Peripheral arterial disease – where are we going?

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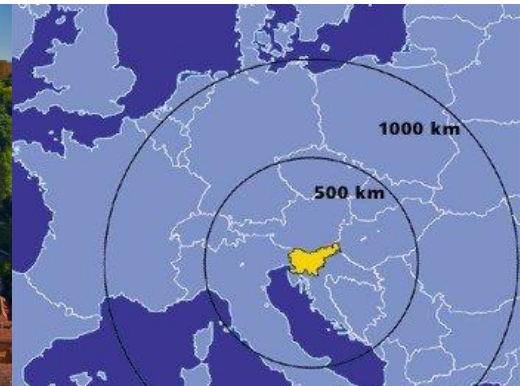
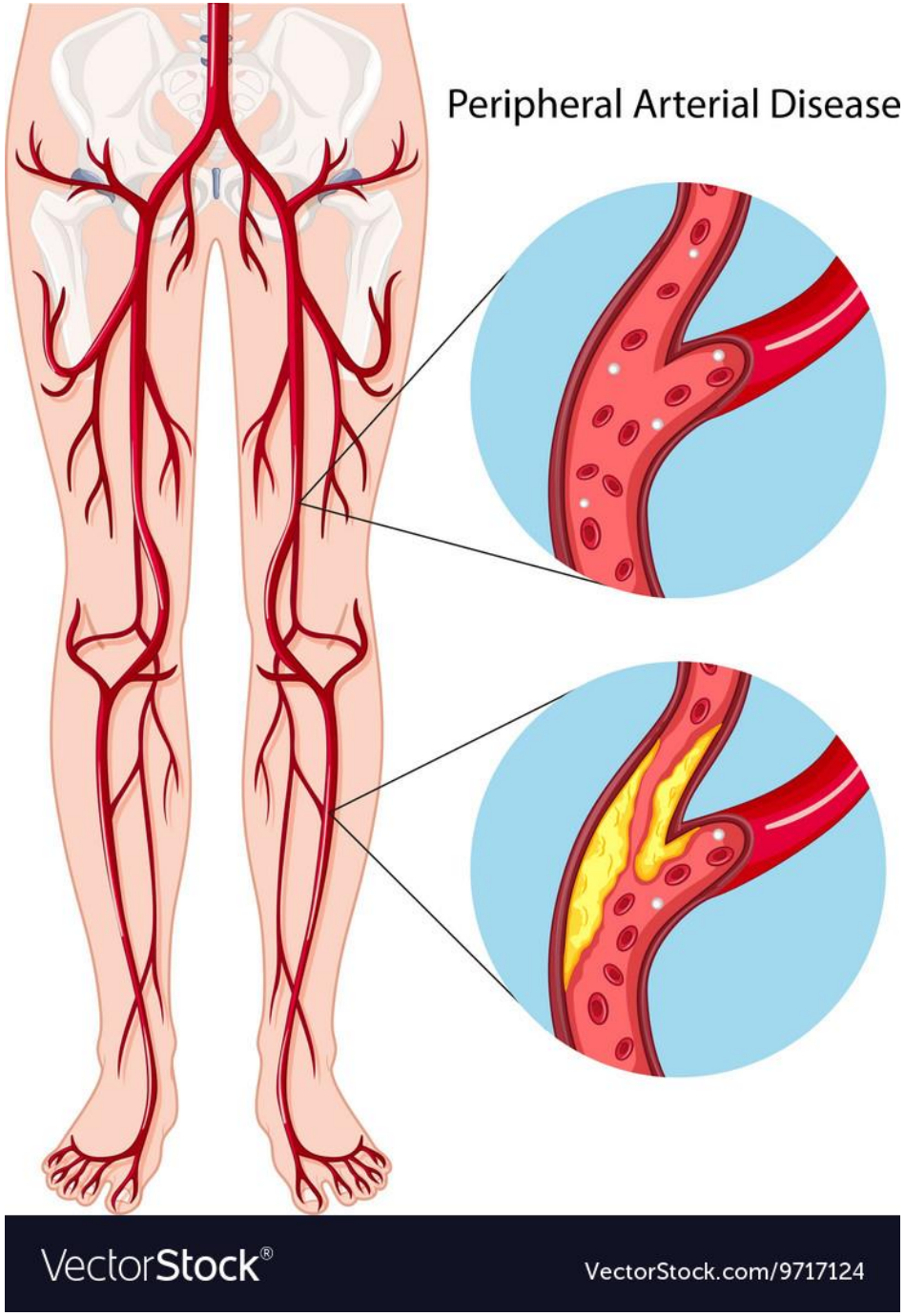


Outline

- Definition and epidemiology of PAD
- Prognosis of PAD & pharmacological prevention of MACE/ MALE
- PAD with intermittent claudication
- Chronic critical limb ischemia = chronic limb-threatening ischemia
- Acute limb ischemia

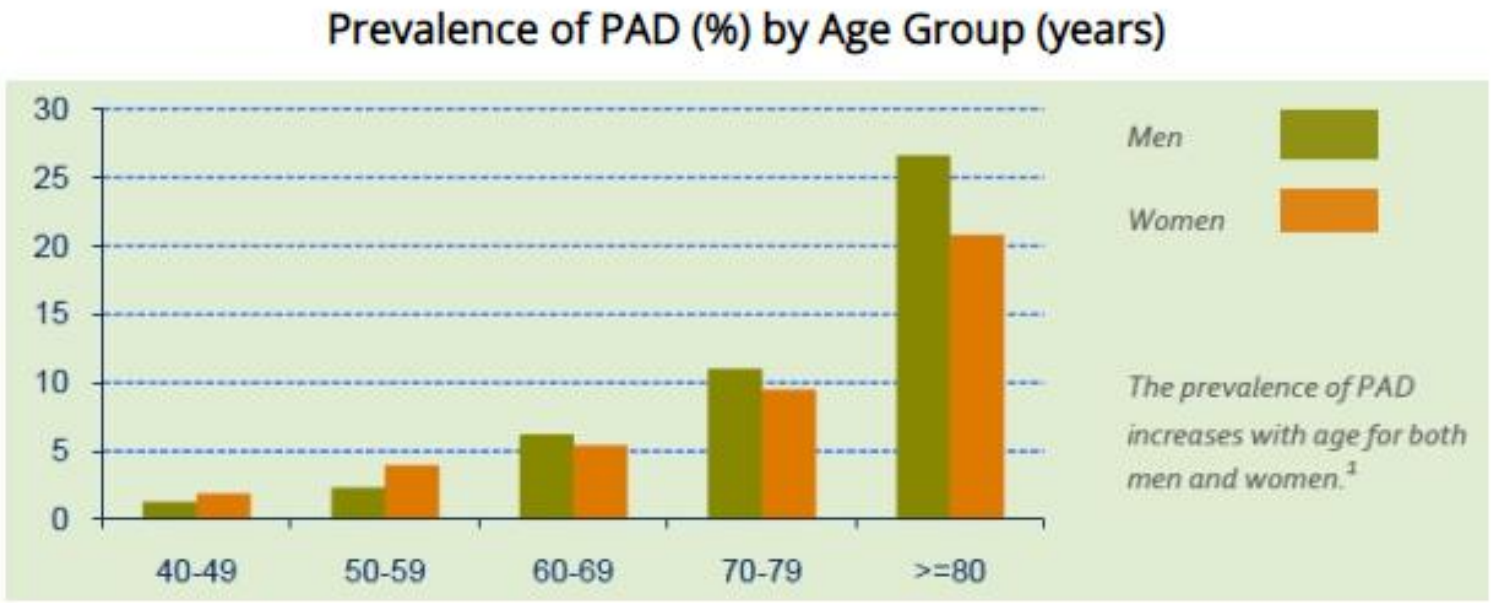


Peripheral arterial disease (PAD) = Lower extremity artery disease (LEAD)

<u>Predominantly</u>:
atherosclerosis and atherothrombosis
of the arteries
below the aortic bifurcation

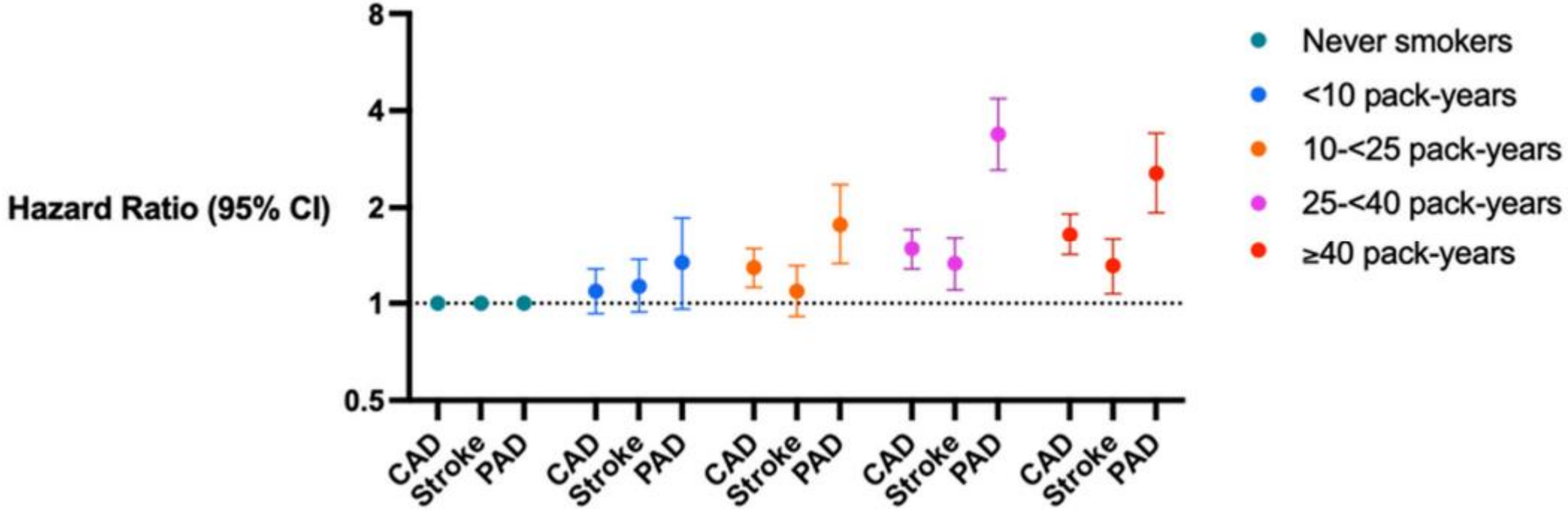
~ 236 million adults were living with PAD worldwide in 2015.

Lancet Glob Health 2020; 8:e721–e729. doi: 10.1016/S2214-109X(20)30117-0



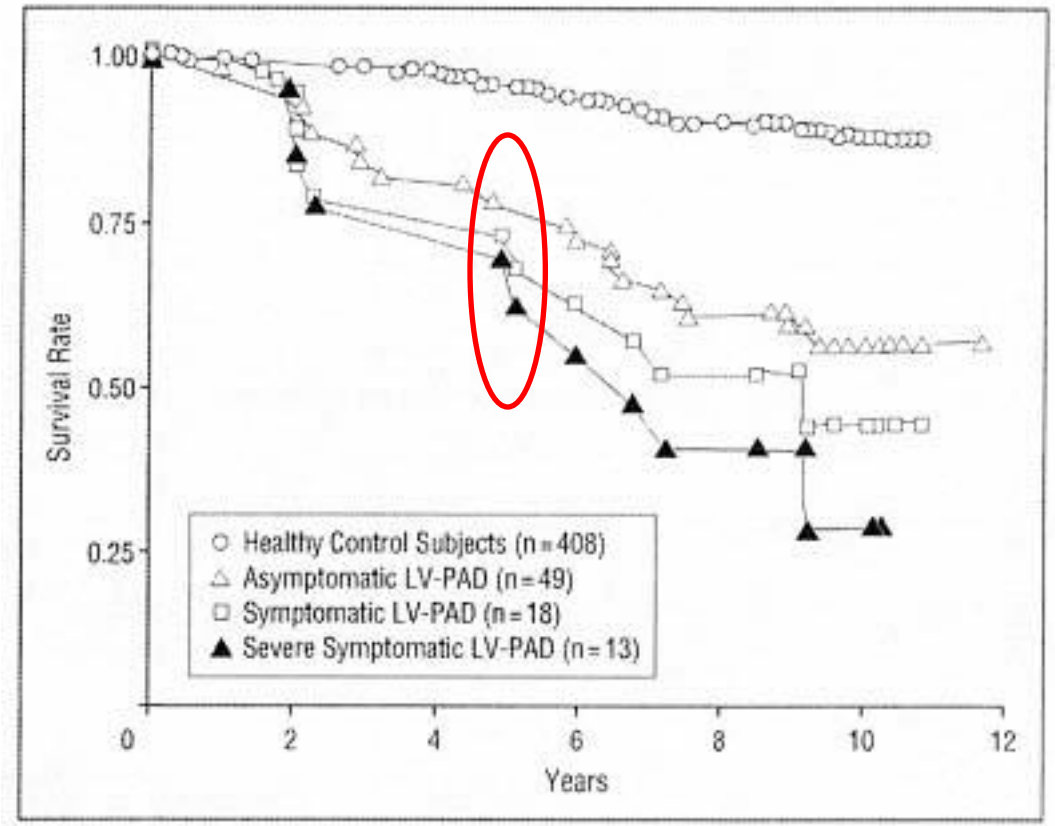
Circulation 2021; 143: e254–e743.

Risk factor	
Smoking	PAD>CAD/stroke
Diabetes	PAD>CAD/stroke
Low-density lipoprotein cholesterol	PAD<CAD/stroke
Triglycerides	PAD>CAD/stroke
Hypertension	PAD=CAD/stroke*
Microvascular disease	PAD>CAD/stroke

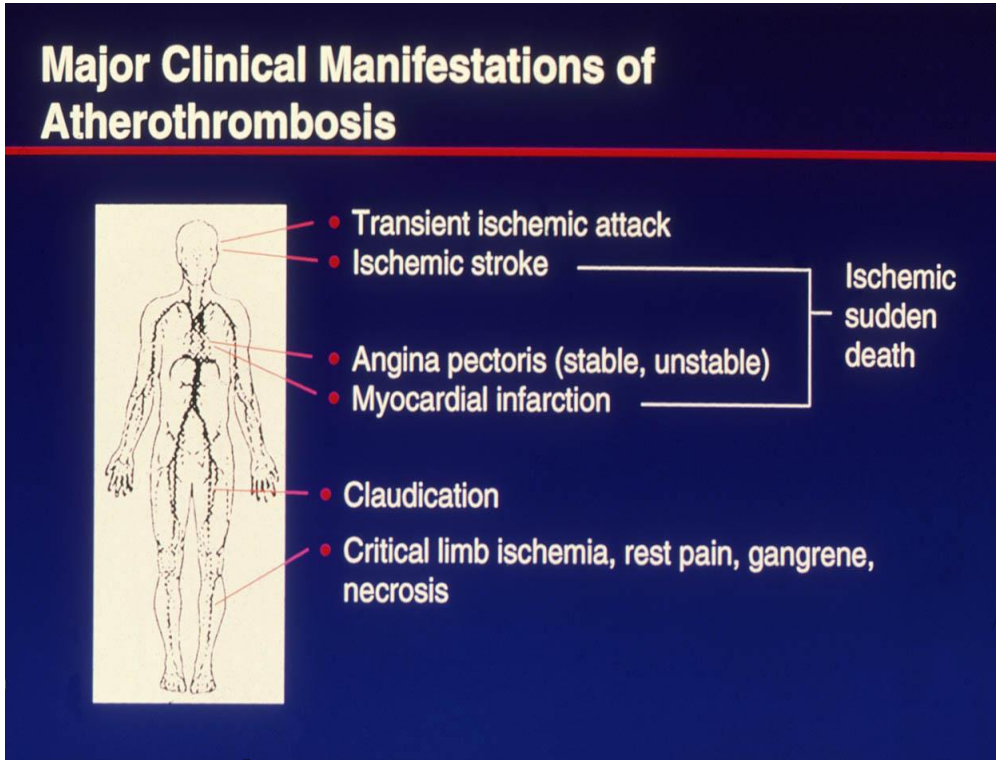


Circulation Research 2021; 128: 1818–1832. DOI: 10.1161/CIRCRESAHA.121.318535

Patients with PAD often succumb to atherothrombotic events



Criqui MH et al. N Engl J Med 1992; 326: 381-6.



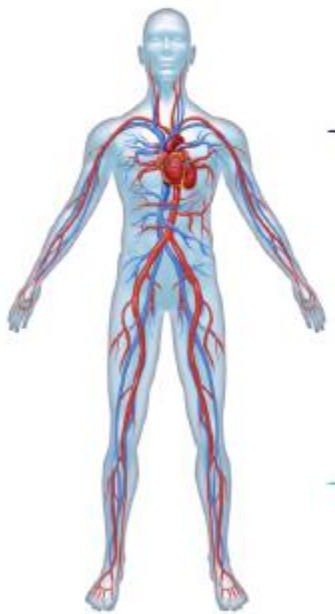
Circulation Research

PERIPHERAL VASCULAR DISEASE COMPENDIUM

Contemporary Medical Management of Peripheral Artery Disease

Circulation Research. 2021;128:1868–1884. DOI: 10.1161/CIRCRESAHA.121.318258

PAD Risk-reduction Therapies



Therapies for all Patients

- Lifestyle Modification & Exercise
- Tobacco Cessation Therapies (behavioral and pharmacologic)
- Targeting blood pressure goals with preference for ACEi
- LDL-C lowering with statin ± ezetimibe and/or PCSK9i
- Antiplatelet monotherapy (symptomatic), preference for $P2Y_{12}$ inhibition

Therapies for MACE Reduction in Selected Patients

Diabetes

- Glucose lowering to reduce microvascular risk
- GLP-1 (n.b. amputation benefit) , SGLT2 inhibitors

Prior MI or CAD (Polyvascular Disease) and low bleeding risk

- ASA + rivaroxaban 2.5 BID (broad polyvascular definition)
- ASA + ticagrelor 60 mg BID (prior MI or other need for DAPT)
- ASA and/or clopidogrel with vorapaxar

Therapies for MALE Reduction in all Patients

- LDL-C / Lp(a) lowering with statin ± ezetimibe and/or PCSK9i

Therapies for MALE Reduction in Selected Patients

Prior peripheral revascularization & low bleeding risk

- ASA + rivaroxaban 2.5 BID – *(only option shown efficacious in the immediate post-revascularization setting)*
- ASA + ticagrelor 60 mg BID (prior MI or other need for DAPT) – chronic PAD
- ASA and/or clopidogrel with vorapaxar – chronic PAD

Therapies for Claudication

Symptomatic Patients

- Cilostazol 100 mg BID

Online version at http://www.minervamedica.it

International Angiology 2017 June;36(3):216-27
DOI: 10.23736/S0392-9590.16.03731-7

ORIGINAL ARTICLE

Survival and event-free survival of patients with peripheral arterial disease undergoing prevention of cardiovascular disease

Aleš BLINC [1, 2] *, Matija KOZAK [1, 2], Mišo ŠABOVIČ [1, 2], Mojca BOŽIČ MIJOVSKI [1, 3], Mojca STEGNAR [1, 3], Pavel POREDOŠ [1, 2], Andrej KRAVOS [4], Breda BARBIČ-ŽAGAR [5], Janez Stare [6], Maja POHAR PERME [6]

[1]Department of Vascular Diseases, University Medical Centre Ljubljana, Ljubljana, Slovenia; [2]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; [3]Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia; [4]Department of Family Medicine, Faculty of Medicine, University of Maribor, Maribor, Slovenia; [5]Krka, d. d., Novo mesto, Slovenia; [6]Institute of Biostatistics and Medical Informatics, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

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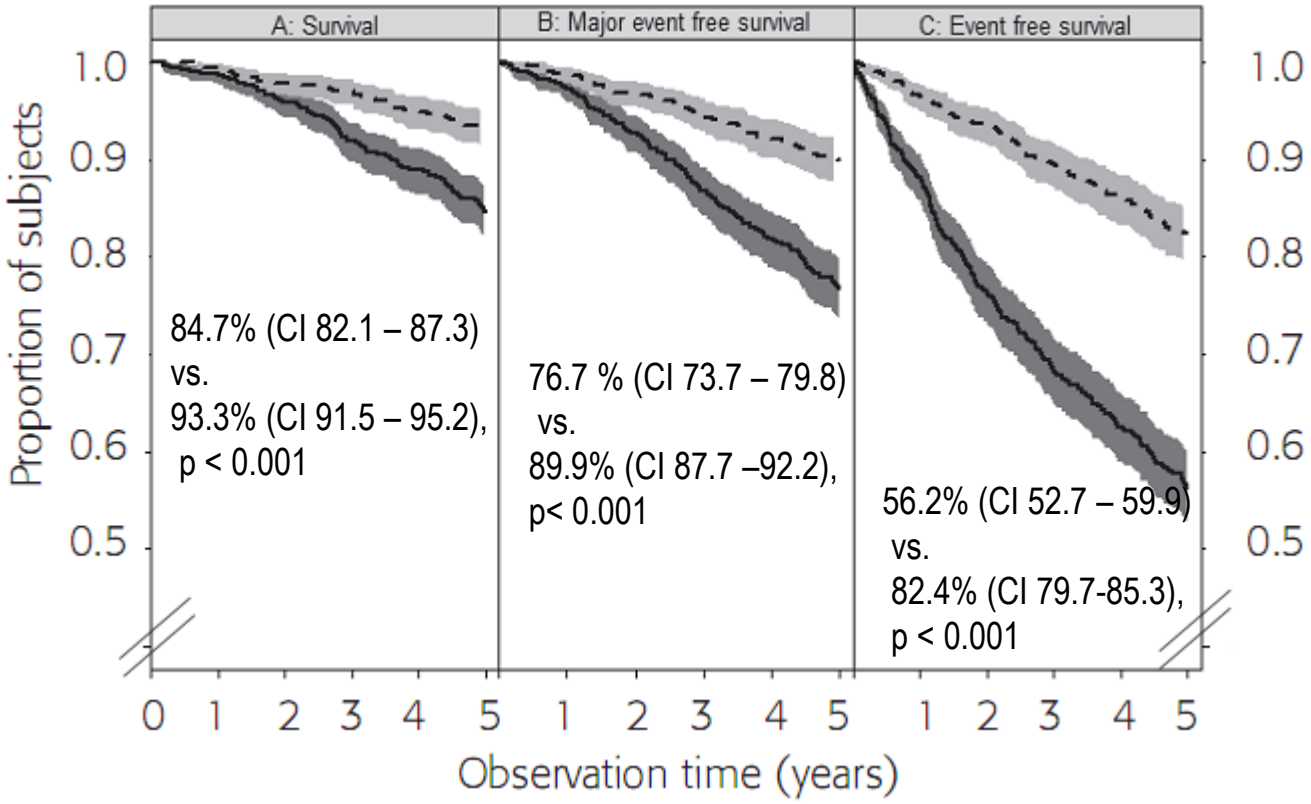
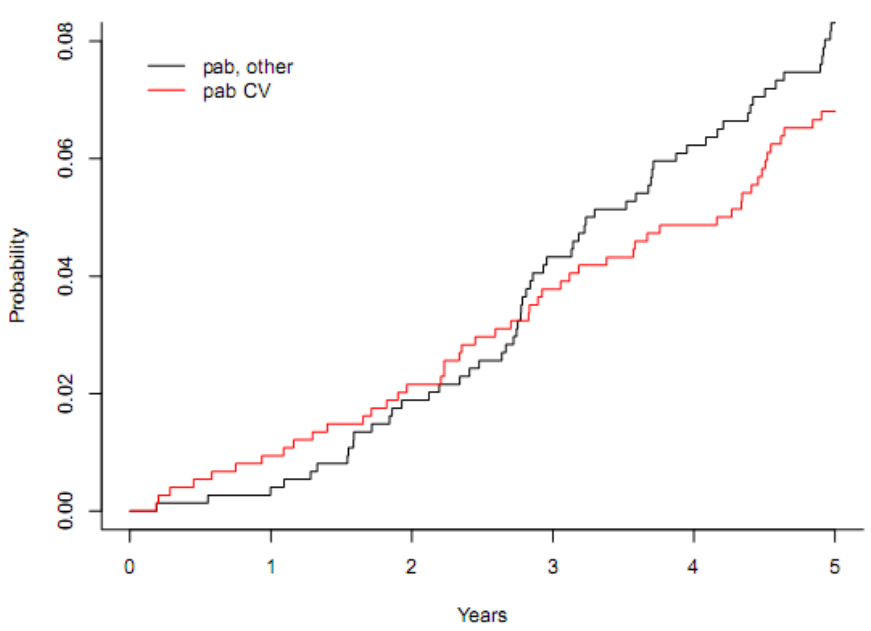
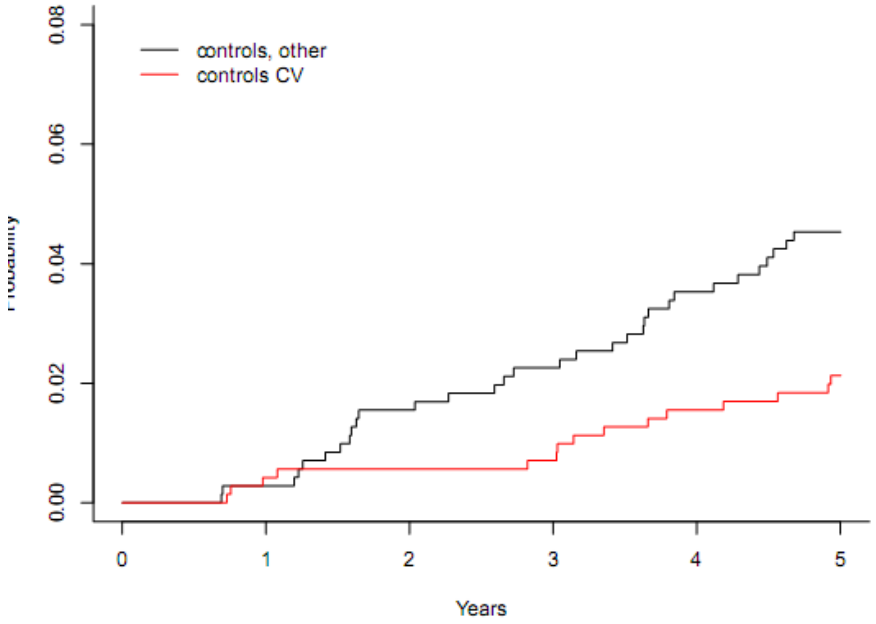
In spite of secondary prevention with platelet inhibition, RAS inhibition and statins, PAD remains an ominous disease.



Int Angiol 2017; 36: 216-27.

Time course of cardiovascular and non-cardiovascular death in patients with PAD and in control subjects:





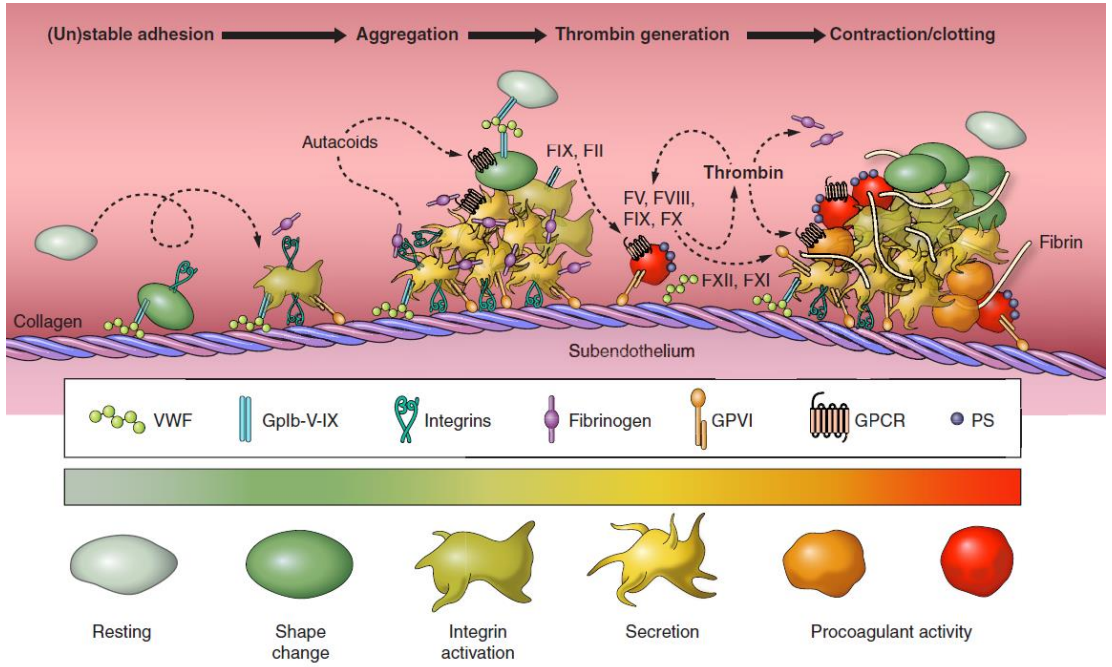
Int Angiol 2017; 36: 216-27.

Improvements in prevention of adverse cardio-vascular outcomes for patients with PAD

- Dual anitithrombotic treatment
- Intensified lipid-lowering treatment
- SGLT2-inhibitors are safe
- *Future: individualized approach*

Dual antihrombotic treatment

Platelet aggregation and fibrin deposition(= coagulation) are interlinked!



Major Adverse Limb Events and Mortality in Patients With Peripheral Artery Disease

The COMPASS Trial

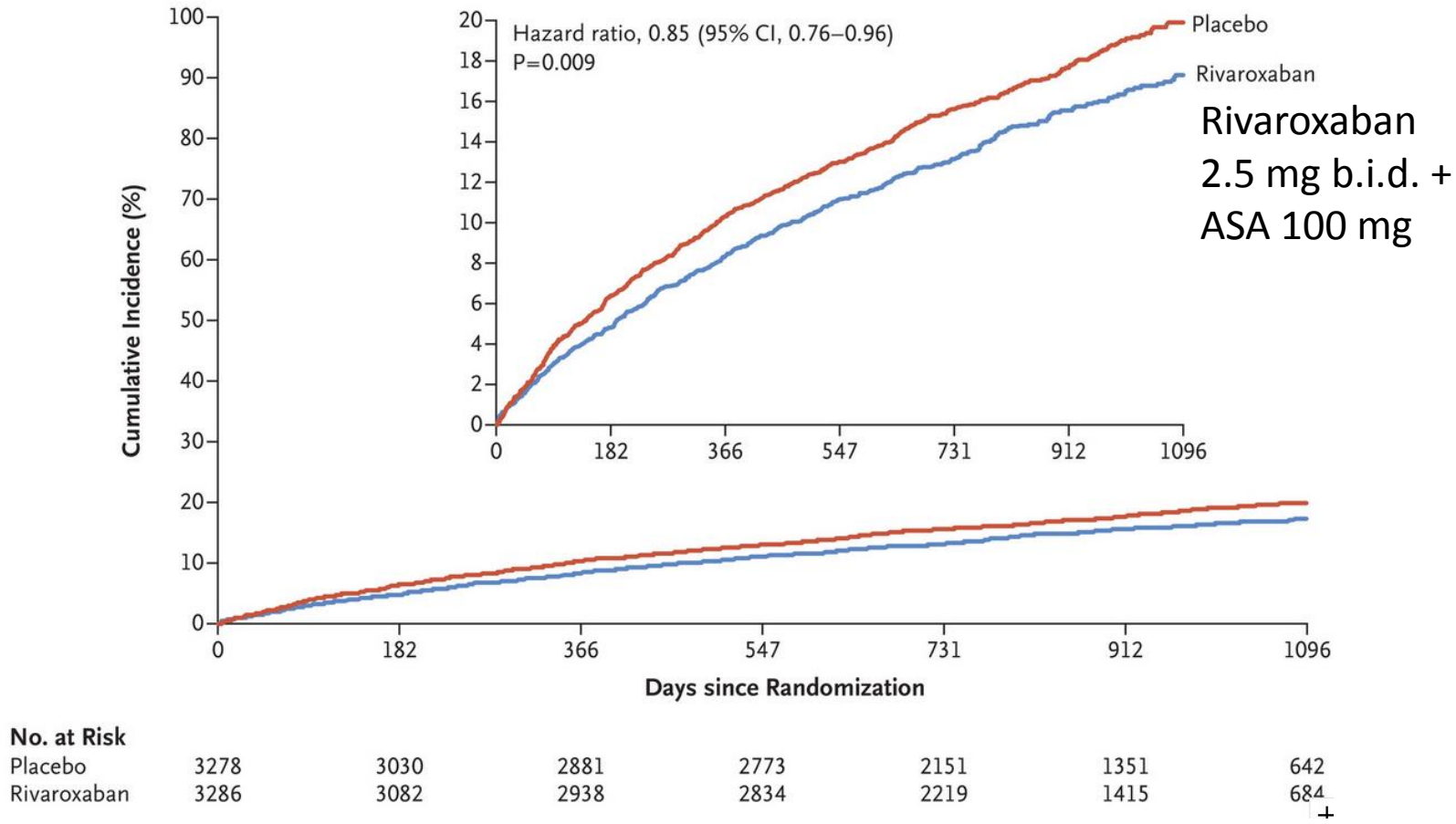
J Am Coll Cardiol 2018;71: 2306-2315

	Rivaroxaban 2.5 mg b.i.d. Plus Aspirin 100 mg (n = 2,139)	Aspirin 100 mg Plus Rivaroxaban Placebo (n = 2,123)	Rivaroxaban 2.5 b.i.d. Plus Aspirin 100 mg	
			HR (95% CI)	p Value
MALE*	32 (1.5)	56 (2.6)	0.57 (0.37-0.88)	0.01
Total vascular amputation	11 (0.5)	26 (1.2)	0.42 (0.21-0.85)	0.01
Major vascular amputation	5 (0.2)	15 (0.7)	0.33 (0.12-0.92)	0.03
All amputations	19 (0.9)	36 (1.7)	0.52 (0.30-0.91)	0.02
Vascular interventions†	117 (5.5)	150 (7.1)	0.76 (0.60-0.97)	0.03
Total outcomes for peripheral artery disease complications‡	132 (6.2)	169 (8.0)	0.76 (0.61-0.96)	0.02
Major bleeding	68 (3.2)	42 (2.0)	1.61 (1.09-2.36)	0.01
Severe bleeding§	24 (1.1)	18 (0.8)	1.32 (0.71-2.42)	0.38

Rivaroxaban in Peripheral Artery Disease after Revascularization

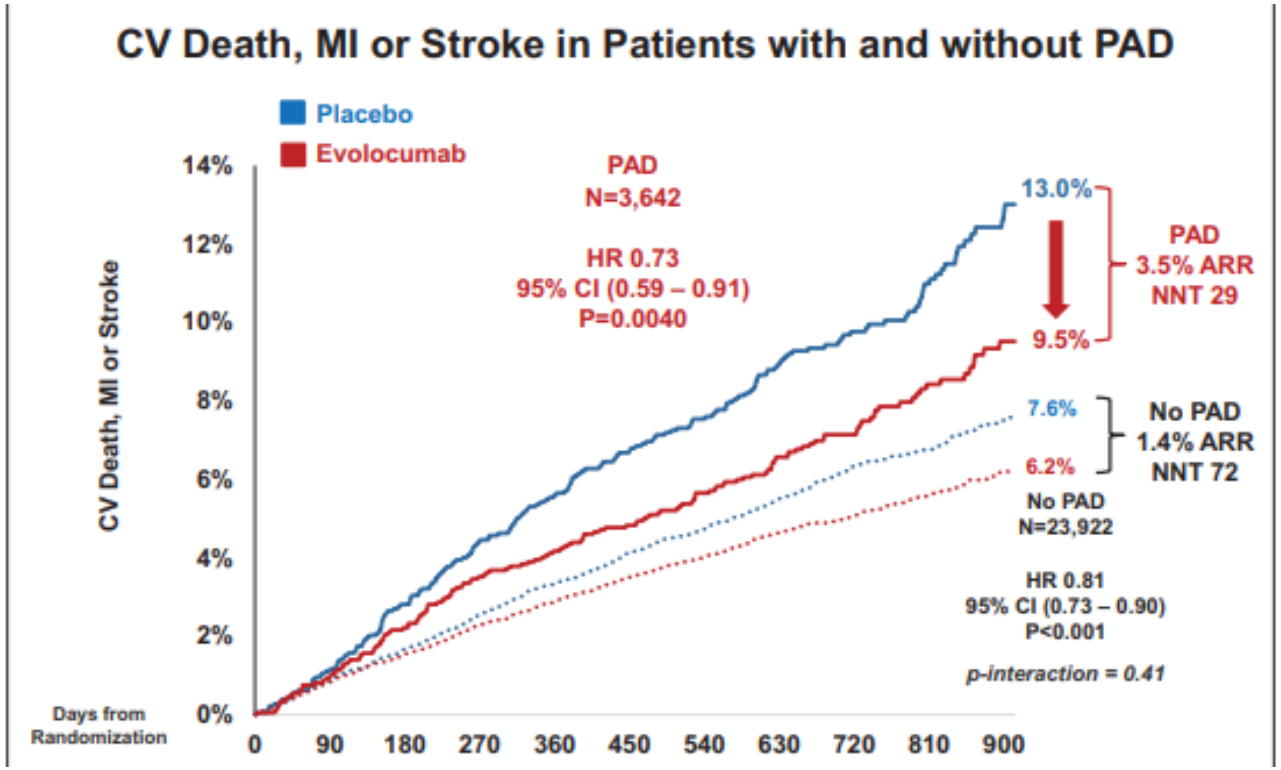
N Engl J Med 2020; 382: 1994-2004. DOI: 10.1056/NEJMoa2000052

acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or cardiovascular death.



Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease

Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)



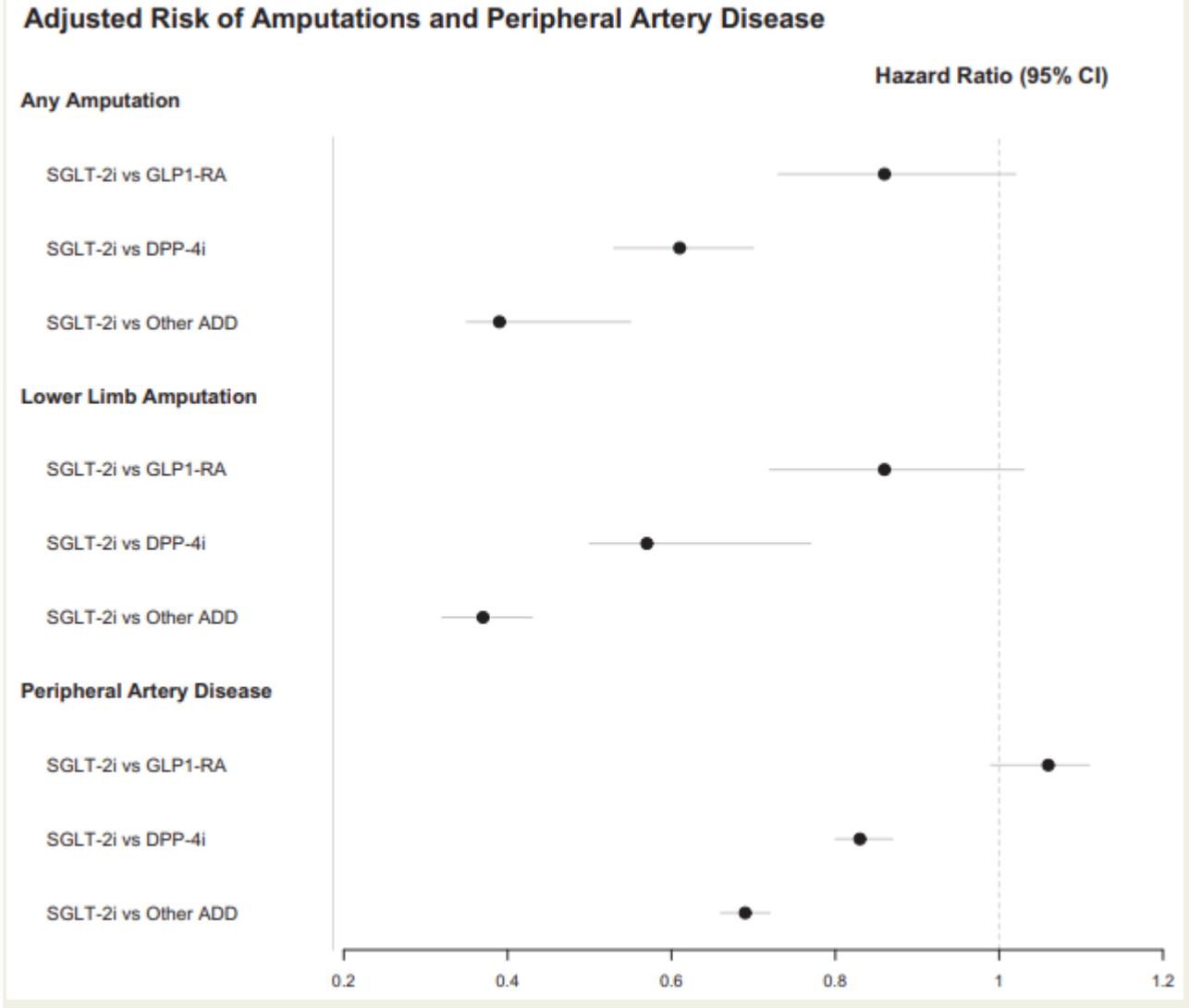
Circulation. 2018;137:338–350. DOI: 10.1161/CIRCULATIONAHA.117.032235

ESC European Society of Cardiology
European Heart Journal (2021) 42, 1728–1738
doi:10.1093/eurheartj/ehaa956

CLINICAL RESEARCH
Vascular biology and medicine

The association of amputations and peripheral artery disease in patients with type 2 diabetes mellitus receiving sodium-glucose cotransporter type-2 inhibitors: real-world study

SGLT2-inhibitors are safe !

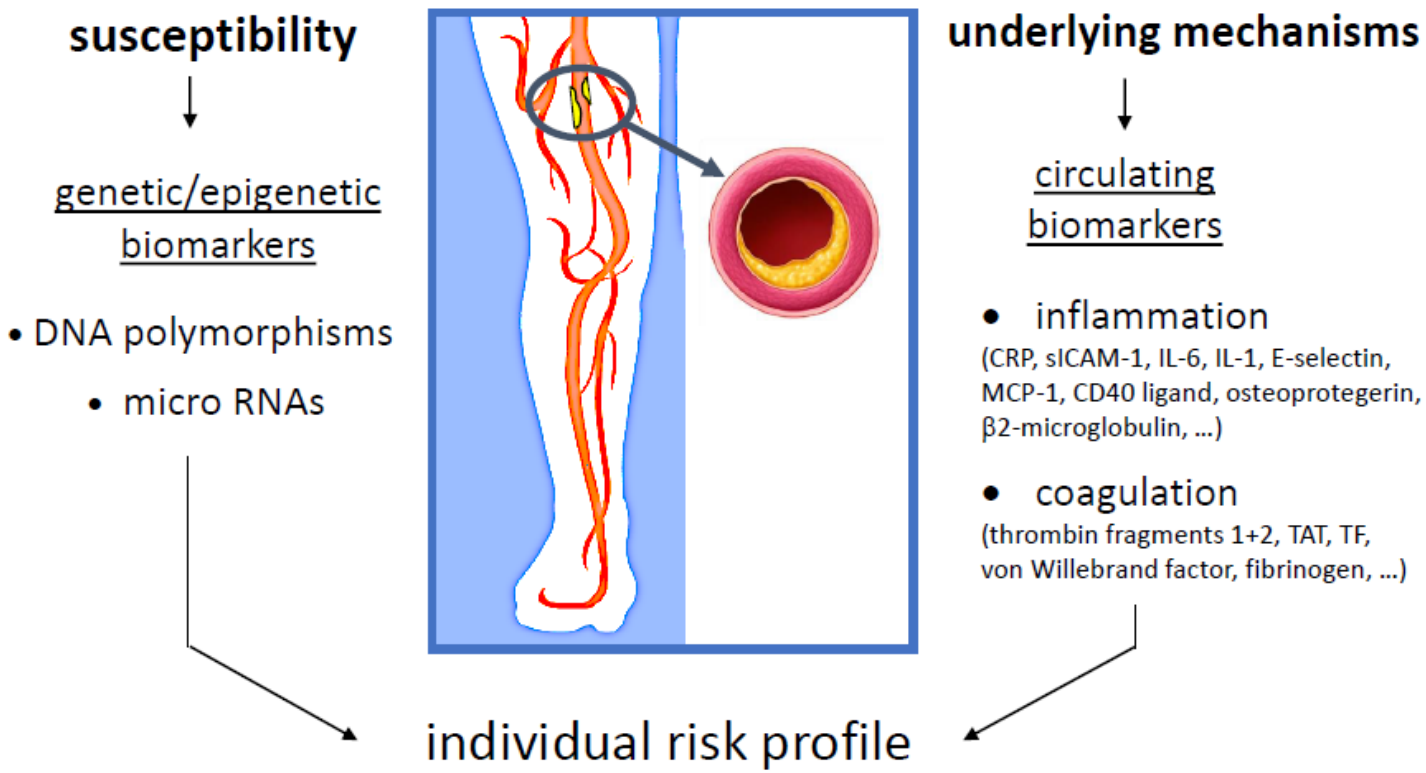


Review

Inflammatory and Prothrombotic Biomarkers, DNA Polymorphisms, MicroRNAs and Personalized Medicine for Patients with Peripheral Arterial Disease

Pavel Poredoš [1], Mišo Šabovič [1,2], Mojca Božič Mijovski [1,3], Jovana Nikolajević [1], Pier Luigi Antignani [4], Kosmas I. Paraskevas [5], Dimitri P. Mikhailidis [6] and Aleš Blinc [1,2,*]

Int. J. Mol. Sci. 2022; 23: 12054. https://doi.org/10.3390/ijms231912054



ESC European Society of Cardiology
European Heart Journal (2018) 39, 763–821
doi:10.1093/eurheartj/ehx095
ESC GUIDELINES

2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)

Intermittent claudication

Recommendations for the management of patients with intermittent claudication

Recommendations	Class[a]	Level[b]
On top of general prevention, statins are indicated to improve walking distance.[30,278]	I	A
In patients with intermittent claudication:		
• supervised exercise training is recommended[273,287–289]	I	A
• unsupervised exercise training is recommended when supervised exercise training is not feasible or available.	I	C
When daily life activities are compromised despite exercise therapy, revascularization should be considered.	IIa	C
When daily life activities are is severely compromised, revascularization should be considered in association with exercise therapy.[288,290]	IIa	B

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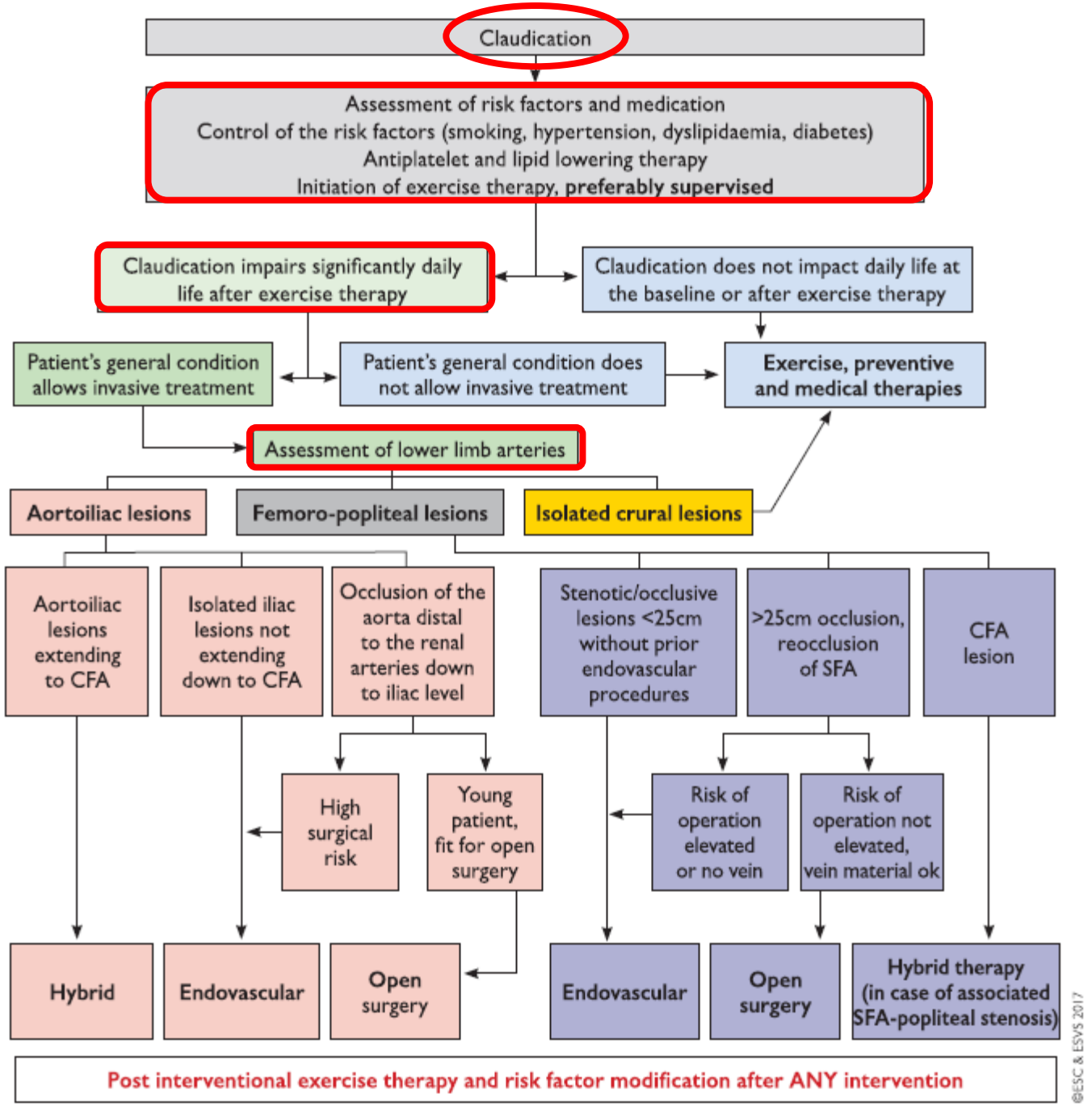
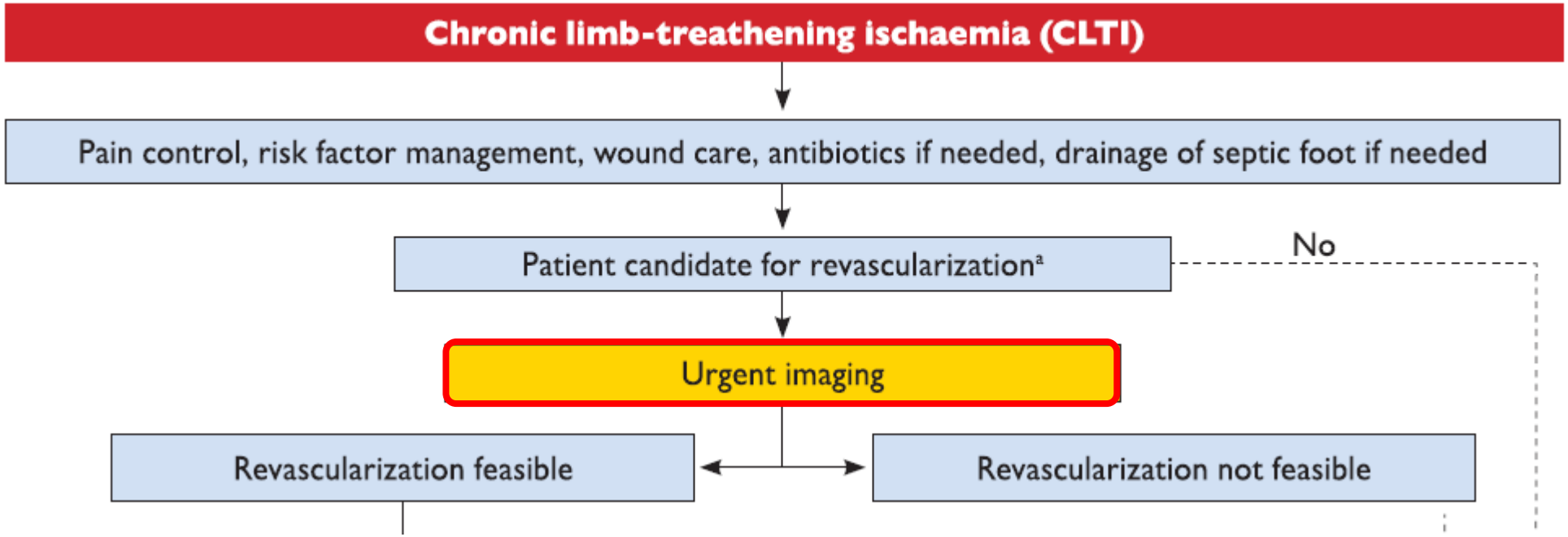


ESC European Society of Cardiology
European Heart Journal (2018) **39**, 763–821
doi:10.1093/eurheartj/ehx095

Chronic critical (=limb-threatening) limb ischemia

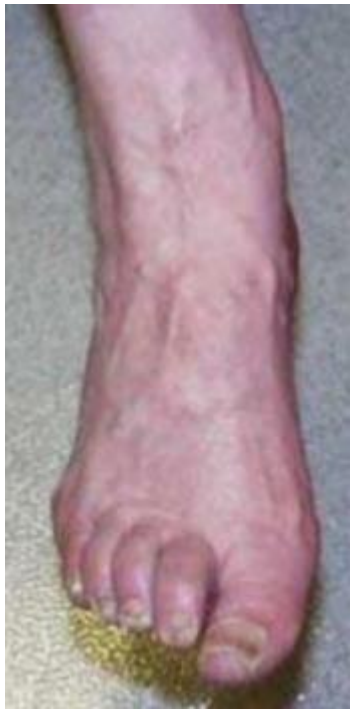


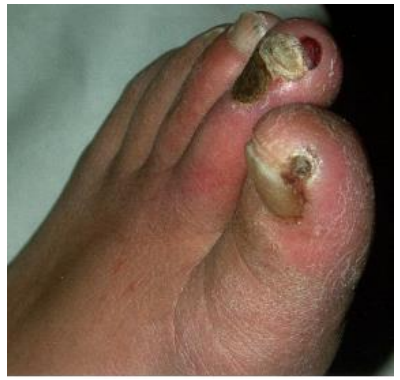
There is no single threshold for ankle pressure or toe pressure in suspected CLI

Presence of chronic ischemic rest pain plus
- ankle pressure <50 mmHg or
- toe pressure <30 mmHg

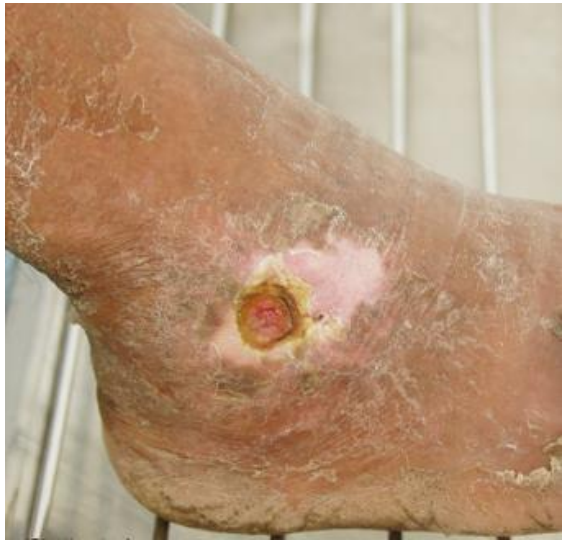
Presence of foot ulcers or gangrene plus
- ankle pressure <70 mmHg
- toe systolic pressure <50 mmHg or
- $TcPO_2$ <30 mmHg

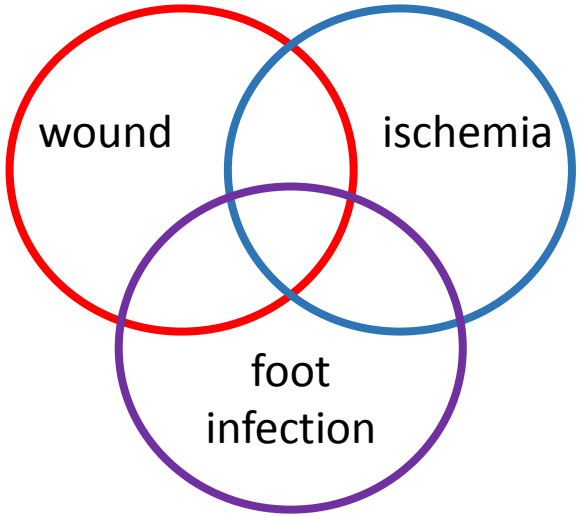
J Vasc Surg. 1995;22(4):485–490.

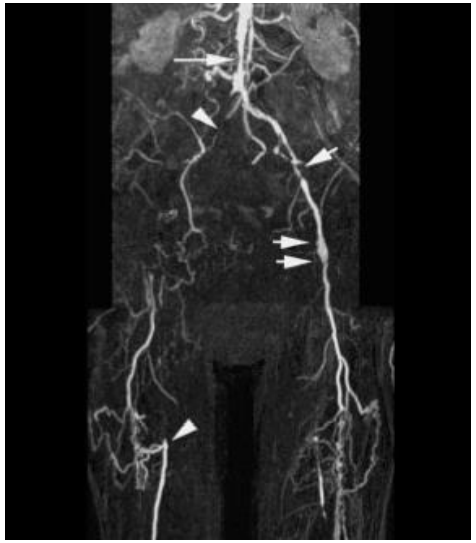


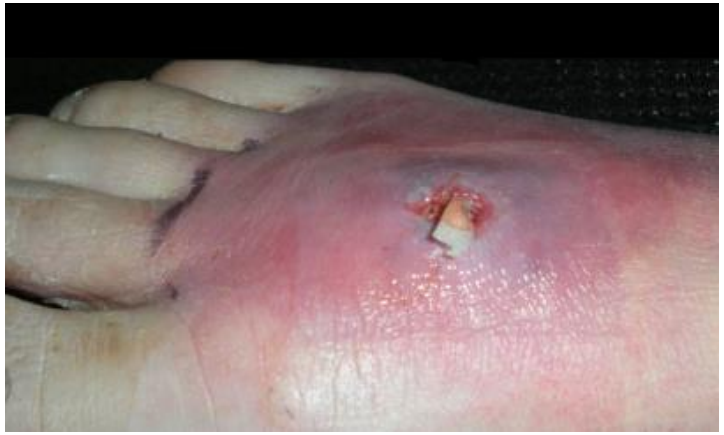


3 components of chronic limb-threatening ischemia









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		

Global vascular guidelines on the management of chronic limb-threatening ischemia

Journal of Vascular Surgery

DOI: https://doi.org/10.1016/j.jvs.2019.02.016

Patient with CLTI, candidate for revascularization

Obtain high quality angiographic imaging including ankle and foot

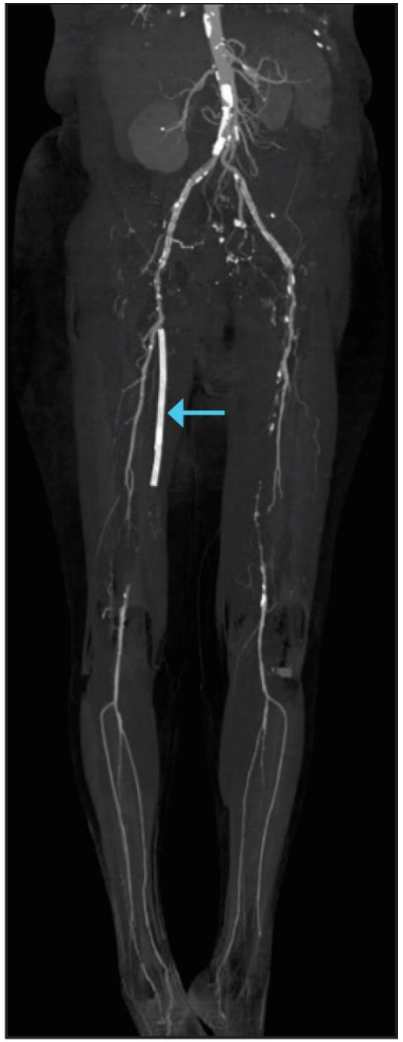
Define the target artery path (TAP)

Grade the femoropoliteal (FP) segment (Fig 5.2)

Grade the infrapopliteal (IP) segment (Fig 5.3)

Look up the overall GLASS stage (Table 5.3)

Define the preferred revascularization strategy by integrating patient risk, limb severity (WIfI) and anatomy (GLASS) according to the PLAN concept (Section 6)



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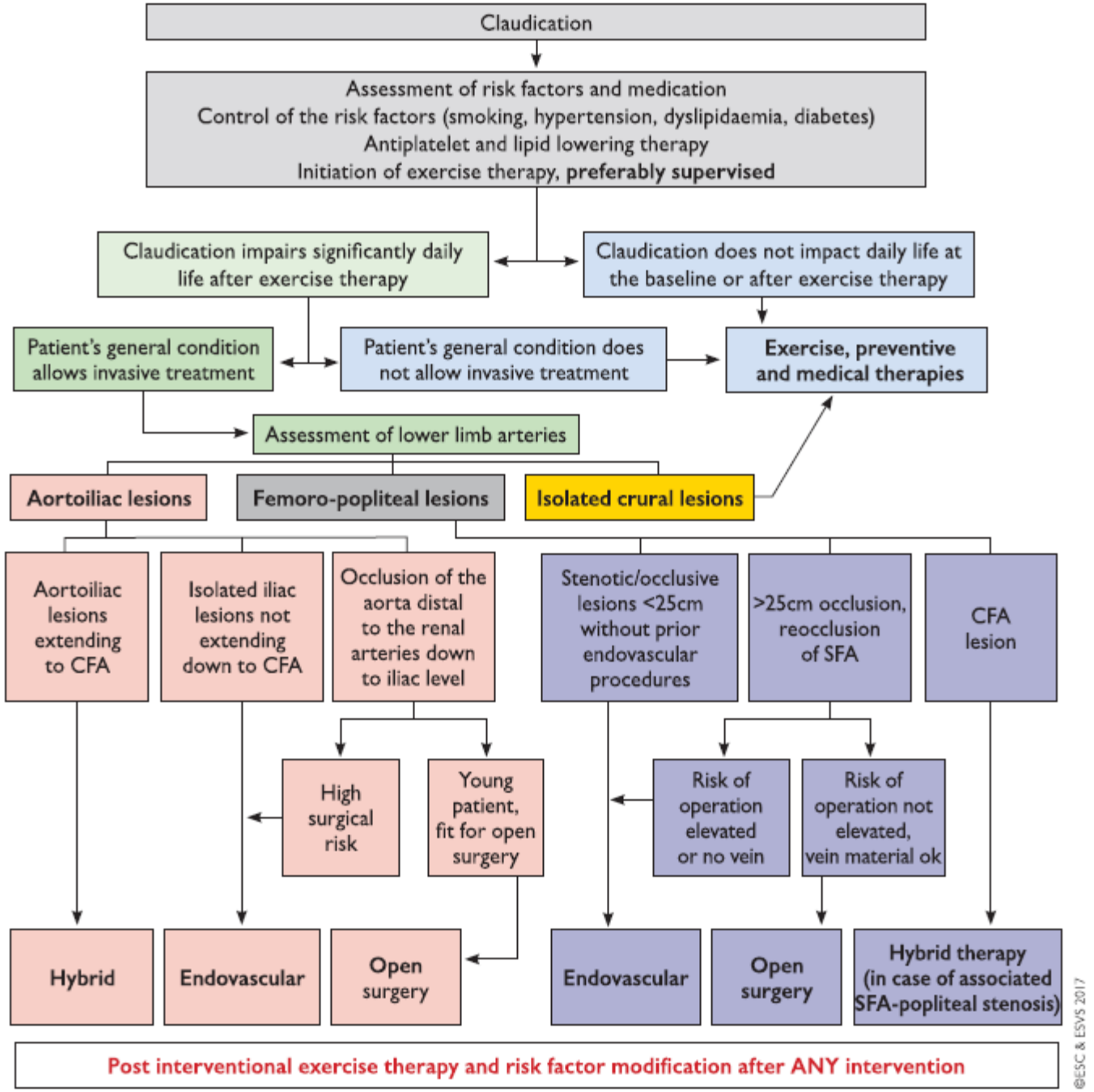
2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)

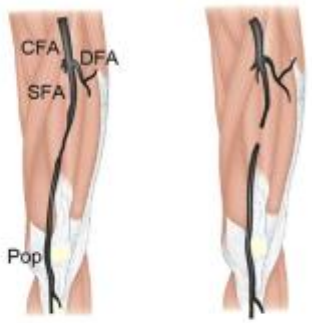
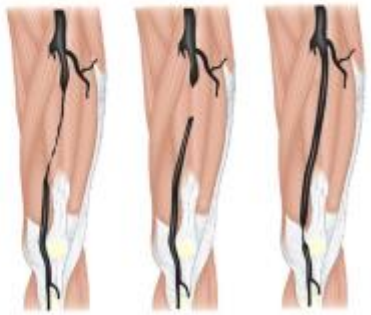


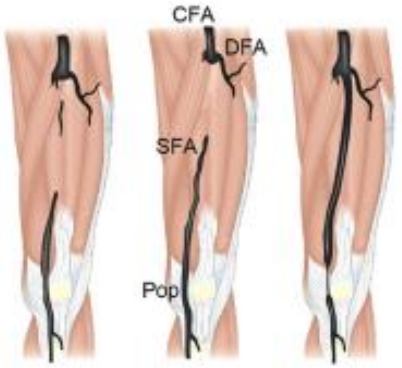
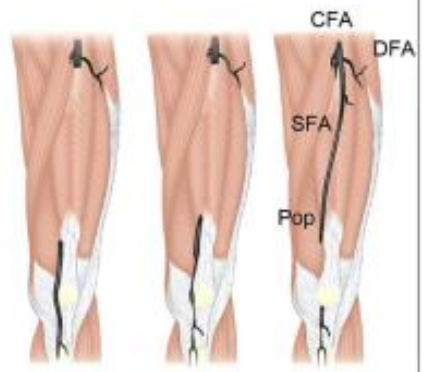
Global vascular guidelines on the management of chronic limb-threatening ischemia

Journal of Vascular Surgery

DOI: https://doi.org/10.1016/j.jvs.2019.02.016

Global Limb Anatomic Staging System (GLASS) for FP segment

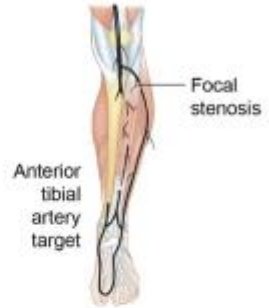
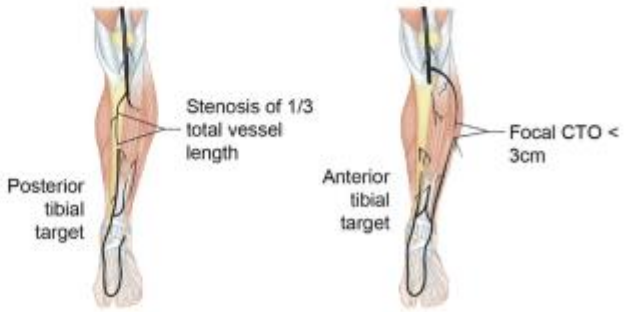
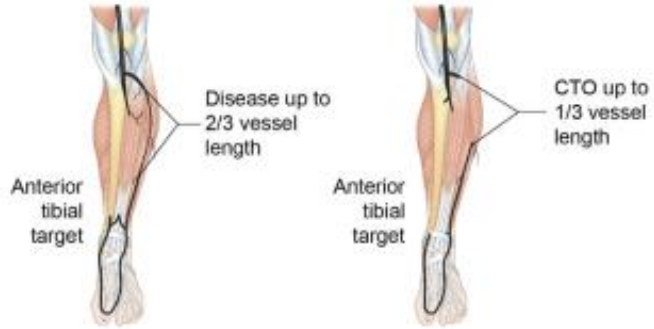
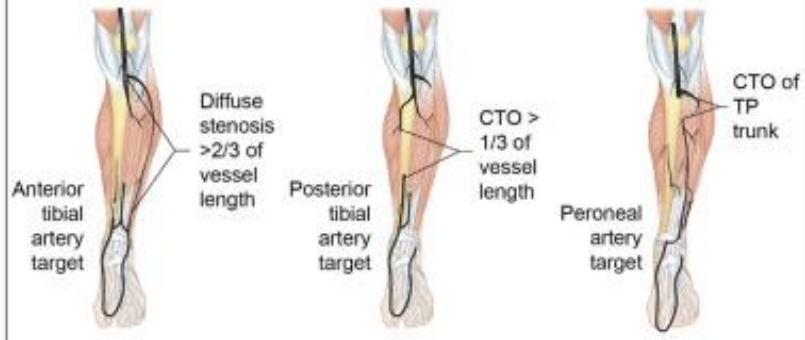
0	Mild or no significant (<50%) disease	
1	• Total length SFA disease <1/3 (<10 cm) • May include single focal CTO (< 5 cm) as long as not flush occlusion • Popliteal artery with mild or no significant disease	
2	• Total length SFA disease 1/3-2/3 (10-20 cm) • May include CTO totaling < 1/3 (10 cm) but not flush occlusion • Focal popliteal artery stenosis <2 cm, not involving trifurcation	

3	• Total length SFA disease >2/3 (>20 cm) length • May include any flush occlusion <20 cm or non-flush CTO 10-20 cm long • Short popliteal stenosis 2-5 cm, not involving trifurcation	
4	• Total length SFA occlusion > 20 cm • Popliteal disease >5 cm or extending into trifurcation • Any popliteal CTO	

Global vascular guidelines on the management of chronic limb-threatening ischemia

Journal of Vascular Surgery

DOI: https://doi.org/10.1016/j.jvs.2019.02.016

0	• Mild or no significant disease in the primary target artery path	
1	• Focal stenosis of tibial artery < 3cm	
2	• Stenosis involving 1/3 total vessel length • May include focal CTO (<3 cm) • Not including TP trunk or tibial vessel origin	
3	• Disease up to 2/3 vessel length • CTO up to 1/3 length (may include tibial vessel origin but not tibioperoneal trunk)	
4	• Diffuse stenosis > 2/3 total vessel length • CTO > 1/3 vessel length (may include vessel origin) • Any CTO of tibioperoneal trunk if AT is not the target artery	

The prediction value of GLASS: differences between endovascular intervention and surgical bypass.

Systematic review (2204 patients) Eur J Vasc Endovasc Surg. 2022;64:32. Epub 2022 Apr 11.

- Following endovascular intervention, the pooled estimates for amputation-free survival and limb salvage were worse for GLASS 3 compared with GLASS 1/2, and major adverse limb events (MALE) were increased for higher GLASS stages. Immediate technical failure also increased with higher GLASS stage (GLASS 1: 3.9 %; GLASS 2: 5.3 %; GLASS 3: 27.9 %).

- Following bypass surgery, observed differences in amputation-free survival, limb salvage rate, and MALE for GLASS 3 versus GLASS 1/2 were not significant.

- For GLASS 2 or GLASS 3, but not GLASS 1, the pooled rate of MALE was significantly better for bypass surgery compared with endovascular therapy.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia

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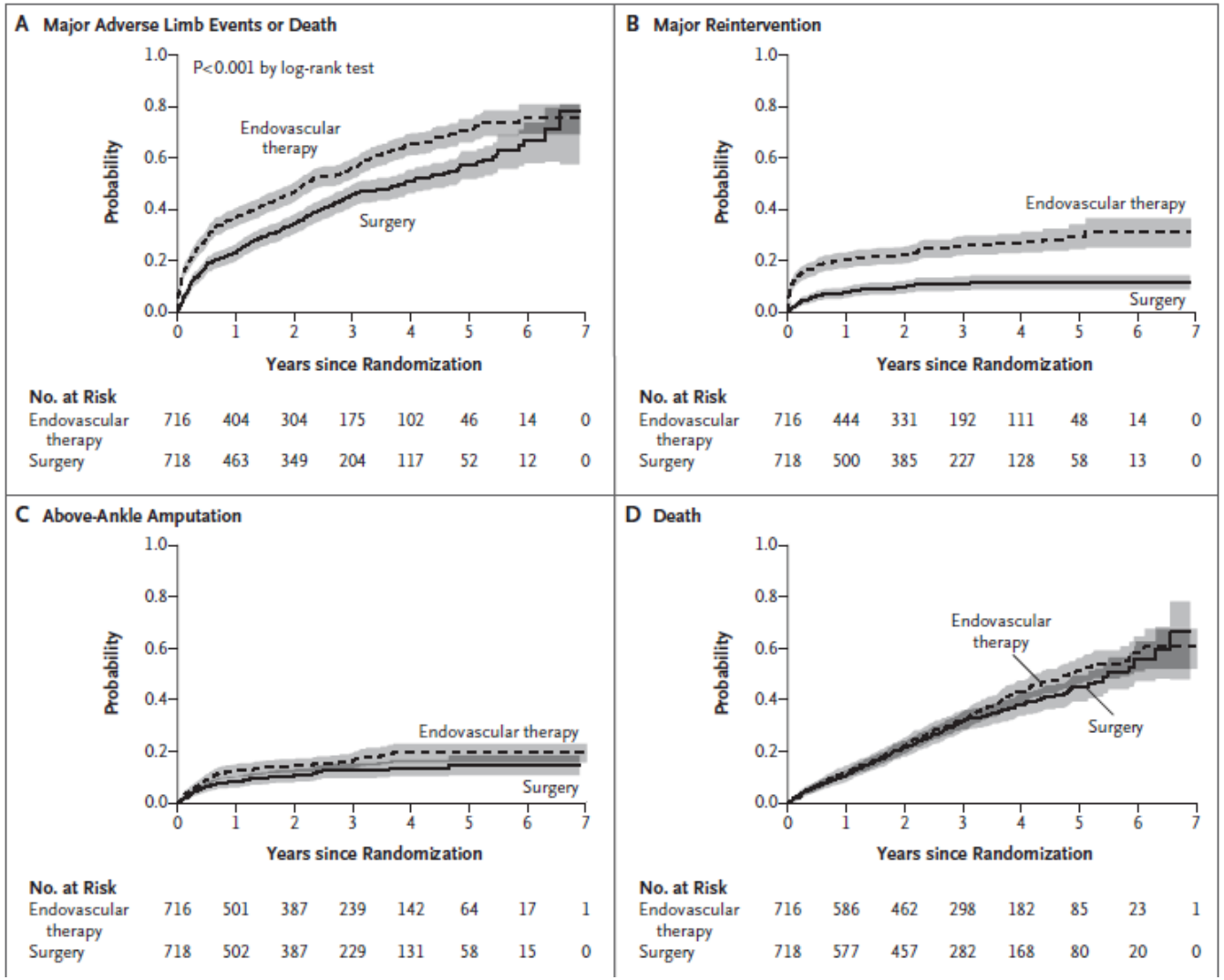
CONCLUSIONS

Among patients with CLTI who had an adequate great saphenous vein for surgical revascularization (cohort 1), the incidence of a major adverse limb event or death was significantly lower in the surgical group than in the endovascular group. Among the patients who lacked an adequate saphenous vein conduit (cohort 2), the outcomes in the two groups were similar. (Funded by the National Heart, Lung, and Blood Institute; BEST-CLI ClinicalTrials.gov number, NCT02060630.)



Global vascular guidelines on the management of chronic limb-threatening ischemia

Joint guidelines of the Society for Vascular Surgery, European Society for Vascular Surgery, and World Federation of Vascular Societies

J Vasc Surg 2019;69:3S-125S

CLTI in patients with no option for revascularization

Recommendations	Grade	Level of evidence	Key references
Consider SCS to reduce the risk of amputation and to decrease pain in carefully selected patients (eg, rest pain, minor tissue loss) in whom revascularization is not possible.	2 (Weak)	B (Moderate)	Ubbink,[106] 2013
Do not use LS for limb salvage in CLTI patients in whom revascularization is not possible.	2 (Weak)	C (Low)	Karanth,[107] 2016
Consider IPC therapy in carefully selected patients (eg, rest pain, minor tissue loss) in whom revascularization is not possible.	2 (Weak)	B (Moderate)	Abu Dabrh,[4] et al 2015

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Recommendations	Grade	Level of evidence	Key references
Do not offer prostanoids for limb salvage in CLTI patients. Consider offering selectively for patients with rest pain or minor tissue loss and in whom revascularization is not possible.	2 (Weak)	B (Moderate)	Vietto,[108] 2018
Do not offer vasoactive drugs or defibrinating agents (ancrod) in patients in whom revascularization is not possible.	1 (Strong)	C (Low)	Smith,[109] 2012
Do not offer HBOT to improve limb salvage in CLTI patients with severe, uncorrected ischemia (eg, WIfI ischemia grade 2/3).	1 (Strong)	B (Moderate)	Kranke,[110] 2015 Game,[111] 2016 Santema,[112] 2018
Recommendation			
Continue to provide optimal wound care until the lower extremity wound is completely healed or the patient undergoes amputation.			Good practice statement

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Trials of gene therapy and cell therapy for CLTI have so far been disappointing.

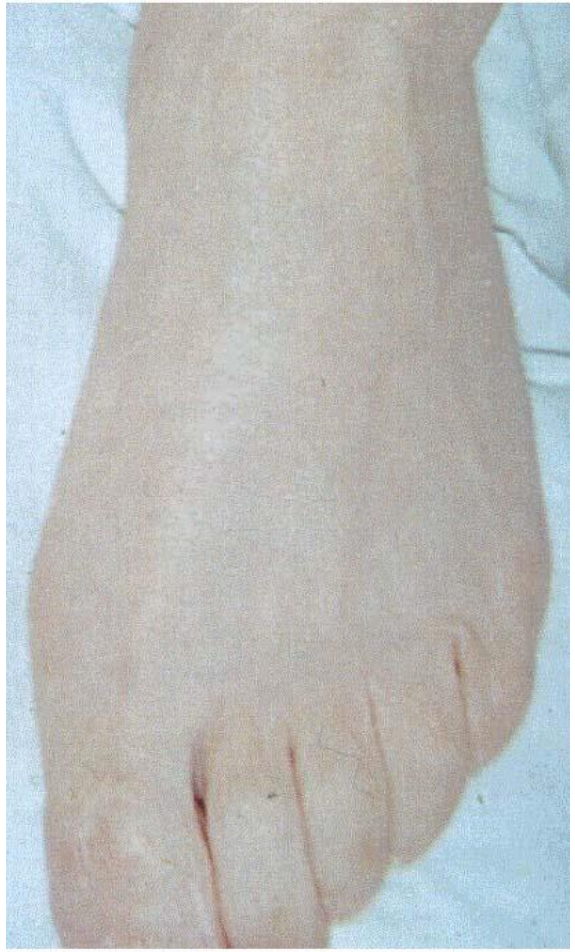
Trial	Treatment	No. of participants	End points: AFS at 12 months (treated vs placebo)	End points: Other end points	End points: Treatment vs placebo	Reference
Gene therapy						
TALISMAN	FGF	125	73% vs 48% ($P = .009$)			Nikol,[522] 2008
TAMARIS	FGF	525	63% vs 67% ($P = .48$)			Belch,[524] 2011
HGF-STAT	HGF	104	No difference	Change in $TcPo_2$ at 6 months	25.2 mm Hg in high-dose group vs 9.4 mm Hg in placebo group ($P = .0015$)	Powell,[526] 2008
HGF-0205	HGF	27	No difference	Change in TBI at 6 months	+0.05 vs −0.17 ($P = 0.047$)	Powell,[525] 2010
Shigematsu et al	HGF	40	No difference	Improvement in rest pain or reduction in ulcer size	70.4% vs 30.8% ($P = .014$)	Shigematsu,[527] 2010
Cell therapy						
Iafrati et al	Autologous bone marrow	97	No difference	Improvement in pain at 6 months	58% vs 26% ($P = .025$)	Iafrati,[528,530] 2011, 2016
				Improvement in TBI at 6 months	0.48 vs 0.012 ($P = .02$)	
RESTORE-CLI	Expanded autologous stem cells	72	No difference	Combined outcomes (1-year freedom from major amputation, mortality, increased wound size, new gangrene)	40% vs 67% ($P = .045$)	Powell,[532] 2012
MOBILE	Autologous bone marrow cells	152	80% vs 69% ($P =$ not significant)			Murphy,[529,531] 2011, 2016
JUVENTAS	BMMNCs	160	77% vs 84% (at 6 months) No difference	Major amputation at 6 months	19% vs 13% ($P =$ not significant)	Teraa,[535] 2015

AFS, Amputation-free survival; *BMMNCs*, bone marrow mononuclear cells; *FGF*, fibroblast growth factor; *HGF*, hepatocyte growth factor; *JUVENTAS*, Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation; *MOBILE*, MarrowStim treatment of limb ischemia in subjects with severe peripheral arterial disease; *TBI*, toe-brachial index; *$TcPo_2$*, transcutaneous oximetry.

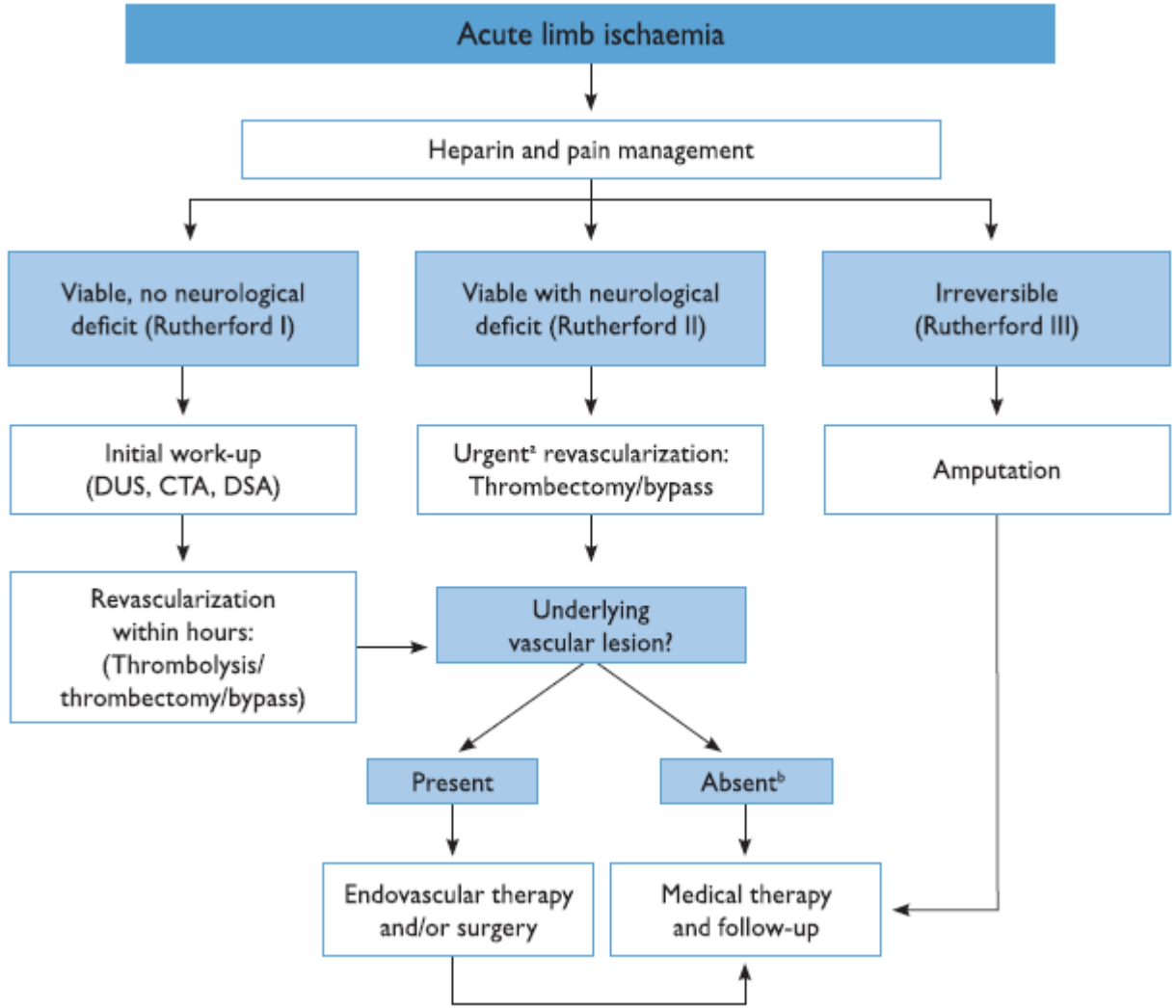
ESC European Society of Cardiology
European Heart Journal (2018) 39, 763–821
doi:10.1093/eurheartj/ehx095

2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)

Acute limb ischemia



- Painful
- Pale
- Pulseless
- Paresthetic
- Paralytic



Conclusions

- PAD is a common manifestation of atherosclerosis.
- In the early stages of PAD, the patient‘s prognosis is dominated by the risk of major adverse cardiovascular events (MACE) in the coronary and cerebral circulation(→ prevention!)
- In the advanced stages of PAD the patient‘s prognosis is dominated by major adverse limb events (MALE > MACE) (→ optimal revascularization strategies + prevention!)


Thank you for your attention!