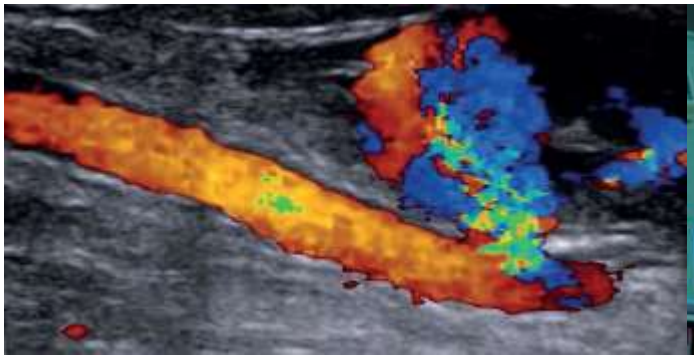
Endovascular Session II.
Below the Knee Intervention

19th CARDIOVASCULAR SUMMIT
TCTAP 2014

The Value of DEB and DES in Below-the-Knee Interventions: When to Use Them and Are They Really Valuable?



Massimiliano Fusaro, MD

German Heart Center, Munich - Germany

Conflicts of interest

Speaker's name: Massimiliano Fusaro

I have the following potential conflicts of interest to report:

☐ Research contracts
☐ Consulting
☐ Employment in industry
☐ Stockholder of a healthcare company
☐ Owner of a healthcare company
☐ Other(s)

X I do not have any potential conflict of interest

Technische Universität München

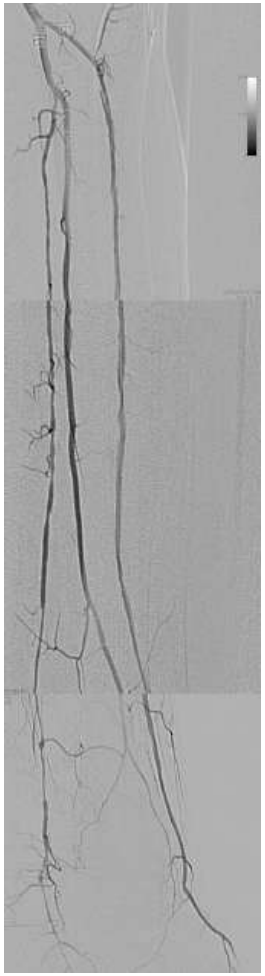
Randomized Trials for Endovascular Treatment of Infrainguinal Arterial Disease: Systematic Review and Meta-analysis (Part 2: Below the Knee)

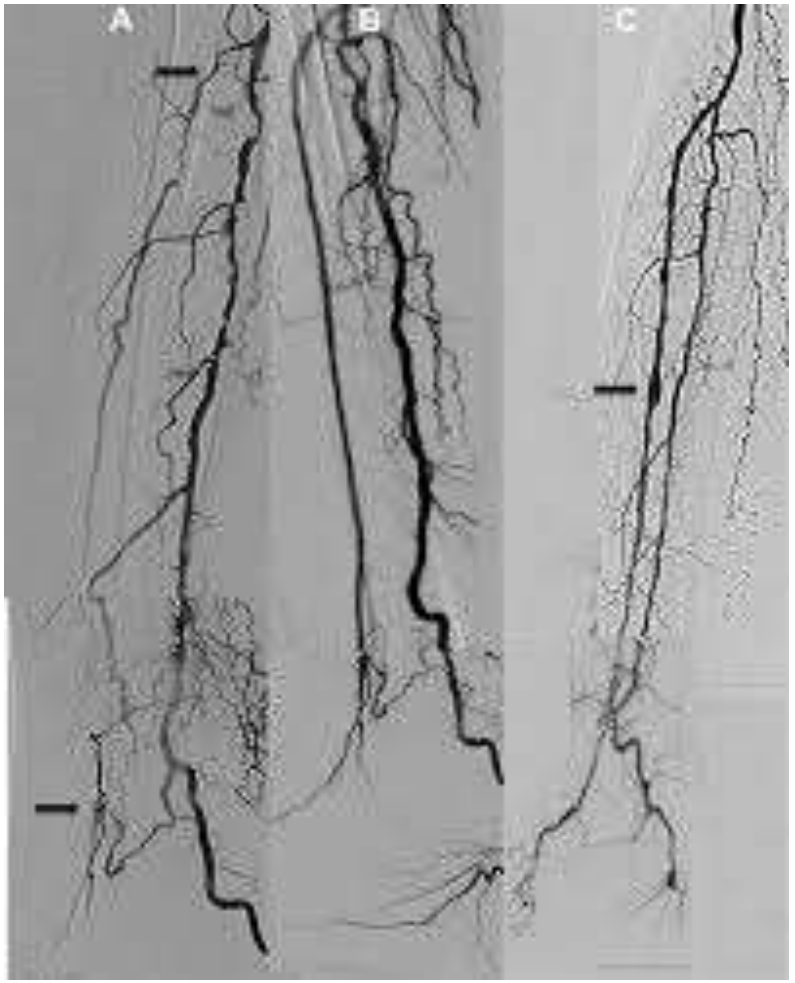
First author	Comparison	Patients, *N*	% FII/FIII/ FIV or IC/CLI	Lesions, *N*	Age (y), mean (SD) or median (range)	Males, *N* (%)	Smoking, *N* (%)	Diabetes, *N* (%)	Renal failure, *N* (%)	CAD, *N* (%)	Stroke, *N* (%)	Hyperlipidemia, *N* (%)	Hypertension, *N* (%)	Occlusions, *N* (%)	Stenosis in %, mean (SD)	Lesion length (mm), mean (SD)	Primary outcome	Industry sponsored
DES vs PTA																		
Scheinert 2012[15]	Sirol-ES	200	FII–FIV	228	73 (9)	143 (72)	65 (33)	129 (65)	—	90 (45)	—	146 (73)	181 (91)	179 (79)	—	27 (21)	12 mo binary restenosis	Yes
Tepe 2010[34]	Sirol-ES abciximab vs POBA abciximab	28	0/0/100	28	71 (—)	16 (57)	4 (14)	21 (75)	—	—	—	12 (43)	22 (79)	8 (29)	90 (—)	29 (21)	6 mo primary restenosis	Not reported
DEB vs PTA																		
Fanelli 2012[16]	PTX-EB	—	FII–FIV	30	—	—	—	—	—	—	—	—	—	12 (40)	86 (5)	—	6 mo LLL	No
Lilstro 2013[17]	PTX-EB	132 (143 limbs)	FIII–FIV	158	75 (10)	106 (80)	20 (15)	132 (100)	—	22 (17)	12 (9)	39 (30)	98 (74)	126 (80)	97 (8)	130 (81)	12 mo binary restenosis	No
DES vs BS																		
Rastan 2011[19]/ 2012[18]	Sirol-ES vs BMS	161	53/47	161	73 (9)	107 (66)	46 (29)	87 (54)	57 (35)	—	—	123 (76)	145 (90)	36 (22)	88 (9)	31 (9)	1 y primary patency rate	Yes
Falkowski 2009[20]	Sirol-ES vs BMS	50	68/20/12	50	mean 69 (53–58)	29 (58)	22 (44)	20 (40)	—	21 (42)	7 (14)	18 (36)	31 (62)	—	—	18 (3)	6 mo restenosis	Not reported
Tepe 2010[34]	Sirol-ES abciximab vs BMS abciximab	30	0/0/100	30	73 (—)	16 (53)	2 (7)	15 (50)	—	—	—	9 (30)	21 (70)	10 (33)	89 (—)	31 (21)	6 mo primary restenosis	Not reported
Bosiers 2012[21]	Everol-ES vs BMS	140	0/45/55	154	76 (8)	89 (64)	45 (32)	77 (55)	44 (31)	—	—	53 (38)	96 (69)	25 (14)	—	17 (10)	1 y primary patency	Yes

Overall, completed randomized trials of drug-based technologies for BTK-revascularization have enrolled <1000 patients and have predominantly mechanistic primary endpoints

Jens S, Eur J Vasc Endovasc Surg. 2014 Mar 17

BTK-lesions in the daily practice





- Drug-coated balloons
- Drug-eluting stents
- Next future

- **Drug-coated balloons**
- Drug-eluting stents
- Next future

Features of lesions included in completed RCT

	Lesions, n		Occlusions, %		Lesion length, mm	
Trial	DEB	PTA	DEB	PTA	DEB	PTA
DEBATE BTK	80	78	77.5	82.1	129±83	131±79
BIOLUX II	50	54	-	-	113±88	115±87
IN.PACT DEEP	239	119	38.6	45.9	102±91	129±85

According to available evidence **DEB** have predominantly been tested in:

- lesions >100 mm (occlusions)
- lesions located at the level of the ankle
- foot arteries

- Drug-coated balloons
- **Drug-eluting stents**
- Next future

Drug-Eluting Stents for Revascularization of Infrapopliteal Arteries

Updated Meta-Analysis of Randomized Trials

Table 2. Main Characteristics of Patients Enrolled Among Trials Included in the Study

Trial/First Author (Ref. #)	No. of Patients	Age, yrs	Males, %	Diabetes, %	CLI, %	Occlusion %	Lesion length, mm	Vessel Diameter, mm	DAPT, mo	Longest FU, months
ACHILLES (7)	200	73.4	71	65	N/A	78.3	26.9	2.60	6	12
BELOW (25)	60	72.4	64	68	100	32.6	27.0	2.90	2	36
DESTINY (8)	140	75.5	64	55	100	16.0	15.9	3.00	12	12
Falkowski et al. (24)	50	69.4	58	66	32	N/A	17.8	2.69	6	6
YUKON-BTK (6)	161	72.9	67	54	47	22.4	30.0	3.00	6	50

Overall mean values are reported.
Trial acronyms as in Table 1.

	CLI, %	Occlusion, %	Lesion length, mm	Vessel diameter, mm
Meta-analysis	73.5	27.5	26.8	2.86

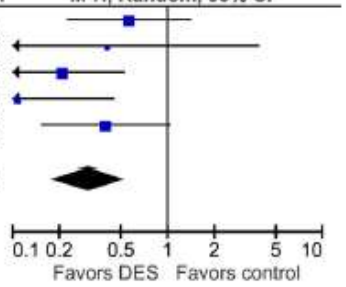
Fusaro M, J Am Coll Cardiol Intv 2013;6:1284–93

Technische Universität München

A Target lesion revascularization

Study or Subgroup	DES Events	DES Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ACHILLES	8	80	14	85	27.6%	0.56 [0.22, 1.43]
BELOW	1	10	6	28	5.6%	0.41 [0.04, 3.88]
DESTINY	7	74	22	66	27.4%	0.21 [0.08, 0.53]
Falkowski et al.	3	25	14	25	13.0%	0.11 [0.03, 0.45]
YUKON-BTK	7	82	15	79	26.3%	0.40 [0.15, 1.04]
Total (95% CI)		**271**		**283**	**100.0%**	**0.31 [0.18, 0.54]**
Total events	26		71			

Heterogeneity: Tau² = 0.06; Chi² = 4.69, df = 4 (P = 0.32); I² = 15%
Test for overall effect: Z = 4.19 (P < 0.0001)

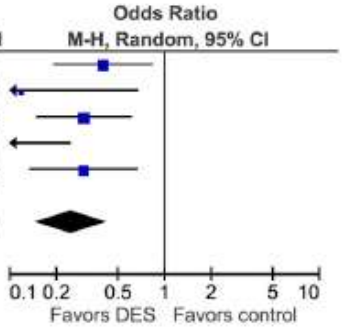


ARR 15.5%
NNT 7

B Restenosis

Study or Subgroup	DES Events	DES Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ACHILLES	15	67	31	74	27.1%	0.40 [0.19, 0.84]
BELOW	2	10	19	28	8.2%	0.12 [0.02, 0.68]
DESTINY	17	75	36	73	28.2%	0.30 [0.15, 0.61]
Falkowski et al.	4	25	19	25	11.6%	0.06 [0.01, 0.25]
YUKON-BTK	12	62	28	63	24.8%	0.30 [0.13, 0.67]
Total (95% CI)		**239**		**263**	**100.0%**	**0.25 [0.15, 0.43]**
Total events	50		133			

Heterogeneity: Tau² = 0.14; Chi² = 6.48, df = 4 (P = 0.17); I² = 38%
Test for overall effect: Z = 5.02 (P < 0.00001)

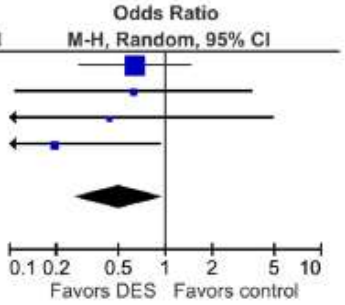


ARR 29.6%
NNT 4

C Amputation

Study or Subgroup	DES Events	DES Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ACHILLES	11	80	17	85	61.7%	0.64 [0.28, 1.46]
BELOW	2	10	8	28	13.8%	0.63 [0.11, 3.61]
DESTINY	1	74	2	66	7.2%	0.44 [0.04, 4.95]
YUKON-BTK	2	82	9	79	17.3%	0.19 [0.04, 0.93]
Total (95% CI)		**246**		**258**	**100.0%**	**0.50 [0.26, 0.97]**
Total events	16		36			

Heterogeneity: Tau² = 0.00; Chi² = 1.82, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.06 (P = 0.04)



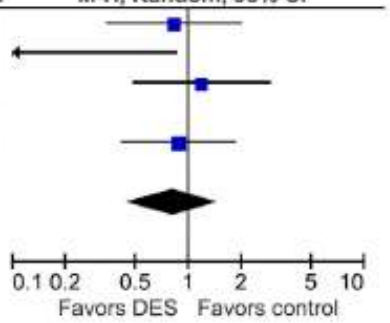
ARR 7.5%
NNT 13

Fusaro M, J Am Coll Cardiol Intv 2013;6:1284–93

D Death

Study or Subgroup	DES Events	DES Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ACHILLES	10	99	12	101	29.0%	0.83 [0.34, 2.03]
BELOW	1	10	15	28	6.9%	0.10 [0.01, 0.87]
DESTINY	13	74	10	66	28.6%	1.19 [0.48, 2.94]
Falkowski et al.	0	25	0	25		Not estimable
YUKON-BTK	17	82	18	79	35.6%	0.89 [0.42, 1.88]
Total (95% CI)		**290**		**299**	**100.0%**	**0.81 [0.45, 1.49]**
Total events	41		55			

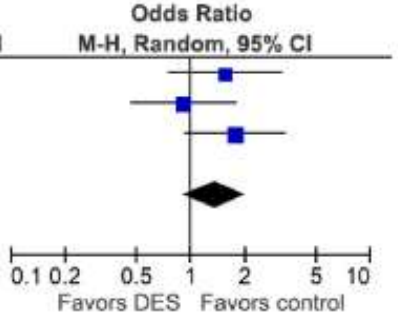
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 4.41$, df = 3 (P = 0.22); $I^2 = 32\%$
Test for overall effect: Z = 0.67 (P = 0.50)



E Rutherford class improvement

Study or Subgroup	DES Events	DES Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ACHILLES	54	71	51	76	29.3%	1.56 [0.75, 3.22]
DESTINY	41	74	38	66	34.0%	0.92 [0.47, 1.79]
YUKON-BTK	37	82	25	79	36.7%	1.78 [0.93, 3.38]
Total (95% CI)		**227**		**221**	**100.0%**	**1.36 [0.91, 2.04]**
Total events	132		114			

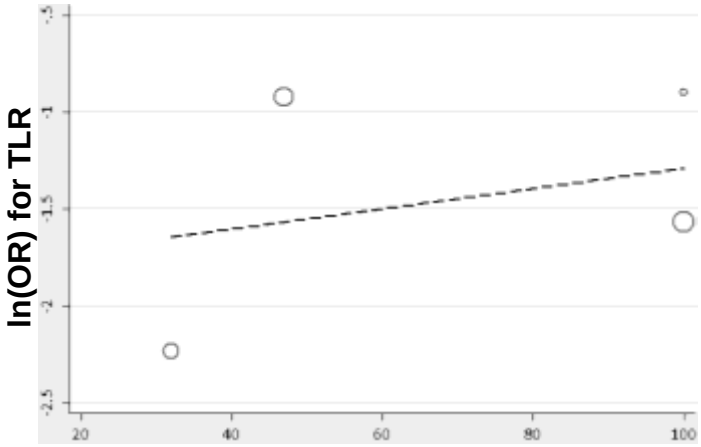
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.14$, df = 2 (P = 0.34); $I^2 = 6\%$
Test for overall effect: Z = 1.50 (P = 0.13)



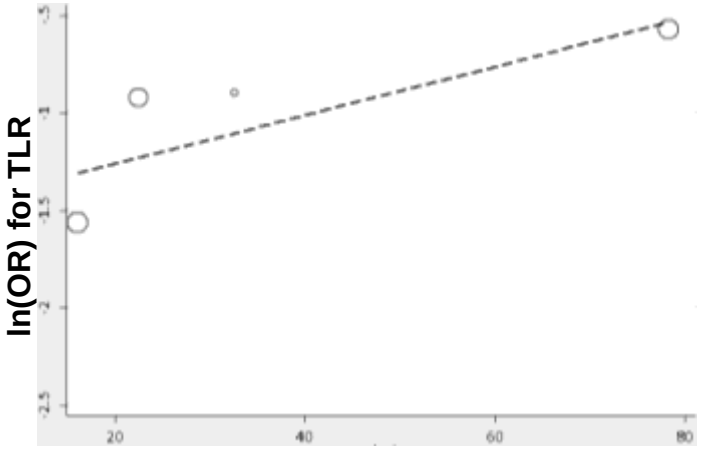
"On adjusted indirect comparison, the everolimus- versus sirolimus-eluting stents, as well as the polymer-free versus durable-polymer DESs did not affect the risk estimates for the main outcomes"

Fusaro M, J Am Coll Cardiol Intv 2013;6:1284–93

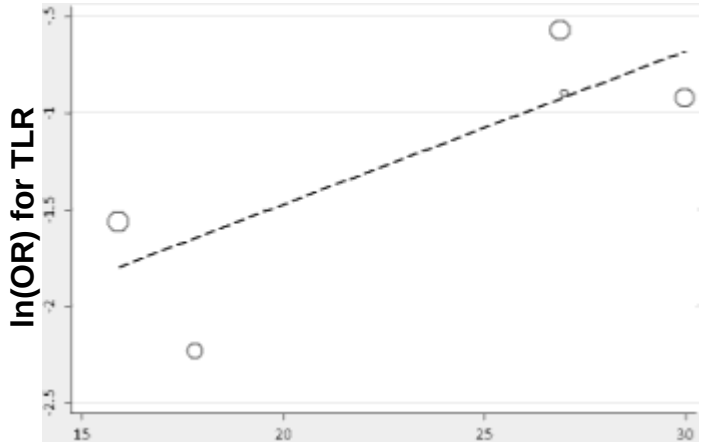
Meta-regression analysis of TLR



A. CLI (%); Exp(b)= 1.00 [0.95-1.06]; SE= 0.01;
B. Δtau= 0.40; p= 0.72



B. Occlusion (%); Exp(b)= 1.01 [0.97-1.04]; SE= 0.008;
Δtau= 1.49; p= 0.27



C. Lesion length (mm); Exp(b)= 1.08 [0.96-1.21]; SE= 0.04;
Δtau= 2.11; p= 0.12

were driven by clinical symptoms. Finally, the population included in this analysis, reporting disabling claudication as well as CLI, with an overall median lesion length of 26.8 mm and a reference vessel diameter of 2.86 mm, could be perceived as not representative of that encountered in daily practice, often presenting with very diffuse disease (>10 cm) and very extensive wounds. For these reasons, the present findings should apply only to patients with characteristics similar to those enrolled in this study and presenting with focal lesions.

Fusaro M, J Am Coll Cardiol Intv 2013;6:1284–93

According to available evidence **DES** have predominantly been tested in:

- lesions <30 mm (with only ACHILLES Trial approaching longer lesions)
- relative low number of patients presenting complete vessel occlusion
- relative high number of patients presenting with CLI
- complex interventions in proximal BTK-segments but no foot arteries

Bifurcation Stenting After Failed Angioplasty of Infrapopliteal Arteries in Critical Limb Ischemia:
Techniques and Short-Term Follow-Up

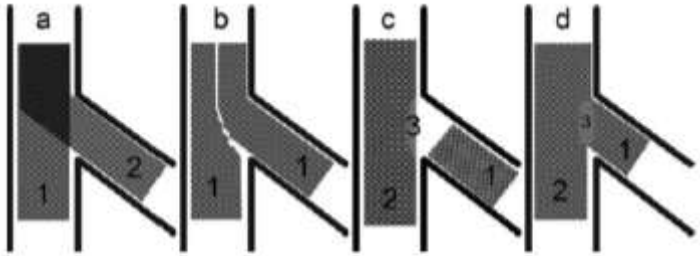


Fig. 1. Schematic overview on the bifurcation stenting techniques performed in this study. The numbers illustrate the sequence of steps. (a) The culotte technique. (b) The kissing stent technique. (c) The T stenting technique, d: The crush stenting technique.

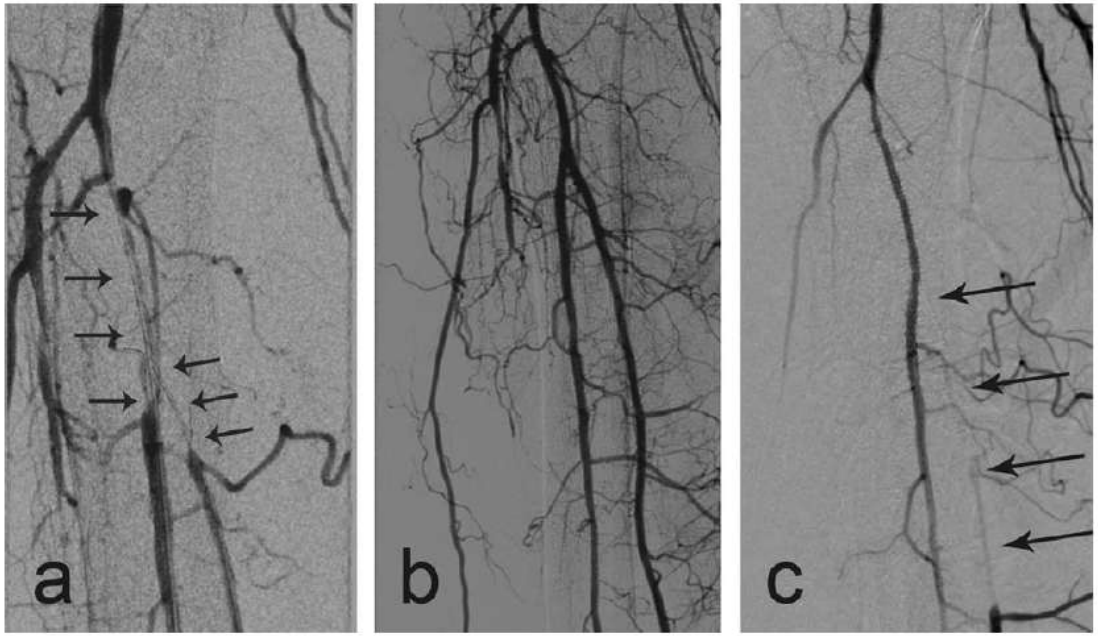


Fig. 2. (a) Total occlusion of the tibioperoneal trunc, the proximal peroneal and posterior tibial arteries. The arrows mark the occluded arteries. (b) After stenting of the bifurcation in culotte technique. (c) Reocclusion of the posterior tibial artery (arrows) 3 months later. The tibioperoneal trunk and peroneal artery remain patent.

Werner M, Cath Cardiovasc Interv 2013 Oct 1;82(4):E522-8

Technische Universität München

Cost-Effectiveness Analysis of Infrapopliteal Drug-Eluting Stents

Stented lesion length <50 mm and/or DES list price <500€ produced the most favorable economical scenario with higher societal monetary savings with an incremental cost-effectiveness ratios <10,000€ per event-free life-year gained

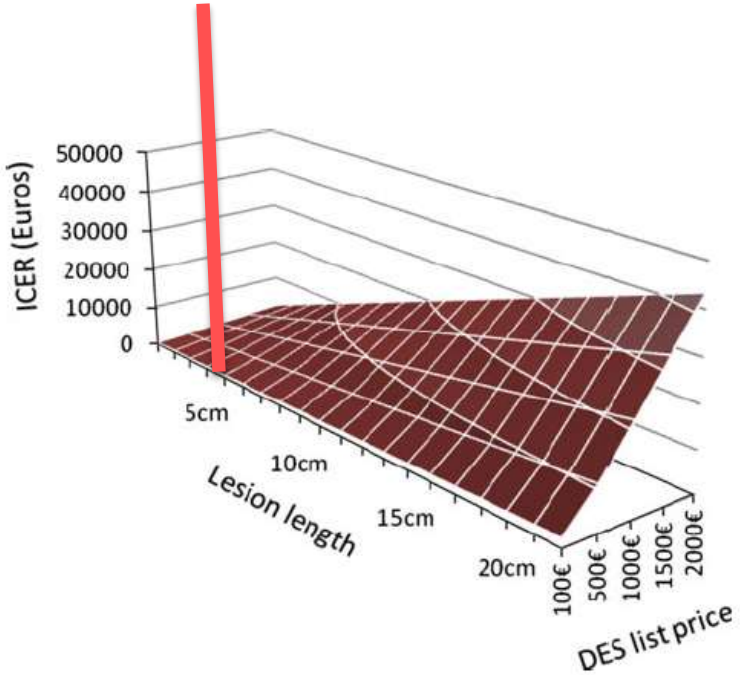


Fig. 3 Two-way sensitivity analysis of ICER estimation of Bail-out SES strategy. Three-dimensional chart was produced by varying stented lesion length from 1 to 20 cm and DES list price from 100 to 2,000€

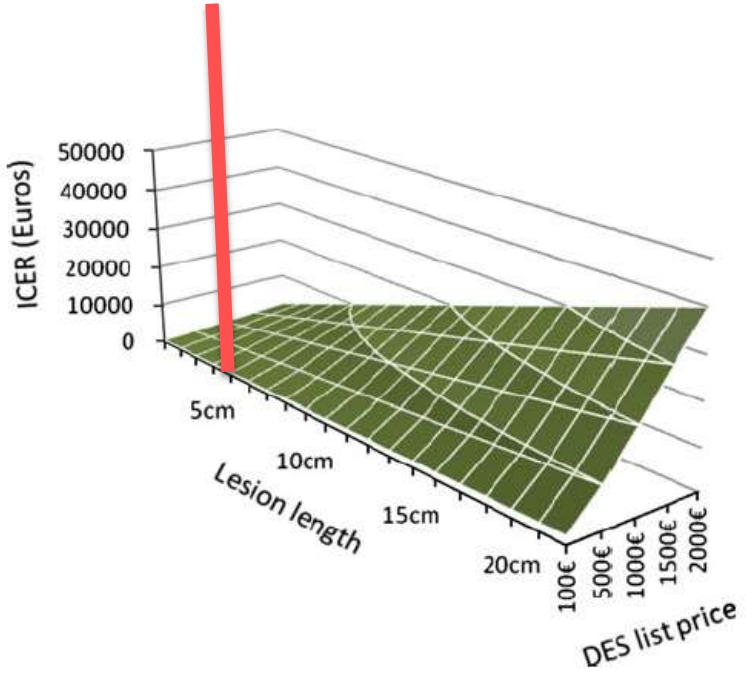


Fig. 4 Two-way sensitivity analysis of ICER estimation of Primary EES strategy. Three-dimensional chart was produced by varying stented lesion length from 1 to 20 cm and DES list price from 100 to 2,000€

Katsanos K, Cardiovasc Intervent Radiol (2013) 36:90–97

- Drug-coated balloons
- Drug-eluting stents
- **Next future**

More technology than evidence…

Table 1 | Currently available drug-coated balloon devices

Device	Company	Coating	Drug dose (μg/mm²)	CE mark*
Peripheral[‖]				
Advance 18 PTX™	Cook Medical, Bloomington, IN, USA	Paclitaxel	3.0	Yes
Cotavance®	Bayer Schering Pharma AG, Berlin, Germany	Paclitaxel–iopromide	3.0	Yes
Freeway™	Eurocor, Bonn, Germany	Paclitaxel–shellac	3.0	Yes
IN.PACT™ Admiral, Amphirion, Pacific	Medtronic Vascular, Santa Clara, CA, USA	Paclitaxel–urea	3.0	Yes
Lutonix DCB® (Moxy)	BARD, Murray Hill, NJ, USA	Paclitaxel–polysorbate/sorbitol	2.0	Yes
Legflow®	Cardionovum, Warsaw, Poland	Paclitaxel–shellac	3.0	Yes
Passeo-18 Lux®	Biotronik, Bülach, Switzerland	Paclitaxel–BTHC	3.0	No
Stellarex®	Covidien, Mansfield, MA, USA	Paclitaxel	2.0	No

*None of the devices is currently approved by the FDA for clinical use. ‡Coronary artery devices are compatible with 0.014 inch guidewires; balloon inflations of 30–60 s are recommended. ‖Peripheral artery devices are compatible with 0.014–0.035 inch guidewires; balloon inflations of up to 180 s are recommended. Abbreviation: BTHC, butyryl-tri-hexyl citrate.

Table 2 | Selected on-going randomized trials with DCBs in coronary or peripheral artery disease

Trial	Inclusion criteria	Treatment devices being compared		Number of patients
		DCB	Comparator(s)	
Peripheral				
ADCAT[105]	Below-the-knee *de novo* stenosis	Paclitaxel–urea-coated balloon	Atherectomy plus paclitaxel–urea-coated balloon	80
BAIR[106]	Below-the-knee in stent restenosis	Paclitaxel–urea-coated balloon	Balloon angioplasty	150
COPA CABANA	Femoropopliteal in-stent restenosis	Paclitaxel–iopromide-coated balloon	Balloon angioplasty	112
CVI drug-coated balloon clinical trial[108]	Femoropopliteal stenosis	Paclitaxel-coated balloon	Balloon angioplasty	360
DEFINITIVE AR[109]	Femoropopliteal *de novo* stenosis	Paclitaxel–iopromide-coated balloon	Atherectomy plus paclitaxel–iopromide-coated balloon	125
FAIR[110]	Superficial femoral artery in-stent restenosis	Paclitaxel–urea coated balloon	Balloon angioplasty	118
IN.PACT SFA II[111]	Femoropopliteal stenosis	Paclitaxel–urea-coated balloon	Balloon angioplasty	450
ISAR-STATH[112]	*De novo* superficial femoral artery stenosis	Paclitaxel–urea-coated balloon plus stent	Atherectomy or stent	150
ISAR-PEBIS[113]	In-stent restenosis of superficial femoral artery	Paclitaxel–urea-coated balloon	Balloon angioplasty	70
LEVANT 2[114]	Femoropopliteal stenosis	Paclitaxel–polysorbate/sorbitol-coated balloon	Balloon angioplasty	476
LUTONIX BTK[115]	Below-the-knee *de novo* arterial stenosis	Paclitaxel–polysorbate/sorbitol-coated balloon	Balloon angioplasty	480
RAPID[116]	Femoropopliteal *de novo* stenosis	Paclitaxel–shellac coated balloon plus stent	Balloon angioplasty plus stent	176

Abbreviations: BTHC, butyryl-tri-hexyl citrate; DCB, drug-coated balloon; DES, drug-eluting stent; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

Byrne RA, Nat Rev Cardiol 11, 13–23 (2014)

Conclusions

Drug-based technologies represent a revolution in the field of revascularization of **peripheral artery disease involving BTK-segments**

Despite **DEB** showed encouraging results in small-sample studies their **safety and biological efficacy** still remain to be proved before further investigate a potential superiority in comparison with established treatment options

On the other hand, the **established superiority of DES** in comparison with other treatment options for BTK-revascularization is confined to specific lesions and patients subsets

A greater effort is required from scientific authorities and investigators to plan future trials with hard clinical endpoints beyond amputation, quality of life and wound healing in order to support the daily practice with adequate evidence

19th CARDIOVASCULAR SUMMIT
TCTAP 2014

Thank You

Massimiliano Fusaro, MD
German Heart Center, Munich – Germany

fusaro@dhm.mhn.de