What Are The Best Current Treatment Options For ISR: What Are The Results Including Recurrence Rates

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ISR can be considered the "Achilles heel" of modern PI !

ISR is a loss of luminal volume from an ingrowth of cells, extracellular matrix, and thrombus within the cylinder of the stented artery and 5-mm margins proximal and distal to the stent.

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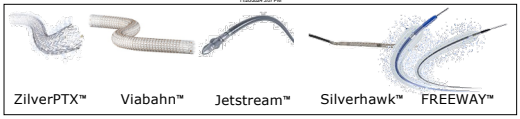

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Disclosure

Speaker name:

Prof. Dr. S. Müller-Hülsbeck

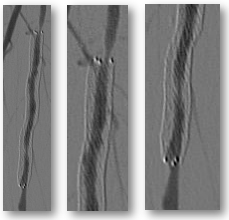
I have the following potential conflicts of interest to report:

- ☒ Consulting: Terumo, Alvimedica, Eurocor
- ☐ Employment in industry
- ☒ Stockholder of a healthcare company: Roche, Novartis, Johnson&Johnson, Novonordisk, Amgen, Chugai, Sandoz
- ☐ Owner of a healthcare company
- ☐ Other(s)

☐ I do not have any potential conflict of interest

In-stent Restenosis (ISR) – Treatment Options and Outcomes

- Objectives and Outline
  - ✓ Relevance, Promotors & Factors
  - ✓ Angiographic Classification
  - ✓ Imaging and Histological Features
  - ✓ Management
    - ✓ Treatment options
    - ✓ Outcome
  - ✓ Future Strategies and Unmet Needs



Relevance*

CAS 6%

PCI 5-10%

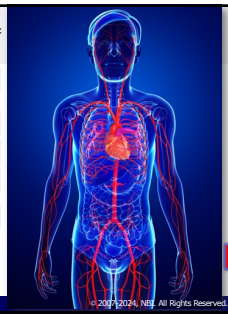
Mesenteric 20-60%

Renal 10%

Aorto-iliac 5-10%

SFA 15-40%

BTK 30%



SFA 15-40%*

*at 2 yrs

*Rough estimates

Promotors of ISR (SFA)

- Excessive stent oversizing
- Long stented segments
- TASC D lesions
- Poor tibial artery runoff
- Mechanical factors
  - ✓ repetitive and dynamic frictional forces between artery and stent caused by musculoskeletal motion
- Anatomic factors
  - ✓ small-caliber arteries
- Clinical factors
  - ✓ smoking and diabetes mellitus

Zhao HQ, Nikanorov A, Virmani R, Jones R, Pacheco E, Schwartz LB. Late stent expansion and neointimal proliferation of oversized Nitinol stents in peripheral arteries. Cardiovasc Intervent Radiol 2009;32:720-6.

Segunner AM, Traupe T, Reiber L, Hess N, Baru Y, Segunner AR, et al. Oversizing and restenosis with self-expanding stents in iliofemoral arteries. Cardiovasc Intervent Radiol 2012;35: 906-13.

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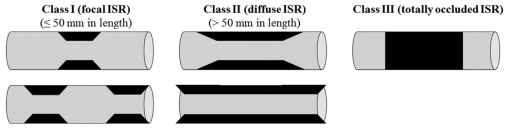
Early M, Lally C, Prendergast PJ, Kelly DJ. Stresses in peripheral arteries following stent placement: a finite element analysis. Comput Methods Biomech Biomed Engin 2009;12: 25-33.

Mahrer PJ, Dangas G, Akiyoat AS, Mintz GS, Lansky AJ, Satler LF, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation 1999;100:1872-8.

Angiographic Classification of ISR



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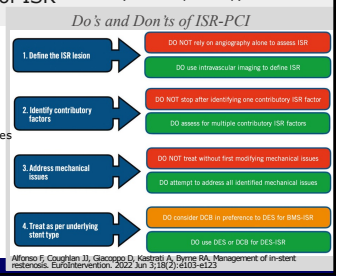
Management of ISR (SFA)

(Coronary Artery)

(1) Bare Metal Stenst (BMS)
(2) Covered Stents (CS)
(3) Drug-Eluting Stent (DES)
(4) Drug-Coated Balloon (DCB)
  (1)Paclitaxel DCBs
  (2)Sirolimus DCBs
(5) Adjunctive therapeutic modalities
  (1)PTA
  (2)Cutting/Scorring Balloon
  (3)Intravascular Brachytherapy
(6) Ablative Strategies
  (1)Excimer Laser Atherectomy
  (2)Rotational Atherectomy
(7) Intravascular Lithotripsy



Alfonso F, Coughlan JJ, Giacoppo D, Kastrati A, Byrne RA. Management of in-stent restenosis. EuroIntervention. 2022 Jun 3;18(2):e103-e123

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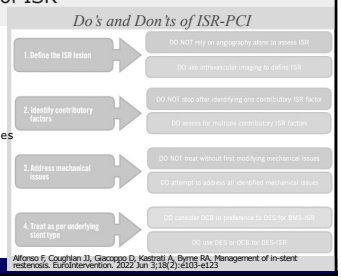

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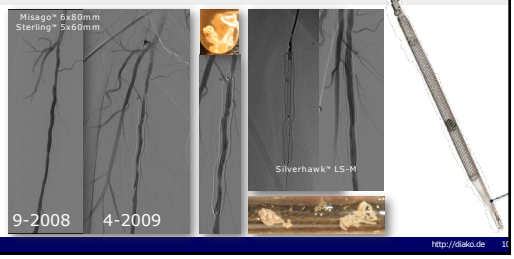
Ablative Strategies – Directional Atherectomy



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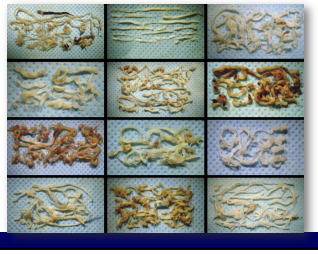
Ablative Strategies - Large Amount of Tissue Captured



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Ablative Strategies – Rotational Atherectomy

- **Combination of rotational atherectomy with DCB angioplasty** offers the advantage of lesion debulking and the antirestenotic effect
- Analysis of 30 pts
- Primary patency at 12 months: 93.4%
- Primary patency at 24 months: 83.4%
- Secondary patency at 24 months: 96.7%.

Cioppa A, Leone A, Puccarelli A, Salemme L, Popusoi G, Franzese M, Di Gioia G, Sada L, Ferrone M, Verdoliva S, Stabile E, Esposito G, Tesorio T. Combined therapy with rotational atherectomy and drug coated balloon for superficial femoral artery in-stent restenosis: safety, efficacy, and two-year results of a single center experience. Minerva Cardiol Angiol. 2023 Oct;71(5):599-605.

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Covered Stents vs. PTA

- 22 patients (27 limbs)
- Primary patency at 3 years 63%
- Analysis of multiple factors showed no association with restenosis occurrence.
- If the Viabahn remained patent for 14 months, the likelihood of restenosis was low.

Gorgani F, Telis A, Narakathu N, LaBarbera M, Babaev A. Long-term outcomes of the Viabahn stent in the treatment of in-stent restenosis in the superficial femoral artery. J Invasive Cardiol. 2013 Dec;25(12):670-4.

- **RELINE-Trial:** Viabahn n=39 vs PTA n=44
- Primary patency at 12 months 74.8% Viabahn group
  28.0% PTA group (p < 0.001).

Bosiers M, Deloose K, Callaert J, Verbist J, Hendriks J, Lauwers P, Schroë H, Lansink W, Scheinert D, Schmidt A, Zeller T, Beschorner U, Noory E, Torsello G, Austermann M, Peeters P. Superiority of stent-grafts for in-stent restenosis in the superficial femoral artery: twelve-month results from a multicenter randomized trial. J Endovasc Ther. 2015 Feb;22(1):1-10.

Treatment of ISR (I) DCB

- Prospective, randomized, single-blind, dualcenter clinical trial
- 74 pts, 51 limbs

	PTA	DCB
Primary patency @ 12 months	13.4	40.7
		p=0.02

FREEWAY™ Balloon

Kinstner CM, Lammer J, Willfort-Ehringer A, Matzek W, Gschwandtner M, Javor D, Funovics M, Schoder M, Koppensteiner R, Lowe C, Ristl R, Wolf F. Paclitaxel-Eluting Balloon Versus Standard Balloon Angioplasty in In-Stent Restenosis of the Superficial Femoral and Proximal Popliteal Artery: 1-Year Results of the PACUBA Trial. JACC Cardiovasc Interv. 2016 Jul 11;9(13):1386-92.

Treatment of ISR (II) DCB

	DCB
Primary Patency @ 12 months	91.26
Primary Patency @ 24 months	80.47
Primary Patency @ 36 months	67.71

- Retrospective observational study
- 105 pts, 103 pts analyzed

MOXY DRUG COATED BALLOON Lutonix™ Balloon

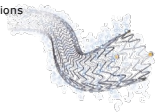
Peclat de Oliveira IC, Alvim Fiorelli RK, Rolim Maia Peclat AP, Peclat de Oliveira LM, Oliveira R, Belczac SO, Almeida RS, Dolo MR, Joviliano SE, Gutfilen B. Superficial Femoral Artery in-Stent Restenosis Treated with Paclitaxel-Coated Balloon Angioplasty - Results of Three-Year Follow-Up. Vasc Endovascular Surg. 2020 Oct;57(7):673-679.

Treatment of ISR (III) DES

	DES
Freedom from TLR @ 6 months	95.7
Freedom from TLR @ 12 months	81
Freedom from TLR @ 24 months	60.8

- Pts from ZILVER-PTX single-arm trial
- 108 pts, 119 ISR lesions

ZilverPTX™



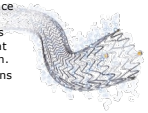
Zeller T, Dake MD, Tepe G, Brechtel K, Noory E, Beschorner U, Kultgen PL, Rastan A. Treatment of femoropopliteal in-stent restenosis with paclitaxel-eluting stents. JACC Cardiovasc Interv. 2013 Mar;6(3):274-81.

Treatment of ISR (IV) DES

	DES
Freedom from clinical driven TLR @ 5 years	73.4
clinical benefit @ 5 years	63.6

- Prospective, multicenter registry Zilver PTX Japan Post-Market Surveillance Study: 904 pts, 1082 femoropopliteal lesions treated with the DES at 95 institutions in Japan.
- 177 pts, 204 ISR lesions

ZilverPTX™



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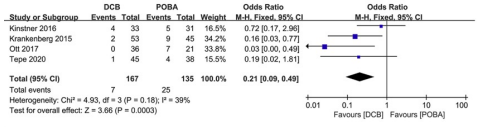
DCB: Systematic Review and Meta-Analysis for ISR

TLR at 12 months - *FAIR* - *PACUBA* - *ISAR PEBIS* - *COPA CABANA*



- 5 randomized controlled trials with 425 patients

Zhan Y, Ren H, Chen J, Chang Z, Wang C, Zheng J. Systematic Review and Meta-Analysis of Drug-Coated Balloon Angioplasty for In-Stent Restenosis in Femoropopliteal Artery Disease. J Vasc Interv Radiol. 2022 Apr;33(4):368-374.e8.

DCB: Systematic Review and Meta-Analysis for ISR

Recurrent ISR at 12 months

Study or Subgroup	DCB Events	DCB Total	POBA Events	POBA Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kinstner 2016	13	33	21	31	22.2%	0.31 [0.11, 0.86]
Krankenberg 2015	8	52	21	47	31.6%	0.23 [0.09, 0.58]
Ott 2017	8	27	16	27	19.1%	0.29 [0.09, 0.89]
Tepe 2020	5	37	16	27	27.1%	0.11 [0.03, 0.36]
Total (95% CI)		**149**		**132**	**100.0%**	**0.22 [0.13, 0.38]**
Total events	34		74			

Heterogeneity: Chi² = 1.98, df = 3 (P = 0.58); I² = 0%
Test for overall effect: Z = 5.55 (P < 0.00001)

Odds Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100
Favours [DCB] Favours [POBA]

- 5 randomized controlled trials with 425 patients

Zhen Y, Ren H, Chen J, Chang Z, Wang C, Zheng J. Systematic Review and Meta-Analysis of Drug-Coated Balloon Angioplasty for In-Stent Restenosis in Femoropopliteal Artery Disease. J Vasc Interv Radiol. 2022 Apr;33(4):368-374.e6.

Systematic Review and Meta-analysis of the Efficacy of Debulking Devices for ISR

Author	Year	Patients	Type	Follow up, months	Lesion length, mm	Occlusive/stenosis	location, SFA/popliteal/both
Armstrong[7]	2015	54	Laser + PTA	24	222 ± 118	37/17	20/5/31
		81	PTA	24	114 ± 106	17/64	53/6/22
Dippel[8]	2015	169	Laser + PTA	6	196 ± 120	50/11x	115/6/27
		81	PTA	6	193 ± 119	31/35	62/4/15
Kokkinidis[10]	2018	62	Laser + DCB	12	256 ± 125	46/16	32/5/25
		50	Laser + PTA	12	242±6 ± 107	37/13	19/3/28
Laird[11]	2012	27	Laser + PTA	12	207 ± 105	NA	NA
Schmidt[15]	2014	90	Laser + PTA	12	123 ± 96	30/60	85/3/2
Shammas[17]	2015	41	SilverHawk + PTA	12	126.2 ± 79.3	NA	NA
		40	Laser + PTA	12	210.4 ± 104	NA	NA
Gandini[18]	2015	24	Laser + DCB	12	200	20/4	NA
		24	DCB	12	233	19/5	NA
Shammas[9]	2016	29	JetStream XC + PTA	6	174 ± 131	8/24	2/3/8
Slingardi[20]	2010	32	Rotarex + PTA	153	160	NA	14/9/5
		1	Rotarex + AngioSculpt	--			
		2	Rotarex + DEB	--			
Trentmann[21]	2010	33	SilverHawk + PTA	12	108 ± 102	7/26	NA
Sixt[22]	2013	29	SilverHawk + DCB	12	153	NA	16/8/5
		60	SilverHawk + PTA	12	180	NA	28/8/24

ABI, Ankle-brachial index; DCB, drug-coated balloon; ISR in stent restenosis; NA, not applicable; PTA, percutaneous transluminal angioplasty; SFA, superficial femoral artery; TLR, target lesion revascularization.

Li X, Zhou M, Ding Y, Wang Y, Cai L, Shi Z. A systematic review and meta-analysis of the efficacy of debulking devices for in-stent restenosis of the femoropopliteal artery. J Vasc Surg. 2020 Jul;72(1):356-366.e5

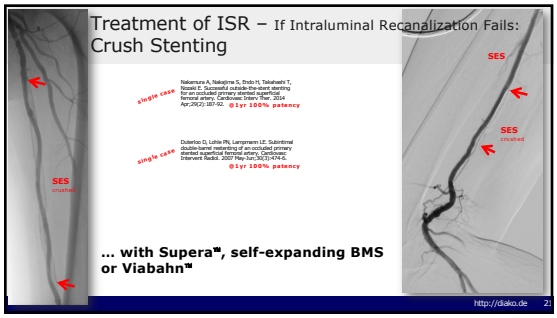
- 12 studies
- 743 patients
- Primary patency at 1 year

58.3% (95%CI, 44.7%-71.9%)

- Freedom from TLR at 1 year

67.0% (95% CI, 56.3%-74.6%)

Treatment of ISR – If Intraluminal Recanalization Fails: Crush Stenting



… with Supera™, self-expanding BMS or Viabahn™

Conclusions

- Guidelines currently do not offer strong recommendations
- Expert opinion is not entirely clear on how to most appropriately treat femoropopliteal ISR
- More research is needed to define what the standard of care should be, and which treatments should be adopted for certain angiographic characteristics (eg, longer lesions, calcified lesions)
- An adequately powered trial examining currently approved treatments for femoropopliteal ISR should be performed:
  - i.e. DCB* alone vs. atherectomy with DCB* vs. DES* vs. Viabahn
- **Without direct comparisons of these treatment strategies, the waters will remain murky on how best to treat the growing population of patients with femoropopliteal ISR.
- Latest meta-analysis suggests that DCB angioplasty is an improvement over PTA for femoropopliteal ISR.

**Rymer JA, Jones WS. Femoropopliteal In-Stent Restenosis. Circ Cardiovasc Interv. 2018 Dec;11(12):e007559

*Paclitaxel or Sirolimus

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