

The LINC logo is located in the top left corner. It features the letters 'LINC' in a white, sans-serif font. To the left of the text is a stylized graphic consisting of two overlapping, curved shapes in red and orange, resembling a flame or a ribbon, set against a dark blue background.

LINC

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DGA @ LINC

CLI is threat to life and limb!

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Disclosure

Speaker name:

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I have the following potential conflicts of interest to report:

- Consulting
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s)

- I do not have any potential conflict of interest



2016 my first party after foot amputation
„I escaped the Grim Reaper“

Peter Degner
Impresario and Event Manager
* 1954 in Leipzig; † 15. Januar 2020

How would you rate this patient's amputation risk?

	RIGHT	LEFT
A. brachialis	140	140
A. tib. ant.	115	120
A. tib. post.	115	120
ABI	0.82	0.86

Toe pressure/tcPO₂ 60 mmHg



	RIGHT	LEFT
A. brachialis	140	140
A. tib. ant.	30	60
A. tib. post.	40	50
ABI	0.21	0.36

Toe pressure/tcPO₂ 30 mmHg



Assessment of the risk of amputation

Component	Score	Description		
W (Wound)	0	No ulcer (ischaemic rest pain)		
	1	Small, shallow ulcer on distal leg or foot without gangrene		
	2	Deeper ulcer with exposed bone, joint or tendon ± gangrenous changes limited to toes		
	3	Extensive deep ulcer, full thickness heel ulcer ± calcaneal involvement ± extensive gangrene		
I (Ischaemia)		ABI	Ankle pressure (mmHg)	Toe pressure or TcPO ₂
	0	≥0.80	> 100	≥60
	1	0.60–0.79	70–100	40–59
	2	0.40–0.59	50–70	30–39
	3	<0.40	<50	<30
fi (foot Infection)	0	No symptoms/signs of infection		
	1	Local infection involving only skin and subcutaneous tissue		
	2	Local infection involving deeper than skin/subcutaneous tissue		
	3	Systemic inflammatory response syndrome		

Interpretation of the WIFI classification



Estimate risk of amputation at 1 year for each combination																
	Ischaemia - 0				Ischaemia - 1				Ischaemia - 2				Ischaemia - 3			
W-0	VL	VL	L	M	VL	L	M	H	L	L	M	M	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	fi-0	fi-1	fi-2	fi-3	fi-0	fi-1	fi-2	fi-3	fi-0	fi-1	fi-2	fi-3	fi-0	fi-1	fi-2	fi-3

fi = foot infection; H = high-risk; L = low-risk; M = moderate risk; VL = very low risk; W = wound.

CLI

What are we talking about?

New terminology - new paradigm for treatment and research

CLI = **critical** limb ischemia

Target population

= patients with objectively documented **PAD** and any of the following clinical symptoms or signs:

- Ischemic **rest pain**
- **lower limb ulceration** present for at least **2 weeks**
- **Gangrene** involving any portion of the lower limb or foot
- **Diabetic foot ulcer (DFU)**

CLTI = **chronic** limb-**threatening** ischemia

!
ankle or toe pressure,
measured to address the PAD severity,
are not a definition component of CLTI



CLTI

- a sad reality.

Clinical burden



Germany

2004-2009:
number of CLI patients increased by 21%
non-CLI PAD patients increased by <10%

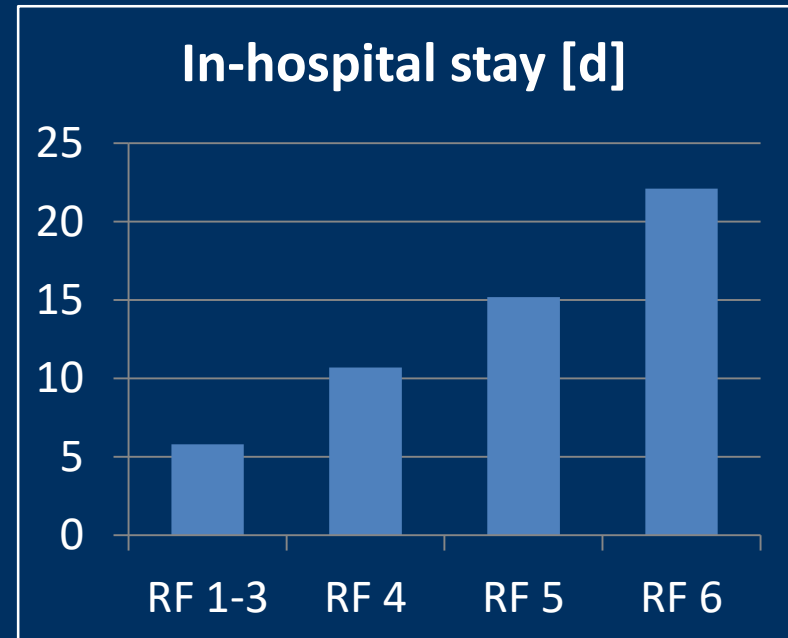


USA

11 % of PAD patients develop CLI → ~ 2 Mio people

CLI hospitalization 325.000-375.000/a

Re-admission 15-30% within 30d
60% at 6 months, with increasing disease severity



Still poor outcome and lack of guideline adherence

	RF 1–3	RF 4	RF 5	RF 6	Total	P
Patients, n (% of all)	21 197 (50.6)	5353 (12.8)	6916 (16.5)	8416 (20.1)	41 882 (100.0)	
Angiography, n (%)	12 339 (58.2)	3128 (58.4)	3567 (51.6)	4032 (47.9)	23 066 (55.1)	<0.001
Endovascular, n (%)	11 602 (54.7)	2043 (38.2)	2450 (35.4)	2481 (29.5)	18 576 (44.4)	<0.001
Surgery, n (%)	5068 (23.9)	2130 (39.8)	1312 (19.0)	2083 (24.8)	10 593 (25.3)	<0.001
TEA, n (%)	2736 (12.9)	932 (17.4)	514 (7.4)	807 (9.6)	4989 (11.9)	<0.001
Bypass, n (%)	2068 (9.8)	1000 (18.7)	816 (11.8)	1326 (15.8)	5210 (12.4)	<0.001
Any revascularization, n (%)	15 963 (75.3)	3817 (71.3)	3518 (50.9)	4140 (49.2)	27 438 (65.5)	<0.001
Acute renal failure, n (%)	76 (0.4)	73 (1.4)	127 (1.8)	235 (2.8)	511 (1.2)	<0.001
MI, n (%)	68 (0.3)	44 (0.8)	58 (0.8)	147 (1.7)	317 (0.8)	<0.001
Ischaemic stroke, n (%)	33 (0.2)	21 (0.4)	29 (0.4)	63 (0.7)	146 (0.3)	<0.001
Infections, n (%)	491 (2.3)	270 (5.0)	1987 (28.7)	3001 (35.7)	5749 (13.7)	<0.001
Sepsis, n (%)	88 (0.4)	81 (1.5)	323 (4.7)	491 (5.8)	983 (2.3)	<0.001
Amputations, n (%)	103 (0.5)	88 (1.6)	679 (9.8)	3531 (42.0)	4401 (10.5)	<0.001
Deaths, n (%)	93 (0.4)	189 (3.5)	234 (3.4)	701 (8.3)	1217 (2.9)	<0.001
In-hospital stay, mean ± SD (days)	5.8 ± 6.7	10.7 ± 11.1	15.2 ± 13.8	22.1 ± 20.3	11.2 ± 14.0	<0.001
Costs, mean ± SD (€)	3662 ± 3186	5316 ± 6139	6021 ± 4892	8461 ± 8515	5227 ± 5650	<0.001

44-54% receive neither angiography nor revascularization before amputation

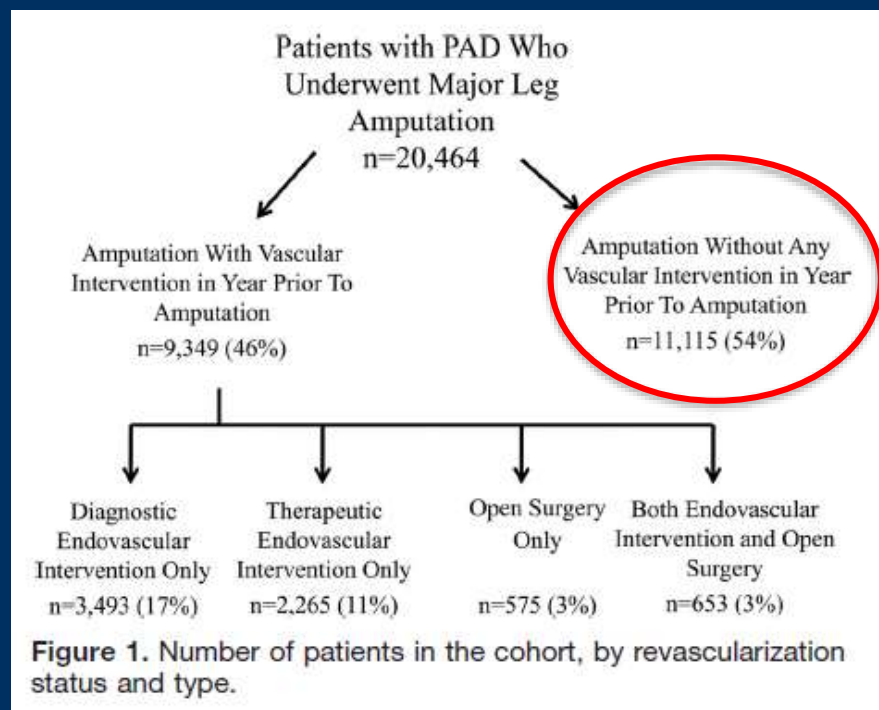
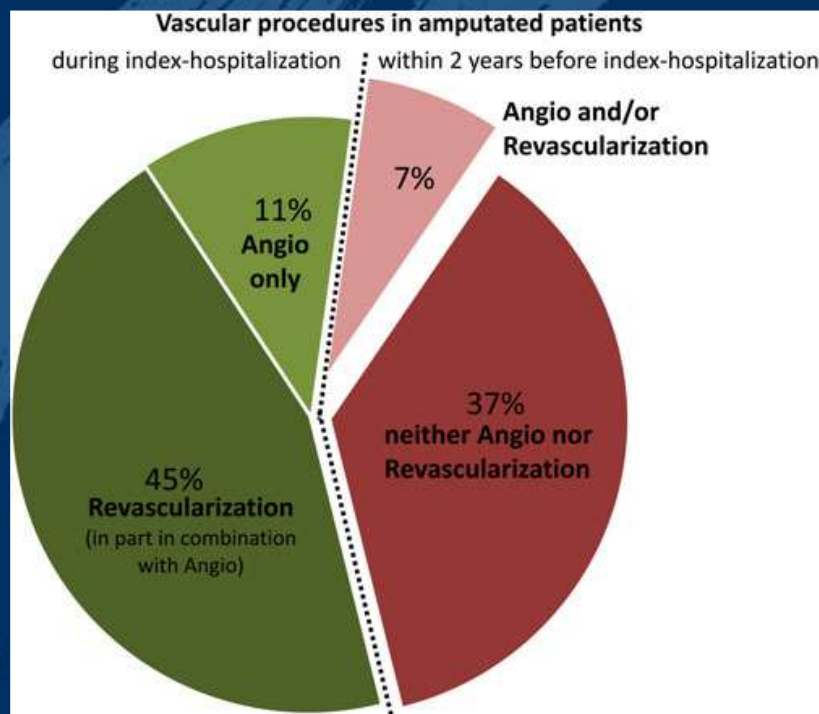
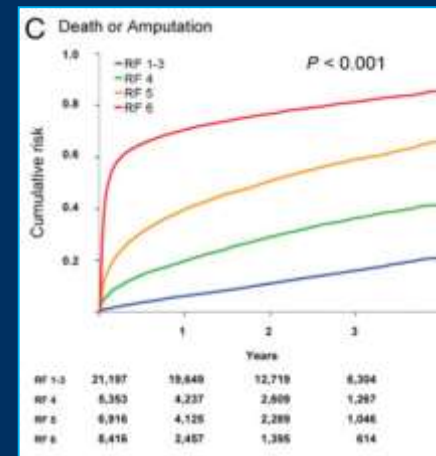
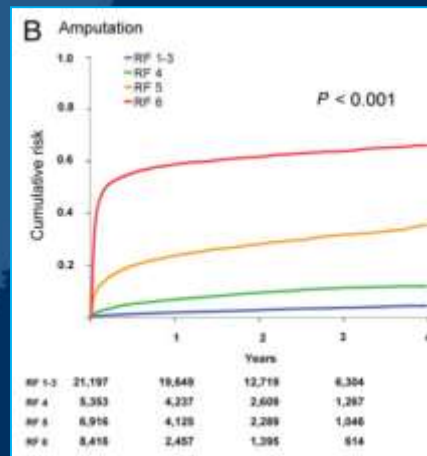
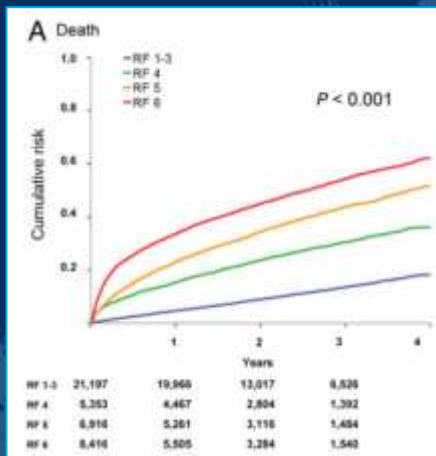


Figure 1. Number of patients in the cohort, by revascularization status and type.

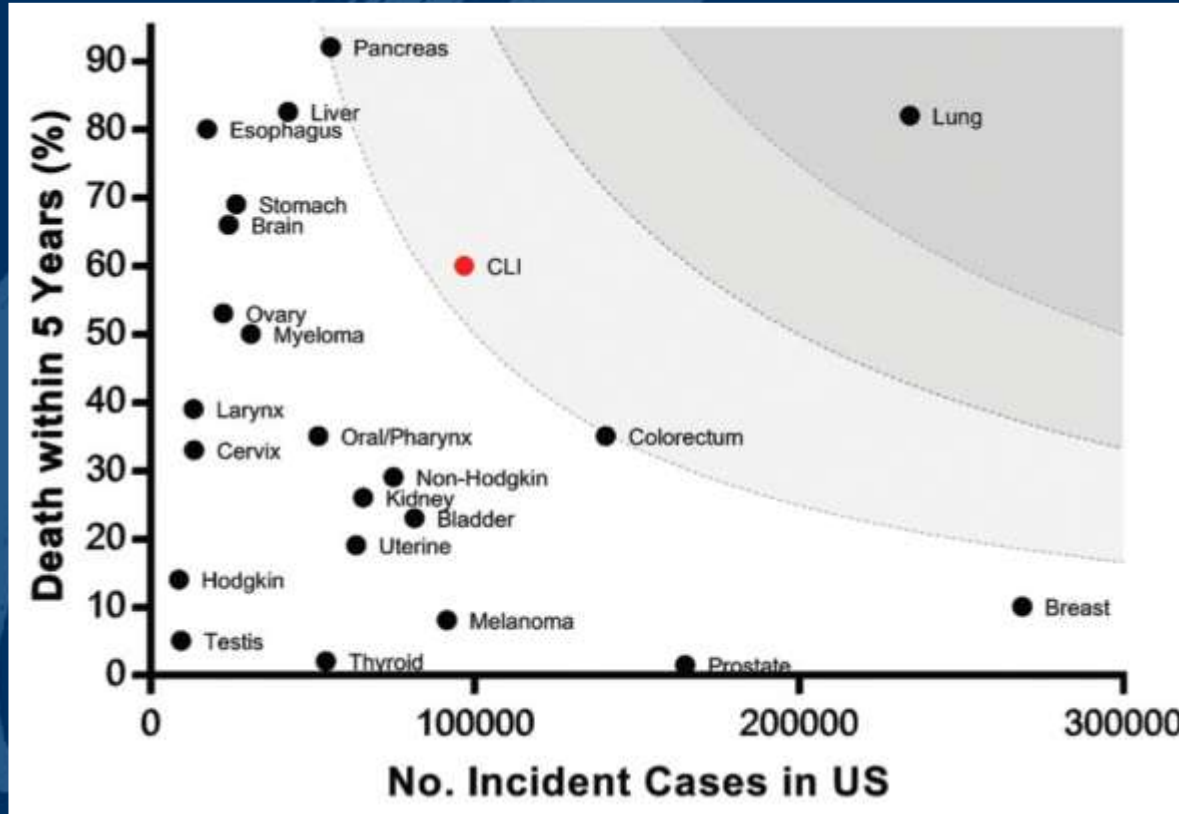
...despite the fact, that CLI patients have a **90% lower risk of amputation** after revascularization!



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MI, n (%)	68 (0.3)	44 (0.8)	58 (0.8)	147 (1.7)	317 (0.8)	<0.001
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1year mortality of CLI patients 24%
5year mortality of CLI patients 60%

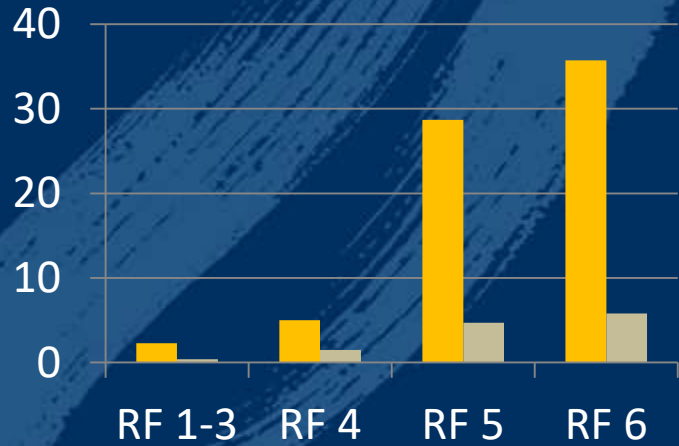


Comparing incident CLI cases with different cancer types, the most deaths over 5 years are:

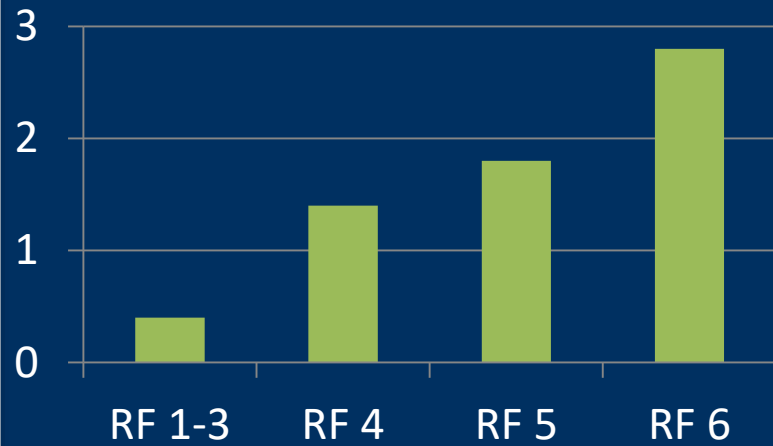
- 1) Lung cancer (192,000)
- 2) CLI (58,000)
- 3) Pancreatic cancer (51,000)
- 4) Colorectal cancer (49,000)
- 5) Liver Cancer (35,000)

Complications

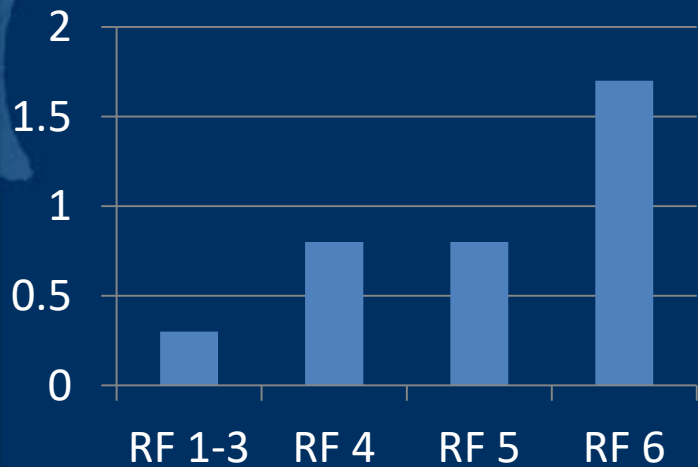
Infection/Sepsis



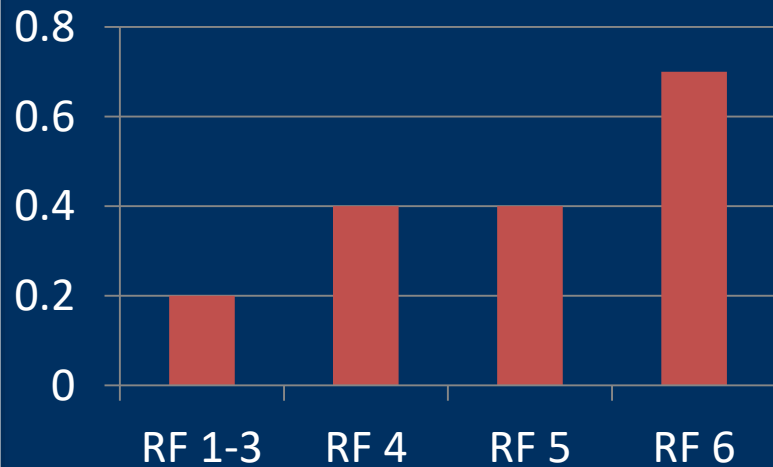
Acute renal failure



MI



Stroke



Causes for poor outcome?

CLI represent not only a disease of peripheral arteries

CLI = multiple systemic alterations

heart failure
brain injury
kidney failure
diabetes
inflammation
hemostasis

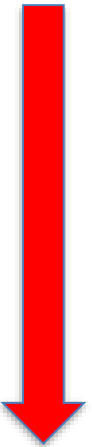
advanced multiorgan
disorders;
no reversible by
peripheral
revascularisation alone

... less than 1/3 of CLI patients are prescribed optimal medical therapy

BMT and multidisciplinary care are essential!

Causes for poor outcome?

RUTHERFORD		
Grade	Category	Clinical
0	0	Asymptomatic
I	1	Mild claudication
I	2	Moderate claudication
I	3	Severe claudication
II	4	Ischemic rest pain
III	5	Minor tissue loss
IV	6	Ulceration or gangrene



CLI patients „...often come too late“

“Approximately 50% of patients presenting with CLI have no prior history of PAD.”

PAD does not progress linearly from IC to CLI!

masked PAD:

- neuropathy
- coxarthrosis
- dyspnoe

Vascular procedures increased markedly, BUT highest in claudicants and not in CLI

???

Screen for PAD in risk patients

Amputation doubles the risk of death over the next year, even after controlling comorbidities!

Revascularization doubles patients survival compared to amputation!

Top priority: Revascularization

MAKRO-vascular

Target population

= patients with objectively documented PAD and any of the following clinical symptoms or signs:

- Ischemic rest pain
- lower limb ulceration present for at least 2 weeks
- Gangrene involving any portion of the lower limb or foot
- Diabetic foot ulcer (DFU)

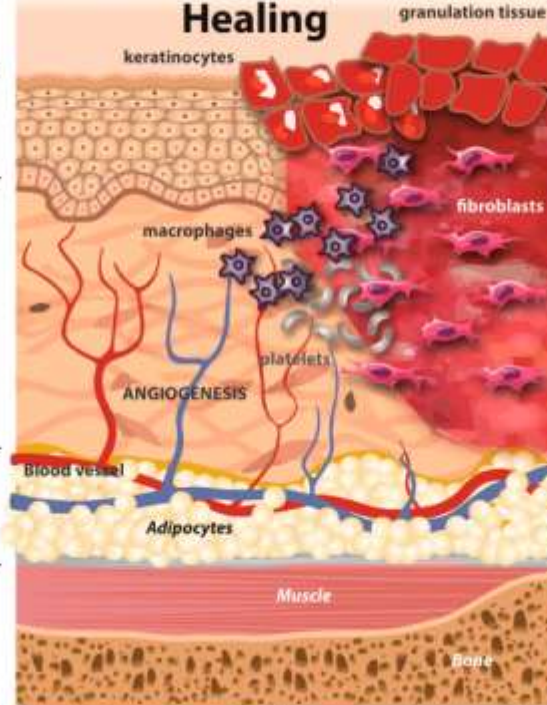
Wound healing takes place in the MICRO-vascular compartment!

50-70% CLI patients present neuro-ischaemic diabetic foot ulcers

Diabetic Foot Ulcer



a) Normal Wound Healing



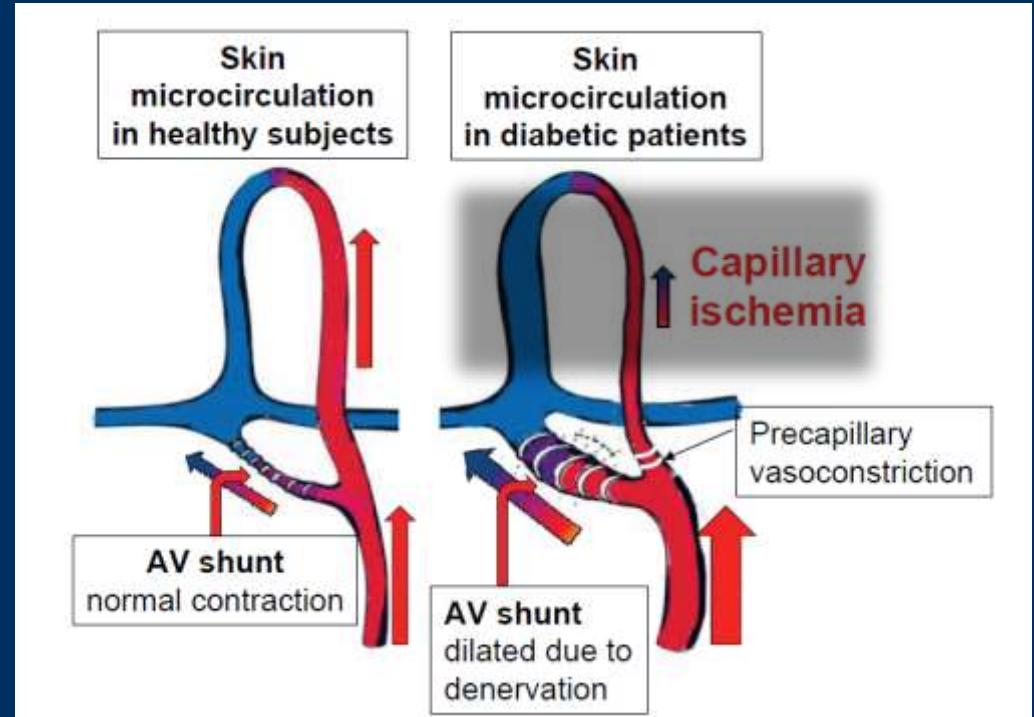
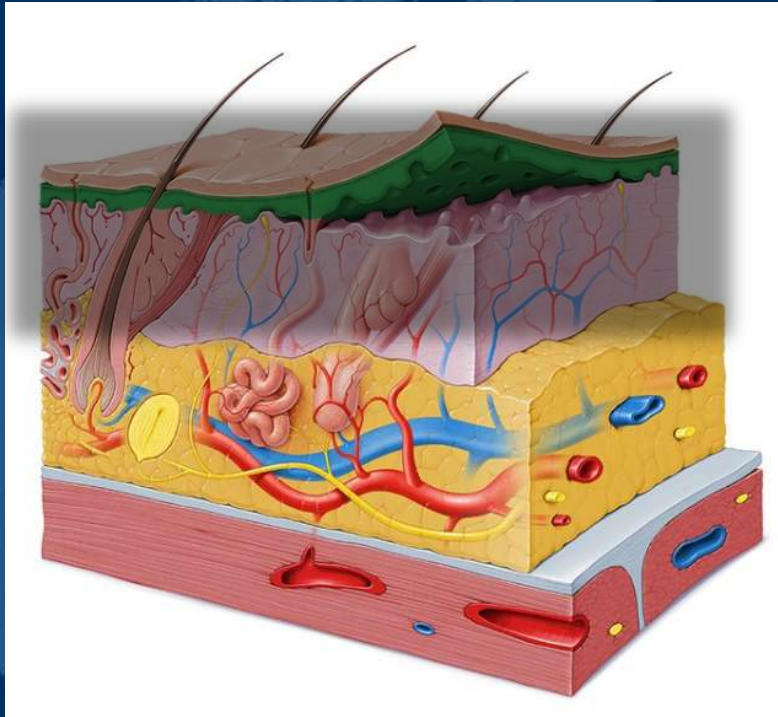
b) Diabetic Wound Healing



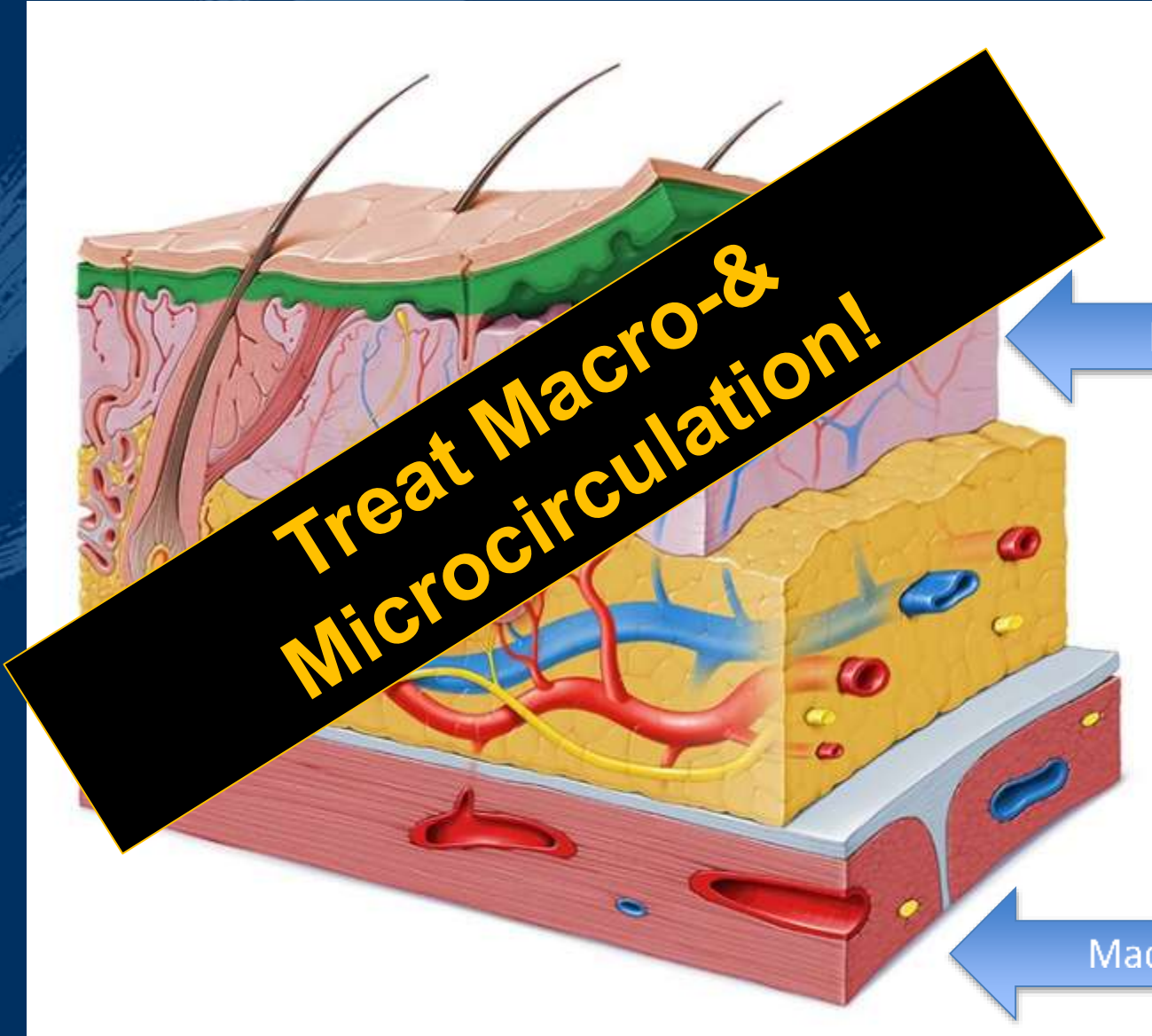
PHASES OF WOUND HEALING (Limit varies within faded interval, mainly by wound severity)	HAEMOSTASIS		INFLAMMATION		PROLIFERATION		CHRONIC WOUND
							REMODELING
EVENTS	- Bleeding - Coagulation - Vasoconstriction-Vasodilatation		- PMN Migration - Phagocytosis - Granulocytosis - Cytolysis		- Angiogenesis (neovascularization) - Fibroplasty - Wound contraction - Extracellular Matrix Synthesis		- Re-epithelization - Decreased vascularity - Degradation of the MEC
CELL FORMS (predominant)	Platelets		Neutrophils, PMNs, Polymorphonuclears, Macrophages		Macrophages, Endothelial Cells, Fibrocytes		Endothelial Cells
TIME	0 - 1 HOURS		1 - 6 DAYS		4 - 21 DAYS		21 DAYS > 2 YEARS

Diabetic Neuropathy = microvascular angiopathy

→ critical reduction of tissue perfusion pressure and nutritive blood supply despite of well perfused big vessels



Decision making in PAD treatment and post-treatment follow-up are still mainly based on large vessels and less on microcirculation.

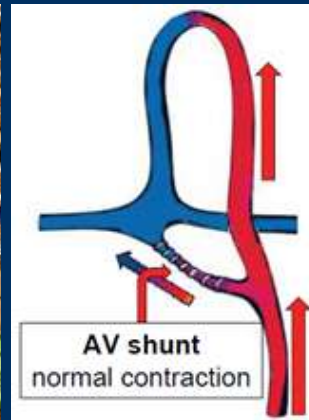
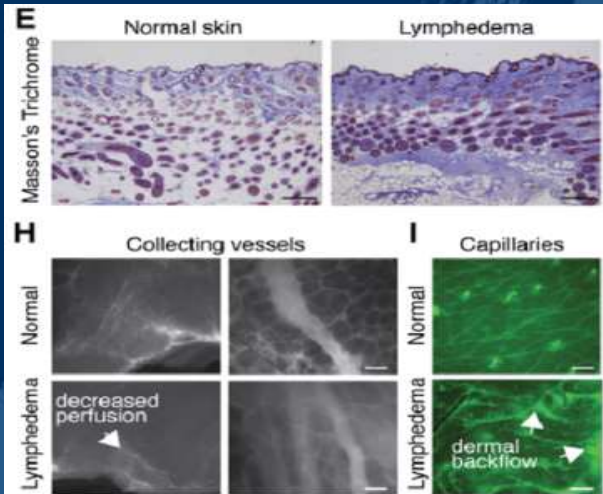


Treat Macro-& Microcirculation!

Micro

Macro

Unmet needs

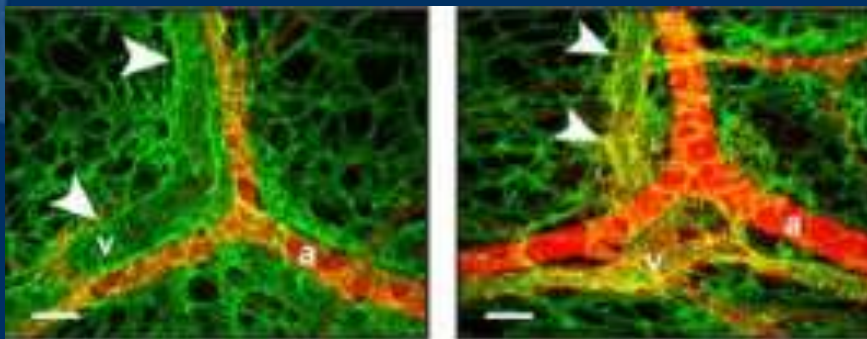


RBC of healthy individual



RBC of a DM patient

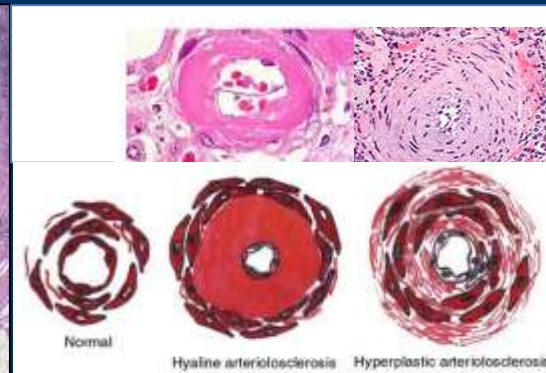
We have still a big gap in well-done studies regarding mechanisms and treatment options in microvascular pathologies of CLI clientel.



Bembe A. *Indian J Hematol Blood Transfus* (2012) 28(2):105–108

Pretorius E et al. *Integr. Biol.*, 2014, 6, 486

Perez-Favila A et al. *Medicina* 2019, 55(11), 714



Morfoisse F et al. *Arterioscler Thromb Vasc Biol.* 2018;38. 1346-1357.

Sharma A et al. *J Inv Dermatol* 2006 (126) 2323-2331.

Bovay E et al. *J. Exp. Med.* 2018 Vol. 215 No. 11 2760–2777.

Take home message

CLTI Target population

= patients with objectively documented PAD and any of the following clinical symptoms or signs:

- Ischemic rest pain
- lower limb ulceration present for at least 2 weeks
- Gangrene involving any portion of the lower limb or foot
- Diabetic foot ulcer (DFU)

Revascularization in every CLTI patient!

→ „Endovascular first/atherectomy for CLI“

Treat the Diabetic Foot Syndrome

→ „Diabetic foot infection“

Make full use of BMT including rheological strategies (microvasculature)

→ „Optimal antithrombotics“

Support the RECCORD registry of DGA

→ „Healthcare research“



Let's come together (with new results?)
next **LINC 2021** *in Leipzig!*