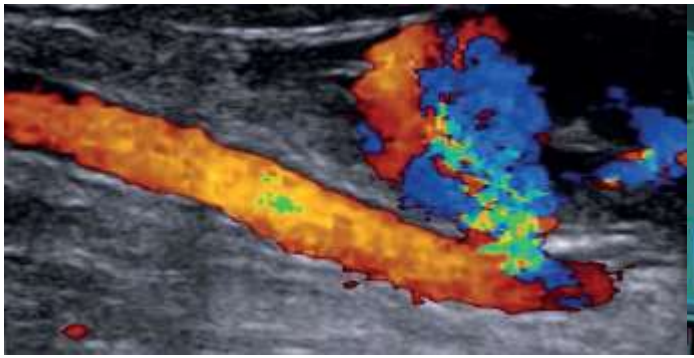
BTK Intervention: Share Breath with Expert

19th CARDIOVASCULAR SUMMIT
TCTAP 2014

How Will Treatment Paradigms Change in a Drug-eluting World?



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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

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Treatment paradigms may change only through high-quality scientific evidence

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

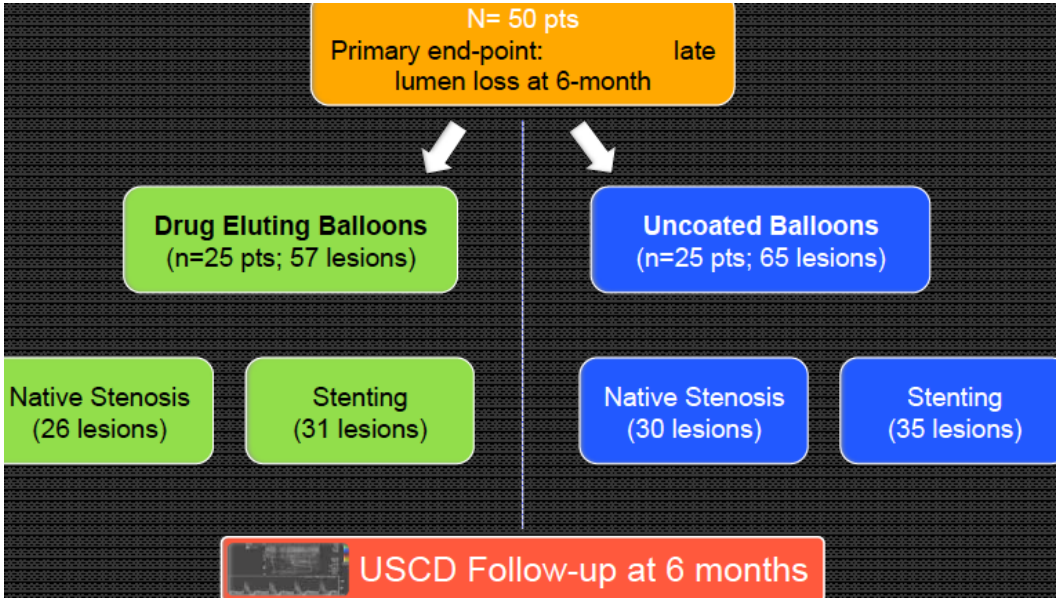
Jens S, Eur J Vasc Endovasc Surg. 2014 Mar 17

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

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

DEBELLUM

Drug Eluting Balloon Evaluation for Lower Limb mUltilevel treatMent



Overall Lesions	122
Femoro-Popliteal Lesions	92 (76%)
BTK Lesions	30 (24%)
Mean lesion Length (cm)	7.5 ± 3.5
Lesion 7-15 cm	63 (51%)
Lesion < 7 cm	38 (27%)
Lesion > 15 cm	21 (22%)
% Stenosis Diameter	85 ± 6.4
Total Occlusion	26 (22%)

Late Lumen Loss at 6-month

Overall analysis: 0.5±1.4 mm (DEB) vs 1.6±1.7 mm (PTA) *p<0.01*

The rate of TLR at 6 months is 9/25 (36%) in the PTA group, 2/25 (8%) in the DEB group (*P<0.001*)

Fanelli F, J Endovasc Ther. 2012 Oct;19(5):571-80

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Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty Evaluation (DEBATE-BTK)

A Randomized Trial in Diabetic Patients With Critical Limb Ischemia

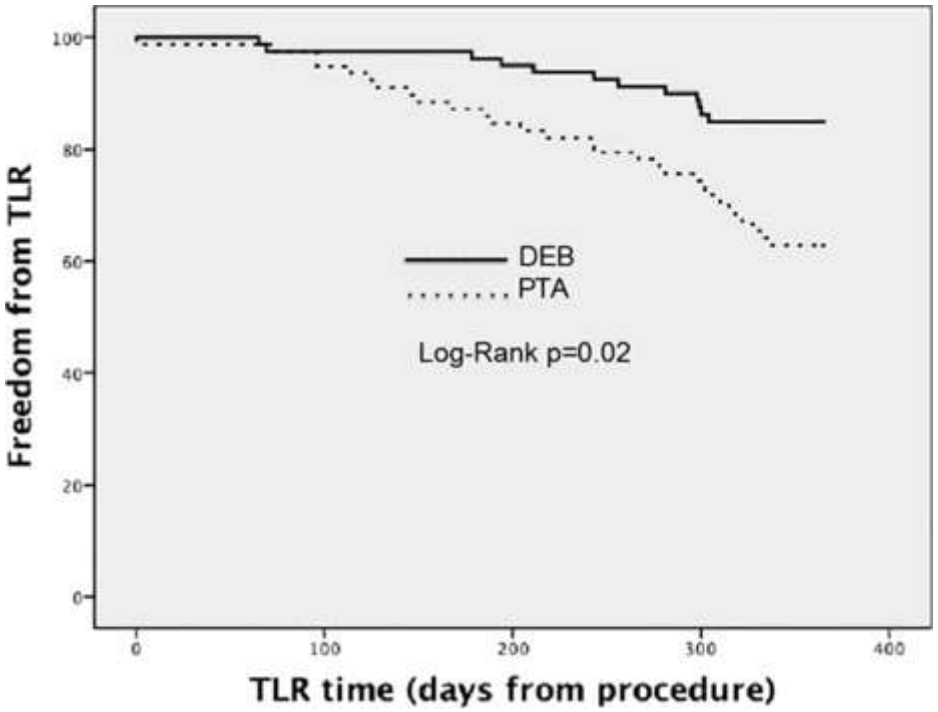


Table 3. Clinical and Angiographic Outcome at 12 Months

	DEB	PTA	*P* Value
Death, n (%)	5 (7.7)	3 (4.5)	0.4
Major amputation, n (%)	0 (0.0)	1 (1.5)	0.9
CVA, n (%)	2 (3.1)	3 (4.5)	0.9
AMI, n (%)	3 (4.6)	3 (4.5)	0.9
MAEs, n (%)	20 (31)	34 (51)	0.05
Limbs available for 12-mo follow-up, n	66	67	
ABI	0.78±0.22	0.47±0.28	<0.001
Mean Rutherford class category, n (%)	0.90±1.8	2.0±2.3	0.004
0–3	57 (86.3)	44 (65.7)	0.06
4	0 (0)	2 (3)	
5	8 (12.2)	19 (28.3)	
6	1 (1.5)	2 (3)	
Complete index ulcer healing, n (%)*	56/65 (86)	43/64 (67)	0.01
Time to index ulcer healing, mo*	4.4±1.5	5.2±1.6	0.01
Lesions available for 12-mo follow-up	74	74	
Binary restenosis (>50%), n (%)†	20 (27.0)	55 (74.3)	<0.001
Vessel occlusion, n (%)†	13 (17.6)	41 (55.4)	<0.001
Occlusion length, mm†	87±88	128±75	<0.001

Values are mean±SD when appropriate. ABI indicates ankle-brachial index; AMI, acute myocardial infarction, CVA, cerebrovascular accident; DEB, drug-eluting balloon; MAE, major adverse event; and PTA, percutaneous transluminal angioplasty.

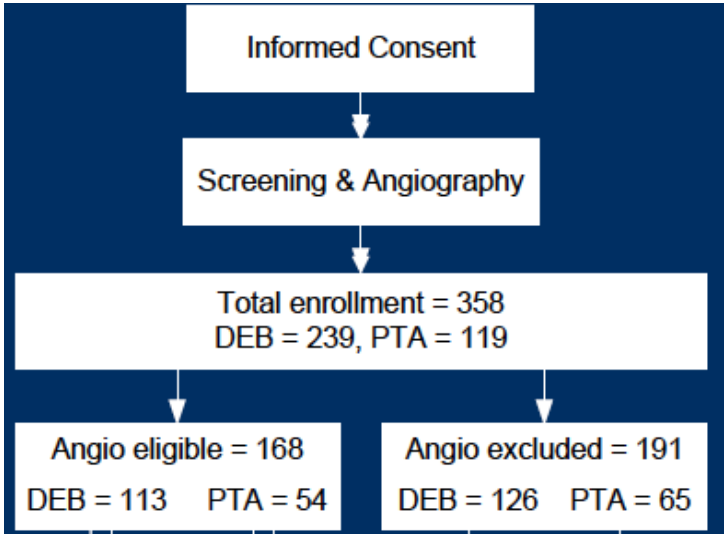
"Patients (n= 132) were enrolled in the study only after successful wiring of the target vessel and therefore the rate of major amputation observed cannot be compared with that derived from studies designed on an intention-to-treat basis"

Liistro F, Circulation. 2013;128:615-621

IN.PACT DEEP

Randomized Trial of IN.PACT Amphirion DEB vs. PTA for Infrapopliteal Revascularization in Critical Limb Ischemia

Objective: Evaluate the safety and efficacy of IN.PACT Amphirion DEB vs. standard PTA for infrapopliteal revascularization in patients with CLI



Primary Efficacy	DEB	PTA	p
12-month LLL (mm) [1]	0.61 ± 0.78	0.62 ± 0.78	*0.950*
12-month CD-TLR [2]	9.2% (18/196)	13.1% (14/107)	*0.291*

Primary Safety	DEB	PTA	p
6-month Death, Major Amputation or CD TLR	17.7% (41/232)	15.8% (18/114)	*0.021* (non-inferiority) *0.662 (superiority)*

1. Angio Cohort, Corelab adjudicated. Angiogaphic Imaging 12-month FU compliance = 70.9% (DEB) vs. 71.4% (PTA)
2. Clinically driven TLR of the target lesion in the (major) amputation free surviving subjects at 12 months. "Clinically driven TLR" defined as any TLR of the target lesion associated with: a) deterioration of RC and / or b) Increase in size of pre-existing wounds and / or c) occurrence of a new wound(s), with b) and c) adjudicated by the Wound Healing Core lab

Zeller T, on behalf of the IN.PACT DEEP Steering Committee, LINC 2014, Leipzig - Germany

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Study Outcome	ITT	Multivariate
Primary Safety	RR 1.12 → PTA p = 0.662	HR 1.15 → PTA p = 0.617
Death (all cause)	RR 1.25 → PTA p = 0.551	HR 1.28 → PTA p = 0.539
Death or Major Amputation	RR 1.40 → PTA p = 0.064	HR 1.81 → PTA p = 0.073
Major Amputation	RR 2.44 → PTA p = 0.080	HR 2.36 → PTA p = 0.119

Randomization status forced into stepwise regression model
Values in orange are safety trends ($0.05 < p < 0.20$)
RR – relative risk, HR – hazard ratio

IN.PACT DEEP did not meet either 1° efficacy endpoint

- PTA outcomes were significantly better than expected

IN.PACT DEEP Trial met the non-inferiority primary safety endpoint

- The safety signal towards major amputations, in conjunction with the absence of significant efficacy, led to market withdrawal

Zeller T, on behalf of the IN.PACT DEEP Steering Committee, LINC 2014, Leipzig - Germany

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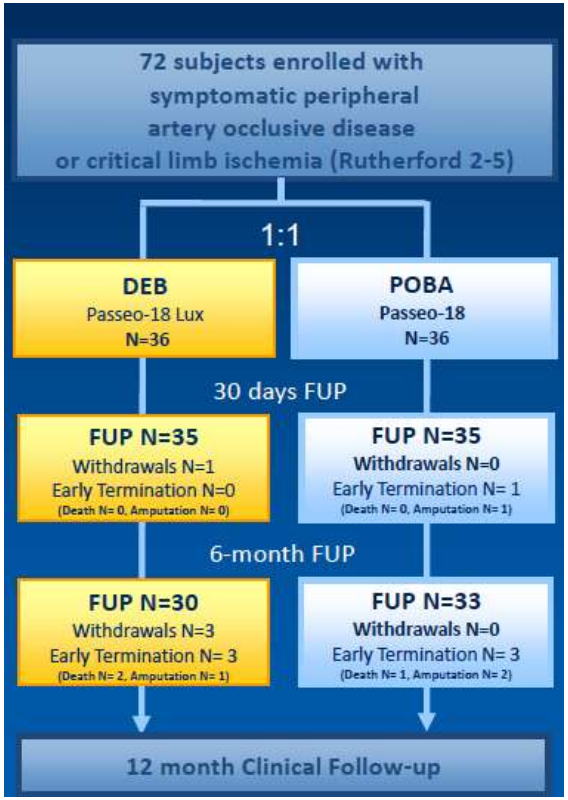
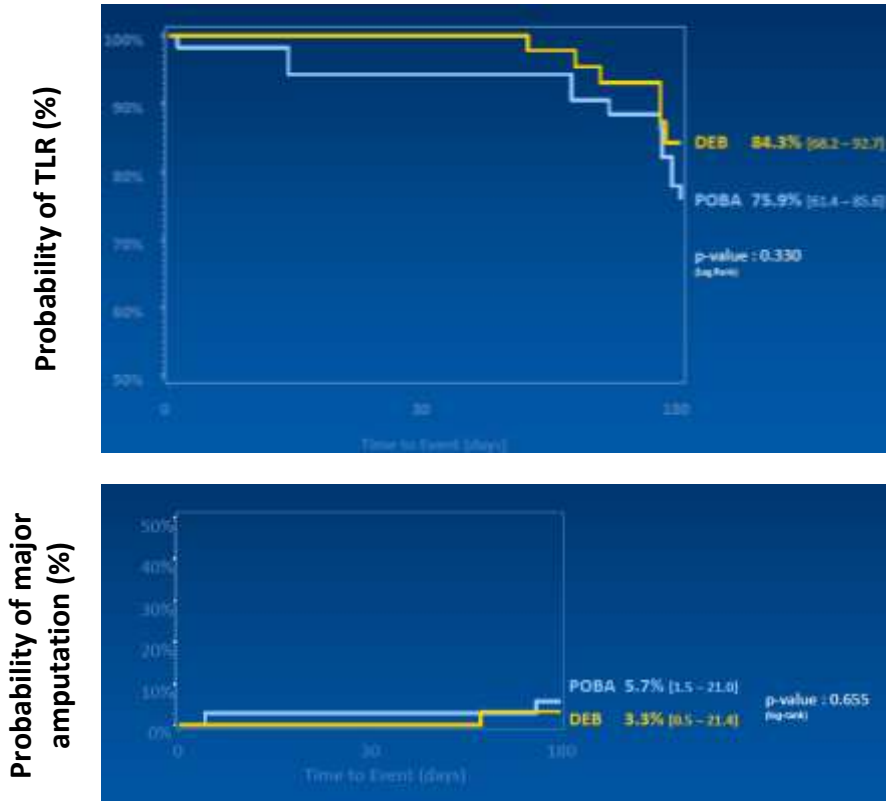
BIOLUX P-II

A randomized clinical trial of DEB vs. PTA for infrapopliteal disease





At 6 months angiographic follow-up, Passeo-18 Lux DRB demonstrated a target lesion primary patency of 84.3% vs. 75.9% compared to the control PTA balloon (p=0.330).

At 6 months, 59% of patients improved in Rutherford Classification in the DEB group vs. 47% in the control group. No patients worsened in the DEB group, vs. 6% in the POBA group.

Zeller T, LINC 2014, Leipzig - Germany

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- 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.

611 patients from **5** trials randomly assigned to DESs (n= 294) versus control therapy (plain balloon angioplasty/BMS implantation, n= 307)

Median lesion length was **26.8** mm with a RVD of **2.86** mm

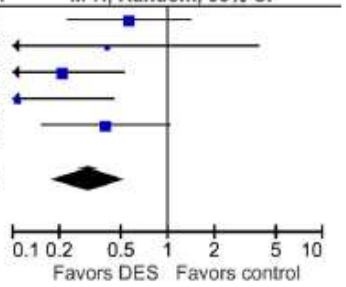
Median follow-up **12** months

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

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)

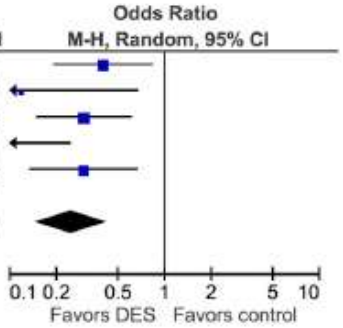


ARR 15.5%
NNT 7

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)

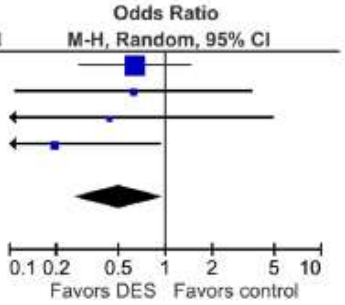


ARR 29.6%
NNT 4

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)



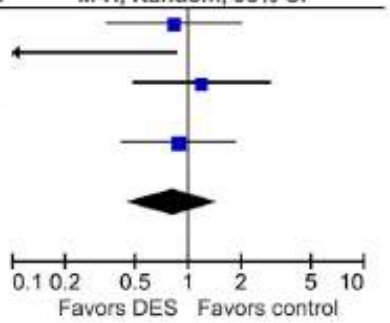
ARR 7.5%
NNT 13

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			

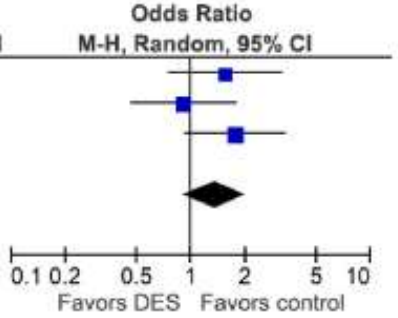
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 4.41$, df = 3 (P = 0.22); $I^2 = 32\%$
Test for overall effect: Z = 0.67 (P = 0.50)



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			

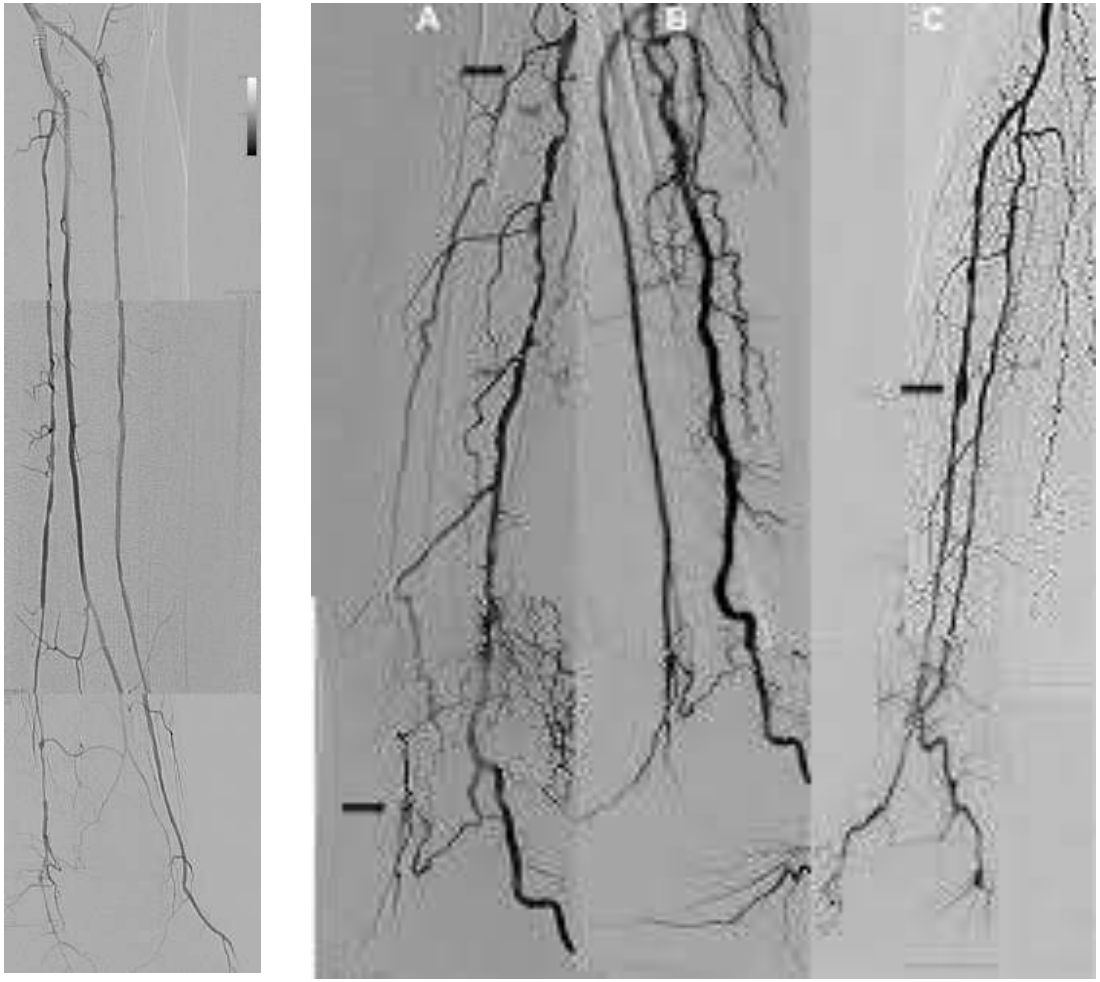
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.14$, df = 2 (P = 0.34); $I^2 = 6\%$
Test for overall effect: Z = 1.50 (P = 0.13)



"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

What's about coronary-DES in the daily BTK-practice?

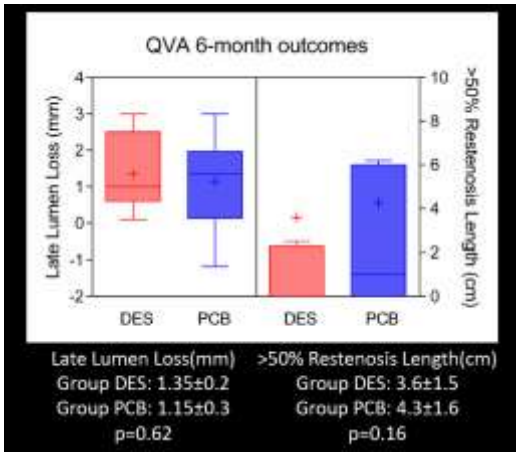


- Drug-coated balloons
- Drug-eluting stents
- **Next future**

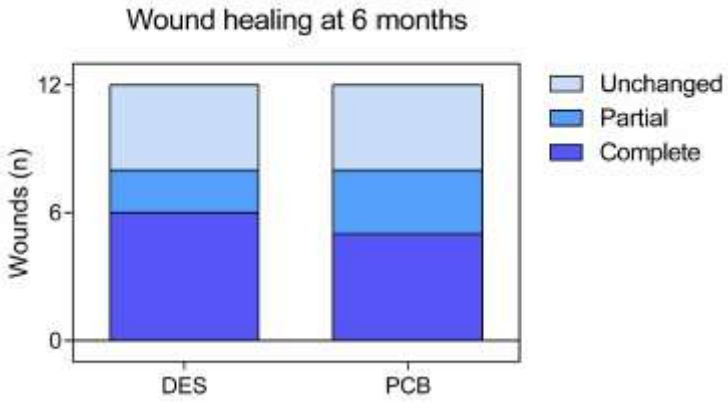
- Do not translate interventional concepts from coronary into BTK-vascular field
- Relevant clinically-driven and patient-oriented rather than marketing-pushed endpoints
- Comparisons between different devices to rule-out a supposed “class effect” in terms of benefit or harm

The IDEAS study
PCB vs. DES
for the long infrapopliteal lesions

	Group DES	Group PCB	p
# patients	25	25	
Men/Total	20/25	18/25	0.25
Age	75.27	67.58	0.03
Diabetes	19/25 (76%)	16/25 (64%)	0.17
C.K.D.	11/25 (44%)	8/25 (32%)	0.19



	DES	PCB	p
Binary Restenosis (>50%)	7/25	11/19	0.0457
Vessel Occlusion	5/25	3/19	1.00
Positive Remodeling	0/25	3/19	0.07
Immediate Residual Stenosis (%)	9.6±2.2	24.8±3.5	<0.0001



Conclusions

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

The **safety and the biological efficacy** of new technologies are prerequisite to further investigate their clinical superiority in comparison with established treatment options

Small-population trials should test how to plan subsequent trials with strong clinical endpoints beyond amputation, quality of life and wound healing

Small single-center trials should not influence standard practice

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TCTAP 2014

Thank You

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