations for ISR ('stent-in-stent'); HR: 2.16; 95%CI: 1.11–4.20; $P = 0.023$ ; ISR in the true bifurcation lesion (HR: 2.98; 95%CI: 1.45–6.14; $P = 0.001$ )
RESTENT-ISR (2016) <sup>[81]</sup>	304	EES vs. ZES	DES-ISR	9-month angio 3-year clinical	LLL: $0.40 \pm 0.56$ vs. $0.45 \pm 0.61$ mm; $P = 0.57$ MACE: 15.8% vs. 22.6%; $P = 0.276$
Nijhoff, et al. registry <sup>[82]</sup>	45	Urea-coated vs. shellac-coated PEB	BMS/DES-ISR	6-month angio	LLL: $-0.03 \pm 0.43$ vs. $0.36 \pm 0.48$ mm; $P = 0.014$ FFR distally: $0.92 \pm 0.07$ vs. $0.84 \pm 0.13$ ; $P = 0.029$ vol%IH: $-16\%$ vs. $+36\%$ ; $P = 0.006$
Pleva, et al. (2017) <sup>[83]</sup>	136	Seal-wing PEB vs. iopromide-coated PEB	BMS-ISR	12-month angio and clinical	LLL: 0.30 vs. 0.02 mm; $P < 0.0001$ MLD: 1.68 vs. 2.13 mm; $P = 0.0006$ Binary restenosis: 28.12% vs. 8.7%; $P = 0.012$ MACE: 26.98% vs. 10.29%; $P = 0.003$ TVR: 20.63% vs. 7.35%; $P = 0.009$
Düsseldorf DCB registry (2017) <sup>[84]</sup>	571	BTHC-coated PEB vs. iopromide-coated PEB	BMS/DES-ISR	in-hospital and clinical	Longer EFS (HR: 0.65; 95%CI: 0.43–0.98; $P = 0.405$ )

BMS: bare-metal stent; BTHC: butyryl-tri-hexyl citrate; Co/Cr: cobalt-chromium; DEB: drug-eluting balloon catheter; DES: drug-eluting stent; EES: everolimus-eluting stent; EFS: event-free survival; FFR: fractional flow reserve; HR: hazard rate; ISR: in-stent restenosis; LLL: late lumen loss; MACE: major adverse cardiac events; MLD: minimal lumen diameter; PEB: paclitaxel-eluting balloon catheter; PES: paclitaxel-eluting stent; %DS: percent diameter stenosis; POBA: plane old balloon angioplasty; Pt/Cr: platinum-chromium; SES: sirolimus-eluting stent; TVF: tagret vessel failure; TVR/TLR: tagret vessel/lesion revascularisation; vol%IH: volume percent intimal hyperplasia; ZES: zotarolimus-eluting stent.

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