The Angiosome Concept in Real Practice -How to Make Revascularization Strategies-

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Definition of CLI (critical limb ischemia)

-Terminal Stage of Peripheral Artery Disease-

- Persistently recurring ischemic pain requiring analgesia for > 2 weeks and ankle systolic pressure< 50mmHg and/ or toe systolic pressure< 30mmHg
- Ulceration or gangrene of the foot or toes and ankle systolic pressure< 70mmHg and/ or toe systolic pressure < 50mmHg

TASC II

Major amputation

Critical limb ischemia (CLI)

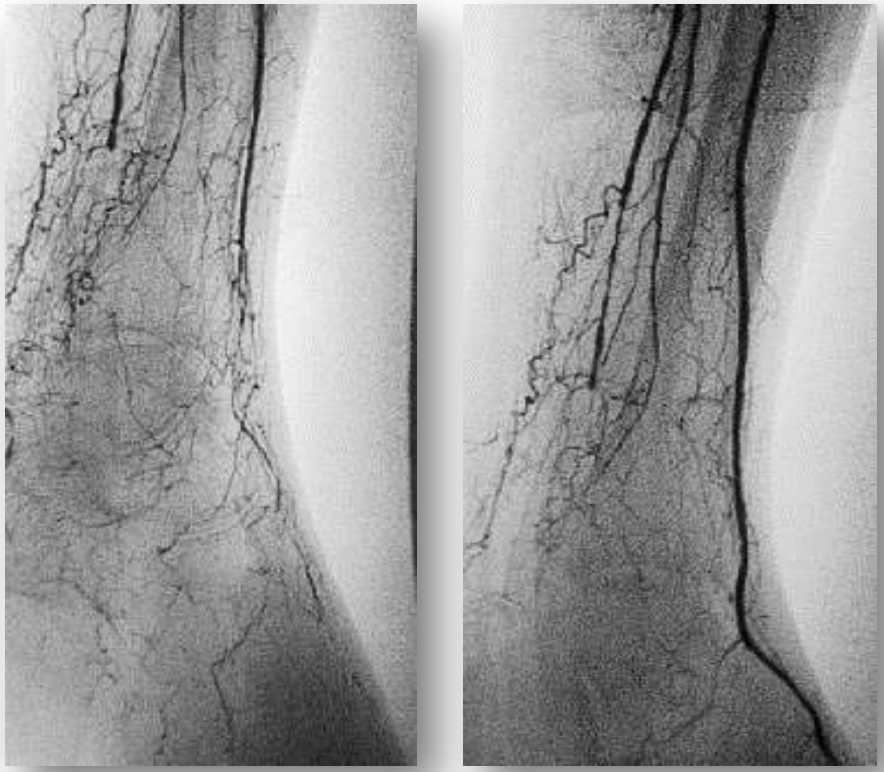
Recommendation 24. Optimal treatment for patients with CLI

➢**Revascularization** is the **optimal treatment** for patients with CLI.

TASC II

Revascularization for the patients critical limb ischemia (CLI)

Bypass therapy (BSX)



Endovascular therapy (EVT)

Meta-analysis of infrapopliteal angioplasty for chronic critical limb ischemia

- Recently, endovascular therapy (EVT) has become commonplace for below the knee (BTK) lesion in patients with critical limbs ischemia (CLI) because it achieve similar limb salvage to bypass therapy (BSX).

Result	*1 month*	*6 months*	*1 year*	*2 years*	*3 years*
Primary patency					
PTA	77.4 ± 4.1	65.0 ± 7.0	58.1 ± 4.6	51.3 ± 6.6	48.6 ± 8.0
Bypass	93.3 ± 1.1	85.8 ± 2.1	81.5 ± 2.0	76.8 ± 2.3	72.3 ± 2.7
P	<.05	<.05	<.05	<.05	<.05
Secondary patency					
PTA	83.3 ± 1.4	73.8 ± 7.1	68.2 ± 5.9	63.5 ± 8.1	62.9 ± 11.0
Bypass	94.9 ± 1.0	89.3 ± 1.6	85.9 ± 1.9	81.6 ± 2.3	76.7 ± 2.9
P	<.05	<.05	<.05		
Limb salvage					
PTA	93.4 ± 2.3	88.2 ± 4.4	86.0 ± 2.7	83.8 ± 3.3	82.4 ± 3.4
Bypass	95.1 ± 1.2	90.9 ± 1.9	88.5 ± 2.2	85.2 ± 2.5	82.3 ± 3.0
Patient survival					
PTA	98.3 ± 0.7	92.3 ± 5.5	87.0 ± 2.1	74.3 ± 3.7	68.4 ± 5.5
Bypass	NA	NA	NA	NA	NA

Romiti Met al J Vasc Surg 2008;47:975-81

Infrapopliteal Percutaneous Transluminal Angioplasty Versus Bypass Surgery as First-Line Strategies in Critical Leg Ischemia

A Propensity Score Analysis

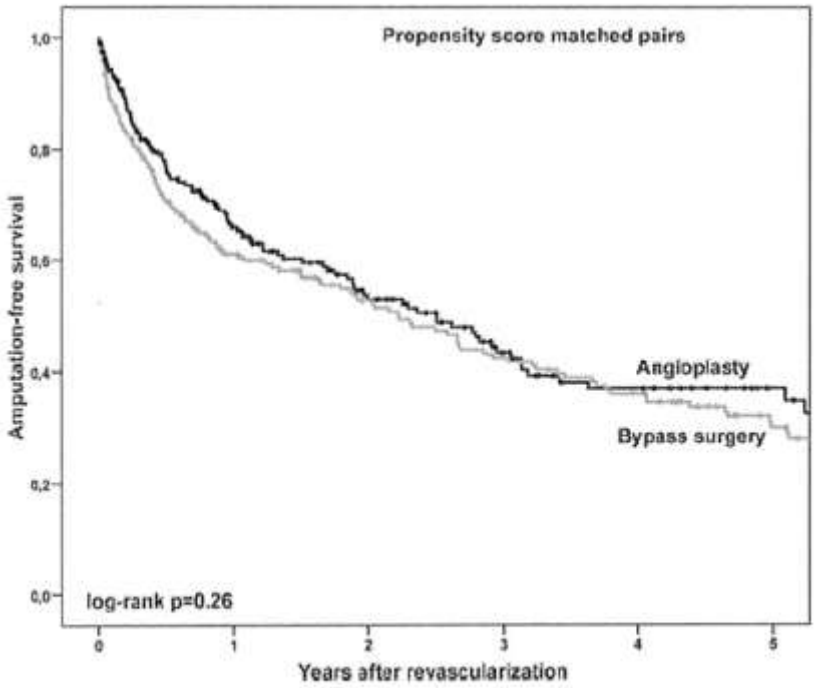
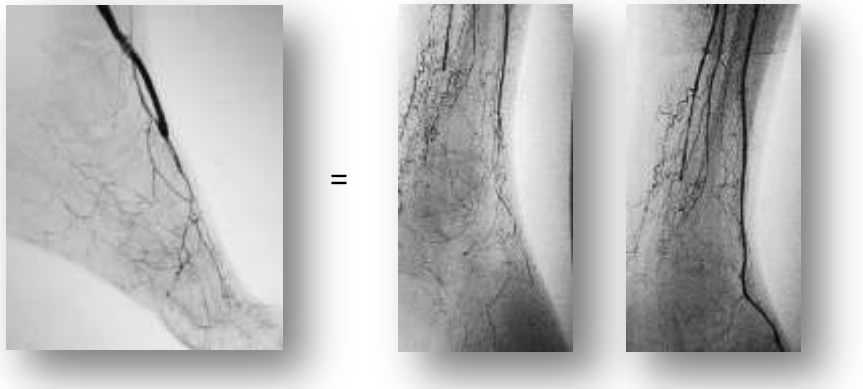


FIGURE 1. Amputation-free survival after infrapopliteal PTA and bypass surgery for CLI in the overall population and in 208 propensity-score–matched pairs.



In propensity-score-matched pairs, PTA and bypass surgery (BSX) achieved similar 5-year amputation-free survival

(BSX: 29.9% vs.PTA: 36.9%, p=0.26)

Ann Surg 2010;252:765-773

Learn From ESC 2011 guideline

Recommendations for revascularization in patients with infrapopliteal lesions

Recommendations	Class[a]	Level[b]
When revascularization in the infrapopliteal segment is indicated, the endovascular-first strategy should be considered.	IIa	C
For infrapopliteal lesions, angioplasty is the preferred technique, and stent implantation should be considered only in the case of insufficient PTA.	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
PTA = percutaneous transluminal angioplasty.

Eur Heart J. 2011;32:2851-906

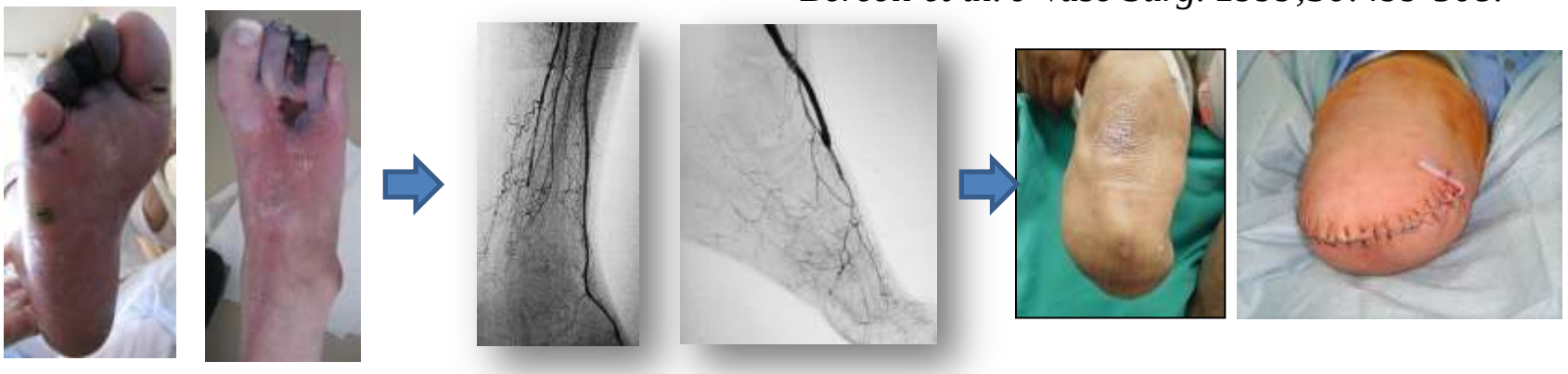
We should discuss on the quality of revascularization

- Nevertheless, it is well known that success in obtaining good flow to the pedal arch does not always result in limb salvage.

Dorros et al. Circulation. 2001;104:2057-62.

- Indeed, major amputation has been reported to be necessary in approximately **15%** of patients with ischemic ulcers of the lower limbs despite a patent bypass.

Berceli et al. J Vasc Surg. 1999;30:499-508.

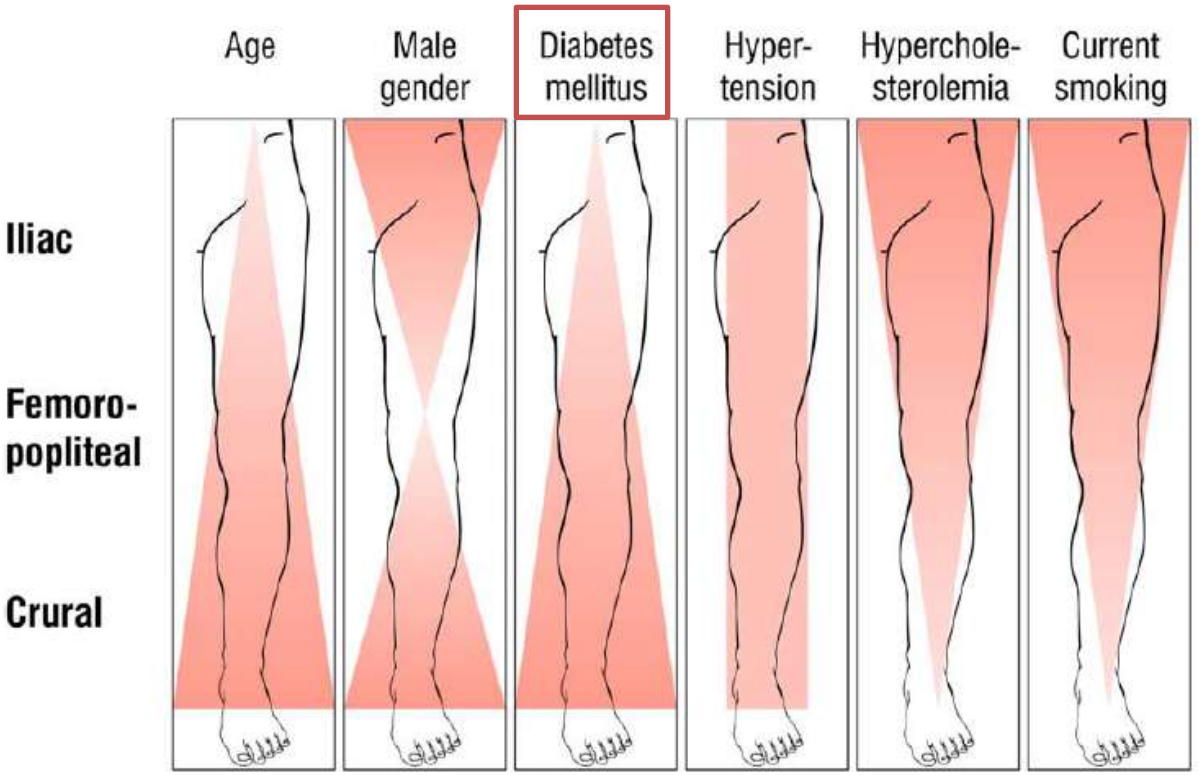


Ischemic ulcer

Revascularization

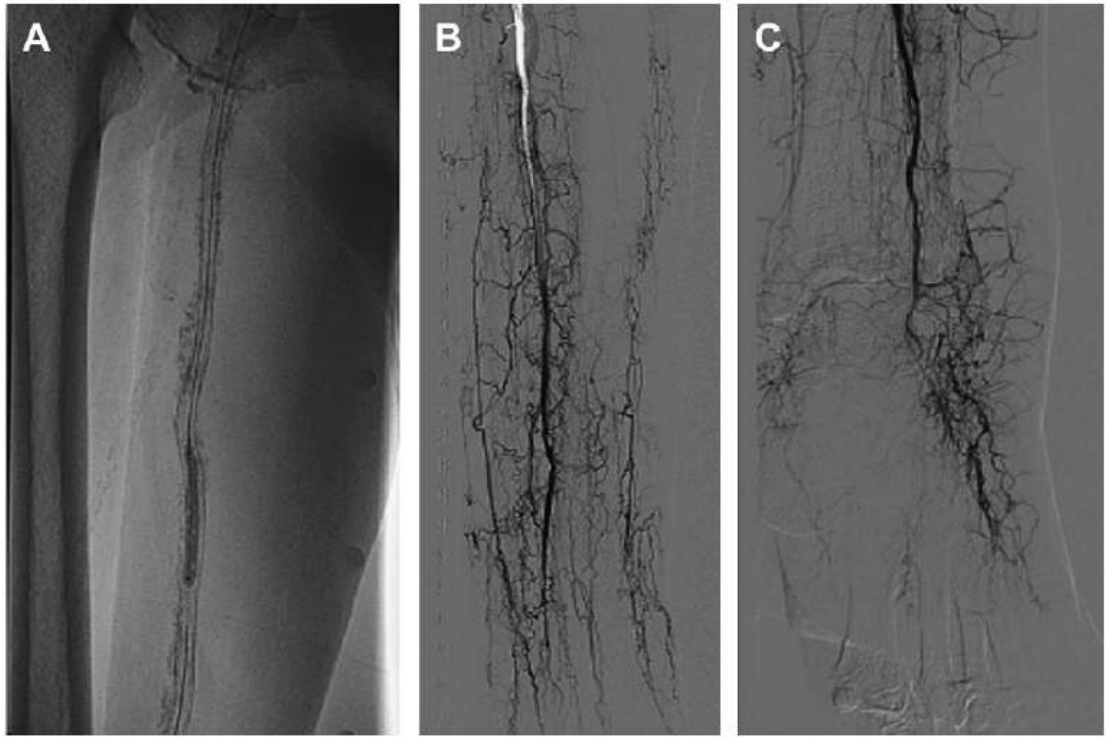
Major amputation

Association of Cardiovascular Risk Factors with Pattern of Lower Limb Atherosclerosis in 2659 Patients Undergoing Angioplasty



Eur J Vasc Endovasc Surg. 2006: 31;59–63

Renal Insufficiency is Independently Associated with a Distal Distribution Pattern of Symptomatic Lower-limb Atherosclerosis



Diffuse severe calcification along the SFA (A), occlusion of the distal ATA and proximal PA and complete occlusion of the PTA (B), occlusion of the plantar and dorsal arterial arches at the foot level (C)

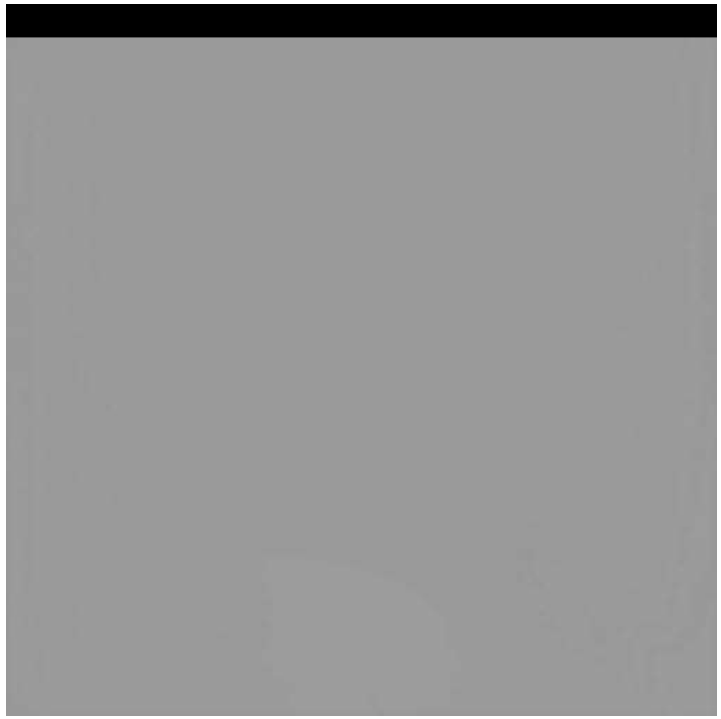
Eur J Vasc Endovasc Surg.2010;39:591-596

74 years, Male, Non-heeling ulcer at the heel (R5)
DM, ESRD on HD

Severe stenosis presnted at ATA to DPA
Poor flow to the calcaneal region was observed. (from DPA-pedal arch)

74 years, Male, Non-heeling ulcer at the heel (R5)
DM, ESRD on HD

Angioplasty for ATA-DPA



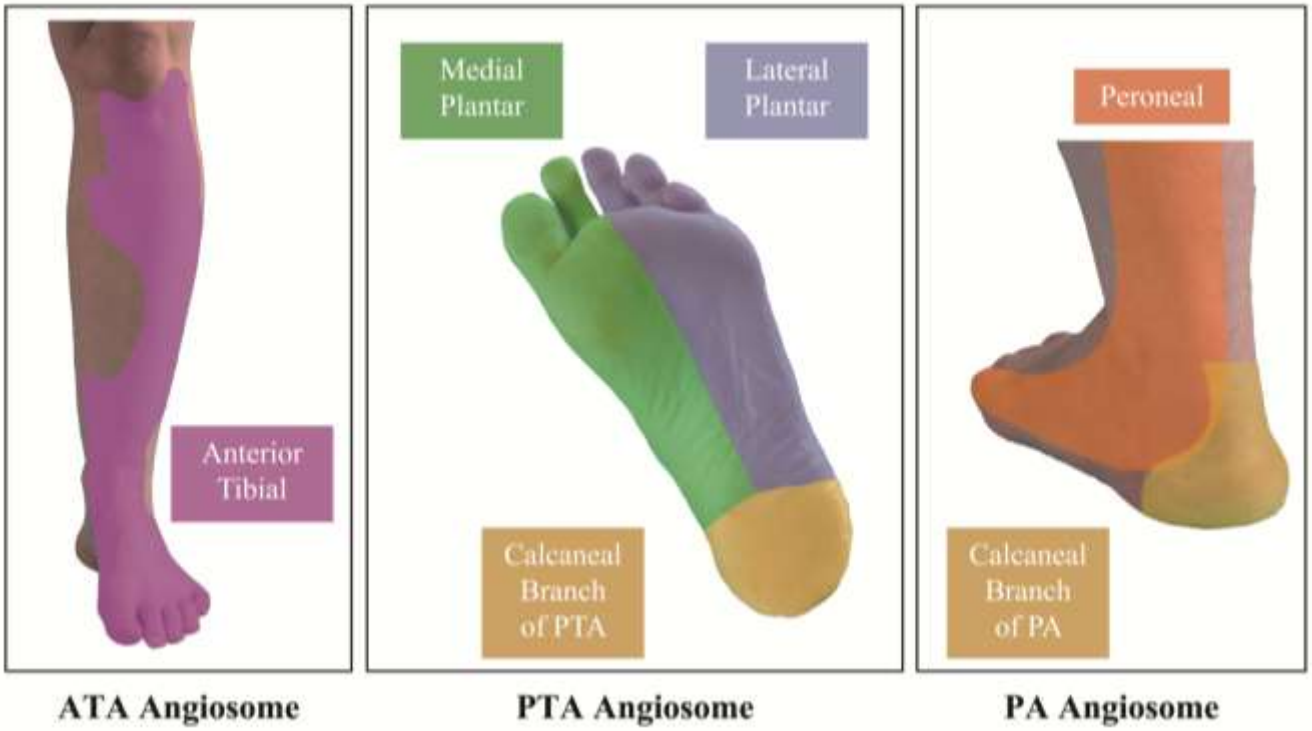
Poor flow to **calcaneal region** despite ATA-DPA revascularization (1-straight line)

74 years, Male, Non-heeling ulcer at the heel (R5)
DM, ESRD on HD

1-straight line

Major amputation (BK amputaion)

Angiosome based revascularization concept is clinically important? or not ?



Alexandrescu VA. J Endovasc Ther. 2008;15:580-93.
Iida O et al. Catheter Cardiovasc Interv. 2009;75:830-6.

Case: 64 y/o male

Risk factors

DM, ESRD on dialysis

Preoperative lower limb examination

ABI: Right 1.27

Skin perfusion Pressure

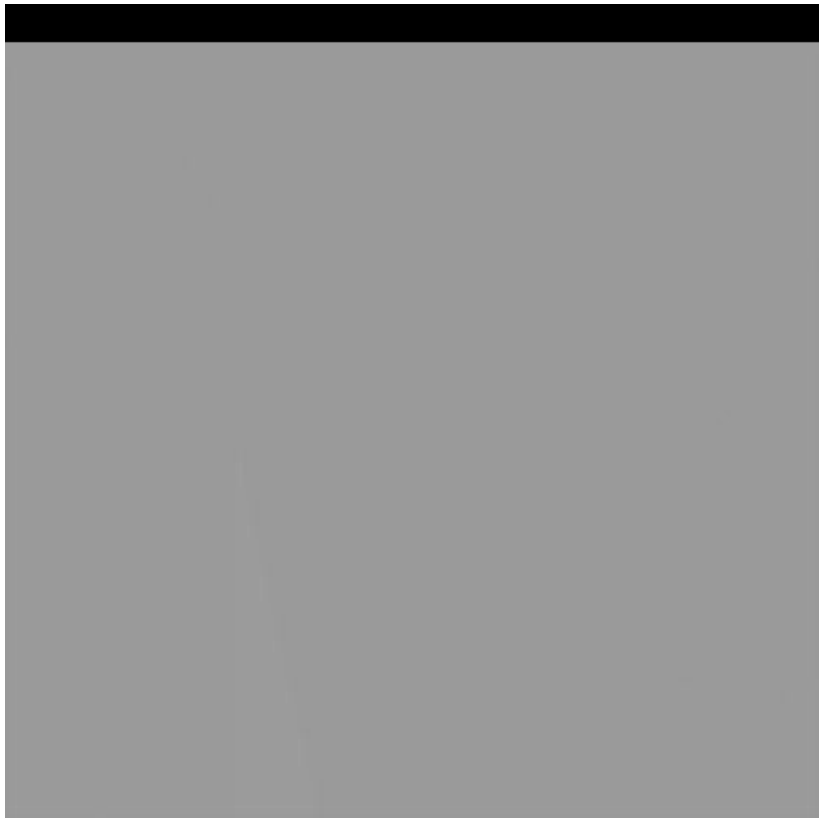
Dorsum side: 26 mmHg

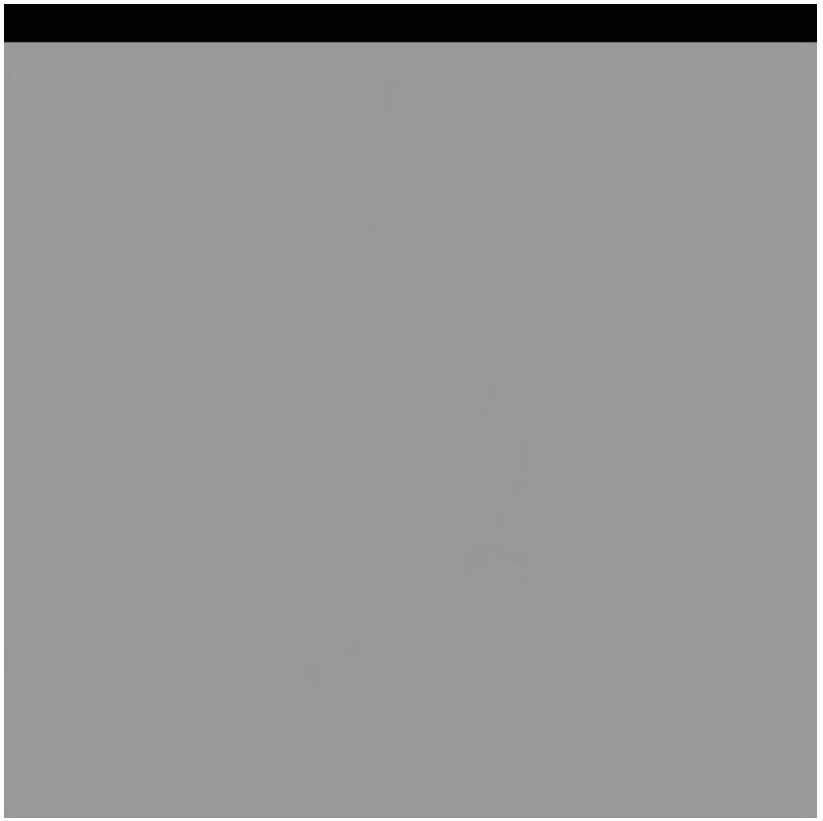
Plantar side: 54 mmHg

Laboratory examination

WBC 6600, CRP 0.8

Case: 64 y/o male





ATA occlusion

Which arteries should we treat?

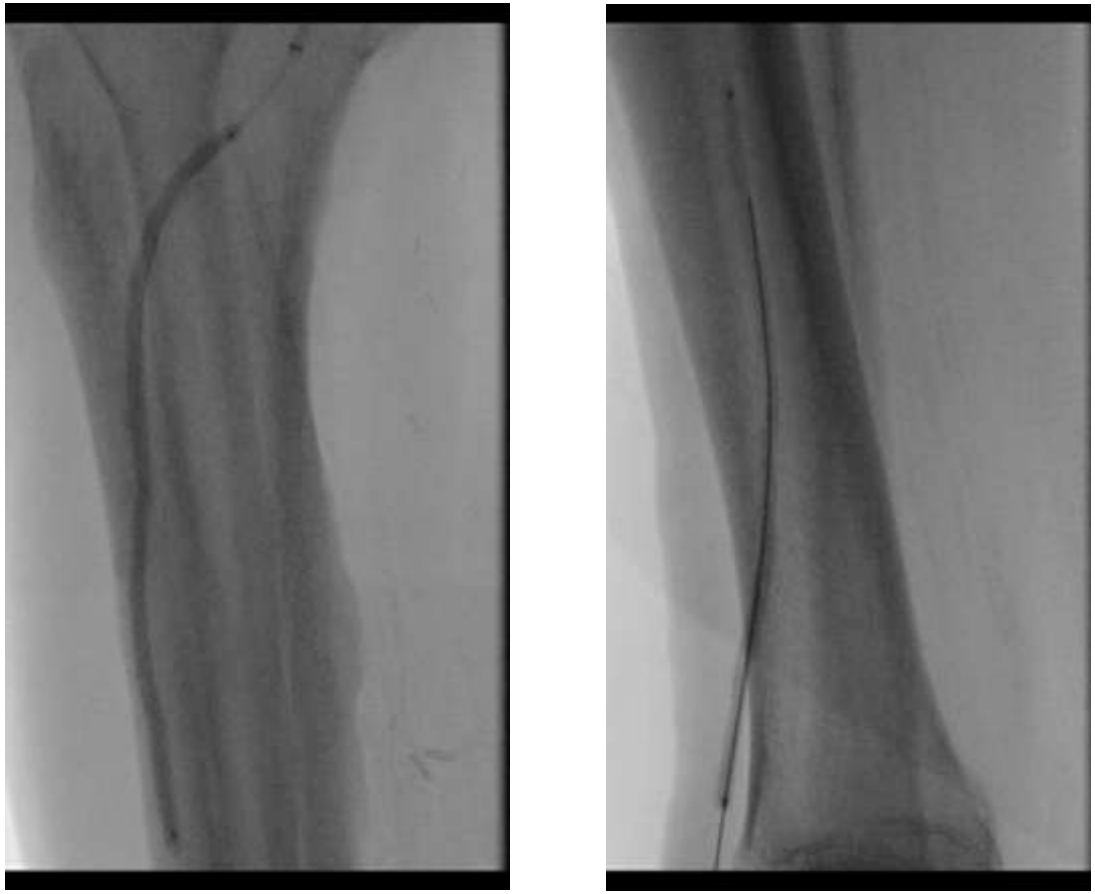
Ulcer/gangrene located at dorsum side of the foot.

ATA Angiosome

This ulcer was supplied from ATA-dorsalis pedis a.

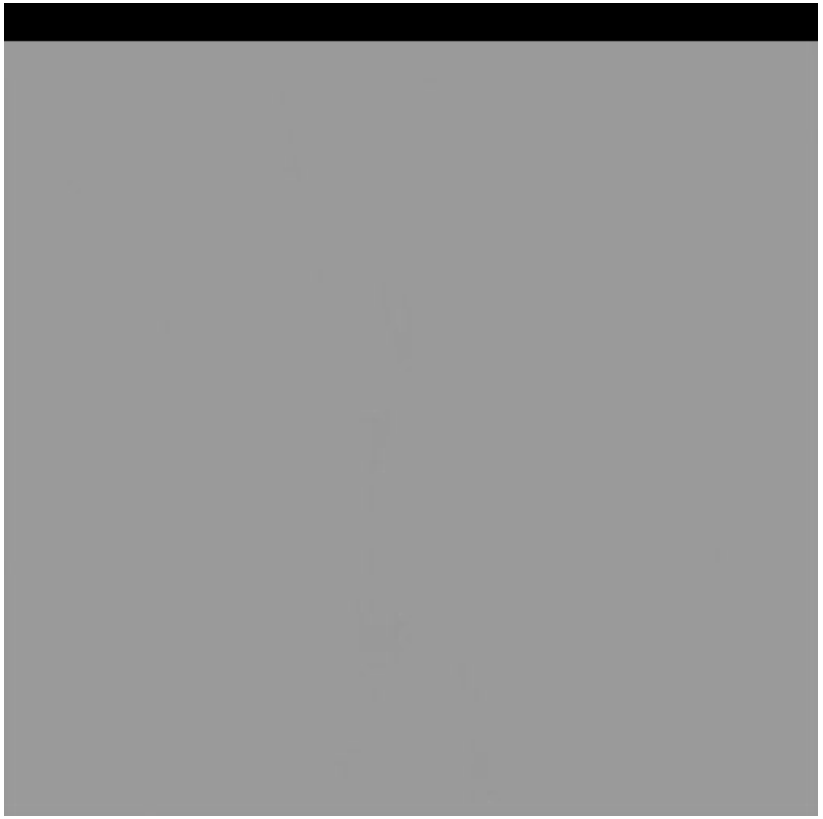
Target lesion was ATA-dorsalis pedis artery.

Endovascular Therapy for ATA-DPA



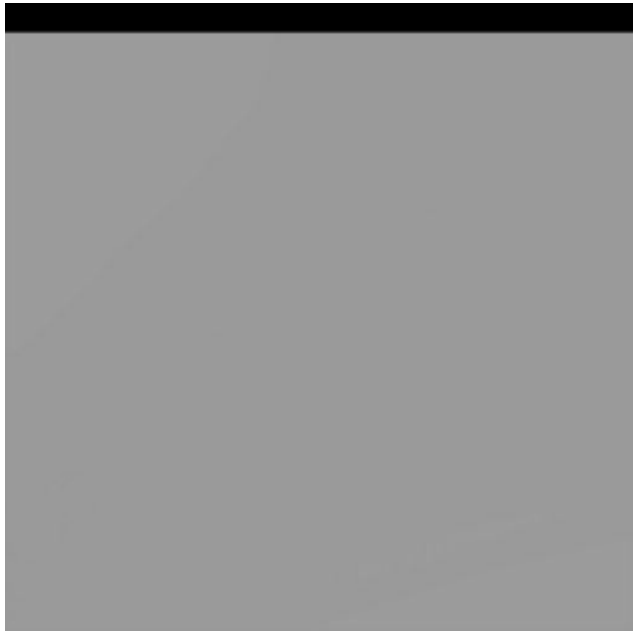
Angioplasy (3.0*120mm)

Endovascular Therapy for ATA-DPA



ATA to DPA 100%→0% (angioplasty alone)

Endovascular Therapy for ATA-DPA



After procedure, angiography for assessing below-the-ankle artery should be conducted to confirm direct perfusion to the ulcer.

Case: 64 y/o male

Postoperative lower limb examination

ABI: Right 1.08

Skin perfusion Pressure

Dorsum side: 70 mmHg

Plantar side: 58 mmHg

Laboratory examination

WBC 5500, CRP 0.1

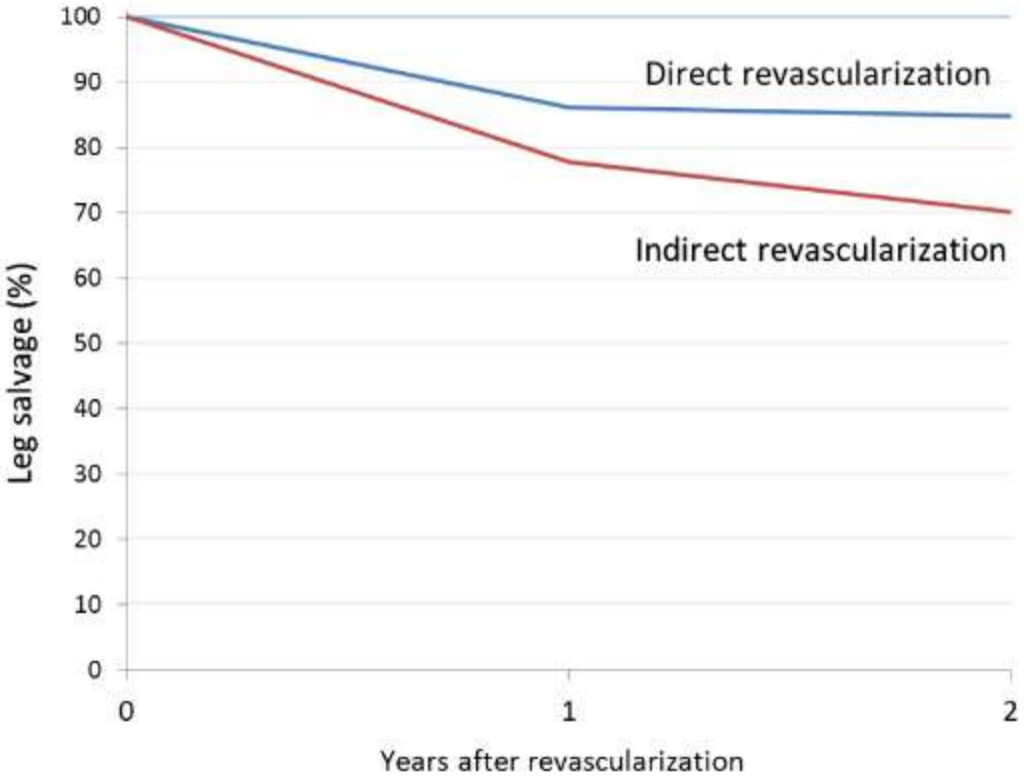
Angiosome-targeted Lower Limb Revascularization for Ischemic Foot Wounds: Systematic Review and Meta-analysis

Characteristics of observational studies evaluating the outcome after direct versus indirect revascularization for ischemic tissue lesions of the foot.

Author	Year of publication	Type of study	Treatment method	Disease stage	No. limbs		Follow-up (months)
					Direct	Indirect	
Varela	2010	retrospective	Endo/Surg	ABI<0.50/TP < 50, wound	45	31	24
Alexandrescu	2011	retrospective	Endo	Diabetic ischemic wound	134	98	54
Blanes Orti	2011	retrospective	Endo	Rutherford 5-6	18	16	21
Azuma	2012	retrospective	Surg	Rutherford 5-6	126	92	24
Iida	2012	retrospective	Endo	AP<70/TP < 50, wound	173	153	48
Ferrufino-Mérida	2012	prospective	Endo	CLI, wound	23	9	6
Söderström	2013	retrospective	Endo	Diabetic ischemic wound	121	129	12
Kabra	2013	prospective	Endo/Surg	Rutherford 4-6	39	25	6
Lejay	2013	retrospective	Surg	Diabetic ischemic wound	36	22	48

Biancari F, Juvonen T. Eur J Vasc Endovasc Surg. 2014 in press.

Angiosome-targeted Lower Limb Revascularization for Ischemic Foot Wounds: Systematic Review and Meta-analysis



WHAT THIS PAPER ADDS

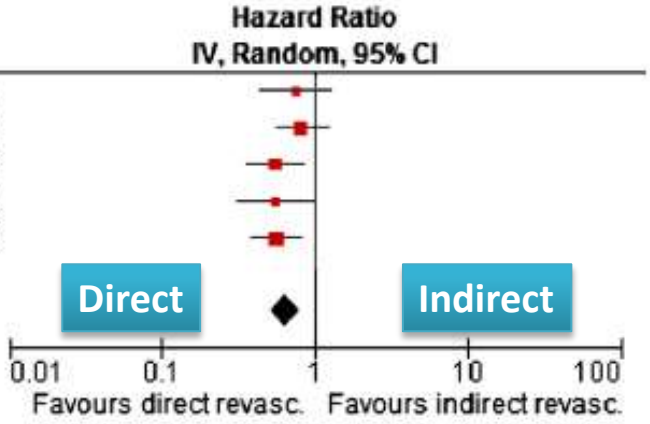
The results of this meta-analysis suggest that, when feasible, direct revascularization of the foot angiosome affected may improve wound healing and limb salvage rates compared with indirect revascularization.

Biancari F, Juvonen T. Eur J Vasc Endovasc Surg. 2014.

Angiosome-targeted Lower Limb Revascularization for Ischemic Foot Wounds: Systematic Review and Meta-analysis

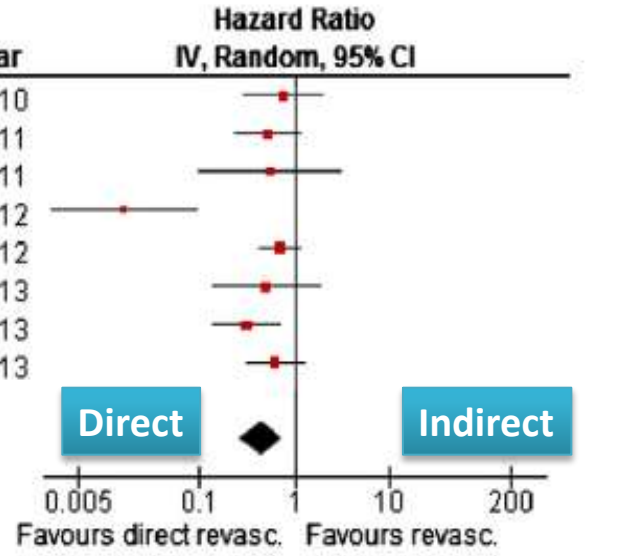
Forest plot for effectiveness in **wound healing**

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Varela 2010	-0.29	0.27	13.9%	0.75 [0.44–1.27]	2010
Azuma 2012 a	-0.2	0.2	25.3%	0.82 [0.55–1.21]	2012
Azuma 2012 b	-0.59	0.22	20.9%	0.55 [0.36–0.85]	2012
Kabra 2013	-0.6	0.29	12.0%	0.55 [0.31–0.97]	2013
Söderström 2013	-0.58	0.19	28.0%	0.56 [0.39–0.81]	2013
Total (95% CI)			**100.0%**	**0.64 [0.52–0.78]**	



Forest plot for effectiveness in **limb salvage**

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Varela 2010	-0.28	0.5	12.7%	0.76 [0.28–2.01]	2010
Alexandrescu 2011	-0.65	0.4	15.1%	0.52 [0.24–1.14]	2011
Blanes Ortí 2011	-0.59	0.88	6.6%	0.55 [0.10–3.11]	2011
Ferrufino-Mérida 2012	-4.16	0.92	6.2%	0.02 [0.00–0.09]	2012
Iida 2012	-0.36	0.25	19.0%	0.70 [0.43–1.14]	2012
Kabra 2013	-0.69	0.67	9.4%	0.50 [0.13–1.86]	2013
Lejay 2013	-1.17	0.42	14.6%	0.31 [0.14–0.71]	2013
Söderström 2013	-0.48	0.36	16.2%	0.62 [0.31–1.25]	2013
Total (95% CI)			**100.0%**	**0.44 [0.26–0.75]**	



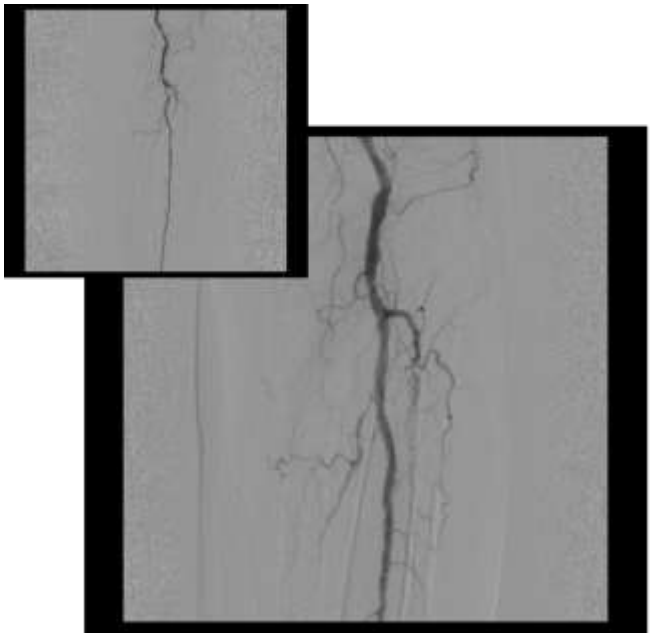
Biancari F, Juvonen T. Eur J Vasc Endovasc Surg. 2014 in press.

Issue of clinical setting (practice) in Angiosome concept

	Verela C et al. Vasc & Endovasc Surgery 2010	Alexandrescu V et al. J Endovasc Ther 2011	Iida O et al. J Vasc Surg 2011	Söderström M et al. J Vasc Surg 2012
Country	Spain	Belgium	Japan	Finland
Subjects (N)	76	232	369	250
Revascularization strategy	Surgical (n=41) Endovascular (n=35)	Endovascular therapy only	Endovascular therapy only	Endovascular therapy only
Direct vs. Indirect revascularization	DR: 59% (45/76) **IR: 41% (31/76)**	DR: 62% (134) **IR: 38% (89)**	DR: 54% (200) **IR: 46% (169)**	DR: 48% (121) **IR: 52% (129)**
Limb salvage rate (DR vs. **IR**)	93% vs. **72%** (P=0.02)	89% vs. **76%** (P=0.04)	82% vs. **68%** (P=0.01)	86% vs. **76%** (P=0.09)

- In the clinical setting, revascularization for ischemic wounds through their specific source artery **is not always successful** because of technical barriers and lesion severity
- Approximately **40-50 %** of patients were reluctantly treated with **indirect revascularization (IR)**

Discrepancy from theory to practice in Angiosome concept



IR (indirect revascularization) → Limb salvage

- Consequently, moderate limb salvage rates **(68-76%)** were obtained by **indirect revascularization (IR)** in earlier studies
- However, it remains unclear which patients derive the most clinical benefit from **direct revascularization (DR)**

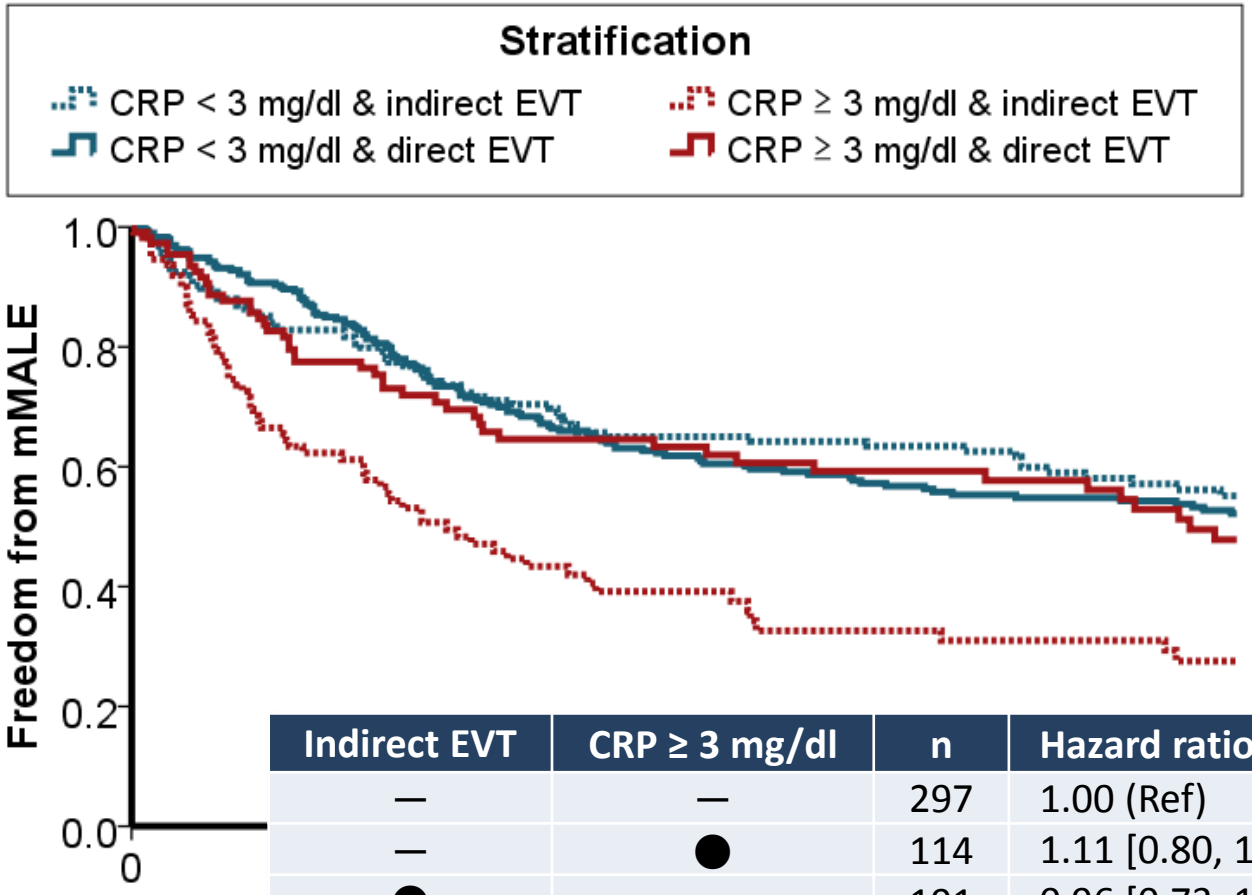
We should seek determinants of patients with CLI who derive the most clinical benefit from **direct revascularization (DR)**

-Interaction between indirect EVT (endovascular therapy) and clinical risk factors-

	Unadjusted hazard ratio of indirect EVT for MALE in each subgroup		Interaction effect p value
	Yes (with risk)	No (without risk)	
Age ≥ 80 years	1.17 [0.66, 2.09]	1.31 [1.04, 1.65]	0.701
Male gender	1.40 [1.08, 1.83]	0.95 [0.65, 1.38]	0.087
Non-ambulatory status	1.20 [0.88, 1.63]	1.26 [0.93, 1.71]	0.781
Serum albumin < 3.0 g/dl	1.86 [1.12, 3.08]	1.14 [0.90, 1.45]	0.084
Diabetes mellitus	1.34 [1.05, 1.72]	1.00 [0.65, 1.54]	0.209
Hypertension	1.16 [0.89, 1.50]	1.56 [1.05, 2.30]	0.251
Hyperlipidemia	1.18 [0.78, 1.78]	1.29 [1.00, 1.66]	0.829
Smoking	1.11 [0.78, 1.58]	1.35 [1.03, 1.77]	0.401
Chronic renal failure	1.34 [1.04, 1.72]	1.24 [0.81, 1.90]	0.820
Coronary artery disease	1.15 [0.86, 1.53]	1.41 [1.01, 1.95]	0.346
Cerebrovascular disease	1.65 [1.06, 2.57]	1.13 [0.88, 1.45]	0.121
Rutherford 6	1.39 [0.94, 2.05]	1.10 [0.84, 1.43]	0.223
CRP ≥ 3 mg/dl	**1.84 [1.28, 2.66]**	**0.96 [0.73, 1.27]**	**0.004**
Three-vessel BK disease	1.31 [0.90, 1.90]	1.25 [0.96, 1.63]	0.802
Calcification	1.27 [0.99, 1.65]	1.25 [0.84, 1.86]	0.984
No below-the-ankle runoff	0.97 [0.65, 1.45]	1.35 [1.04, 1.74]	0.169
Overall	1.25 [1.01, 1.55]		----

Iida O, et al. Eur J Vasc Endovasc Surg. 2013.

- Indirect EVT increased risk for MALE only in patients with CRP ≥ 3 mg/dl



Indirect EVT	CRP ≥ 3 mg/dl	n	Hazard ratio for MALE
—	—	297	1.00 (Ref)
—	●	114	1.11 [0.80, 1.53]
●	—	191	0.96 [0.73, 1.27]
●	●	116	2.08 [1.56, 2.78]**

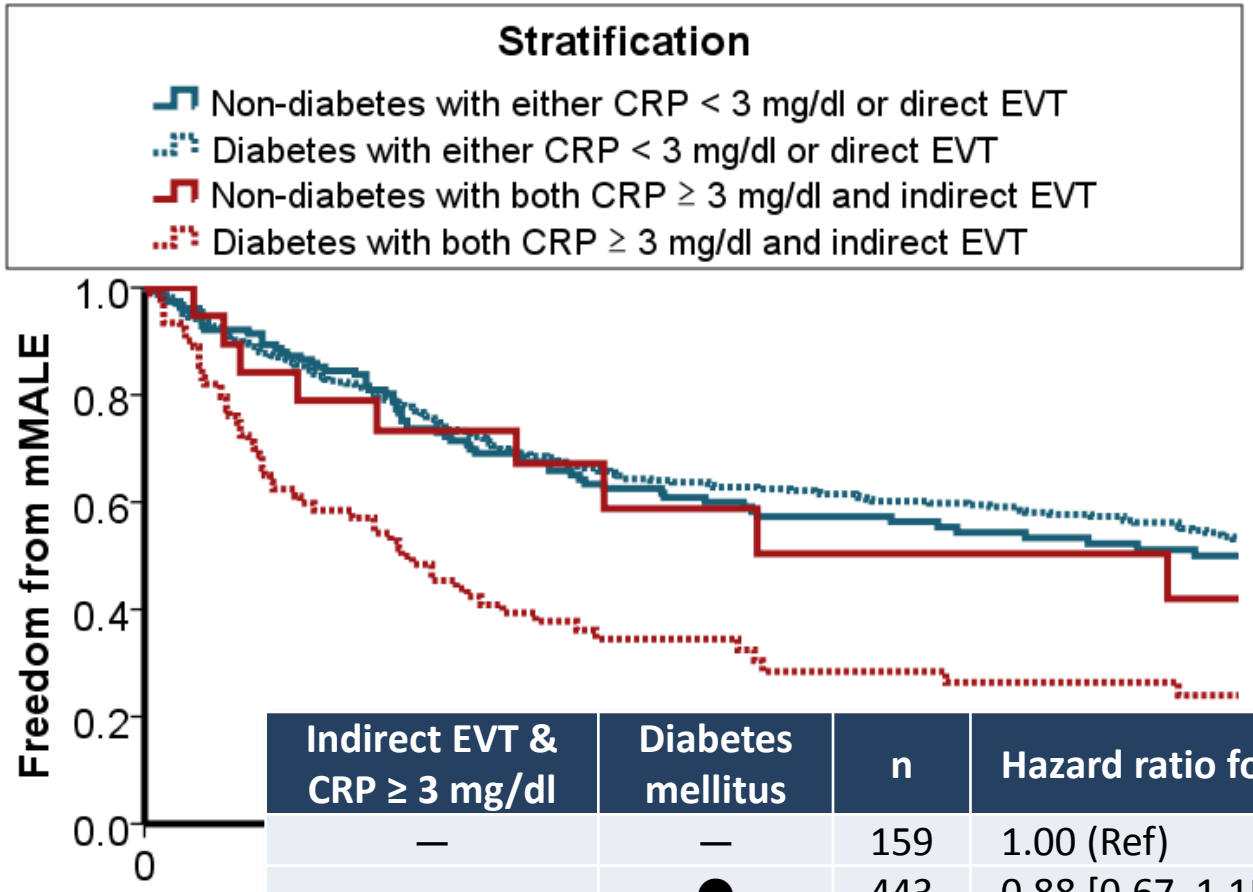
Iida O, et al. Eur J Vasc Endovasc Surg. 2013.

-Interaction between "indirect EVT for CLI with CRP ≥ 3" and other clinical risk factors-

	Unadjusted hazard ratio of "indirect EVT for CLI with CRP ≥ 3 mg/dl" for MALE in each subgroup		Interaction effect p value
	Yes (with risk)	No (without risk)	
Age ≥ 80 years	1.27 [0.50, 3.20]	2.11 [1.59, 2.79]	0.318
Male gender	2.17 [1.56, 3.02]	1.77 [1.13, 2.79]	0.452
Non-ambulatory status	1.90 [1.34, 2.70]	2.16 [1.42, 3.29]	0.735
Serum albumin < 3.0 g/dl	2.71 [1.62, 4.52]	1.81 [1.30, 2.51]	0.124
Diabetes mellitus	**2.43 [1.81, 3.27]**	**1.07 [0.55, 2.07]**	**0.021**
Hypertension	2.11 [1.54, 2.89]	2.05 [1.25, 3.36]	0.900
Hyperlipidemia	1.87 [1.13, 3.11]	2.25 [1.65, 3.09]	0.585
Smoking	2.37 [1.54, 3.64]	1.92 [1.37, 2.70]	0.505
Chronic renal failure	2.21 [1.63, 3.02]	1.95 [1.15, 3.33]	0.740
Coronary artery disease	2.02 [1.42, 2.87]	2.18 [1.45, 3.29]	0.691
Cerebrovascular disease	1.88 [1.05, 3.37]	2.09 [1.55, 2.81]	0.731
Rutherford 6	1.86 [1.24, 2.81]	1.59 [1.09, 2.31]	0.270
Three-vessel BK disease	2.07 [1.29, 3.33]	2.09 [1.51, 2.88]	0.915
Calcification	2.26 [1.66, 3.07]	1.64 [0.94, 2.85]	0.323
No below-the-ankle runoff	1.80 [1.17, 2.78]	2.11 [1.49, 2.98]	0.681
Overall	2.06 [1.58, 2.69]		----

Iida O, et al. Eur J Vasc Endovasc Surg. 2013.

- Indirect EVT for CLI with CRP ≥ 3 mg/dl increased risk for mMALE only in diabetic patients-

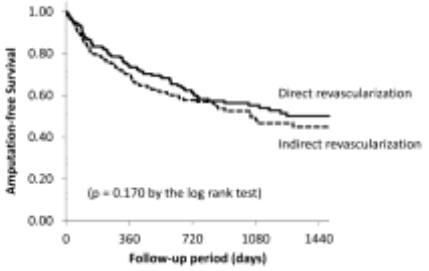


Indirect EVT & CRP ≥ 3 mg/dl	Diabetes mellitus	n	Hazard ratio for mMALE
—	—	159	1.00 (Ref)
—	●	443	0.88 [0.67, 1.15]
●	—	21	1.05 [0.54, 2.04]
●	●	95	2.17 [1.54, 3.06]**

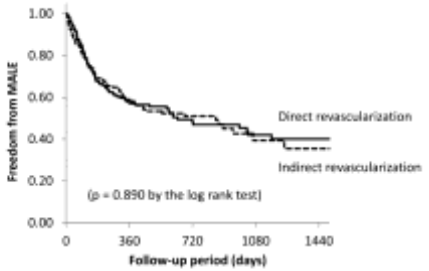
Iida O, et al. Eur J Vasc Endovasc Surg. 2013.

Background

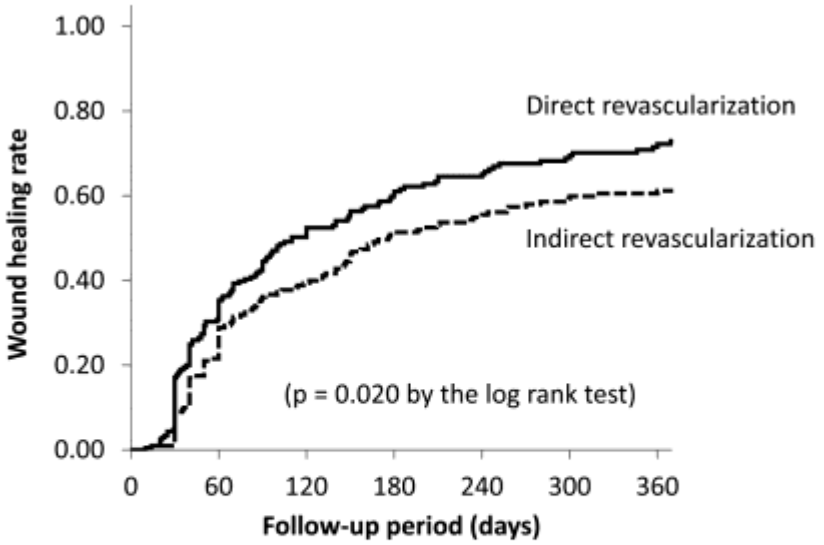
- ✓ We previously reported favorable impact of angiosome-oriented revascularization on limb prognosis in patients with critical limb ischemia (CLI) complicated with both diabetes and wound infection.
- ✓ The current study investigated the impact of angiosome-oriented revascularization on clinical outcomes in CLI patients excluding those with both diabetes and wound infection.



Follow-up period (days)		0	360	720	1080	1440
Direct revascularization	No. at risk	207	125	76	47	14
	Rate±SE	100±0%	74±3%	62±4%	55±4%	48±5%
Indirect revascularization	No. at risk	207	119	71	33	20
	Rate±SE	100±0%	70±3%	58±4%	48±4%	45±5%



Follow-up period (days)		0	360	720	1080	1440
Direct revascularization	No. at risk	207	74	40	21	13
	Rate±SE	100±0%	59±4%	48±4%	40±5%	40±5%
Indirect revascularization	No. at risk	207	73	36	11	6
	Rate±SE	100±0%	58±4%	51±4%	39±6%	35±6%



Follow-up period (days)		0	120	240	360
Direct revascularization	No. at risk	207	90	58	40
	Rate±SE	0±0%	52±4%	65±3%	72±3%
Indirect revascularization	No. at risk	207	109	73	60
	Rate±SE	0±0%	39±4%	56±4%	61±4%

Conclusion: In propensity matching analysis, complete wound healing rate was higher in DR than IR groups (72±3% vs. 61±4% at 12 months, P=0.02) while freedom from MALE (P=0.89) and AFS (P=0.17) was not significantly different. In multivariate analysis, IR was an independent predictor of wound healing

Conclusion

- The recent meta-analysis suggest that direct revascularization of the foot angiosome affected may improve wound healing and limb salvage rates compared with indirect revascularization.

- Based on our analysis for angiosome concept, indirect EVT is an acceptable strategy for most patients with CLI due to isolated BTK lesion, however, when wounds are complicated by both diabetes and infection, an effort should be made to accomplish direct EVT.