DIPARTIMENTO DI MEDICINA-DIMED
UNIVERSITA' DEGLI STUDI DI PADOVA

MASTER MEDICINA VASCOLARE E MALATTIE TROMBOTICO-EMORRAGICHE

Direttore PROF. PAOLO SIMIONI

AA 2024-25

TERAPIA MEDICA DELLE MALATTIE VASCOLARI ARTERIOSE

Arteriopatia periferica arti inferiori (PAD)

Inquadramento clinico e terapia medica

13 12 2024

Adriana Visonà

già Direttore UOC Angiologia Azienda ULSS 2 Marca Trevigiana

Past President SIAPAV e ESVM

adrianavisona@gmail.com

PAD

Definizione ed Epidemiologia

PAD: Un’epidemia orfana

- Si stima che circa 240 milioni di persone al mondo soffrano di PAD. Sebbene la PAD condivida con la coronaropatia e con l’ischemia cerebrale il terreno predisponente dell’arteriosclerosi, si fa crescente l’evidenza che **PAD rappresenti una connotazione peculiare della malattia aterosclerotica,** caratterizzata da un alto rischio non solo di complicanze a carico degli arti **(MALE),** ma anche di eventi avversi cardiovascolari **(MACE).**
- La **rivascolarizzazione**, anche se migliora la sintomatologia della maggior parte dei pazienti, **non impedisce che molti sviluppino successivamente** complicanze vascolari, tra cui **l’ischemia acuta dell’arto**, che è attesa con una frequenza **4 volte superiore** che in soggetti che non hanno subito la rivascolarizzazione
- Studi recenti hanno dimostrato che **strategie anti-trombotiche più potenti** riducono il **MACE e il MALE** ma aumentano il **sanguinamento** nei pazienti con PAD. L'identificazione **di sottogruppi di pazienti con PAD a più alto rischio** di **MACE e MALE** che ottengono maggiori benefici assoluti per compensare il rischio di sanguinamento è di interesse clinico, come pure **la stratificazione del rischio di sanguinamento**, che deve fare i conti con eterogeneità del rischio in base alle caratteristiche cliniche

PAD (Peripheral Artery Disease) - Definizioni

"Peripheral arterial diseases (PADs)"

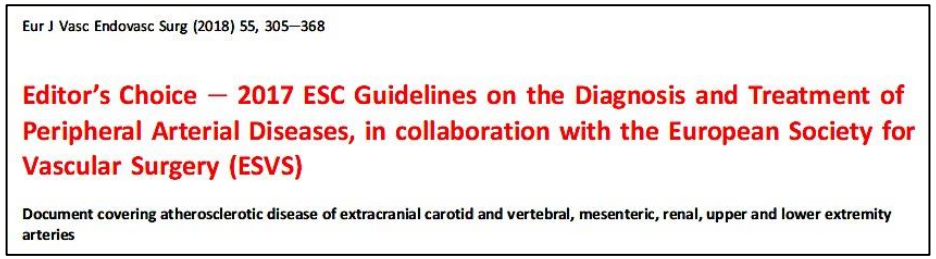
Tutte le malattie che coinvolgono le arterie, escluse le coronarie e l'aorta

- arterie degli arti inferiori
- arterie carotidi e vertebrali
- arterie arti superiori
- arterie mesenteriche
- arterie renali

"Peripheral arterial disease (PAD)"

Arteriopatia obliterante degli arti inferiori

European Society for Vascular Medicine **(ESVM).** Guideline on peripheral arterial disease. **Vasa. 2019**;48, Supplement 102, doi 10.1024/0301-1526/a000834.


Eur J Vasc Endovasc Surg (2018) 55, 305–368

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

Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries

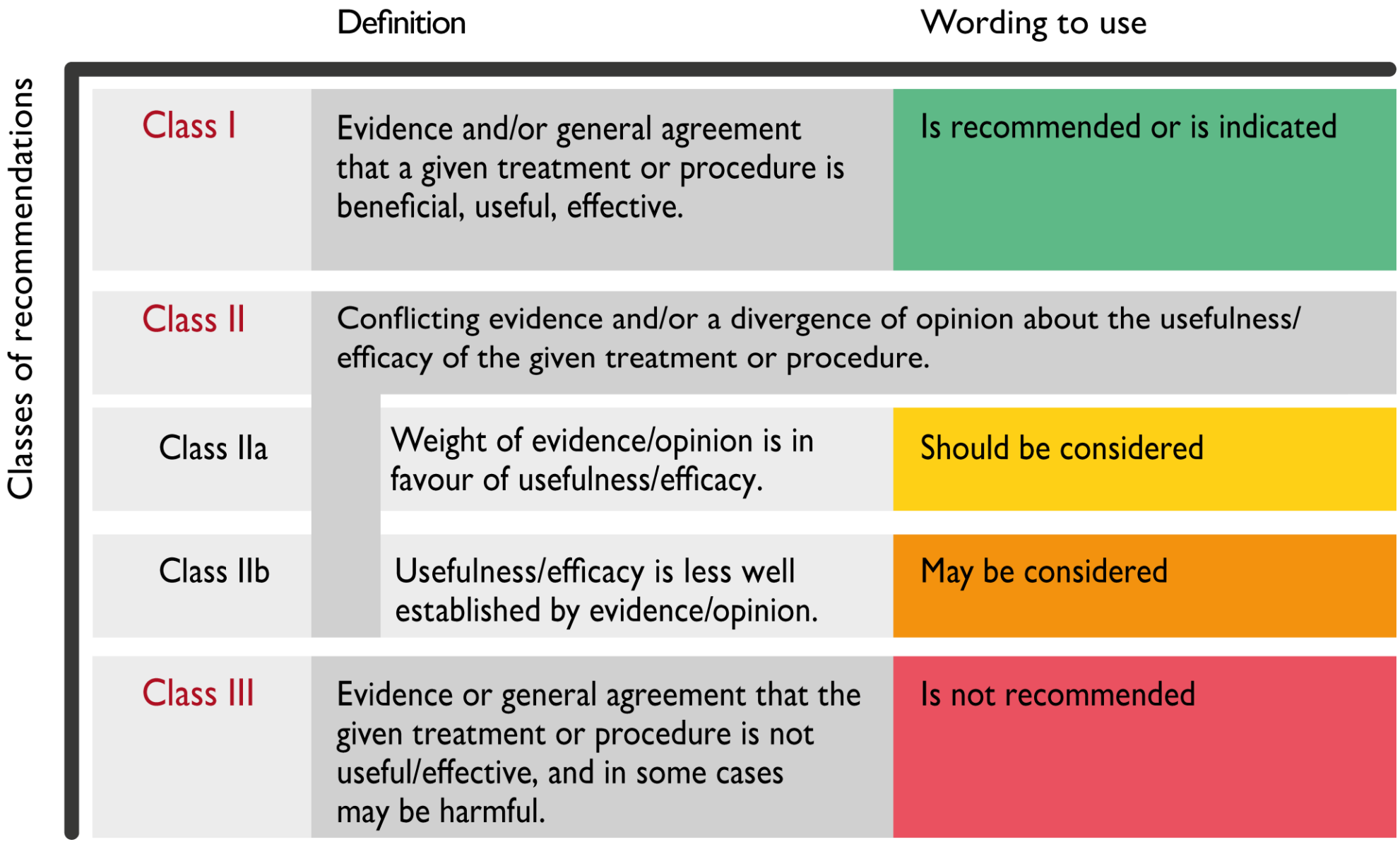
2024 ESC Guidelines for the management of peripheral arterial and aortic diseases

Authors/Task Force Members:

Lucia Mazzolai (Chairperson) (Switzerland), Jose F. Rodriguez-Palomares (Chairperson) (Spain), Gisela Teixido-Tura (Task Force Co-ordinator) (Spain), Stefano Lanzi (Task Force Co-ordinator) (Switzerland), Vinko Boc (Slovenia), Eduardo Bossone (Italy), Marianne Brodmann[1] (Austria), Alessandra Bura-Rivière (France), Julie De Backer[2] (Belgium), Sebastien Deglise (Switzerland), Alessandro Della Corte (Italy), Christian Heiss (United Kingdom), Marta Kałużna-Oleksy (Poland), Donata Kurpas (Poland), Carmel M. McEniery (United Kingdom), Tristan Mirault (France), Agnes A. Pasquet (Belgium), Alex Pitcher (United Kingdom), Hannah A.I. Schaubroeck (Belgium), Oliver Schlager (Austria), Per Anton Sirnes (Norway), Muriel G. Sprynger (Belgium), Eugenio Stabile (Italy), Françoise Steinbach (France), Matthias Thielmann (Germany), Roland R.J. van Kimmenade (Netherlands), Maarit Venermo (Finland).

[1]Representing the European Society of Vascular Medicine (ESVM).
[2] Representing the European Reference Network on Rare Multisystemic Vascular Diseases (VASCERN).

ESC Classes of recommendations



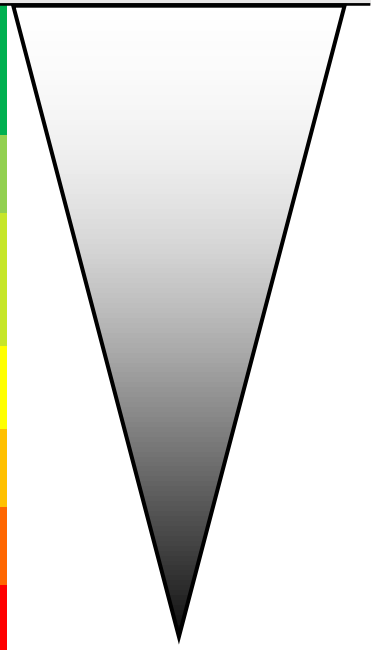
2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

ESC Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Progressive Atherosclerosis Underlying Lower Extremity PAD Results in a Spectrum of Limb Symptoms

	Fontaine stage[1–3]		Rutherford category[1–3]		Proportion of patients[3]
	I	Asymptomatic	0	Asymptomatic	
	II	IIa Non-disabling intermittent claudication*	1	Mild claudication*	
			2	Moderate claudication*	
		IIb Disabling intermittent claudication*	3	Severe claudication*	
CLI	III	Ischaemic rest pain	4	Rest pain	
CLI	IV	Ulceration or gangrene	5	Minor tissue loss	
CLI			6	Major tissue loss	

- ALI is caused by either native atherosclerotic plaque disruption and thrombus formation, or *in situ* stent or graft thrombosis in revascularized patients[4]

*Or atypical leg pain

1. Aboyans V *et al*, *Eur Heart J* 2017: doi:10.1093/eurheartj/ehx095; 2. Aboyans V *et al*, *Eur J Vasc Endovasc Surg* 2017: doi:10.1016/j.ejvs.2017.07.018; 3. Norgren L *et al*, *J Vasc Surg* 2007;45:S5–S67; 4. Hirsch AT *et al, Vasc Med* 2016;21:535–538

Ischemia acuta 6 P di Pratt

Pain	Dolore
Pallor	Pallore
Pulselessness	Assenza dei polsi periferici
Paresthesia	Parestesie (disestesie, iperestesia, ipo-anestesia)
Paralysis	Paralisi periferica (deficit motorio più o meno esteso)
Poikilothermia	Freddo

Peripheral arterial disease categorized according to clinical presentation

Clinical characteristics of PAD	Rutherford classification		Fontaine classification	
	Category	Signs and symptoms	Stage	Signs and symptoms
Asymptomatic PAD	0	Asymptomatic	I	Asymptomatic
Symptomatic (effort-related) PAD	1	Mild claudication	IIa	Non-disabling intermittent claudication
	2	Moderate claudication	IIb	Disabling intermittent claudication
	3	Severe claudication		
Chronic limb-threatening Ischaemia	4	Ischaemic rest pain	III	Ischaemic rest pain
	5	Minor tissue loss	IV	Ischaemic ulceration or gangrene
	6	Major tissue loss		

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Prevalenza stimata di PAD nel mondo

Pazienti con PAD ➡ 202.000.000 nel mondo (2010)

236.000.000 nel mondo (5,56%) (2015)

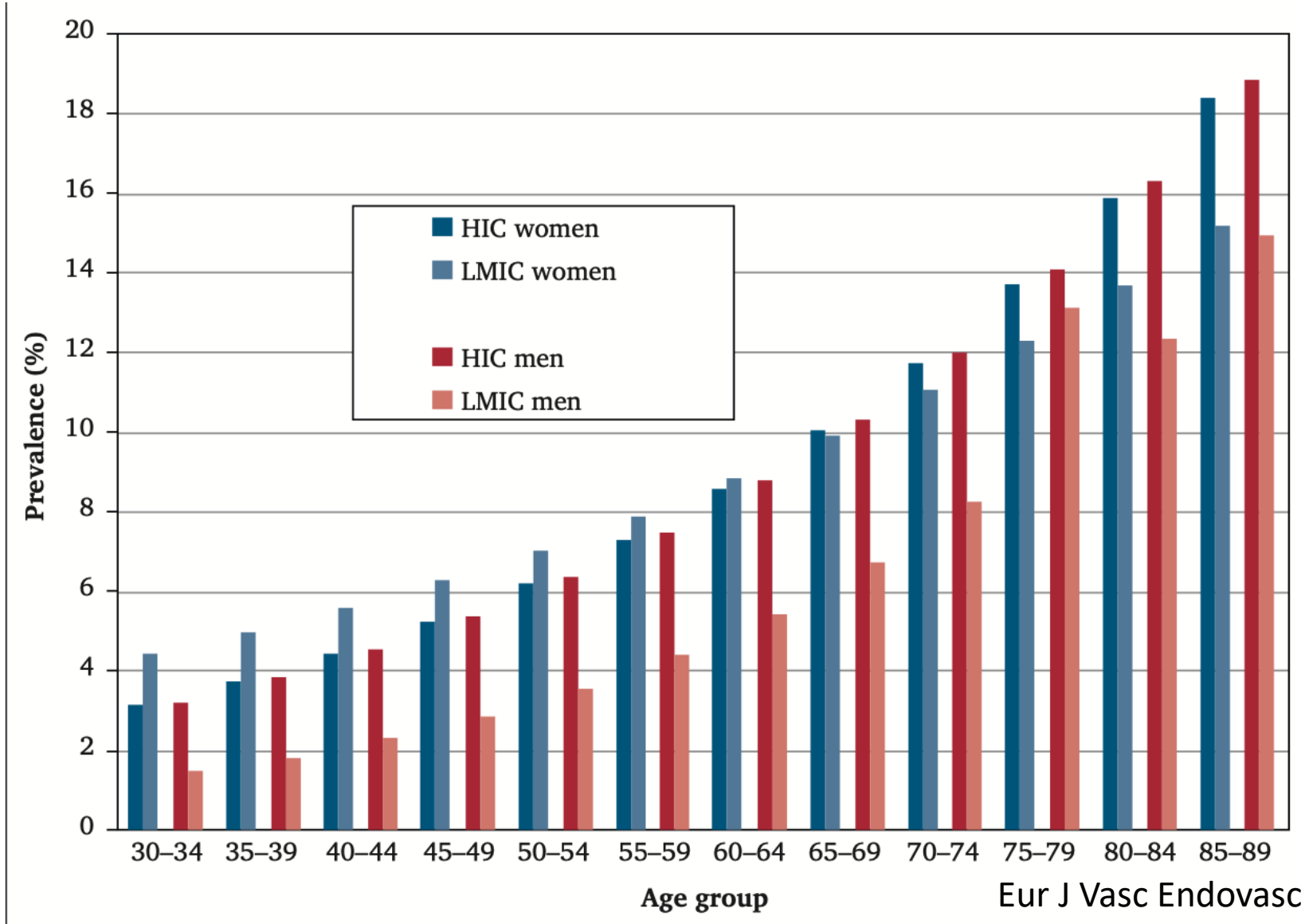
Bangladesh, Brasile, Cina, Francia, Germania, India, Indonesia, Italia, Giappone, Messico, Pakistan, Russia, Spagna, Regno Unito, USA

⬇

Più di 2/3 dei casi

Fowkes FGR, et al. Lancet 2013;382:1329-40
Song P, et al. Lancet 2019;7:1020-30

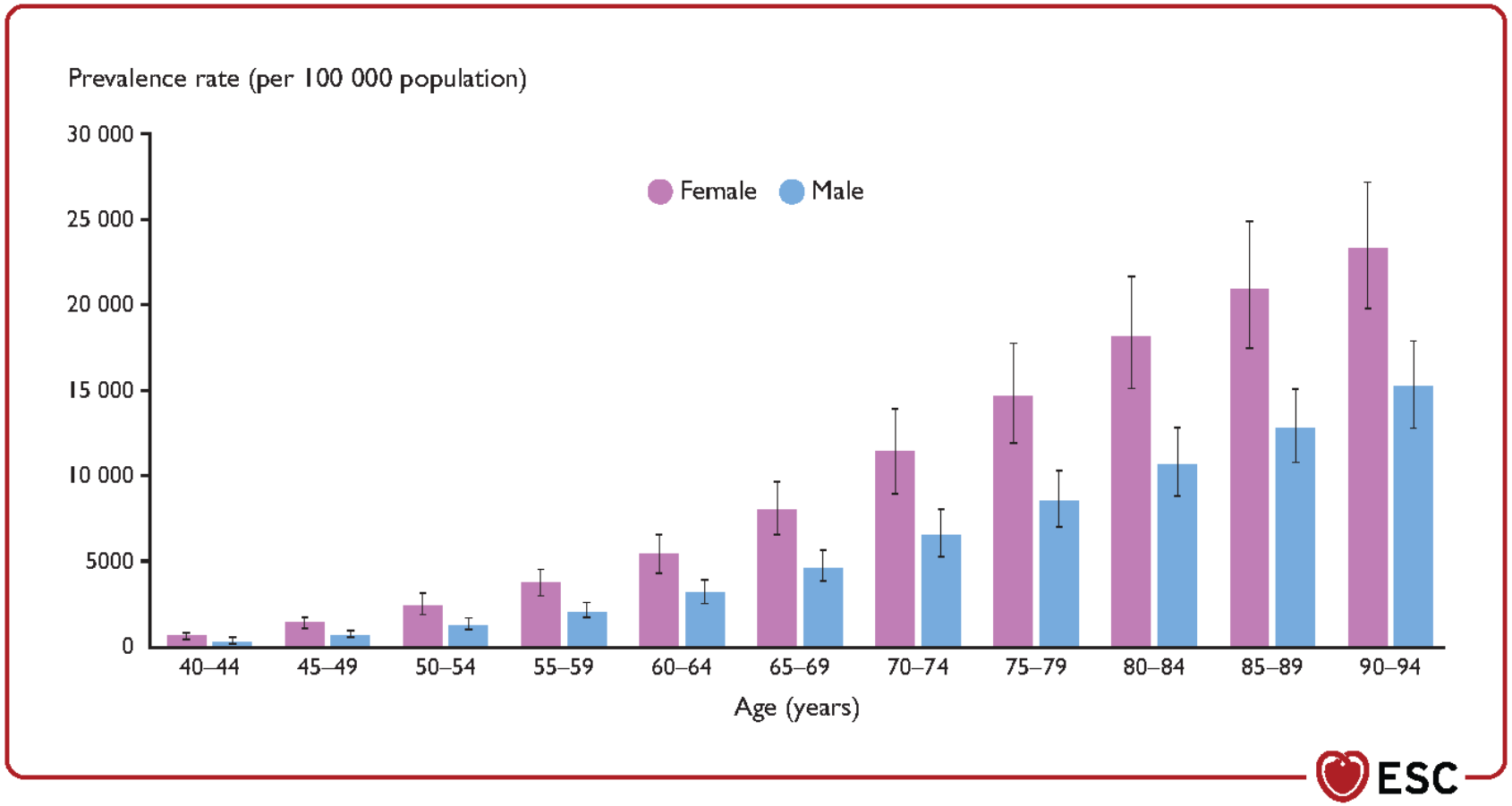
Prevalence of peripheral artery disease (PAD; ankle-brachial index [ABI] <0.9) by age and sex in high-income countries (HICs) and in low- and middle-income countries (LMICs)



Eur J Vasc Endovasc Surg (2019) 58, S1eS109

Figure 2

Estimated specific prevalence of peripheral arterial disease, by sex, in people aged 40 years and older



2024 ESC Guidelines for the management peripheral arterial and aortic diseases
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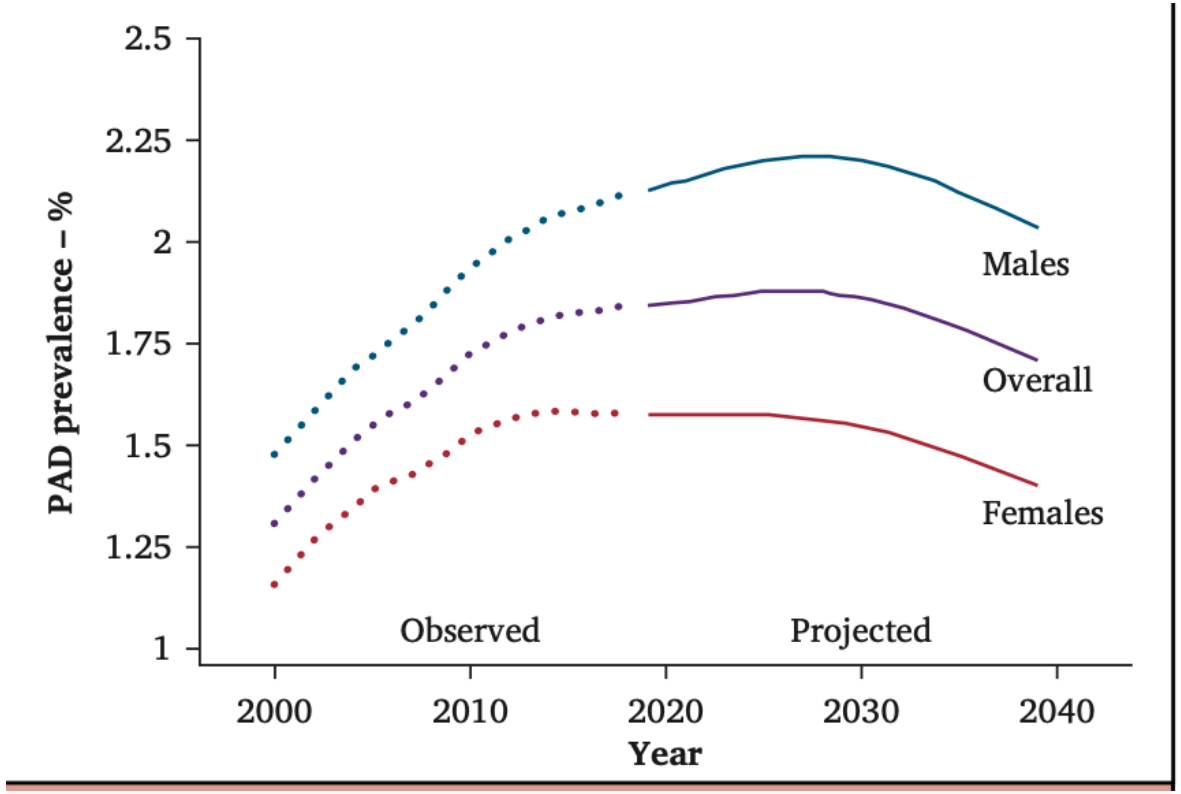


Peripheral Arteries

Eur J Vasc Endovasc Surg (2023) 66, 662–669

EJVES Open Access

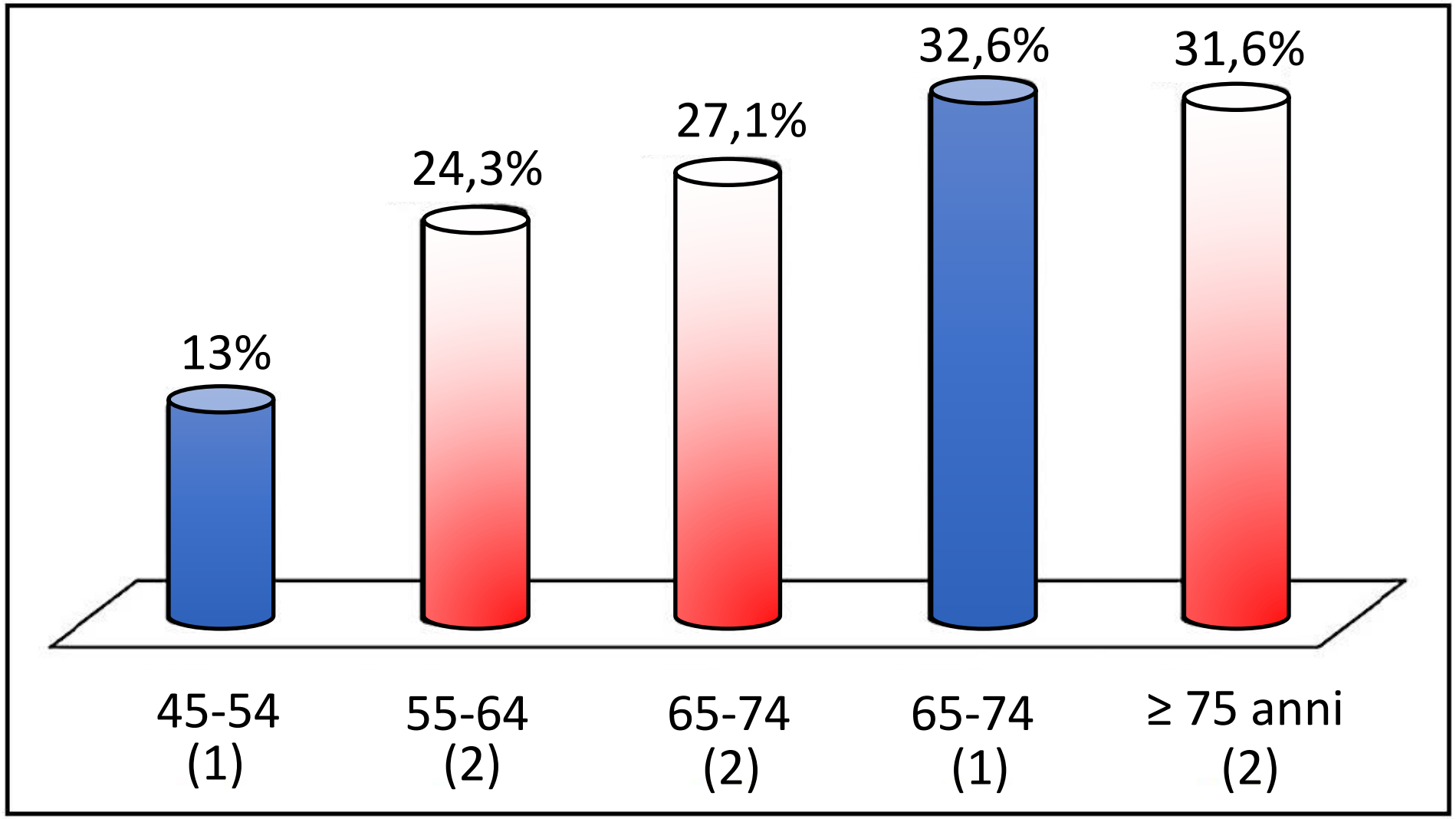
Epidemiological Trends and Projections of Incidence, Prevalence, and Disease Related Mortality Associated With Peripheral Arterial Disease: Observations Using Nationwide Danish Data

Mette Søgaard [a,b,*], Peter Brønnum Nielsen [a,b], Nikolaj Eldrup [c], Christian-Alexander Behrendt [d], Chalotte W. Nicolajsen [a,b,e], Gregory Y.H. Lip [b,f], Flemming Skjøth [b,g]

Le proiezioni della prevalenza della PAD hanno dimostrato che l'aumento della prevalenza della PAD continuerà fino al 2030 circa, seguito da un calo verso il 2040. Tra gli individui di 80 anni di età, si prevede che la prevalenza si attesti all'8,9% per gli uomini e al 6,2% per le donne prima di diminuire.

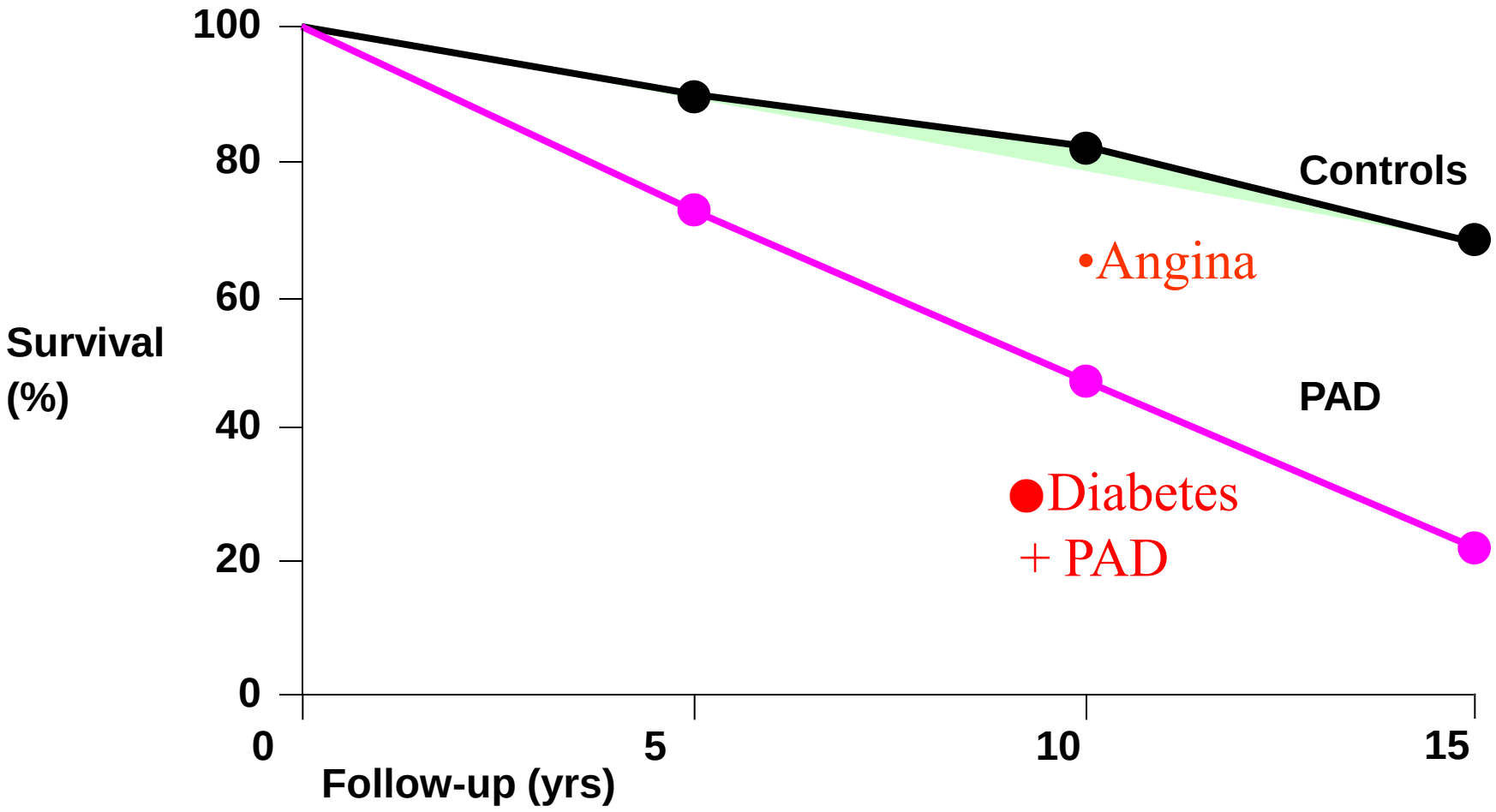
Nonostante il cauto ottimismo sulla diminuzione dell'incidenza e della mortalità, l'aumento della prevalenza sottolinea che la PAD rimane un onere per la sanità pubblica, con una continua necessità di servizi sanitari ottimali e costi elevati negli anni a venire.

La prevalenza della PAD aumenta con l'età



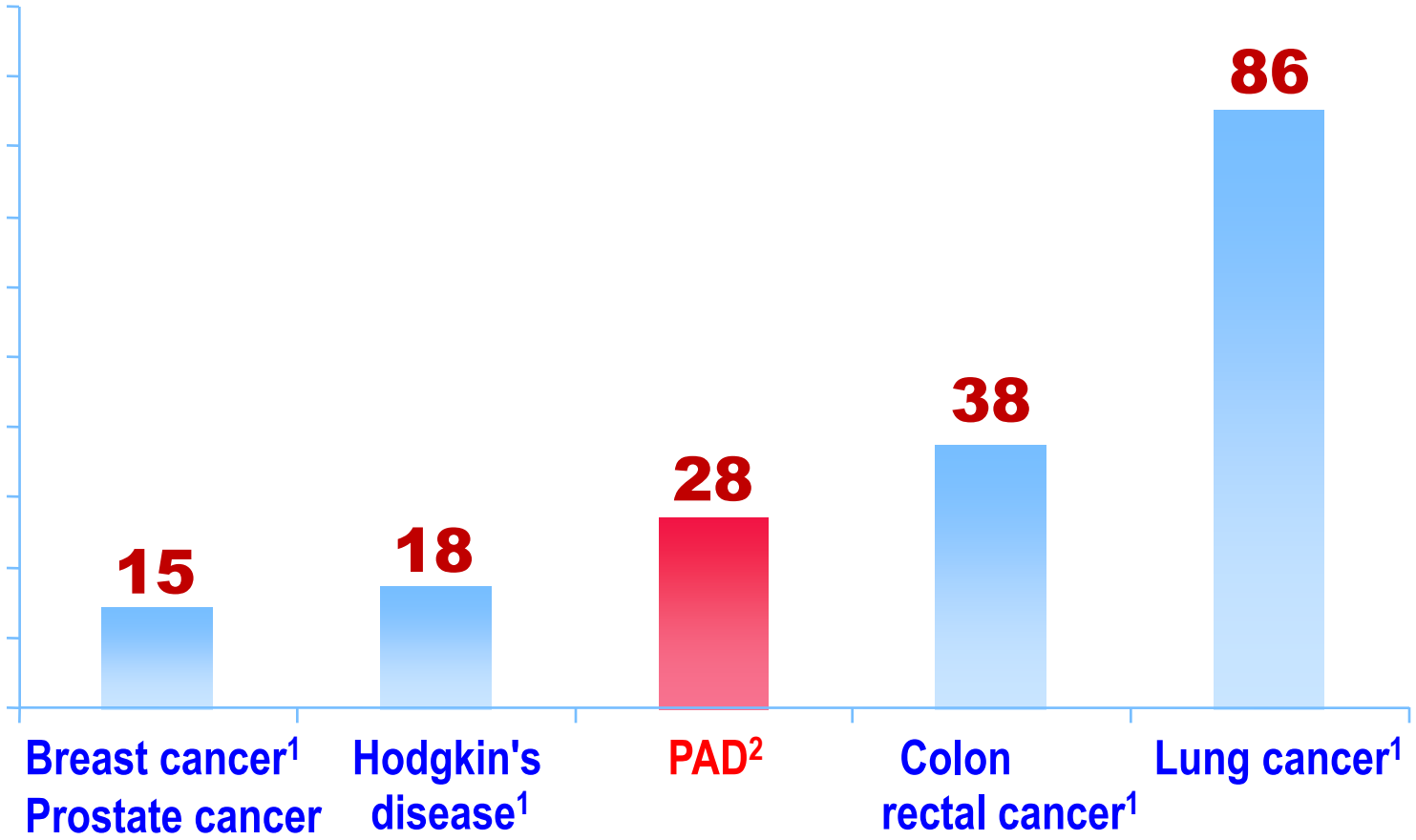
1. Cimminiello C, et al. Intern Emerg Med 2011;6:509-19
2. Cacoub P, et al. Int J Clin Pract 2009;63:63-70

Link between presence of PAD and survival



Modified from Criqui MH et al. N Engl J Med 1992;326:381–386 & Dormandy JA et al. J Vasc Surgery. 2000;31(1):S1-S296

Relative 5-year PAD mortality rates versus other common pathologies

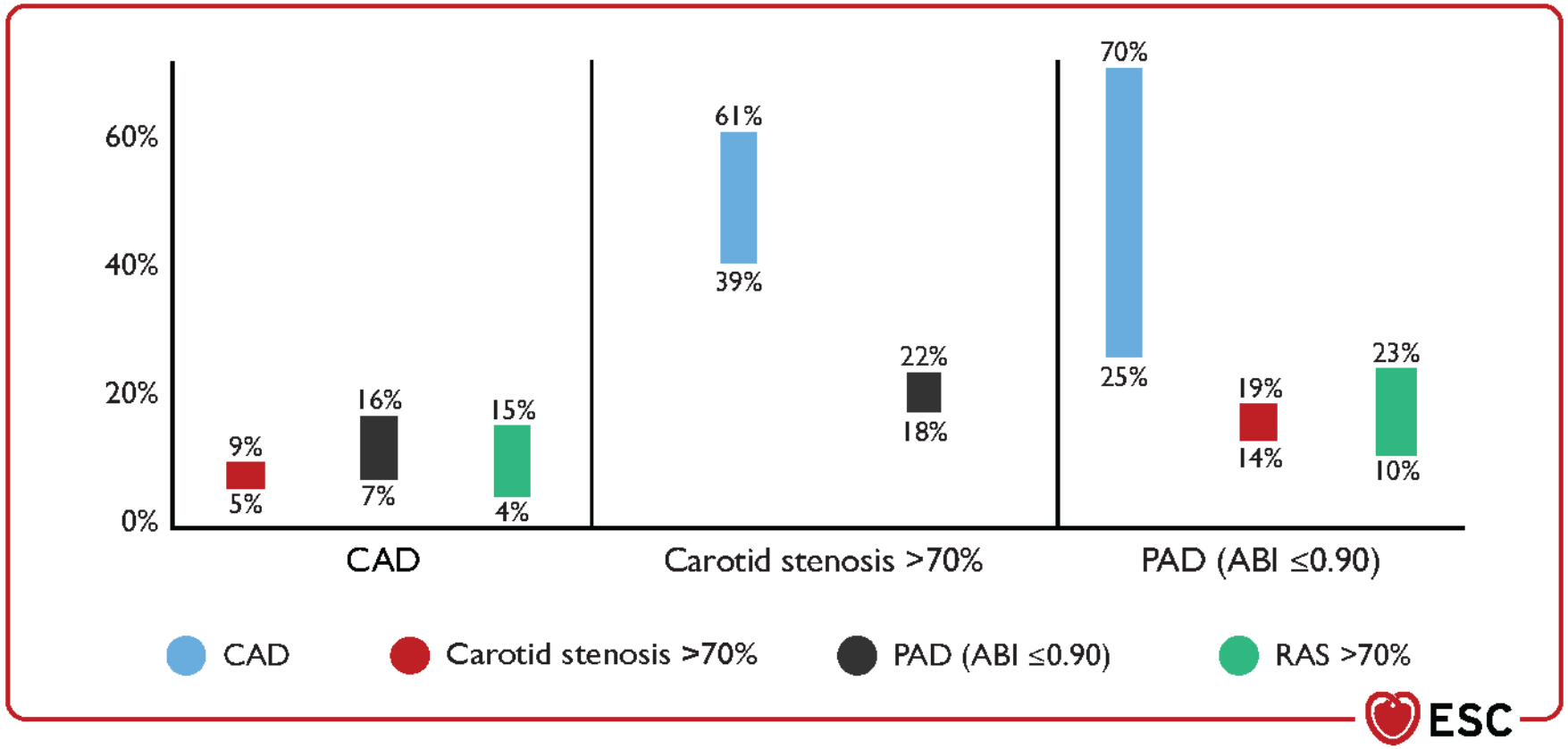


[1]American Cancer Society. Cancer Facts and Figures – 1997.

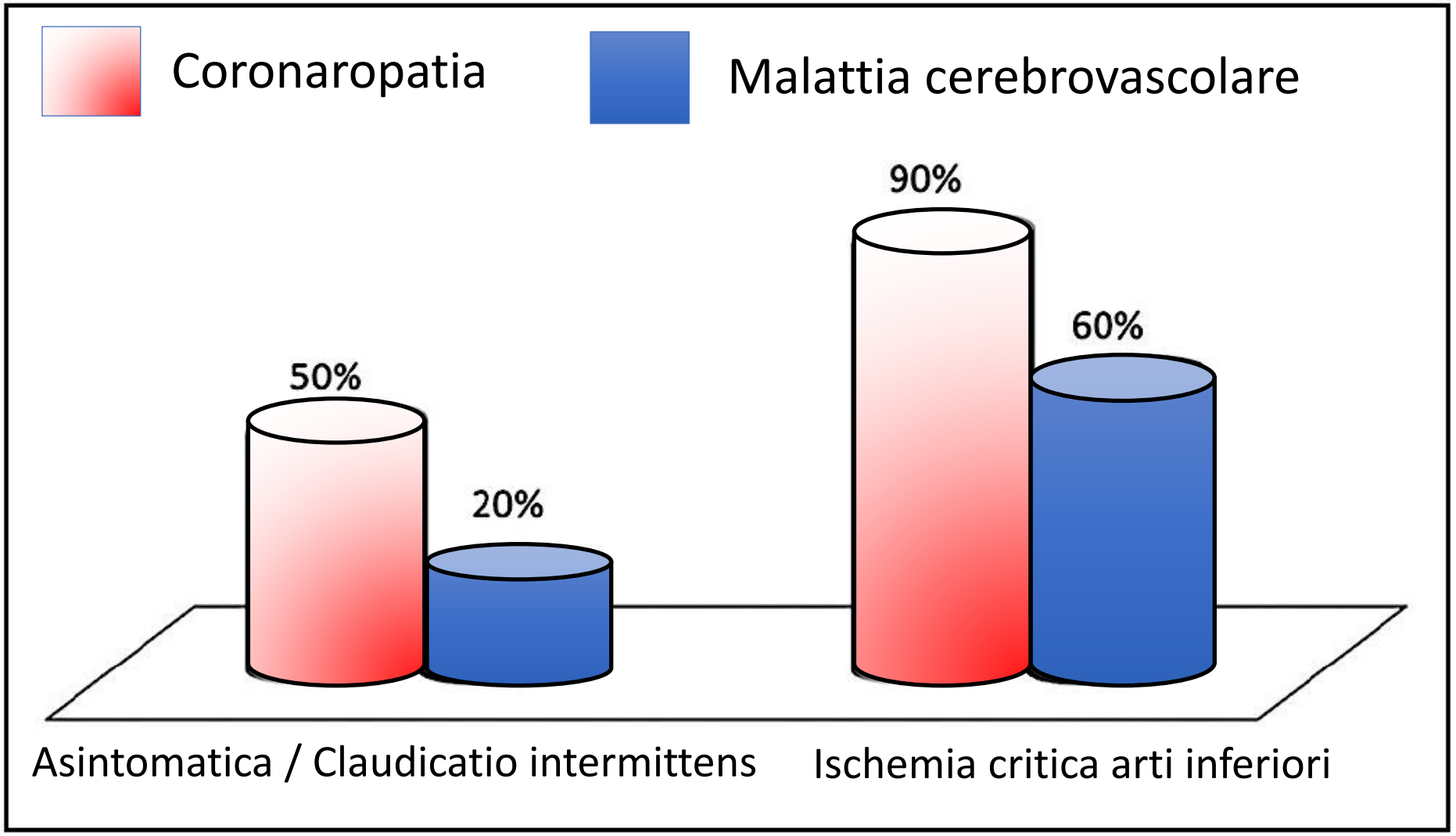
[2]Kampozinski RF, Bernhard VM. In: Vascular Surgery (Rutherford RB, ed). Philadelphia, PA: WB Saunders: 1989;chap 53.

Figure 45

Reported rate ranges of other localizations of atherosclerosis in patients with a specific arterial disease

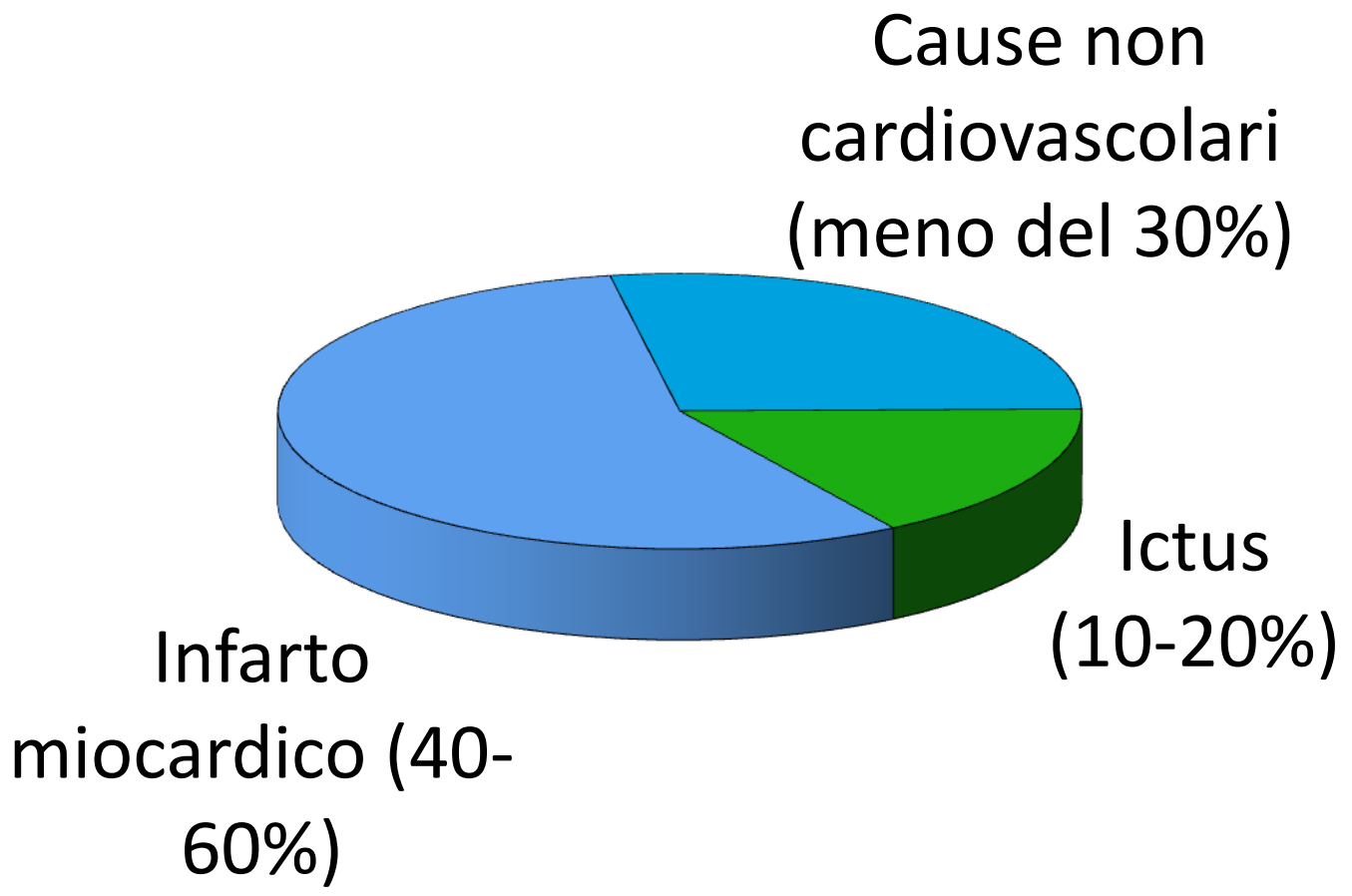


Comorbilità cardiovascolari concomitanti in pazienti con PAD



Gallino A, et al. Eur Heart J 2014;35:1112-9

Cause di morte nei pazienti con arteriopatia periferica



Fowkes FG, et al. Eur J Vasc Surg 1988;2:283-91

Il rischio cardiovascolare del paziente con PAD

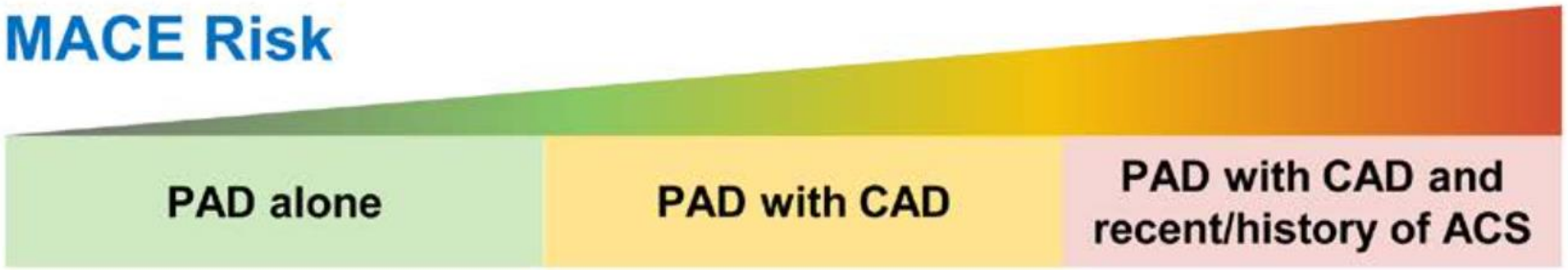
Aumento del rischio vs popolazione generale

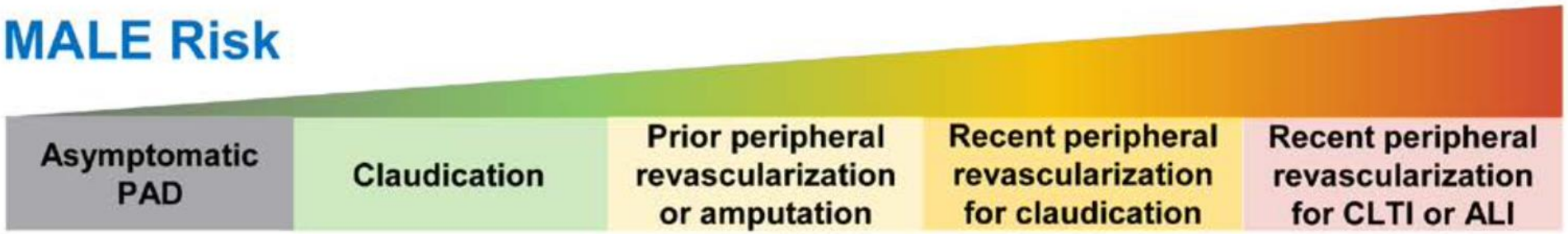
Condizione iniziale	Infarto miocardico	Ictus
Infarto miocardico	**5-7 volte**[1] (inclusa la morte)	**3-4 volte**[2] (incluso TIA)
Ictus	**2-3 volte**[2] (inclusa angina e morte improvvisa*)	**9 volte**[3]
Arteriopatia obliterante periferica	**4 volte**[4] (inclusi solo IM fatale e altre morti CV†)	**2-3 volte**[3] (incluso TIA)

Morte documentata entro 1 ora e attribuita a cardiopatia ischemica
†Inclusi solo IM fatali e altre morti cardiache; non sono inclusi gli IM non fatali

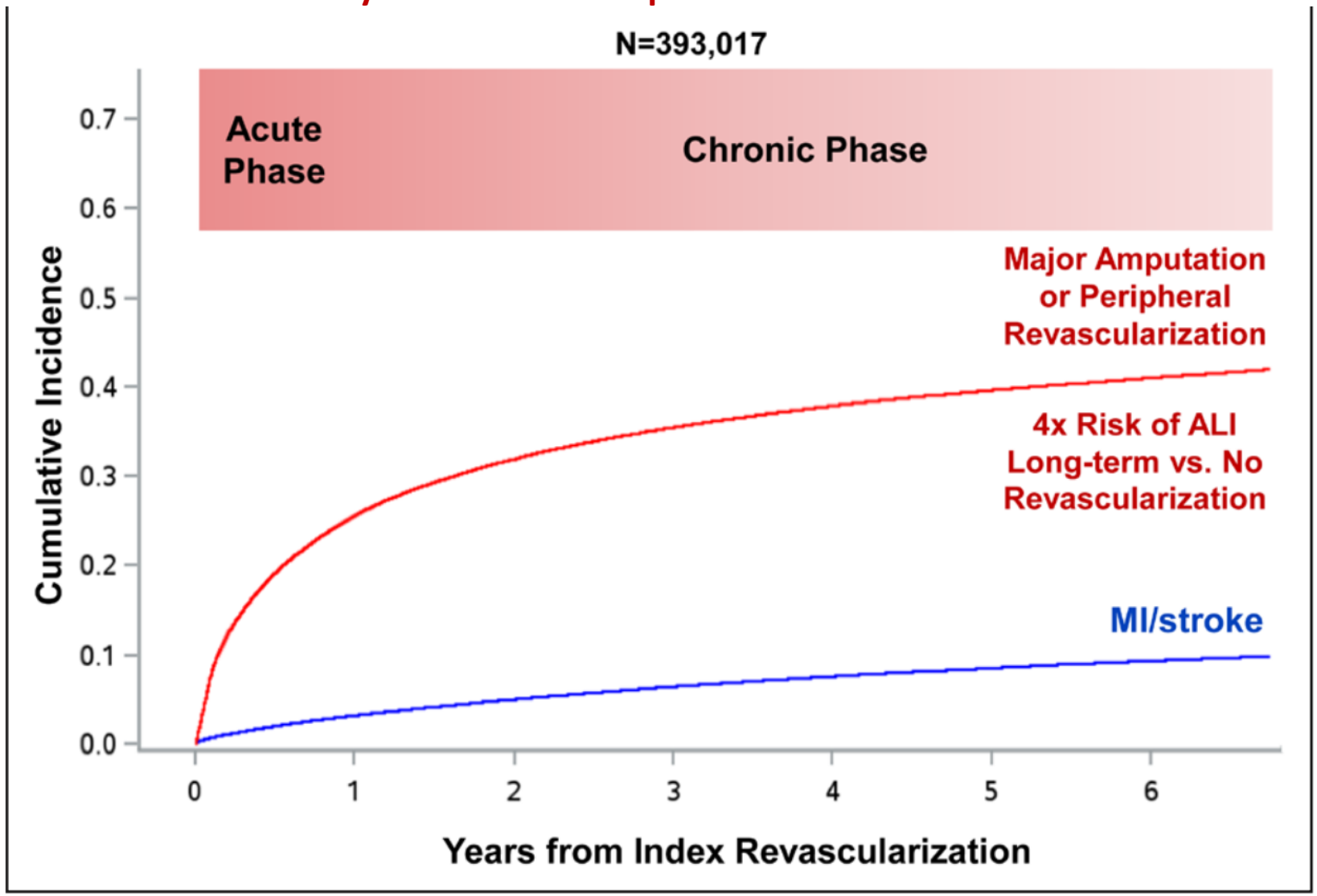
[1]Adult Treatment Panel II Circulation 1994;89:1333-1363; [2]Kannel WB J Cardiovasc Risk 1994;1:333-339
[3]Wilterdink JI, Easton JD Arch Neurol 1992;49:857-863; [4]Criqui MH et al. N Engl J Med 1992;326:381-386

RISCHI NEI PAZIENTI CON ARTERIOPATIA PERIFERICA (PAD)





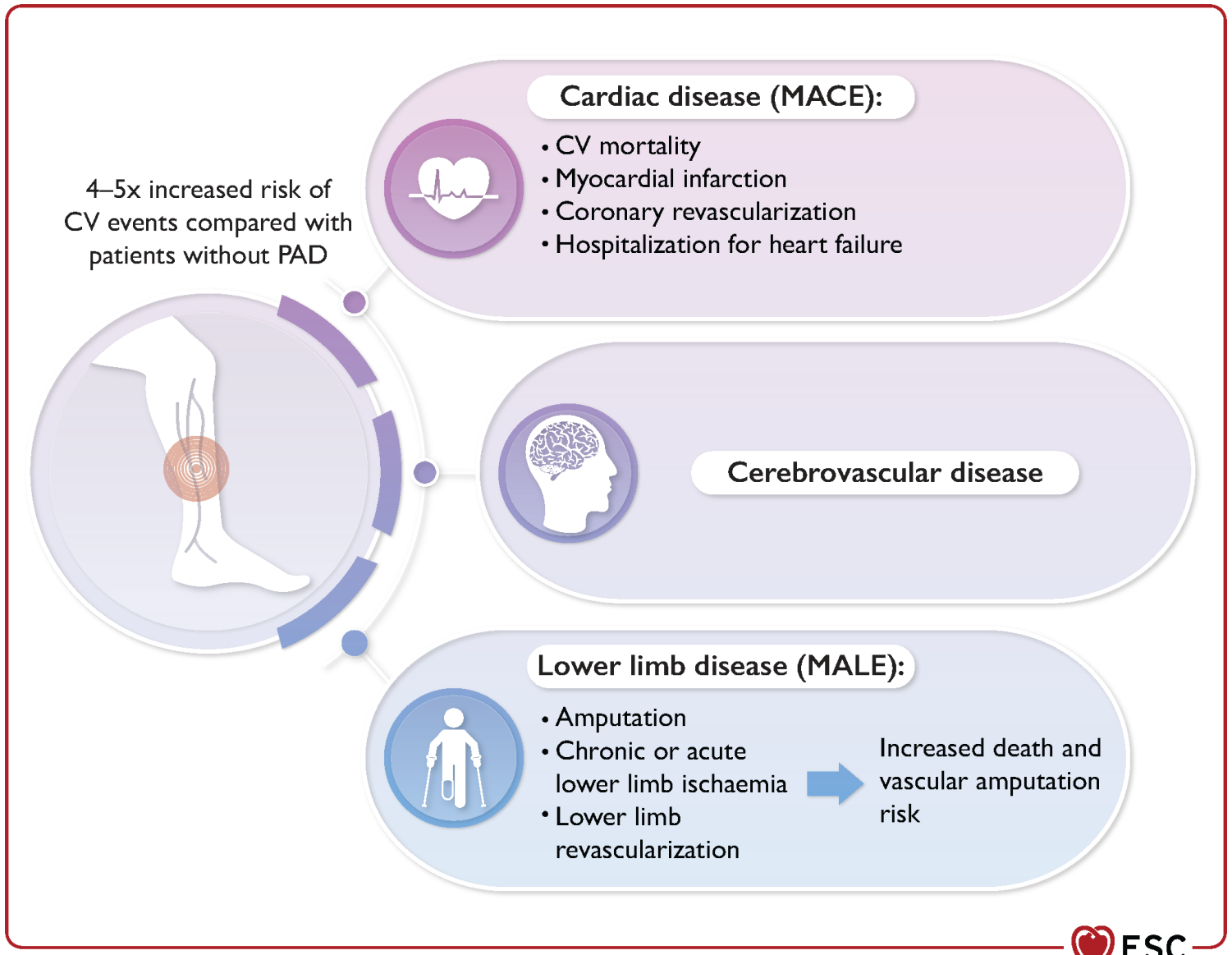
Mortality and vascular Amputation after MALE in PAD



Hess CN, *J Am Coll Cardiol*. 2020

Figure 8

Cardiovascular risk in patients with peripheral arterial disease



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Consapevolezza della PAD

Peripheral Arterial Disease Detection, Awareness, and Treatment in Primary Care

Gaps in Public Knowledge of Peripheral Arterial Disease
The First National PAD Public Awareness Survey

1 su 4 conosce la PAD

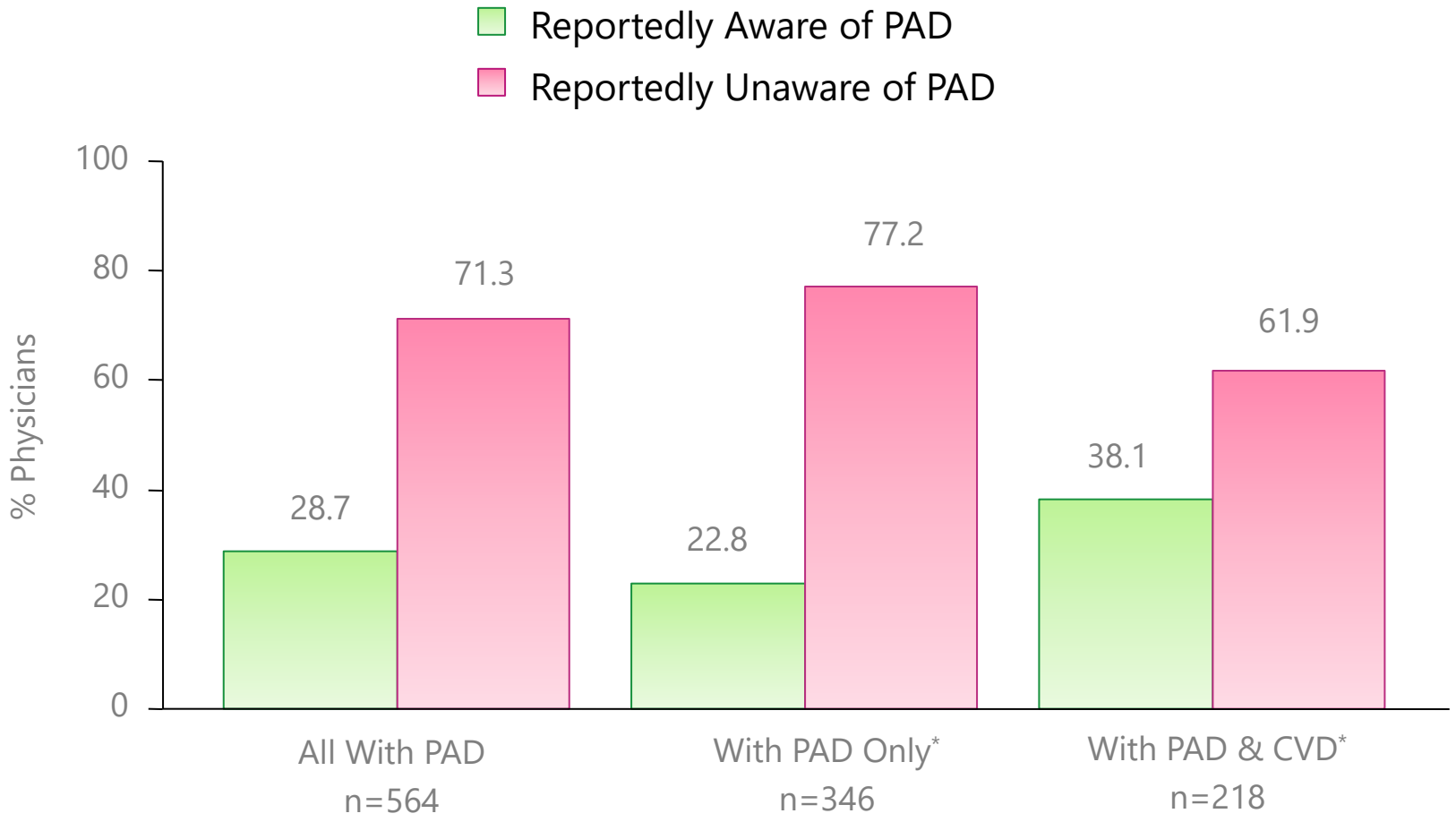
- 1 su 2 sa che diabete e fumo aumentano il rischio di PAD
- 1 su 4 sa che la PAD si associa a un aumento del rischio di IMA e stroke
- 1 su 7 sa che la PAD può portare ad amputazione

Peripheral arterial disease: Lack of awareness in Canada

Peripheral Artery Disease: A Marked Lack of Awareness in Ireland

Hirsch AT, et al. JAMA 2001;286:1317-24
Hirsch AT, et al Circulation. 2007;116:2086-94
Lovell M, et al. Can J Cardiol 2009;25(1):39-45
Cronin CT, et al. Eur J Vasc Endovasc Surg 2015;49:556-62

Physician Awareness of PAD



**P<.001.*

Hirsch et al PARTNERS study JAMA, Sept. 19, 2001, Vol. 286, No. 11.

PAD → **ancora sottodiagnosticata e sottotrattata**

Diagnosi precoce	facilita la precoce identificazione di individui con rischio cardiovascolare molto alto
Trattamento precoce	può portare a riduzione degli eventi aterosclerotici futuri e della mortalità cardiovascolare

Olinic DM. et al. International Angiol 2018;37(4):327-34

PAD
INQUADRAMENTO CLINICO

Multidisciplinary and Holistic Approach

- **Shared decision-making** to involve patients, explore treatment options, assess patient values, and reach decisions collaboratively.
- **Multidisciplinary approach in expert and high-volume PAAD centres for complex patients or procedures**.

These centres provide diverse services, including diagnosis, treatment planning minimally invasive procedures, open surgery, post-operative and outpatient care, and ideally, **research and innovation**.

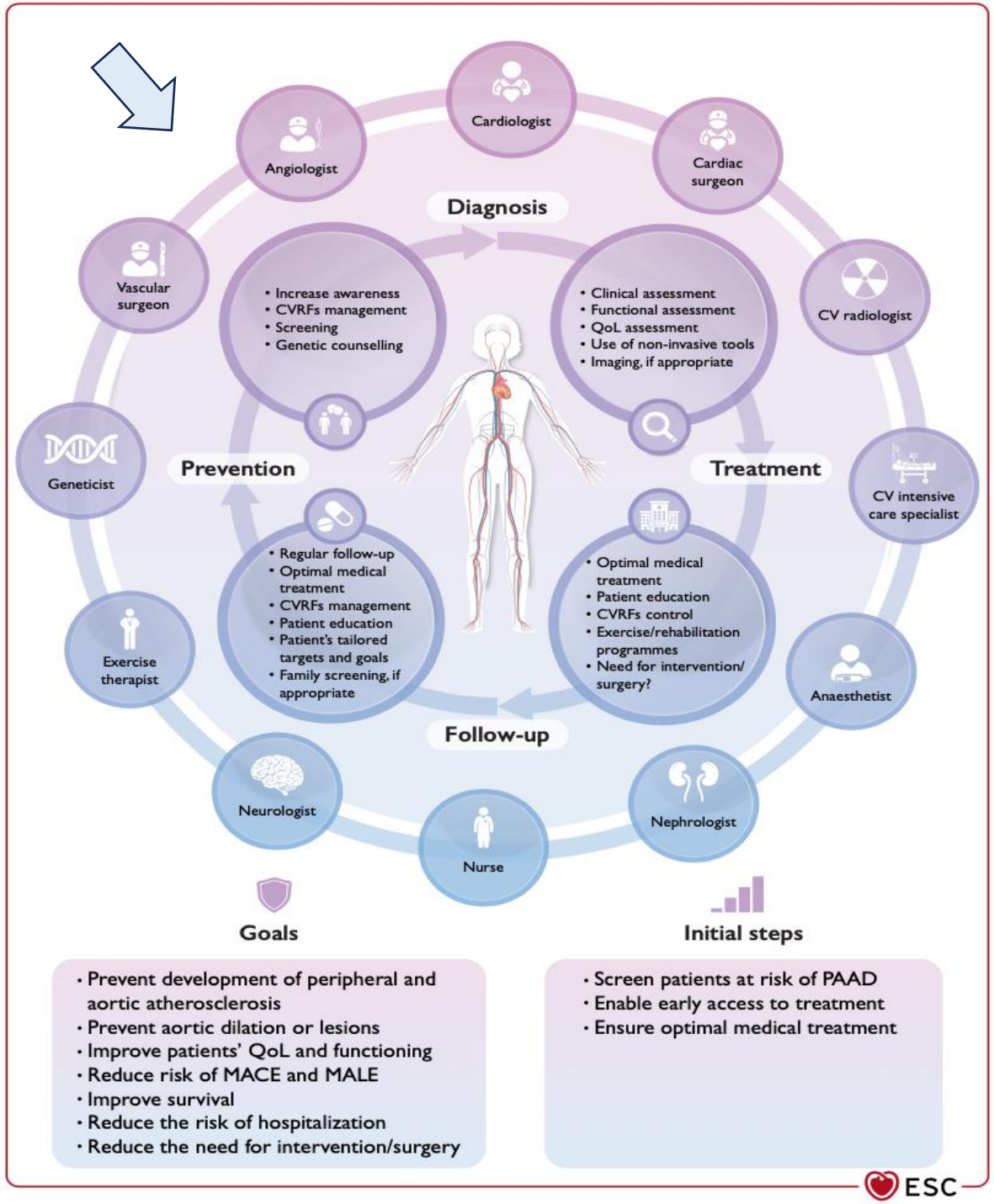
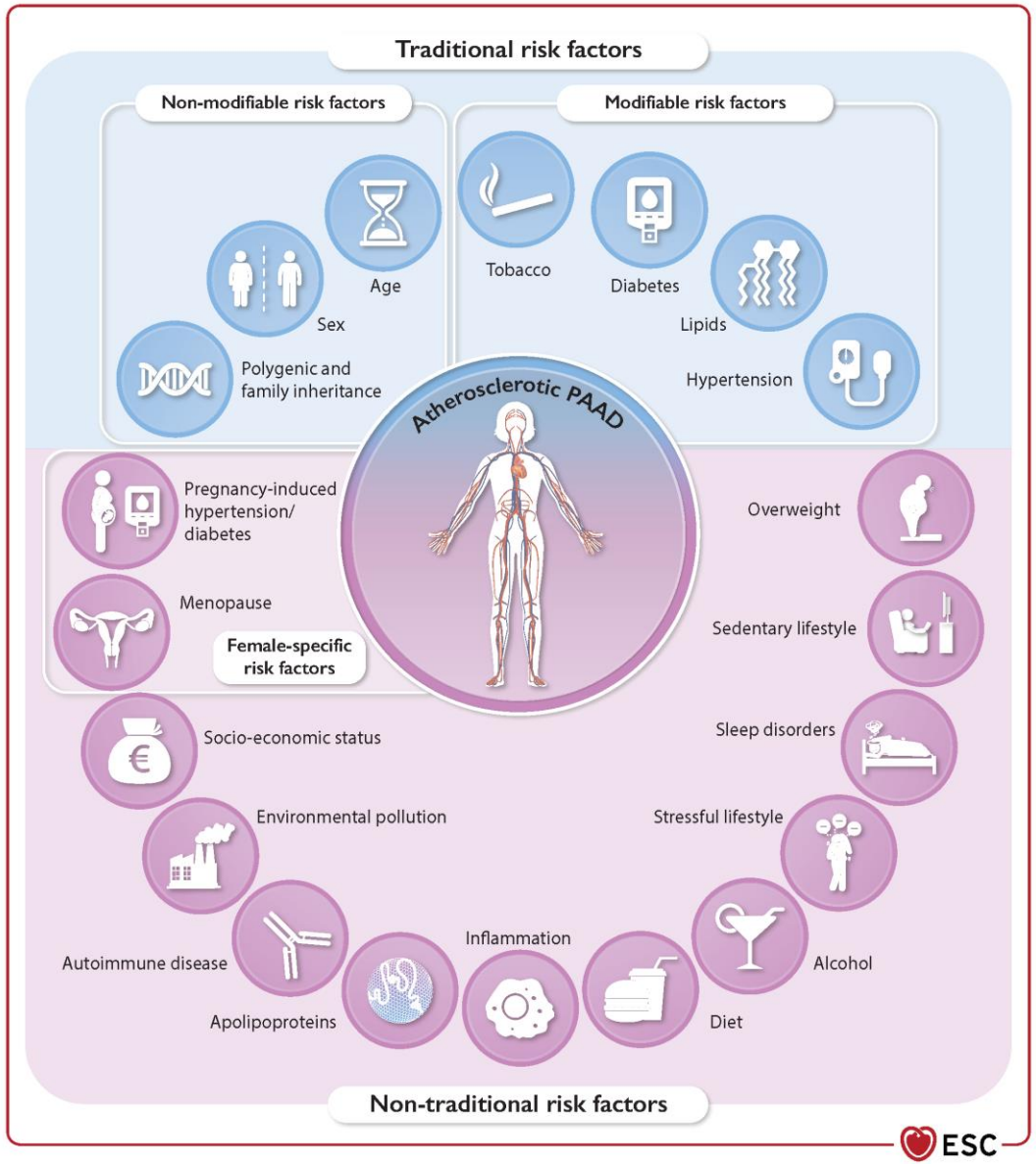


Figure 3

Main risk factors associated with atherosclerosis in peripheral arterial and aortic diseases



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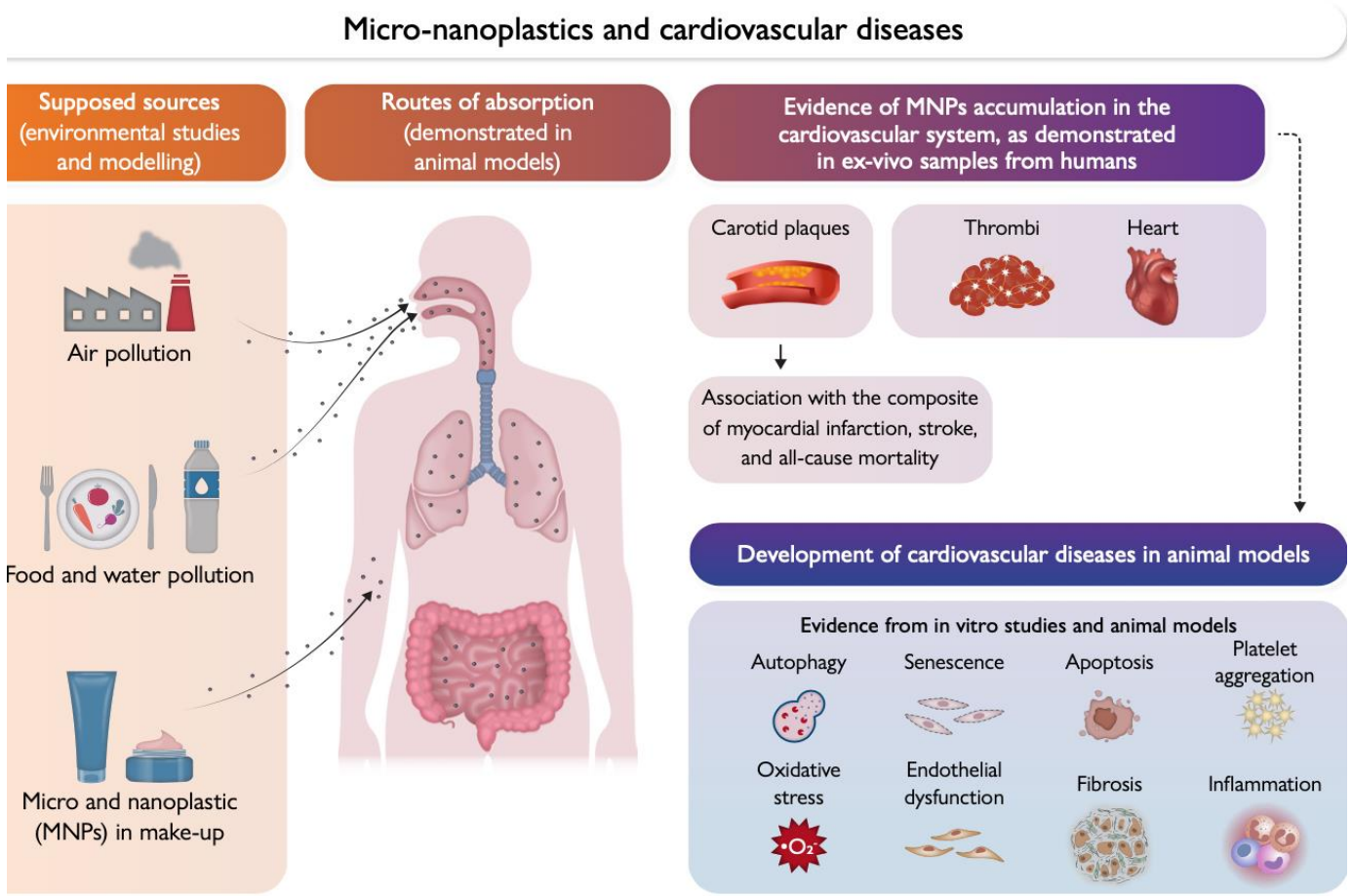
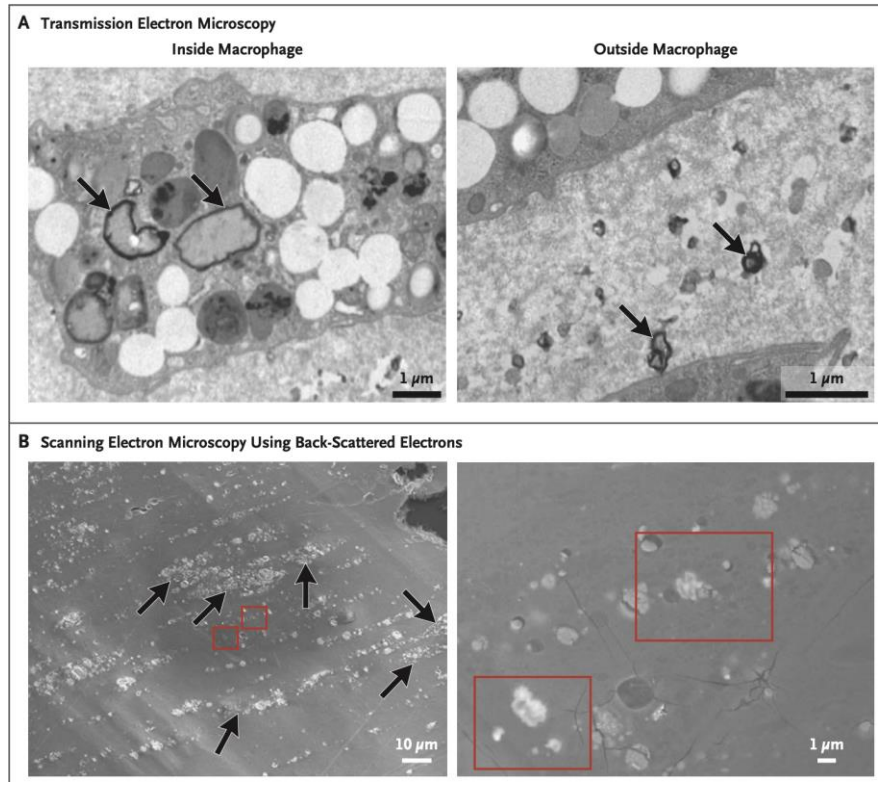


The possible role of micro- and nanoplastics (MNPs) in cardiovascular disease

Prattichizzo et al. European Heart Journal (2024) 00, 1–12



Microplastics and Nanoplastics in Atheromas and Cardiovascular Events

R. Marfella, F. Prattichizzo N Engl J Med 2024;390:900-10.

VALUTAZIONE CLINICA

Main points of medical history for assessment of peripheral arterial diseases *(continued)*

ESC European Society of Cardiology

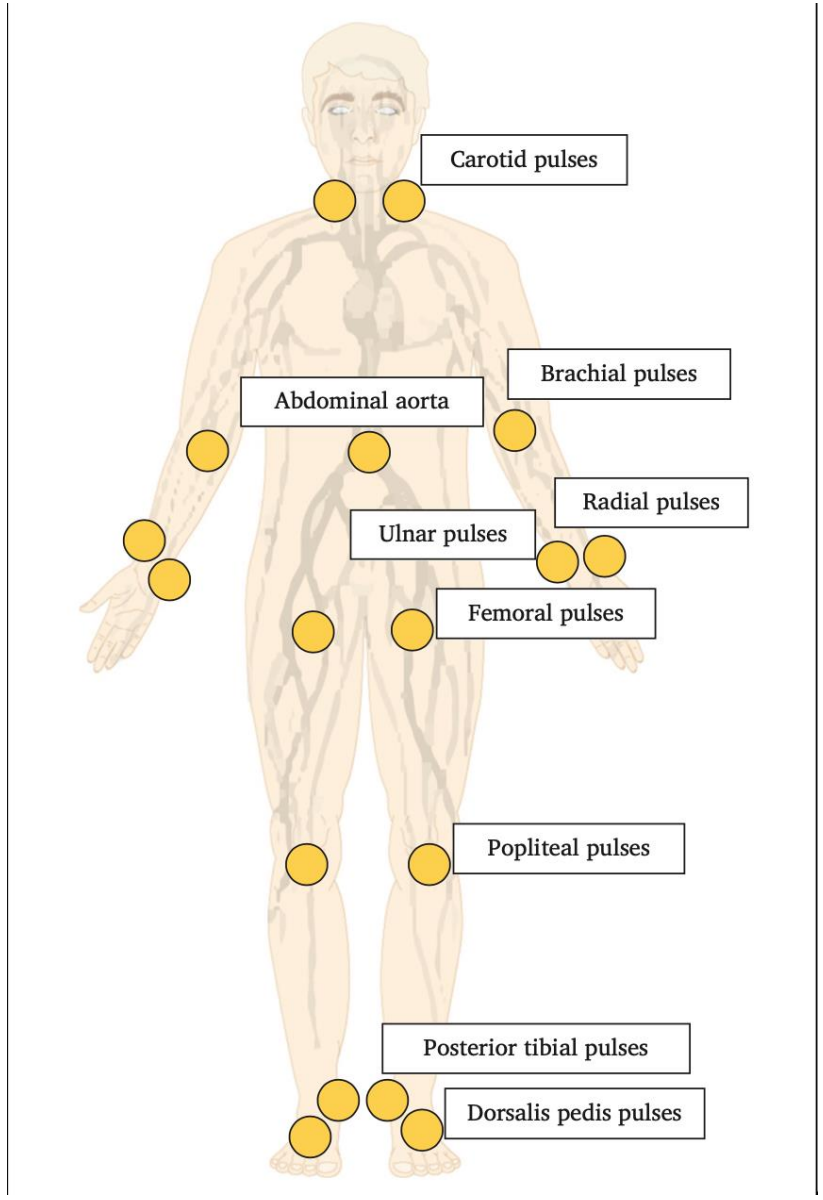
Abdominal pain, particularly if related to eating and associated with weight loss.
Walking impairment/claudication: • type: fatigue, aching, cramping, discomfort, burning, • location: buttock, thigh, calf, or foot, • timing: triggered by exercise, uphill rather than downhill, quickly relieved with rest; chronic, • distance.
Lower limb pain (including foot) at rest, and evolution at upright or recumbent position.
Poorly healing wounds of the extremities.
Physical activity assessment: • functional capacity and causes of impairment.
Erectile dysfunction.

Physical examination for assessment of peripheral arterial diseases

ESC European Society of Cardiology

Auscultation and palpation of cervical and supraclavicular areas.
Careful inspection of upper extremities, including hands (i.e. colour, skin integrity).
Palpation of upper extremity pulses.
Blood pressure measurement of both arms and notation of inter-arm difference.
Auscultation at different levels including the flanks, peri-umbilical region, and groin.
Abdominal palpation, palpation of femoral, popliteal, dorsalis pedis, and posterior tibial artery pulses, temperature gradient assessment.

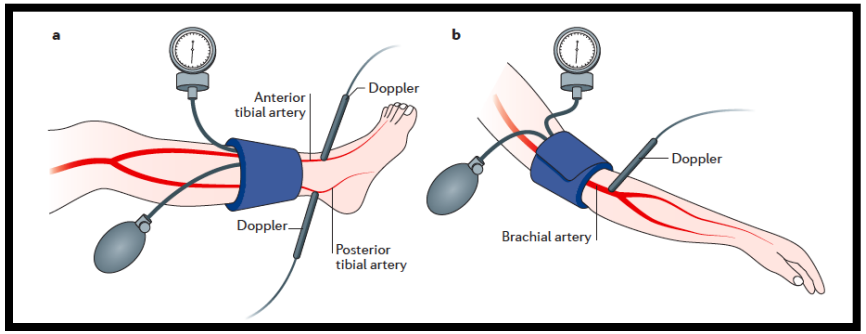
Pulse examination of patients with lower extremity peripheral arterial disease



ESVS Guidelines 2024

Indice caviglia/braccio

Raccomandazioni	Classe	Livello
La misurazione dell'indice caviglia/braccio è indicata come test non invasivo di prima linea per lo screening e la diagnosi di arteriopatia periferica	I	C



Sensibilità 95% e specificità 100%

(rispetto ad angiografia)

AHA Scientific Statement

Measurement and Interpretation of the Ankle-Brachial Index

A Scientific Statement From the American Heart Association

Aboyans V, et al. Eur J Vasc Endovasc Surg 2018;55: 305-68

Aboyans V, et al. Circulation 2012;126:2890-909

1. Who should have an ABI measurement in clinical practice?

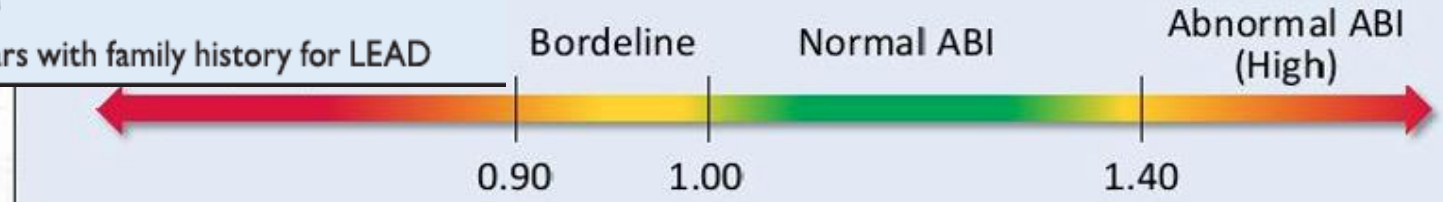
- **Patients with clinical suspicion for LEAD:**
  - Lower extremities pulse abolition and/or arterial bruit
  - Typical intermittent claudication or symptoms suggestive for LEAD
  - Non-healing lower extremity wound
- **Patients at risk for LEAD because of the following clinical conditions:**
  - Atherosclerotic diseases: CAD, any PADs
  - Other conditions: AAA, CKD, heart failure
- **Asymptomatic individuals clinically-free but at-risk for LEAD:**
  - Men and women aged >65 years
  - Men and women aged <65 years classified at high CV risk according the ESC Guidelines[a]
  - Men and women aged >50 years with family history for LEAD

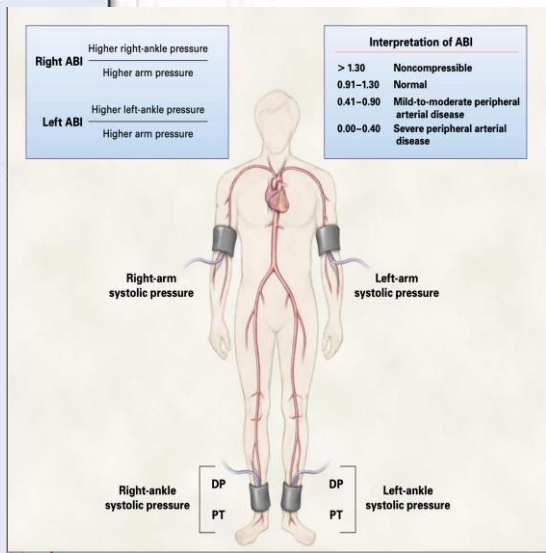
ial Index *(continued)*

ESC European Society of Cardiology

ABI?

AD interpret each leg separately (one ABI per leg).
ification: take the lowest ABI between the two legs.

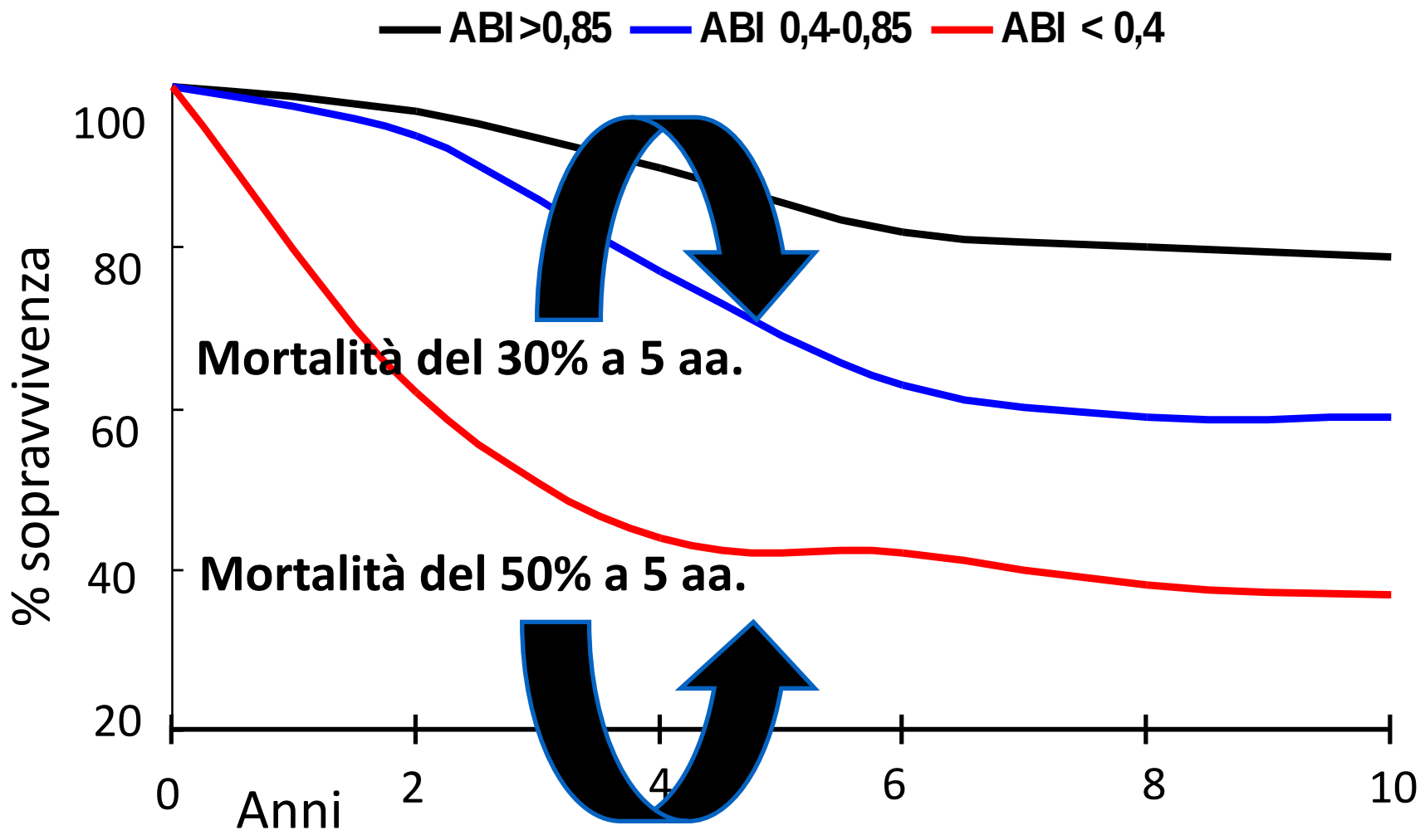




2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with ESVS (European Heart Journal 2017; doi:10.1093/eurheartj/ehx095)

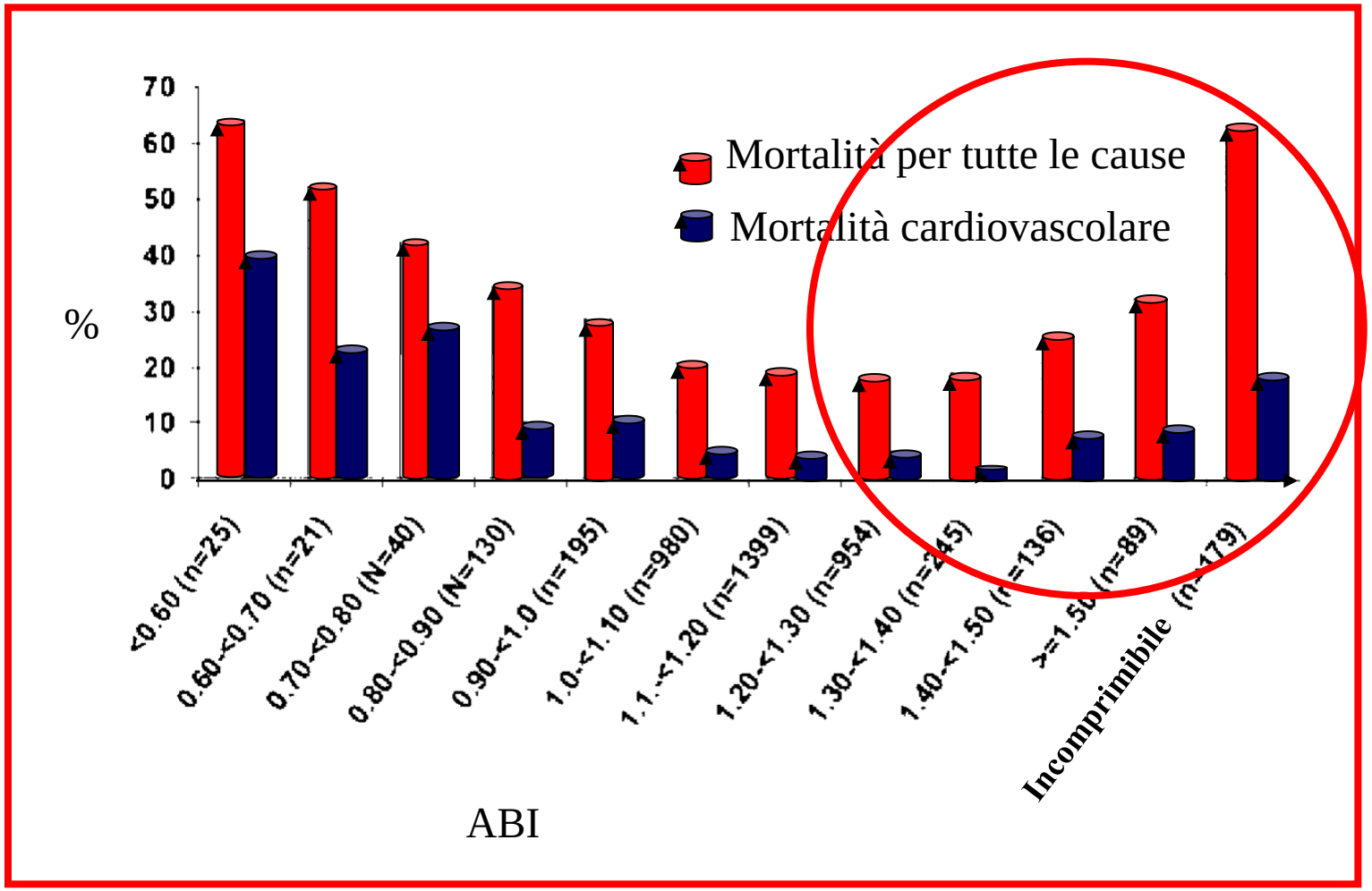
Vi è la necessità di diffondere la cultura della PAD e di documentarla mediante la misurazione dell'ABI

Declino della sopravvivenza associata con la gravità dell'arteriopatia periferica



McKenna M, Wolfson S, Kuller L. Atherosclerosis 1991;87:119-28

Mortalità per tutte le cause e mortalità cardiovascolare in base all'ABI (n=4393)



Resnick HE et al. Circulation 2004;109:733-9

Recommendation 8

When the ankle brachial index is used as a cardiovascular risk marker, it is recommended that it is calculated by dividing the lowest recorded systolic pressure at ankle level by the highest systolic arm pressure due to the higher sensitivity to detect peripheral arterial disease.

Class	Level	References	ToE
I	B	Niazi *et al.* (2006)[199] Le Bivic *et al.* (2019)[202] O'Hare *et al.* (2006)[203] Espinola-Klein *et al.* (2008)[201] Pereira Fihlo *et al.* (2022)[208]	

ESVS Guidelines 2024

Contents lists available at ScienceDirect

European Journal of Internal Medicine

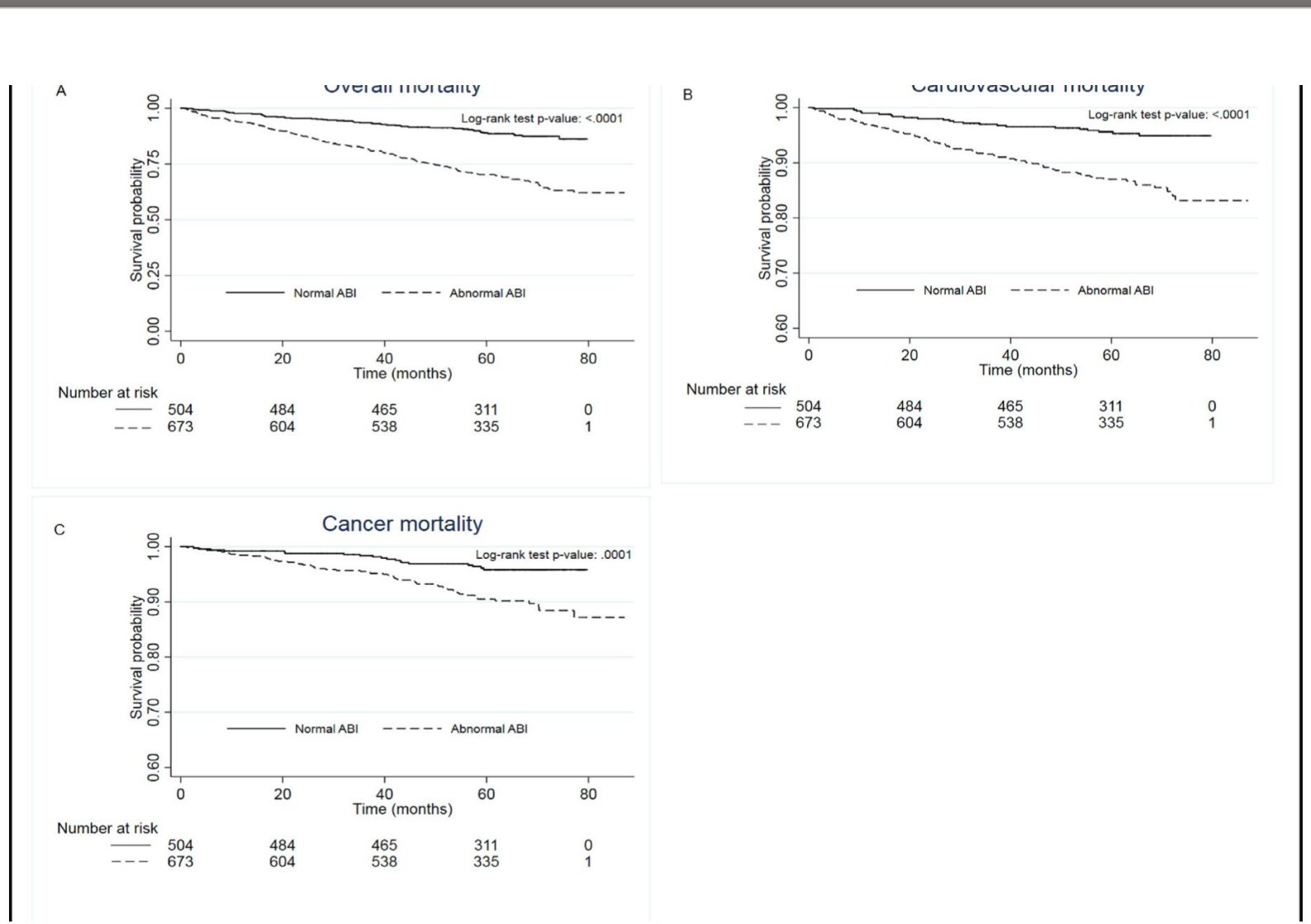
journal homepage: www.elsevier.com/locate/ejim

Original article

Abnormal ankle-brachial index (ABI) predicts primary and secondary cardiovascular risk and cancer mortality

A. Visonà[a], A. De Paoli[b], U. Fedeli[b], D. Tonello[a], B. Zalunardo[a,i], N. Zanatta[c], R. Martini[d], R. Pesavento[e], S. Cuppini[f], M. Prior[g], S. Benazzi[h], C. Cimminiello[i,*], F. Avossa[b]

Eur J Intern Med. 2020 Jul;77:79-85



Overall mortality (A), cardiovascular mortality (B) and cancer mortality (C) in relation to normal and abnormal ABI and presence or absence of history of CV events.

Eur J Intern Med. 2020 Jul;77:79-85

ABI

- The first is the confirmation of ABI as a **prognostic tool to predict mortality and vascular events, including non-fatal ones such as AMI and S**. With its ease of execution and low cost, this tool confirms its potential role in **refining the assessment of CV risk.** Instead, the role of **ABI as a predictor of cancer mortality** is entirely new. This is of course only a preliminary finding and needs to be confirmed in ad hoc studies.
- The second aspect relates to the **specific predictive utility of an abnormal ABI in patients with a history of coronary or cerebral events.** In defining the management strategies for **secondary prophylaxis**, it is crucial to recognize patients at high risk of recurrent events. Subjects with abnormal ABI and a **history of CV events form a subgroup likely to require more aggressive management strategies**.

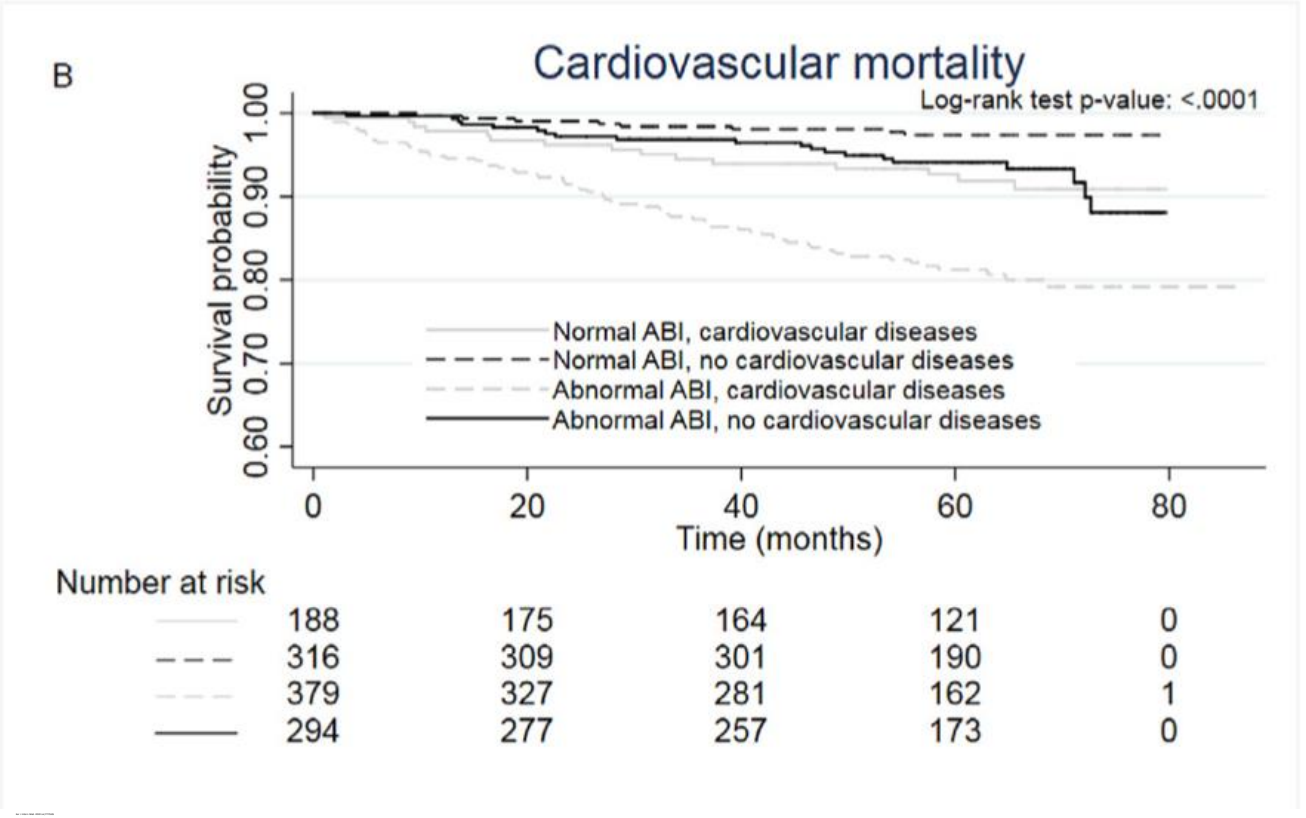
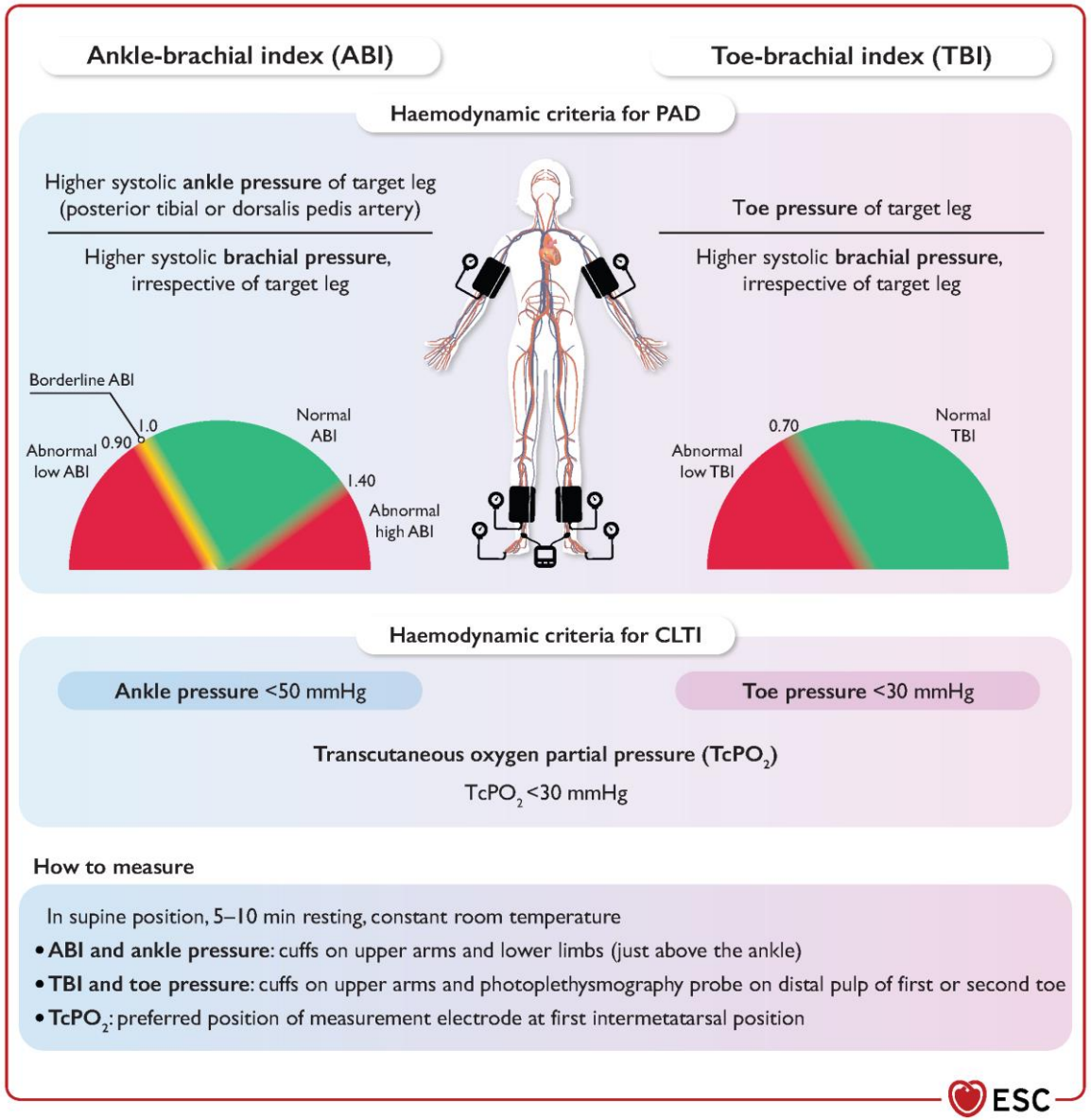


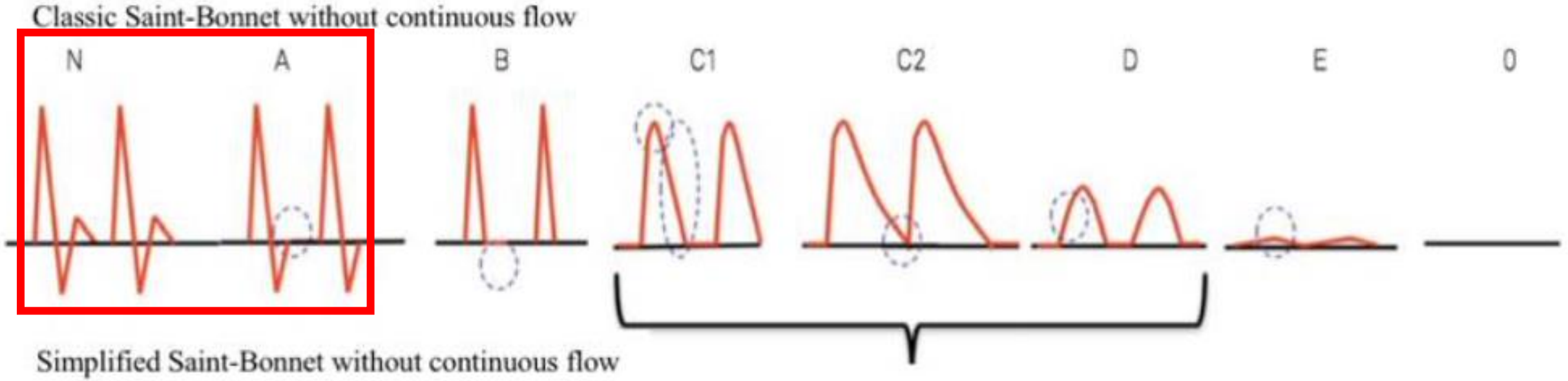
Figure 4

Haemodynamic assessment of peripheral arterial disease



2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Saint Bonnet classification



The different arterial Doppler waveform classifications.

Triphasic of biphasic types are considered normal. Monophasic and poor monophasic types describe differen levels of peripheral artery disease (PAD)

Types N and A are considered normal.

Guilcher A et al, *J. Clin. Med.* **2021**, *10*, 464

New recommendations (1)

Recommendations	Class	Level
Recommendations for clinical and laboratory, and for functional quality of life, assessment in patients with peripheral arterial and aortic disease		
When managing PAAD, it is recommended to adopt a comprehensive approach that addresses the entirety of arterial circulation.	I	B
Recommendations for peripheral arterial disease screening		
In patients with AAA, femoro-popliteal aneurysm screening with DUS should be considered.	IIa	C
In patients needing intervention with transfemoral access, screening for iliofemoral artery disease may be considered.	IIb	C
In patients with two or more CVRFs, screening for asymptomatic CS may be considered.	IIb	C
Recommendations for abdominal aortic aneurysm screening		
Opportunistic AAA screening with DUS should be considered in symptomatic/asymptomatic PAD patients.	IIa	B

Recommendations for clinical and laboratory, and for functional and QoL, assessment in patients with PAAD

Recommendations	Class	Level
When managing PAAD, it is recommended to adopt a comprehensive approach that addresses the entirety of the arterial circulation.	I	B
To assess PAAD, it is recommended to perform thorough clinical, vascular, and CVRFs laboratory evaluation.	I	C
Overall evaluation of functional (physical functioning) performance with objective tests should be considered in patients with symptomatic and asymptomatic chronic PAD.	IIa	B
Overall evaluation of self-reported (i.e. by questionnaire) physical and mental/social HRQoL should be considered in patients with PAAD.	IIa	B

Recommendations for diagnostic tests in patients with peripheral arterial disease

Recommendations	Class	Level
Measurement of the ABI is recommended as the first-line non-invasive test for screening and diagnosis of PAD, using an ABI ≤0.90 as a diagnostic criterion.	I	B
In the case of non-compressible ankle arteries or ABI >1.40, additional methods such as TP, TBI or Doppler waveform analysis are recommended.	I	B

Recommendations for peripheral arterial disease screening

Recommendations	Class	Level
In patients with diabetes or chronic kidney disease, and normal resting ABI, TBI measurement should be considered.	IIa	B
In patients ≥65 years of age with CVRFs, screening for PAD by ABI or TBI should be considered.	IIa	C
In patients with AAA, femoro-popliteal aneurysm screening with DUS should be considered.	IIa	C
In patients ≥65 years without CVRFs, screening for PAD by ABI or TBI may be considered.	IIb	C
In patients needing intervention with transfemoral access, screening for iliofemoral artery disease may be considered.	IIb	C
In patients with two or more CVRFs, screening for CS may be considered.	IIb	C

Recommendations for diagnostic tests in patients with PAD and diabetes, renal failure, and wounds

Recommendations	Class	Level
Measuring TP or TBI is recommended in patients with diabetes or renal failure if resting ABI is normal.	I	C
In patients with PAD and chronic wounds, the WIfI classification system should be considered to estimate individual risk of amputation.	IIa	C

Recommendations for imaging in patients with peripheral arterial disease

Recommendations	Class	Level
DUS is recommended as the first-line imaging method to confirm PAD lesions.	I	C
In symptomatic patients with aorto-iliac or multisegmental/complex disease, CTA and/or MRA are recommended as adjuvant imaging techniques for preparation of revascularization procedures.	I	C
Analysis of anatomical imaging tests in conjunction with symptoms and haemodynamic tests prior to an invasive procedure is recommended.	I	C

PAD
SINDROMI CLINICHE

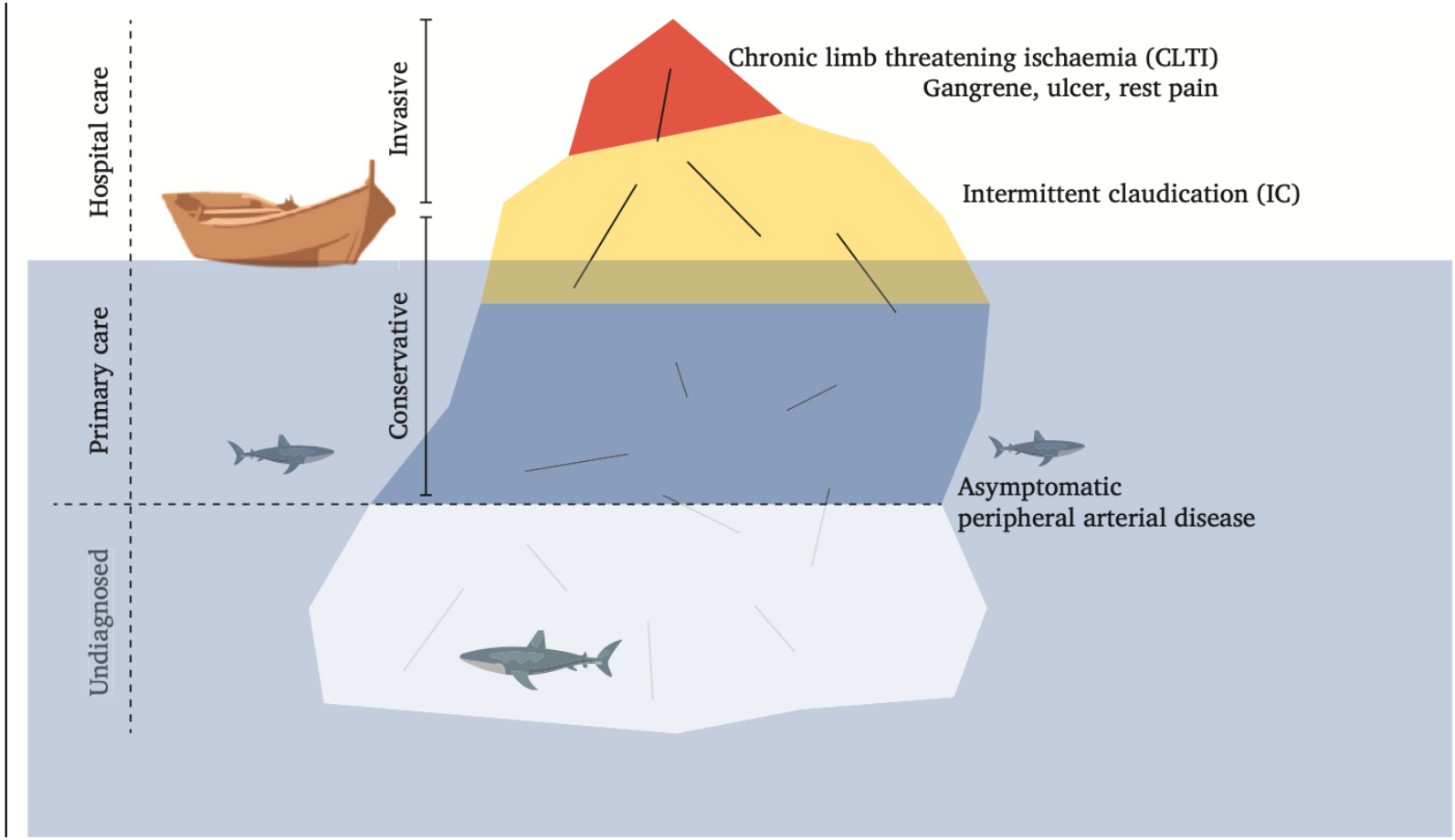
Peripheral arterial disease categorized according to clinical presentation

Clinical characteristics of PAD	Rutherford classification		Fontaine classification	
	Category	Signs and symptoms	Stage	Signs and symptoms
Asymptomatic PAD	0	Asymptomatic	I	Asymptomatic
Symptomatic (effort-related) PAD	1	Mild claudication	IIa	Non-disabling intermittent claudication
	2	Moderate claudication	IIb	Disabling intermittent claudication
	3	Severe claudication		
Chronic limb-threatening Ischaemia	4	Ischaemic rest pain	III	Ischaemic rest pain
	5	Minor tissue loss	IV	Ischaemic ulceration or gangrene
	6	Major tissue loss		

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

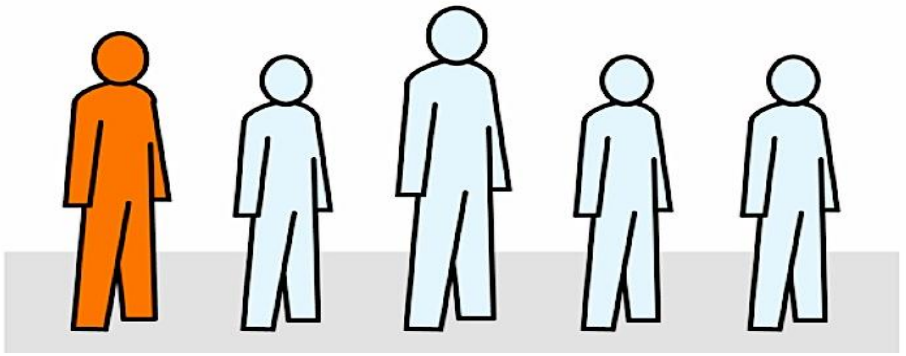
PAD ASINTOMATICA

Epidemiologia dell'iceberg della malattia arteriosa periferica (PAD) degli arti inferiori, che illustra indirettamente le reali sfide associate al raggiungimento dell'intera popolazione di pazienti con qualsiasi intervento sanitario.

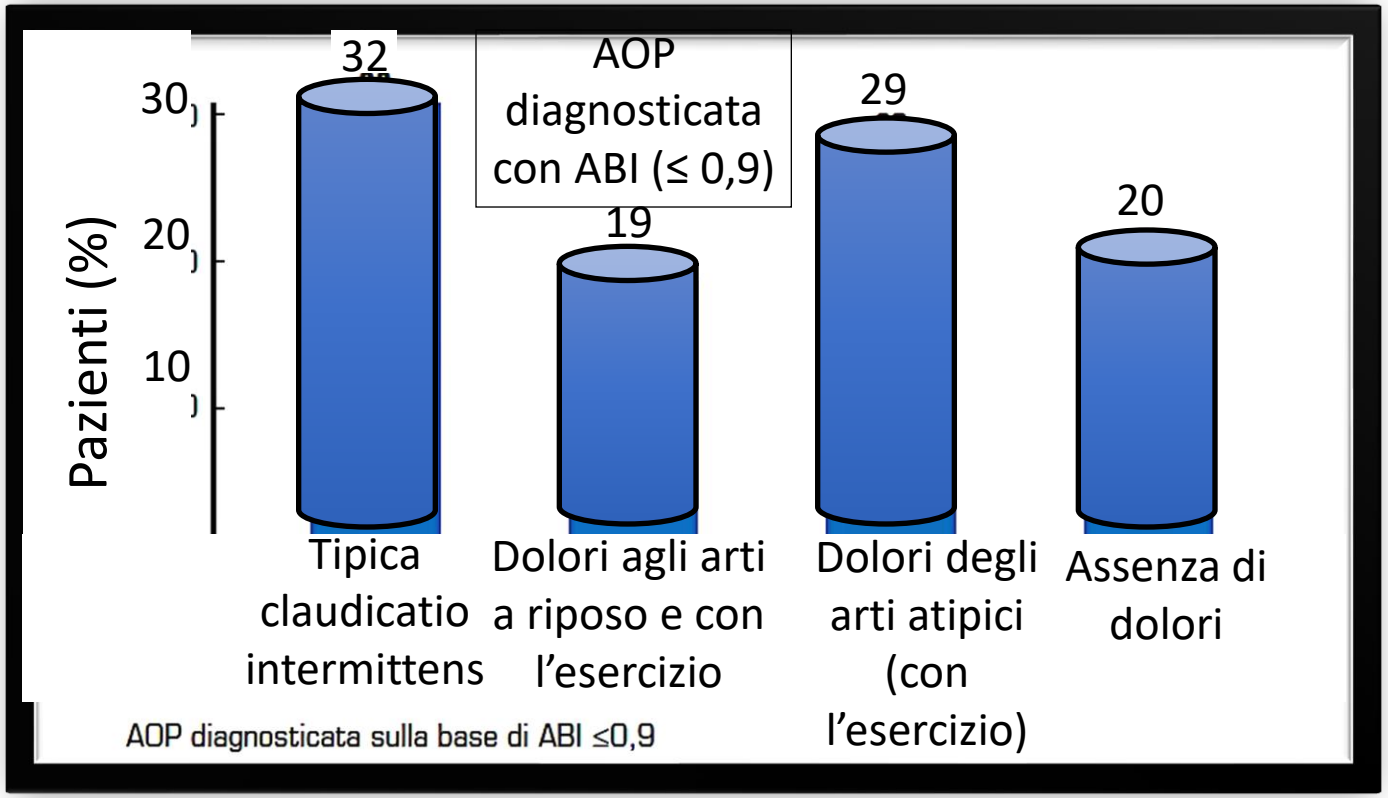


Søgaard et al. Vasa. 2023;52:77-80.72)

Per ogni paziente con PAD sintomatica ci sono altri 3-4 pazienti con PAD asintomatica



45-50% dei pazienti hanno sintomi atipici



McDermott MM, et al. JAMA 2001;286:1599-606
McDermott MM. Circ Res. 2015;116:1540-1550

«Masked» PAD

What is new in the 2017 PAD Guidelines? *(continued)*

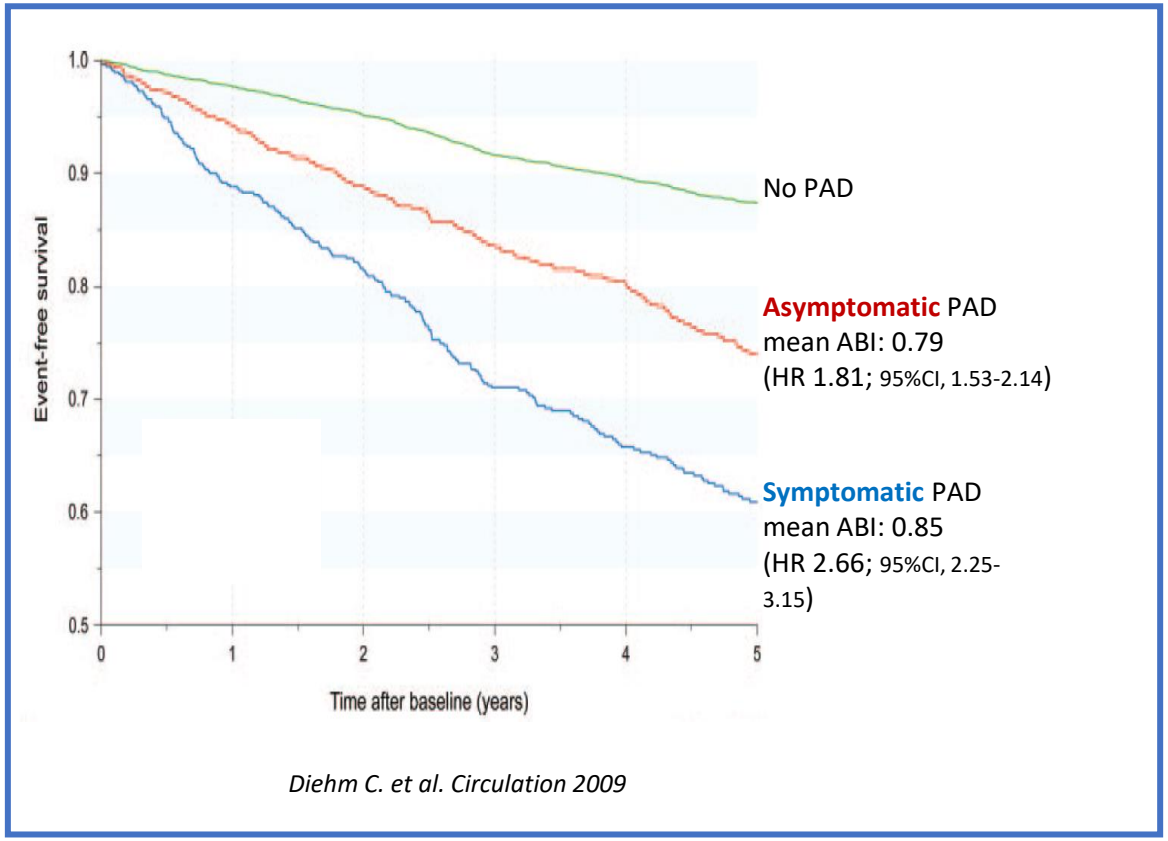
ESC European Society of Cardiology

2017 New/Revised concepts

Lower extremity artery disease:

- Masked LEAD should be individualized from asymptomatic disease.

- "Masked PAD" → pazienti "asintomatici" perché incapaci di camminare una distanza sufficiente a scatenare il dolore.
- In genere si tratta di pazienti con insufficienza cardiaca, problemi articolari, neuropatia diabetica
- I pazienti asintomatici hanno un rischio aumentato di eventi CV
- Quelli con "masked PAD" hanno in aggiunta un rischio aumentato di eventi sfavorevoli (MALE) agli arti inferiori → PAD piu' severa



Diehm C. et al. Circulation 2009

Prima di fare una stima del dolore durante la marcia é quindi necessario stimare le **capacità di deambulazione** di un paziente

Aboyans V, et al, EHJ, 2017; Mc Dermott M., et al, JAMA 2001

PAD SINTOMATICA

Peripheral arterial disease categorized according to clinical presentation

Clinical characteristics of PAD	Rutherford classification		Fontaine classification	
	Category	Signs and symptoms	Stage	Signs and symptoms
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	3	Severe claudication		
Chronic limb-threatening Ischaemia	4	Ischaemic rest pain	III	Ischaemic rest pain
	5	Minor tissue loss	IV	Ischaemic ulceration or gangrene
	6	Major tissue loss		

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Potential differential diagnostic alternatives causing lower limb pain, that may either present with intermittent claudication symptoms or be misclassified as intermittent claudication.

Condition	Location	Characteristics	Effect of exercise	Effect of rest	Effect of position
Baker's cyst	Behind knee	Swelling behind knee and distally. When ruptured, tenderness and calf pain	Worsening of symptoms	None	None
Deep vein thrombosis and venous claudication caused by chronic venous obstruction	Entire lower limb	Ipsilateral oedema, tightness, worse in calf	Worsening of symptoms	Subsides slowly	Relief by elevation
Thromboangiitis obliterans — Buerger's disease	Often bilateral	Young age smokers, pain (most commonly) located in the foot	Worsening of symptoms	Relief with rest	Worse with elevation
Spinal cord stenosis	Often bilateral buttock and lower limbs	Pain, weakness, numbness	May mimic claudication	Variable relief and may take a long time to recover	Relief with lumbar spine flexion
Nerve root compression	Radiates down along the posterior aspect of the lower limb	Sharp pain	Induced mainly by standing and walking	Present at rest and on sitting	Improved by change in position
Hip arthritis	Ipsilateral lower limb — thigh	Pain and discomfort	Worse with exercise	Relief but it takes time	Less symptoms when not weight bearing
Foot or ankle arthritis	Ankle or foot	Pain and discomfort	Worse with exercise	Relief but it takes time	Fewer symptoms when not weight bearing or related to activity level
Chronic exertional compartment syndrome	Lower limb	Pain, swelling, disability	Worse with exercise	Pain even at rest, relief takes time	Worsening or improvement according to position
Popliteal artery entrapment syndrome	Lower limb	Cold feet after exercise Tingling or burning in calf Numbness in the calf area	Worse with exercise	Relief with rest	Flexion of foot results in worsening of symptoms
Cystic adventitial degeneration of the popliteal artery	Calf, always unilateral	Exercise induced pain and discomfort, most common in younger patients	Worse with exercise	Relief with rest	None
Lymphangitis or cellulitis	Entire lower limb, mostly in calf	Ipsilateral pitting oedema, worse in calf	Heaviness	None	None

SVS 2024 Guidelines on Asymptomatic Lower Limb Peripheral Arterial Disease and Intermittent Claudication

CLTI
(Chronic limb threatening ischemia)

Ischemia cronica che minaccia gli arti

Peripheral arterial disease categorized according to clinical presentation

Clinical characteristics of PAD	Rutherford classification		Fontaine classification	
	Category	Signs and symptoms	Stage	Signs and symptoms
Asymptomatic PAD	0	Asymptomatic	I	Asymptomatic
Symptomatic (effort-related) PAD	1	Mild claudication	IIa	Non-disabling intermittent claudication
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	3	Severe claudication		
Chronic limb-threatening Ischaemia	4	Ischaemic rest pain	III	Ischaemic rest pain
	5	Minor tissue loss	IV	Ischaemic ulceration or gangrene
	6	Major tissue loss		

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Assessment of the risk of amputation: the Wound, Ischaemia, and foot Infection classification (1)

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		

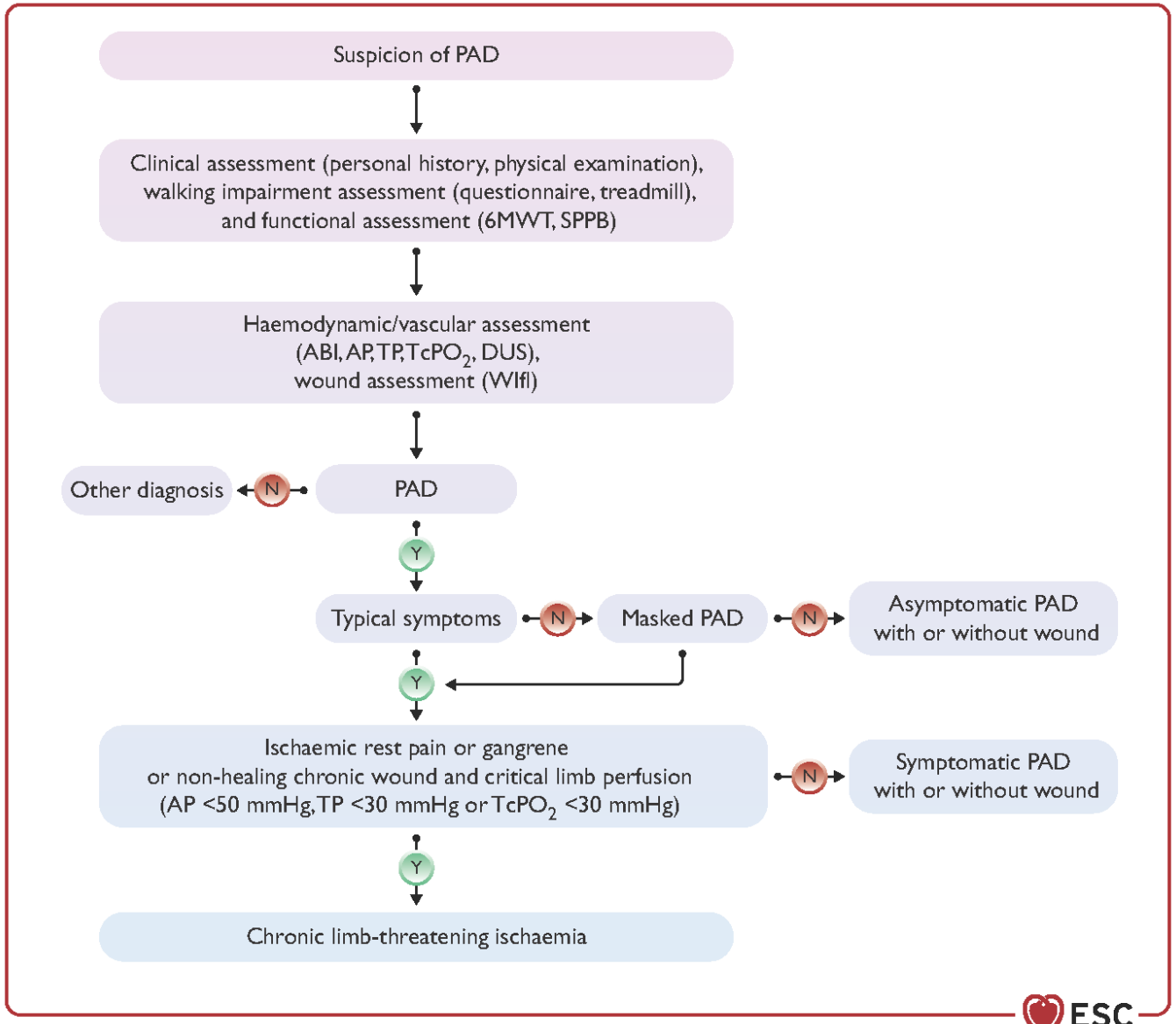
2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Assessment of the risk of amputation: the Wound, Ischaemia, and foot Infection classification (2)

	Ischaemia – 0				Ischaemia – 1					Ischaemia – 2				Ischaemia – 3			
W–0	VL	VL	VL	VL	VL	L	L	M		L	L	M	M	M	H	H	H
W–1	VL	VL	VL	VL	L	M	M	M		M	H	H	H	H	H	H	H
W–2	VL	VL	VL	VL	M	M	H	H		H	H	H	H	H	H	H	H
W–3	VL	VL	VL	VL	M	M	M	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

Figure 9

Diagnostic algorithm for peripheral arterial disease



Caso Clinico

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

ALI
ISCHEMIA ACUTA ARTI INFERIORI

Ischemia acuta 6 P di Pratt

Pain	Dolore
Pallor	Pallore
Pulselessness	Assenza dei polsi periferici
Paresthesia	Parestesie (disestesie, iperestesia, ipo-anestesia)
Paralysis	Paralisi periferica (deficit motorio più o meno esteso)
Poikilothermia	Freddo

Clinical categories of acute limb ischaemia

Grade	Category	Sensory loss	Motor deficit	Arterial Doppler signal	Venous Doppler signal	Capillary refill	Biomarkers	Prognosis
I	Viable	None	None	Yes	Yes	Yes	Not elevated	No immediate threat
IIA	Marginally threatened	None or minimal (toes)	None	No	Yes			Salvageable if promptly treated
IIB	Immediately threatened	More than toes	Mild-moderate	No	Yes			Salvageable if promptly revascularized
III	Irreversible	Profound, anaesthetic	Profound paralysis (rigor)	No	No	No	Massively elevated	Major tissue loss, permanent nerve damage inevitable

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Recommendations for the management of patients presenting with acute limb ischaemia (1)

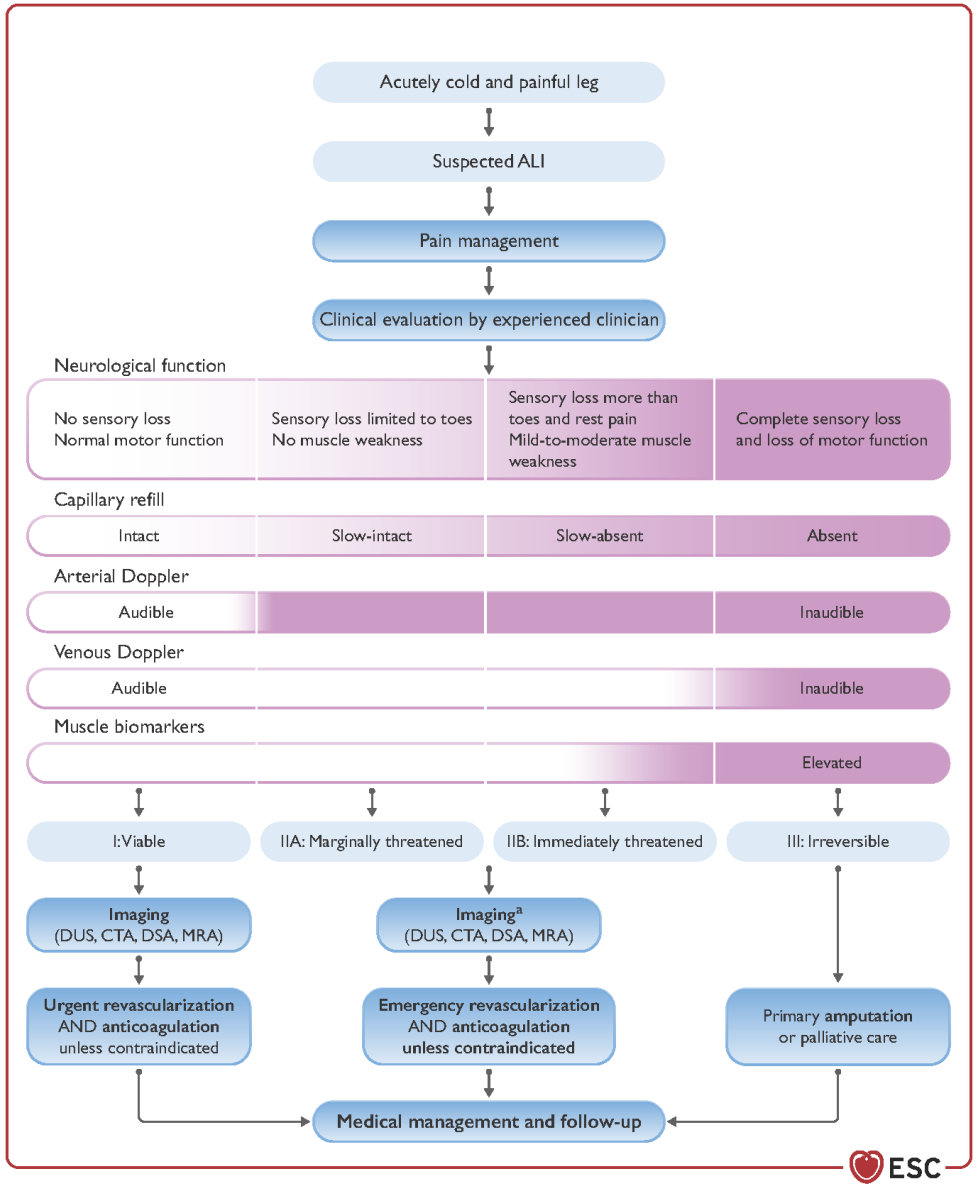
Recommendations	Class	Level
In patients with ALI, it is recommended that an urgent evaluation is performed by a vascular clinician with sufficient experience to assess limb viability and implement appropriate therapy.	I	C
In cases of neurological deficit, urgent revascularization is recommended; diagnostic imaging is recommended to guide treatment, provided it does not delay treatment, or if the need for primary amputation is obvious.	I	C
In the absence of severe neurological deficit, revascularization is recommended within hours of initial imaging in a case-by-case decision.	I	C
Treatment with analgesics is recommended as soon as possible for pain control.	I	C
It is recommended to monitor for compartment syndrome after revascularization and treat (fasciotomy).	I	C
It is recommended to assess clinical and haemodynamic success following revascularization.	I	C

Recommendations for the management of patients presenting with acute limb ischaemia (2)

Recommendations cont.	Class	Level
In patients with ALI, it is recommended to obtain a comprehensive medical history and determine the cause of thrombosis and/or embolization.	I	C
In patients with ALI, following revascularization if not on anticoagulation for other reasons, DAPT or rivaroxaban (2.5 mg b.i.d.) and aspirin (100 mg o.d.) should be considered.	IIa	C
Upon confirmation of ALI diagnosis, treatment with heparin may be considered.	IIb	C

Figure 16

Management of acute limb ischaemia



2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

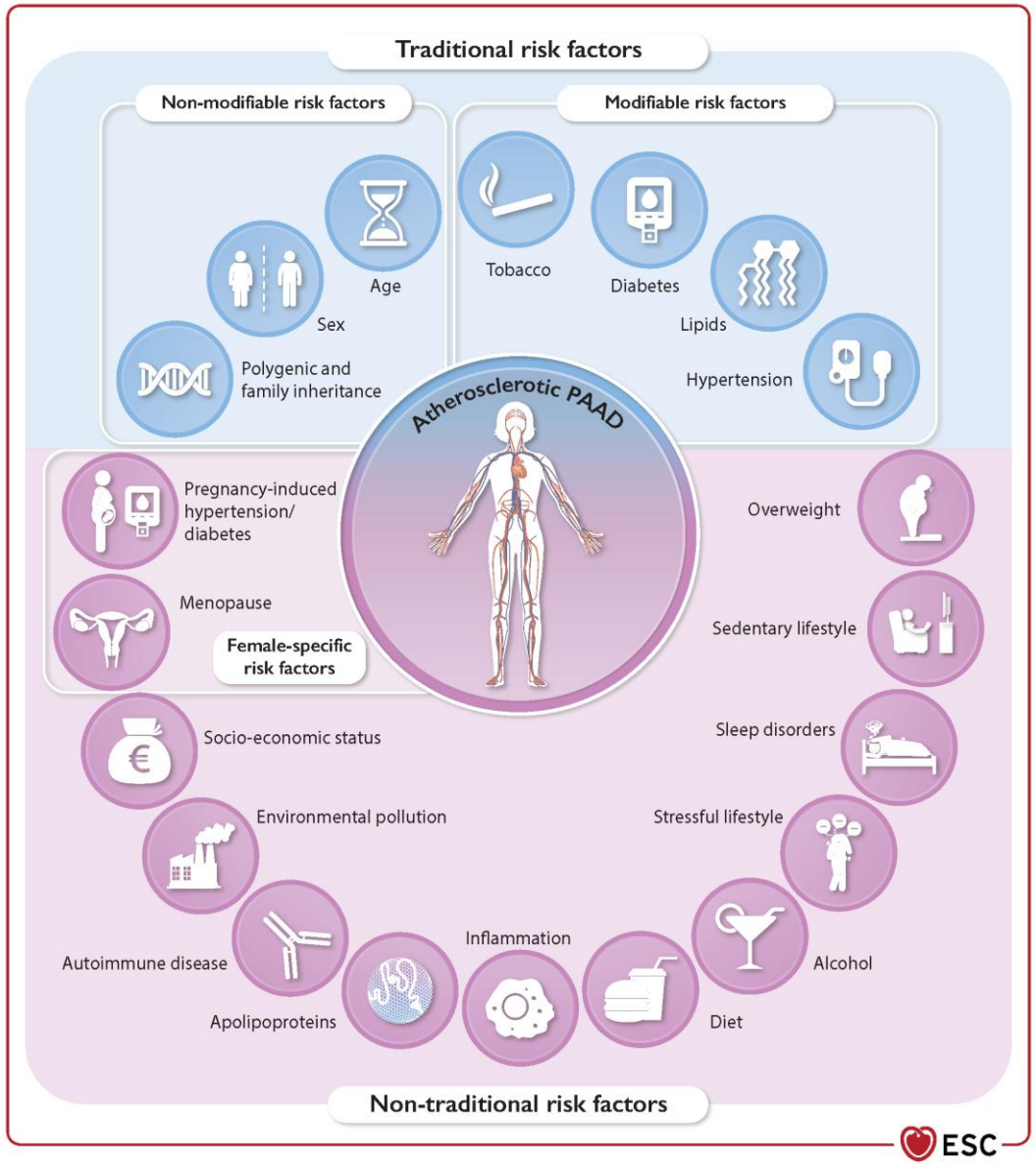
ALI
Ischemia acuta

…….. Caso Clinico atipico

PAD
TERAPIA MEDICA

Figure 3

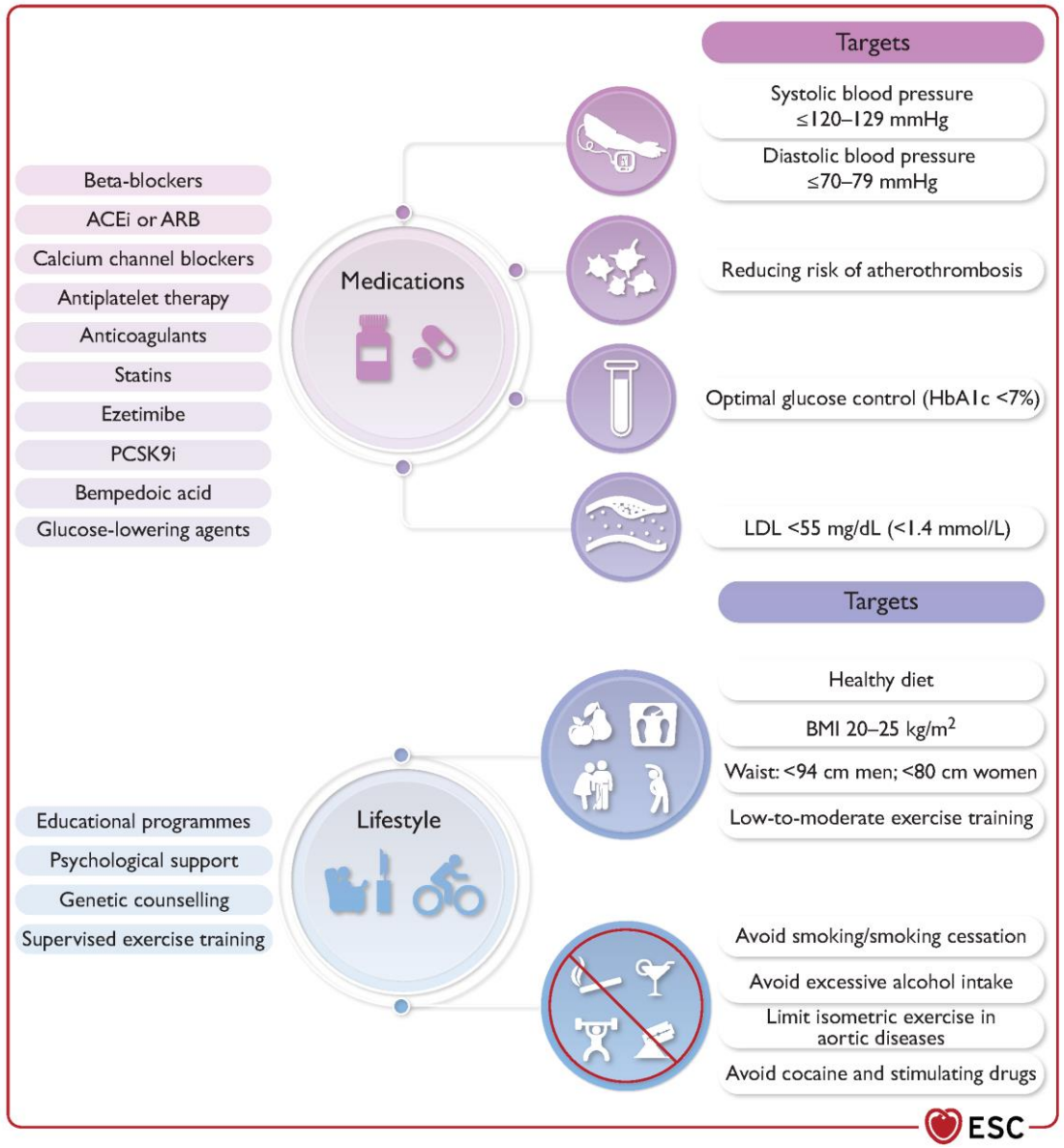
Main risk factors associated with atherosclerosis in peripheral arterial and aortic diseases



2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Figure 7

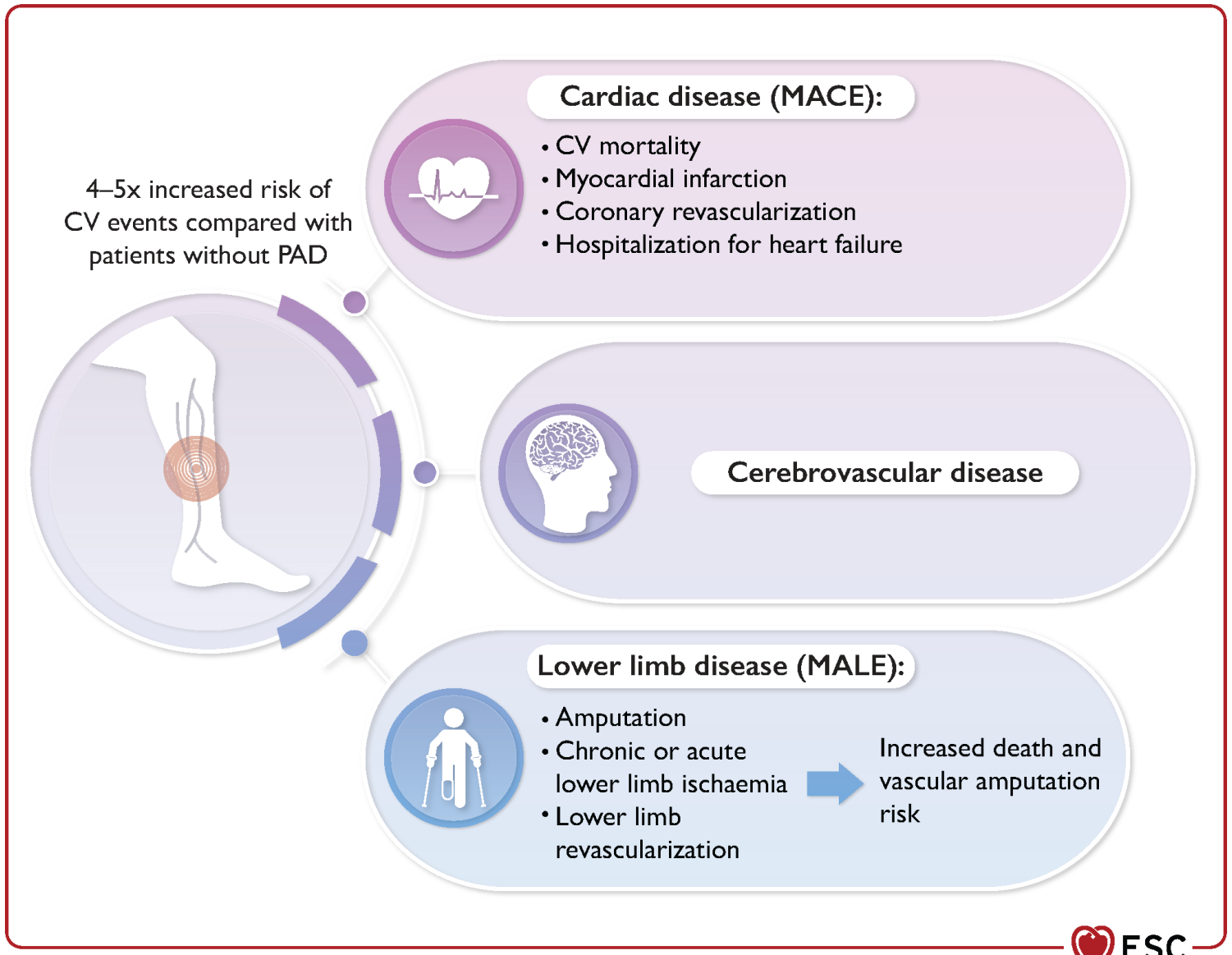
Cardiovascular risk modification and healthy lifestyle interventions and targets in patients with peripheral arterial and aortic diseases



2024 ESC Guidelines for the management peripheral arterial and aortic diseases (European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Figure 8

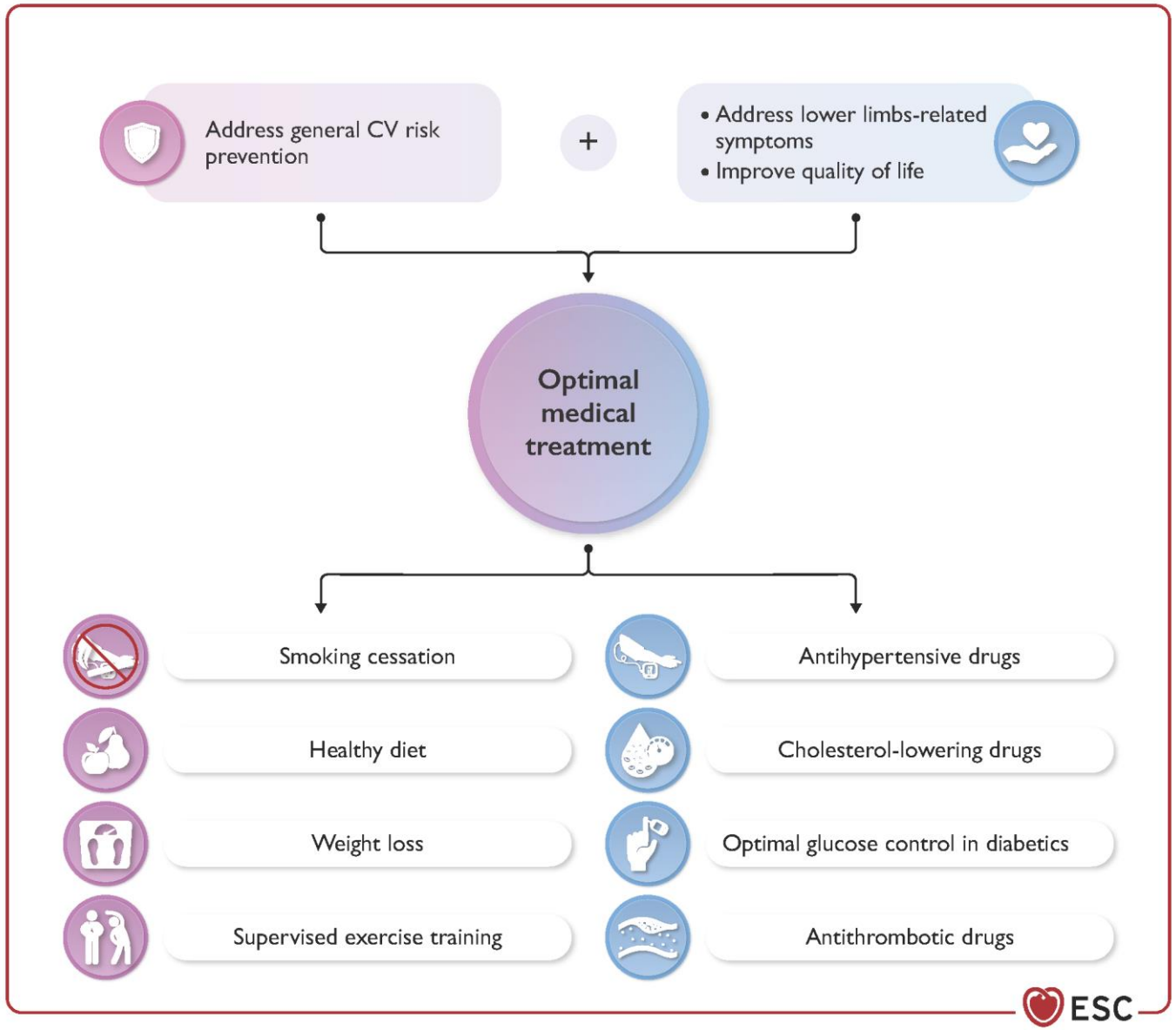
Cardiovascular risk in patients with peripheral arterial disease



2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Figure 10

Optimal medical treatment in patients with peripheral arterial disease



2024 ESC Guidelines for the management peripheral arterial and aortic diseases (European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

PAD e CI

Stili di vita
Esercizio fisico
Terapia Farmacologica per sintomi

Figure 1. Life's Essential 8.
Life's Essential 8 includes the 8 components of cardiovascular health: healthy diet, participation in physical activity, avoidance of nicotine, healthy sleep, healthy weight, and healthy levels of blood lipids, blood glucose, and blood pressure.

Lloyd-Jones et al, Circulation 2022

FUMO

Recommendations for patients with lower extremity artery disease: best medical therapy		
Smoking cessation is recommended in all patients with LEAD.	I	B
Healthy diet and PA are recommended for all patients with LEAD.	I	C
In patients with intermittent claudication: • Supervised exercise training is recommended	I	A
• Non-supervised exercise training is recommended when supervised exercise training is not feasible or available.	I	C
Antiplatelet therapy is recommended in patients with symptomatic LEAD.	I	C
In patients with LEAD and hypertension, it is recommended to control BP at <140/90 mmHg.	I	A
In patients with LEAD and DM, strict glycaemic control is recommended.	I	A

ESC Prevention 2021

‘Very brief advice’ for smoking cessation

‘Very brief advice’ on smoking is a proven 30-second clinical intervention, developed in the UK, which identifies smokers, advises them on the best method of quitting, and supports subsequent quit attempts. There are three elements to very brief advice:

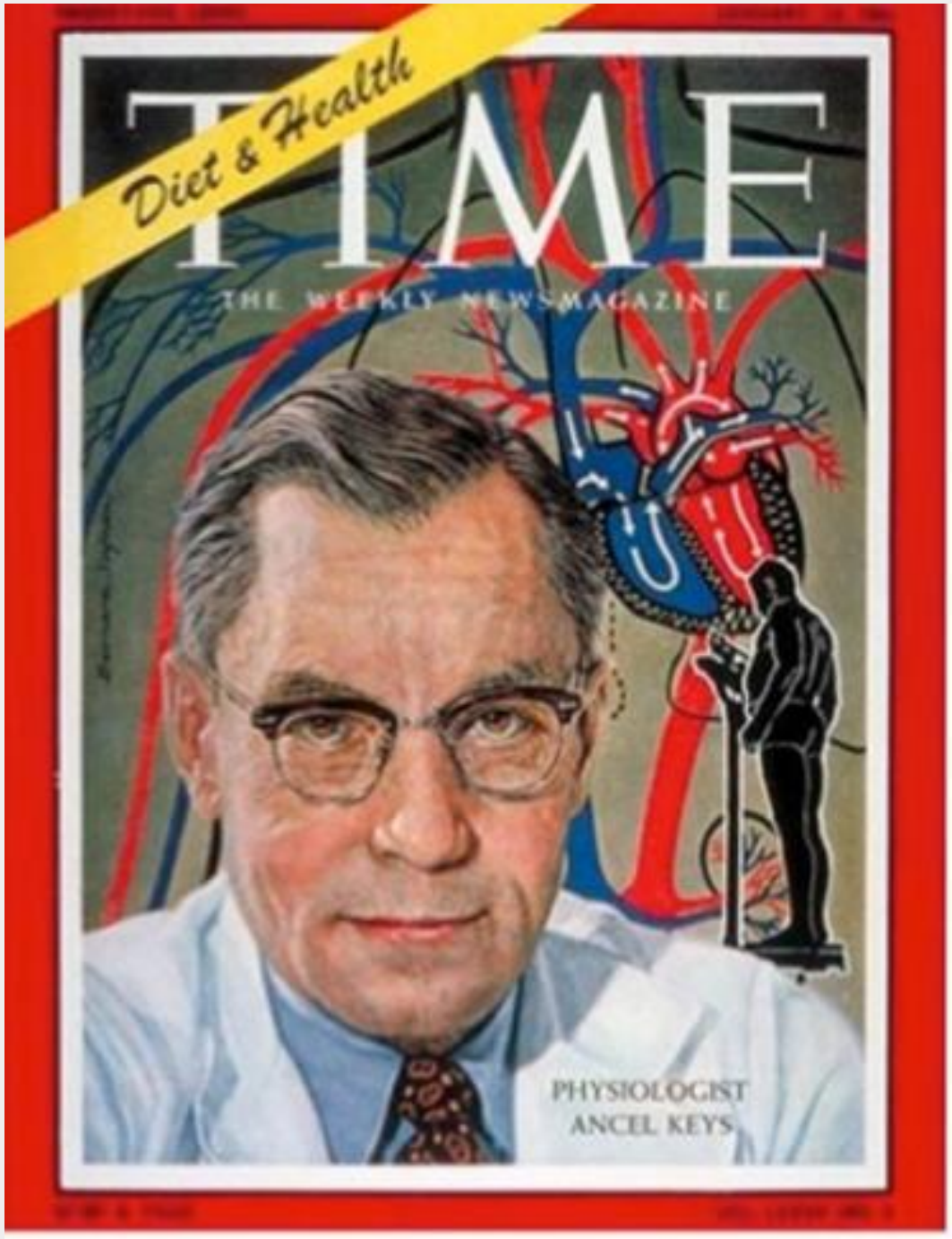
- ASK - establishing and recording smoking status
- ADVISE - advising on the best ways of stopping
- ACT - offering help

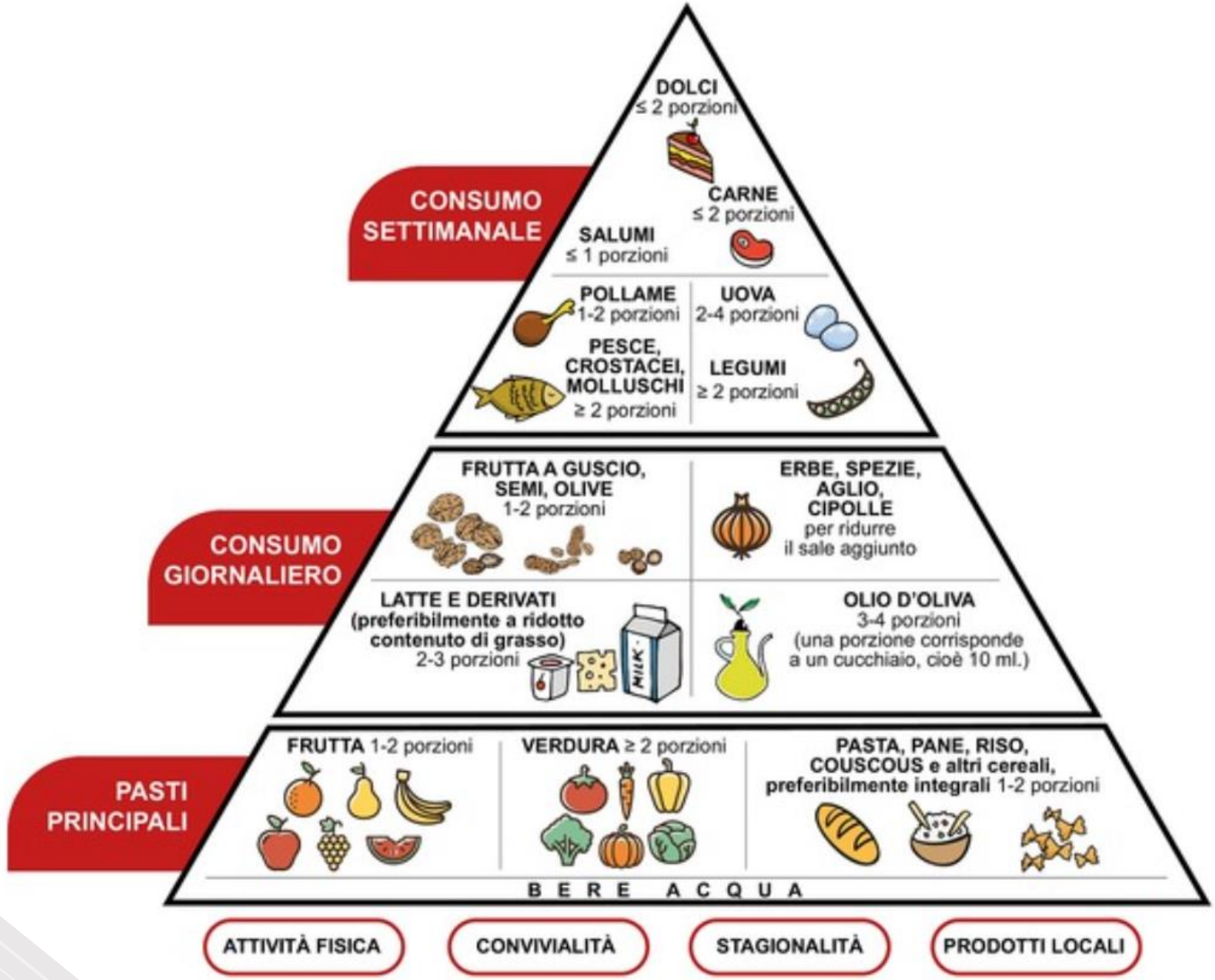
Recommendations for smoking intervention strategies

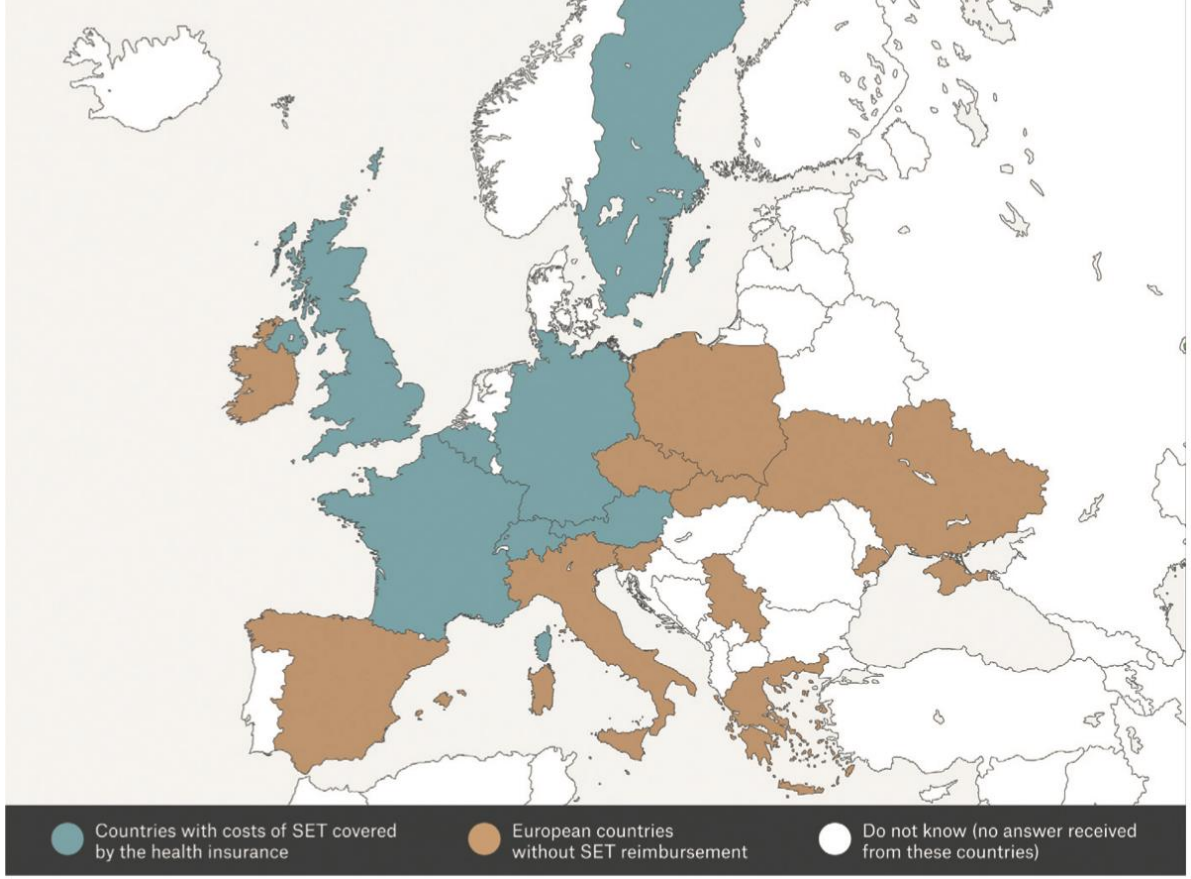
Recommendations	Class[a]	Level[b]
All smoking of tobacco should be stopped, as tobacco use is strongly and independently causal of ASCVD.[487,488]	I	A
In smokers, offering follow-up support, nicotine replacement therapy, varenicline, and bupropion individually or in combination should be considered.[489–494]	IIa	A
Smoking cessation is recommended regardless of weight gain, as weight gain does not lessen the ASCVD benefits of cessation.[495]	I	B

ASCVD = atherosclerotic cardiovascular disease.
[a]Class of recommendation.
[b]Level of evidence.

Recommendations	Class[a]	Level[b]
Smoking cessation is recommended in all patients with LEAD.[29,781]	I	B
Healthy diet and PA are recommended for all patients with LEAD.	I	C
In patients with intermittent claudication: • Supervised exercise training is recommended[782–784]	I	A
• Non-supervised exercise training is recommended when supervised exercise training is not feasible or available.	I	C
Antiplatelet therapy is recommended in patients with symptomatic LEAD.[c]	I	C
In patients with LEAD and hypertension, it is recommended to control BP at <140/90 mmHg.[776,785,786]	I	A
In patients with LEAD and DM, strict glycaemic control is recommended.[768]	I	A
ACE inhibitors or ARBs should be considered as first-line therapy in patients with PAD and hypertension.[d] [575,787]	IIa	B
In patients with DM and chronic symptomatic LEAD without high bleeding risk, a combination of low-dose rivaroxaban (2.5 mg *b.i.d.*) and aspirin (100 mg *o.d.*) may be considered.[774]	IIb	B


Diet & Health
TIME
THE WEEKLY NEWSMAGAZINE
PHYSIOLOGIST
ANCEL KEYS


CONSUMO SETTIMANALE
DOLCI
≤ 2 porzioni
CARNE
≤ 2 porzioni
SALUMI
≤ 1 porzioni
POLLAME
1-2 porzioni
UOVA
2-4 porzioni
PESCE, CROSTACEI, MOLLUSCHI
≥ 2 porzioni
LEGUMI
≥ 2 porzioni
CONSUMO GIORNALIERO
FRUTTA A GUSCIO, SEMI, OLIVE
1-2 porzioni
ERBE, SPEZIE, AGLIO, CIPOLLE
per ridurre il sale aggiunto
LATTE E DERIVATI
(preferibilmente a ridotto contenuto di grasso)
2-3 porzioni
MILK
OLIO D'OLIVA
3-4 porzioni
(una porzione corrisponde a un cucchiaio, cioè 10 ml.)
PASTI PRINCIPALI
FRUTTA 1-2 porzioni
VERDURA ≥ 2 porzioni
PASTA, PANE, RISO, COUSCOUS e altri cereali, preferibilmente integrali 1-2 porzioni
BERE ACQUA
ATTIVITÀ FISICA
CONVIVIALITÀ
STAGIONALITÀ
PRODOTTI LOCALI

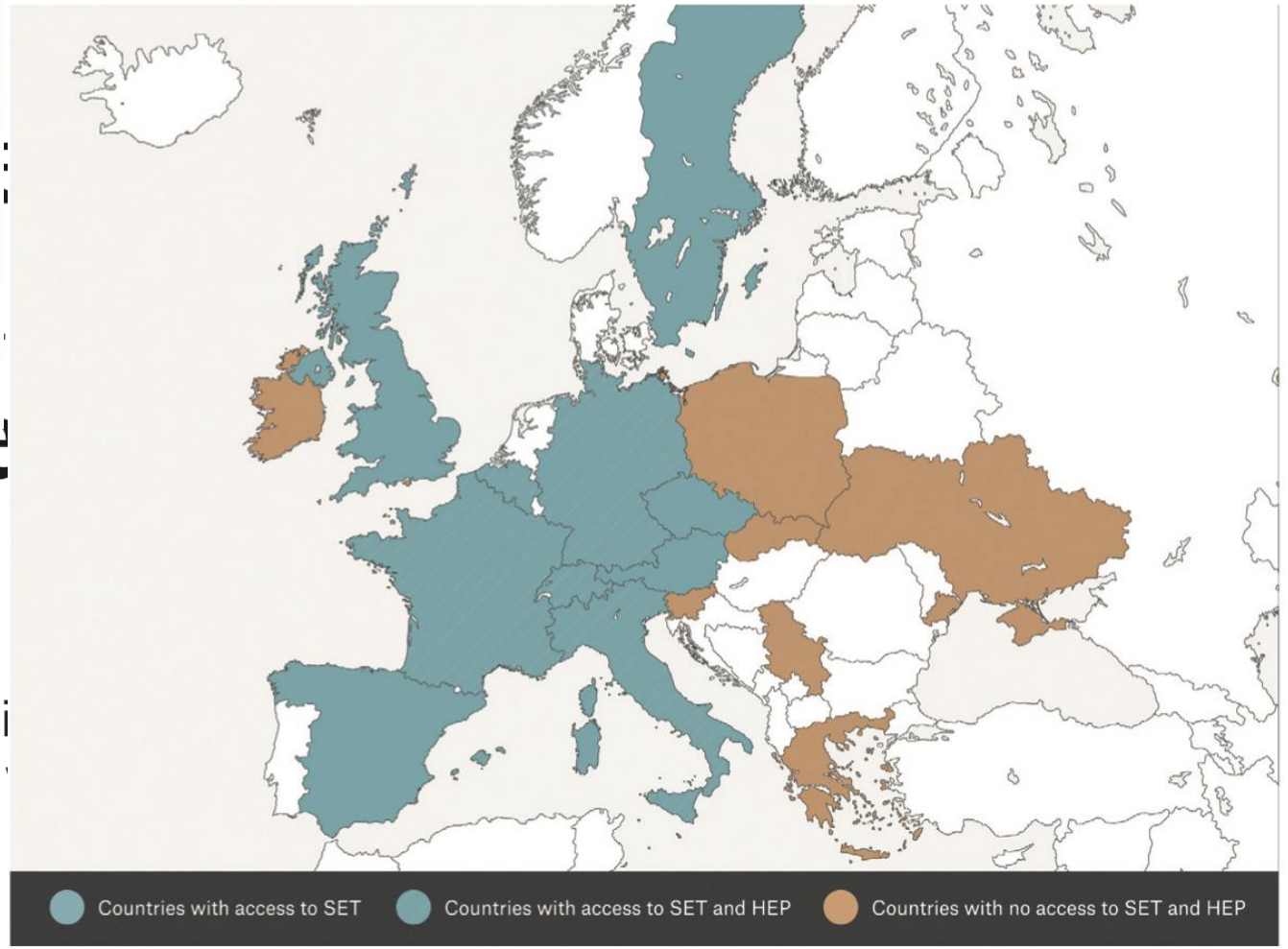


European Society of Vascular Medicine

peripheral arte

A European overview

Stefano Lanzi[1], Jill Belch[2], Mari
Alessandra Bura-Riviere[5], Adriana



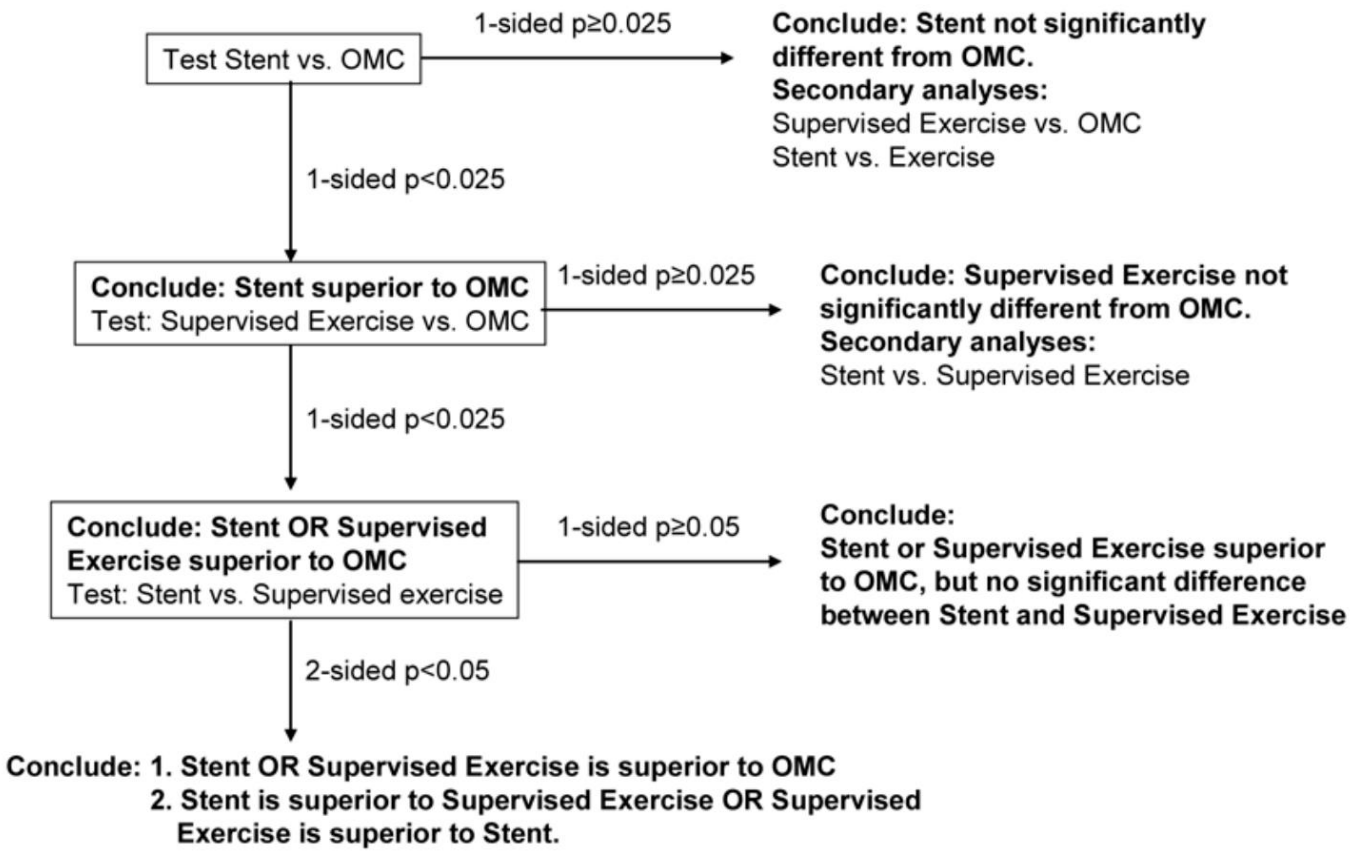


Figure 2.
Claudication: Exercise Vs. Endoluminal Revascularization (CLEVER) trial statistical analysis

CLEVER

Primary Endpoints:

- Peak walking time on a graded treadmill test

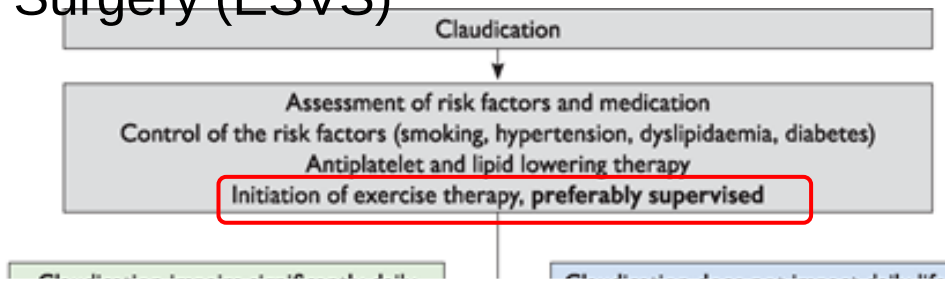
Secondary Endpoints:

- Free-living step activity
- Quality of life
- Cardiovascular disease markers
- Major adverse cardiac events

Murphy TP, JVS 2008

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

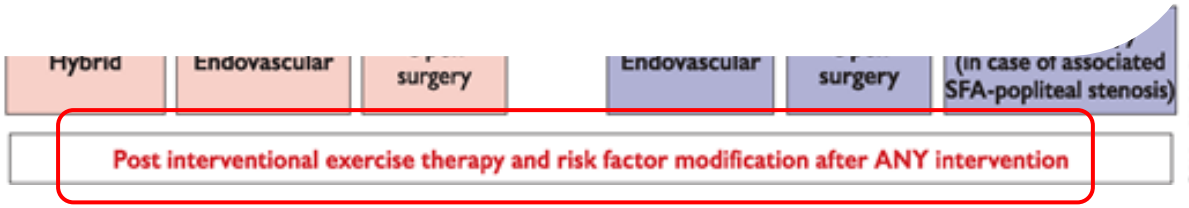
ement of patients with intermittent claudication **audication**



In patients with intermittent claudication:		
• supervised exercise training is recommended,	I	A
• unsupervised exercise training is recommended when supervised exercise training is not feasible or available.	I	C

ESC European Society of Cardiology

esvs



Cochrane Library

Cochrane Database of Systematic Reviews

Exercise for intermittent claudication (Review)

Lane R, Harwood A, Watson L, Leng GC.

Exercise for intermittent claudication.

Cochrane Database of Systematic Reviews 2017, Issue 12.

CONCLUSIONS

High-quality evidence shows that exercise programmes provided **important benefit** compared with placebo or usual care **in improving both pain-free and maximum walking distance** in people with **leg pain from IC who were considered to be fit for exercise intervention**.

Exercise **did not improve ABI, and we found no evidence of an effect of exercise on amputation or mortality.** Exercise may improve quality of life when compared with placebo or usual care. As time has progressed, the trials undertaken have begun to include exercise versus exercise or other modalities; therefore we can include fewer of the new trials in this update.

Cochrane Library

Cochrane Database of Systematic Reviews

Supervised exercise therapy versus home-based exercise therapy versus walking advice for intermittent claudication (Review)

Hageman D, Fokkenrood HJP, Gommans LNM, van den Houten MML, Teijink JAW.

Supervised exercise therapy versus home-based exercise therapy versus walking advice for intermittent claudication. *Cochrane Database of Systematic Reviews* 2018, Issue 4.

Conclusions

- Evidence of moderate and high quality shows that **SET provides an important benefit for treadmill-measured walking distance (MWD and PFWD)** compared with HBET and WA, respectively. Although its clinical relevance has not been definitively demonstrated, this benefit translates to increased MWD of 120 and 210 meters after three months in SET groups. These increased walking distances are likely to have a positive impact on the lives of patients with IC.
- Data provide **no clear evidence of a difference between HBET and WA.** Trials show no clear differences **in quality of life parameters nor in self-reported functional impairment between SET and HBET.** However, evidence is of low and very low quality, respectively. Investigators detected some improvements in quality of life **favoring SET over WA, but analyses were limited by small numbers of studies and participants**. Future studies should focus on disease-specific quality of life and other functional outcomes, such as walking behavior and physical activity, as well as on long-term follow-up.

MWD= Maximal walking distance; PFWD= Pain free walking distance *HBET*= Home based exercise Therapy; *WA*= Walking Advice

Cochrane Library

Cochrane Database of Systematic Reviews

Endovascular revascularisation versus conservative management for intermittent claudication (Review)

Fakhry F, Fokkenrood HJP, Spronk S, Teijink JAW, Rouwet EV, Hunink MGM. Endovascular revascularisation versus conservative management for intermittent claudication. *Cochrane Database of Systematic Reviews* 2018, Issue 3.

CONCLUSIONS

- In the management of patients with IC, **endovascular revascularisation does not provide significant benefits compared with supervised exercise alone in terms of improvement in functional performance or QoL.**
- Although the number of studies is small and clinical heterogeneity underlines the need for more homogenous and larger studies, evidence suggests that a **synergetic effect may occur when endovascular revascularisation is combined with a conservative therapy of supervised exercise or pharmacotherapy with cilostazol**: the combination therapy seems to result in greater improvements in functional performance and in QoL scores than are seen with conservative therapy alone.

European Society for Vascular Medicine

GUIDELINE ON PERIPHERAL ARTERIAL DISEASE

Recommendation	Class of recommendation	Level of evidence
It is recommended that structured walking training is to be offered to all PAD patients with intermittent claudication as an inherent part of basic treatment.	I	B
It is recommended that supervised training programs under regular instruction be offered as they are more effective than unstructured vascular training.	I	B
It is recommended that a supervised Vascular workout in patients with intermittent claudication should take place at least 3 times a week for at least 30-minutes over at least 3 months.	I	B
Daily individual vascular training should be considered in the conservative treatment of patients with intermittent claudication, if no supervised training programs are available. It is less effective than supervised programmes.	IIa	B

VASA 2019

Circulation

AHA SCIENCE ADVISORY

Implementation of Supervised Exercise Therapy for Patients With Symptomatic Peripheral Artery Disease

A Science Advisory From the American Heart Association

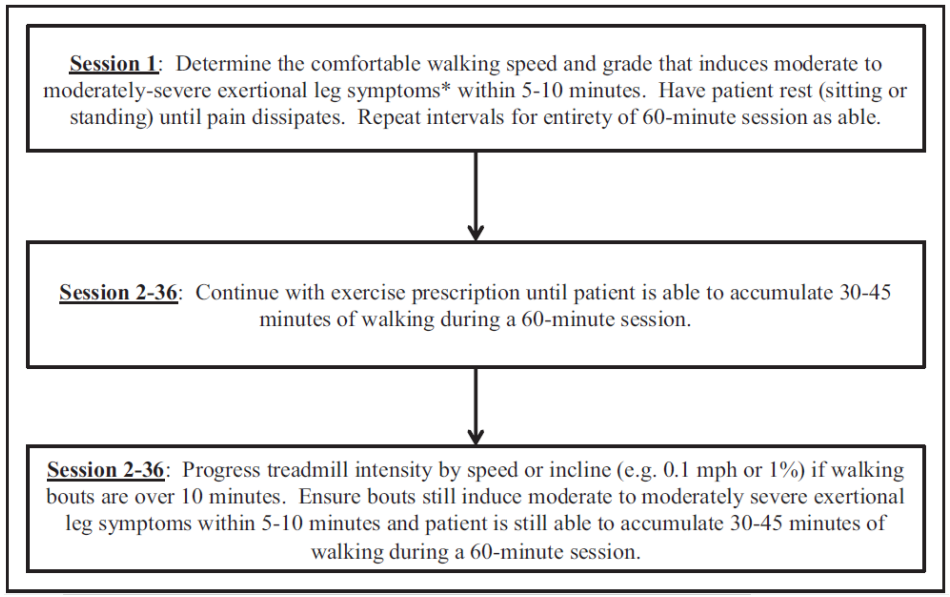
Supervised Exercise Training Must	Physician Referral Must Include	What Is Covered
Consist of at least 30- to 60-min sessions of therapeutic exercise training in patients who have symptomatic PAD	A face-to-face visit with the physician responsible for PAD treatment	Up to 36 individual sessions
Be conducted in a hospital outpatient setting or a physician's office	Patient receipt of information on cardiovascular disease and PAD risk factor reduction, which should include education, counseling, behavioral interventions, and outcome assessments; smoking cessation should be a cornerstone of risk factor counseling	Delivered over 12 wk
Be delivered by qualified personnel to ensure that benefits exceed harms; personnel should be trained in SET for PAD	A statement or *ICD-10* code that demonstrates that the patient is diagnosed with symptomatic PAD	May cover additional 36 sessions over an extended period of time with MAC approval
Be under the direct supervision of a physician [as defined in section 1861(r)(1)] of the Social Security Act, physician assistant, or nurse practitioner/clinical nurse specialist [as identified in Section 1861(aa)(5) of the Social Security Act] who must be trained in both basic and advanced life support techniques	An ABI is not required	A second referral is required for the additional 36 sessions
	Pain level rating is not required	Medicare covers a lifetime limit of 72 sessions (fee for service)

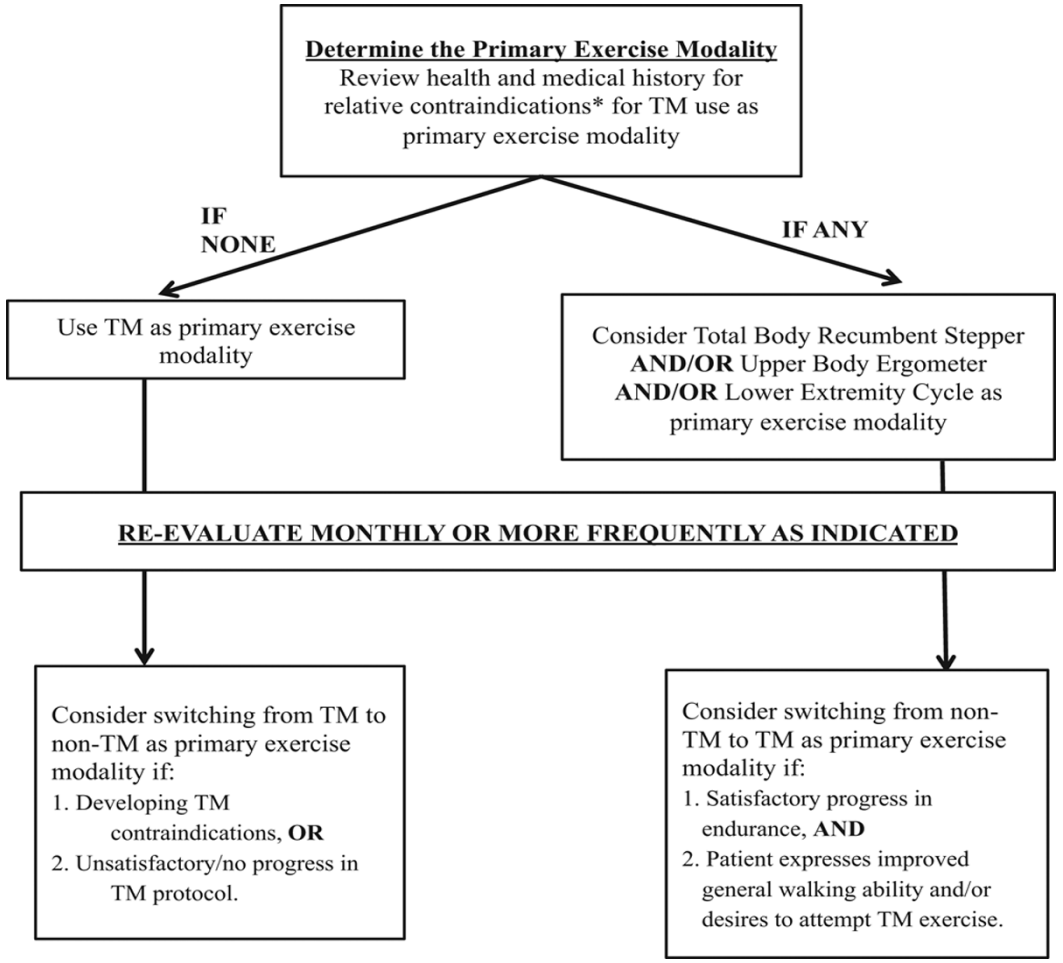
DT JACOBSON, AHA Circulation 2019

Modalità di esercizio per arteriopatia periferica

Table 3. An Exercise Test Is Indicated for the Following Underlying Cardiac Conditions

Myocardial infarction in the past 12 mo
History of stable angina pectoris
Heart failure
Prior coronary artery bypass surgery
Prior coronary angioplasty or coronary stent
Prior heart valve repair or replacement
Heart or heart-lung transplantation





*Relative contraindications to treadmill exercise include moderate to severe claudication within 1 to 2 minutes of normal paced walking, current foot wound, history of falls, shuffling or unsteady gait, or patient desire to avoid treadmill exercise.

DT JACOBSON, AHA Circulation 2019

ESC European Society of Cardiology

European Heart Journal (2024) **45**, 1–19
https://doi.org/10.1093/eurheartj/ehad734

SPECIAL ARTICLE
Vascular biology and medicine

Exercise therapy for chronic symptomatic peripheral artery disease

A clinical consensus document of the European Society of Cardiology Working Group on Aorta and Peripheral Vascular Diseases in collaboration with the European Society of Vascular Medicine and the European Society for Vascular Surgery

Lucia Mazzolai [1*†], Jill Belch[2†], Maarit Venermo [3,4†], Victor Aboyans [5,6], Marianne Brodmann[7], Alessandra Bura-Rivière[8], Sebastien Debus[9], Christine Espinola-Klein [10], Amy E. Harwood[11], John A. Hawley[12], Stefano Lanzi [1], Juraj Madarič[13,14], Guillaume Mahé[15,16], Davide Malatesta[17], Oliver Schlager [18], Arno Schmidt-Trucksäss[19], Chris Seenan[20], Henrik Sillesen[21,22], Garry A. Tew[23], and Adriana Visonà[24]

Exercise training approaches in patients with peripheral artery disease.

Exercise therapy for peripheral artery disease

Included patients

- Women and men with symptomatic chronic peripheral artery disease
- Patients undergoing revascularization

Initial exercise training

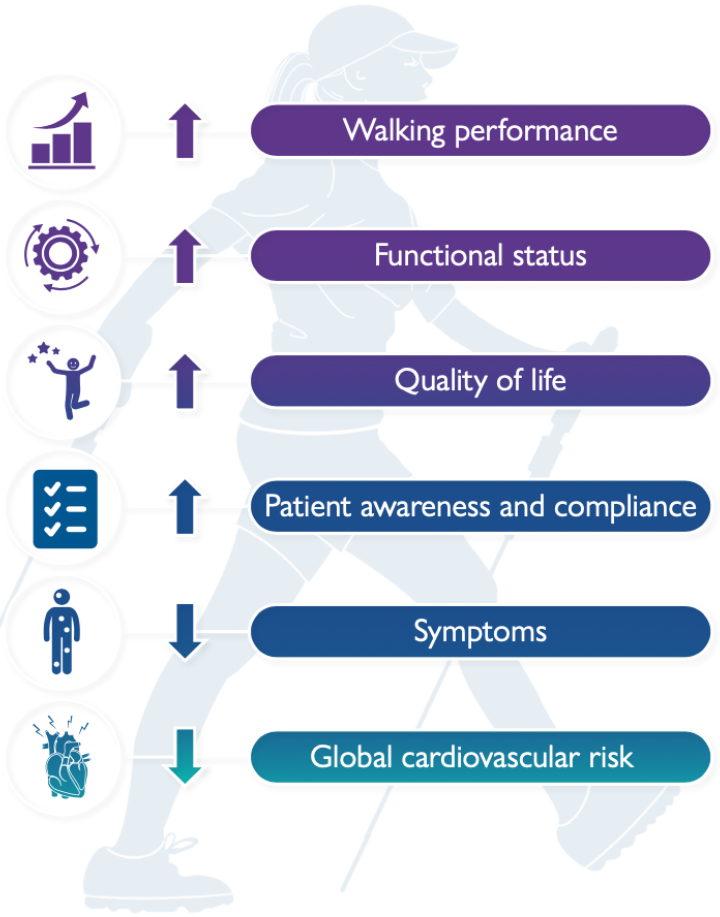
- Supervised exercise or home-based training programmes
- ***Training frequency***: at least 3 times per week
- ***Training modality***: intermittent bouts of walking alternating with periods of rest are the first option.
- ***Claudication pain intensity***: Based on strong evidence, patients should exercise to moderate-high claudication pain.
- ***Exercise intensity:*** begin with a "lead-in period" of low-to-moderate intensity followed by, if tolerated, a graduate progression to vigorous exercise intensity
- ***Session duration***: at least 30 minutes
- ***Programme duration***: at least 12 weeks
- Programmes should include information and guidance on peripheral artery disease, cardiovascular risk factors, and lifestyle aiming for longer-term behaviour change

Assessments before and after exercise therapy

- Complete medical history, physical examination, and screening for contraindications
- Functional assessment
- Quality of life assessment
- Vascular assessments

Chronic exercise training

- Following initial exercise training (supervised or home-based), patients are encouraged to sustain lifelong and high levels of regular physical activity



Dynamic exercise training induces extensive remodelling of the vascular system. Skeletal muscle contraction is associated with several physiological, metabolic, and mechanical mechanisms that when repeated over several weeks and months result in mitochondrial biogenesis, angiogenesis, and increases in the functional capacity of individuals with peripheral arterial disease.

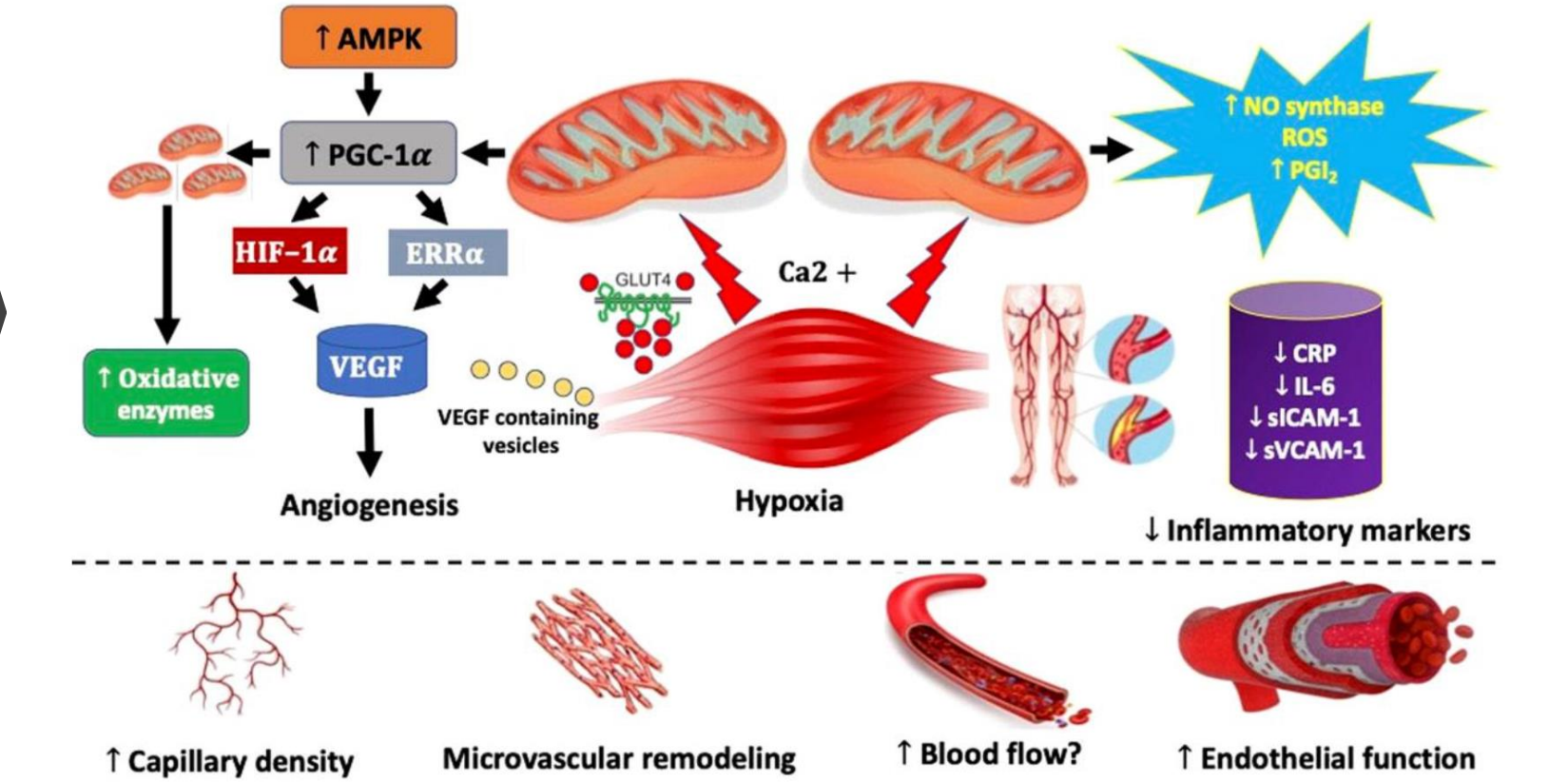
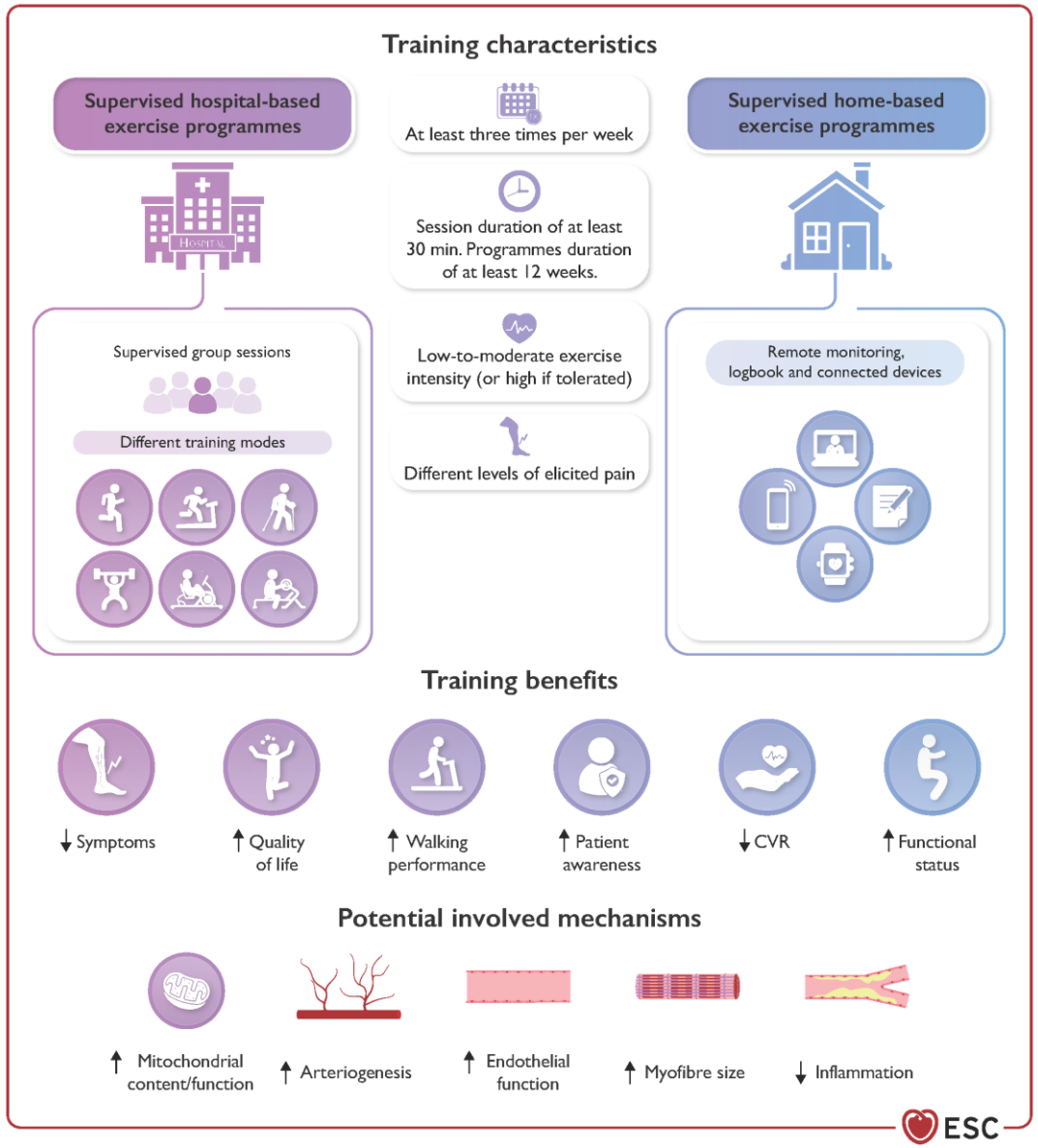
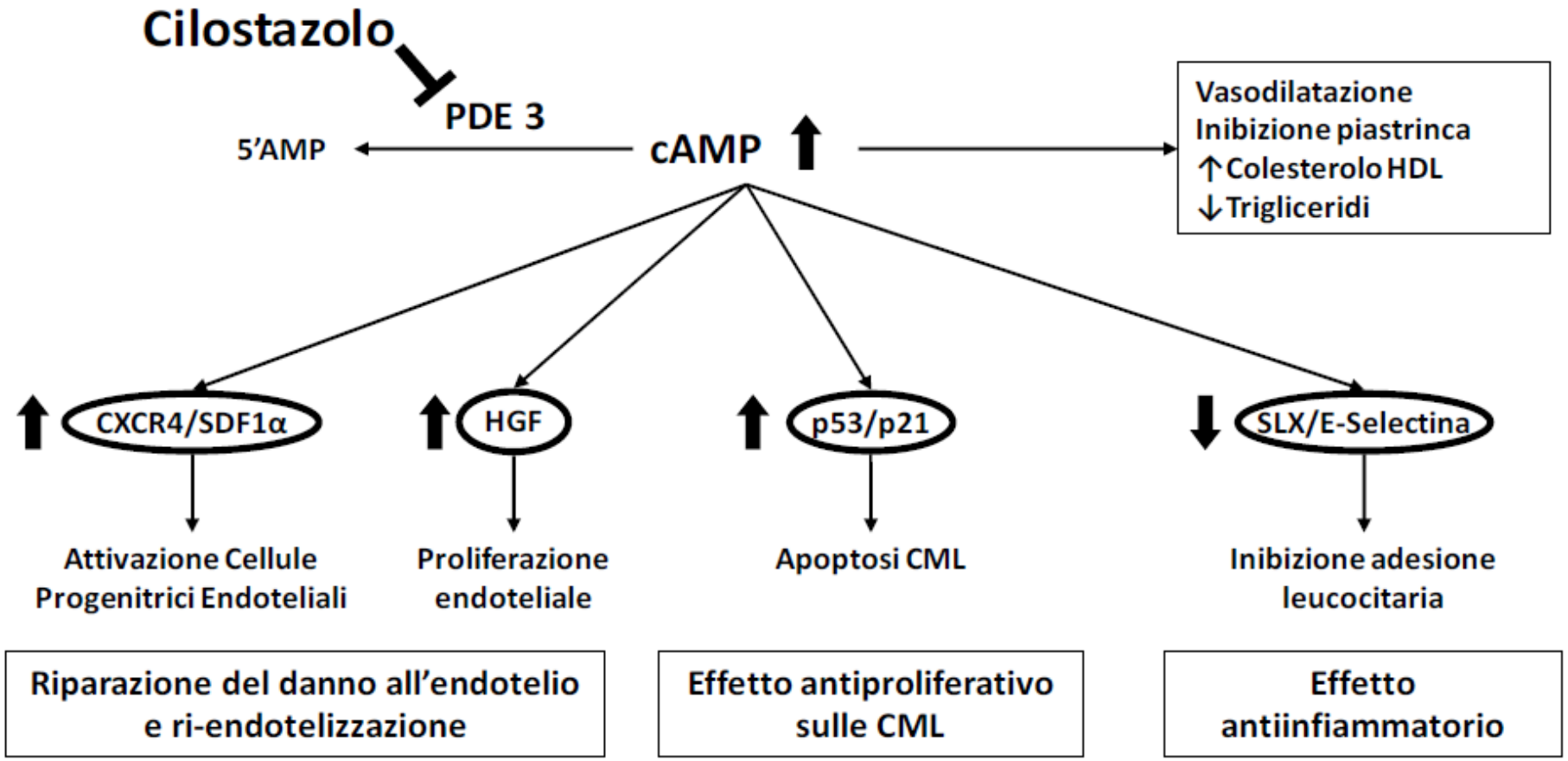


Figure 13

Exercise training characteristics and benefits in patients with peripheral arterial disease



2024 ESC Guidelines for the management peripheral arterial and aortic diseases (European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)



Cilostazolo: meccanismo d'azione

Azione del cilostazolo sull'endotelio

- **Cilostazolo è l'unico agente antitrombotico a bersaglio endoteliale:**
  - Migliora la funzione endoteliale
  - Riduce il numero di piastrine attivate interagendo con le cellule endoteliali attivate
  - Inibisce la produzione di MCP-1 (Nishio Y e coll., Horm Metab Res, 1997) *
  - A differenza di ASA e ticlopidina non prolunga il tempo di emorragia

* MCP1 Monocyte Chemotactant Protein 1

Indicazioni

- **CILOSTAZOLO** è indicato per aumentare la distanza percorsa a piedi senza dolore e la distanza massima in pazienti con claudicatio intermittens, senza dolore a riposo e senza necrosi dei tessuti periferici (arteriopatia periferica – classe Fontaine II);

- **CILOSTAZOLO** è indicato in seconda linea, in pazienti nei quali modifiche dello stile di vita (compreso smettere di fumare e programmi di attività fisica [con supervisione]) e altri interventi appropriati non hanno migliorato in modo sufficiente i sintomi della claudicatio intermittens.

Obiettivi della terapia con CILOSTAZOLO

- Prevenzione della progressione della vasculopatia
- Prevenzione complicanze cardiovascolari
- Riduzione dei sintomi
- Miglioramento dell’attività fisica
- Miglioramento della qualità della vita

Efficacia del cilostazolo nei trial clinici

Cochrane Library
Cochrane Database of Systematic Reviews

Cilostazol for intermittent claudication (Review)

Bedenis R, Stewart M, Cleanthis M, Robless P, Mikhailidis DP, Stansby G

Analysis 4.1. Comparison 4 Ankle brachial index (ABI), Outcome 1 ABI cilostazol 100 mg twice daily versus placebo.

Review: Cilostazol for intermittent claudication

Comparison: 4 Ankle brachial index (ABI)

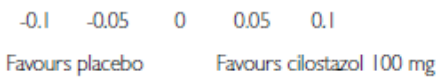
Outcome: 1 ABI cilostazol 100 mg twice daily versus placebo

Study or subgroup	Cilostazol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Dawson 2000	227	0.04 (0.18)	239	-0.01 (0.19)		16.5 %	0.05 [0.02, 0.08]
Elam 1998	95	0.07 (0.02)	94	0 (0.02)		41.5 %	0.07 [0.06, 0.08]
Money 1998	119	0.06 (0.02)	120	0.01 (0.02)		41.9 %	0.05 [0.04, 0.06]
Total (95% CI)	**441**		**453**			**100.0 %**	**0.06 [0.04, 0.08]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 26.65$, df = 2 (P<0.00001); I^2 =92%

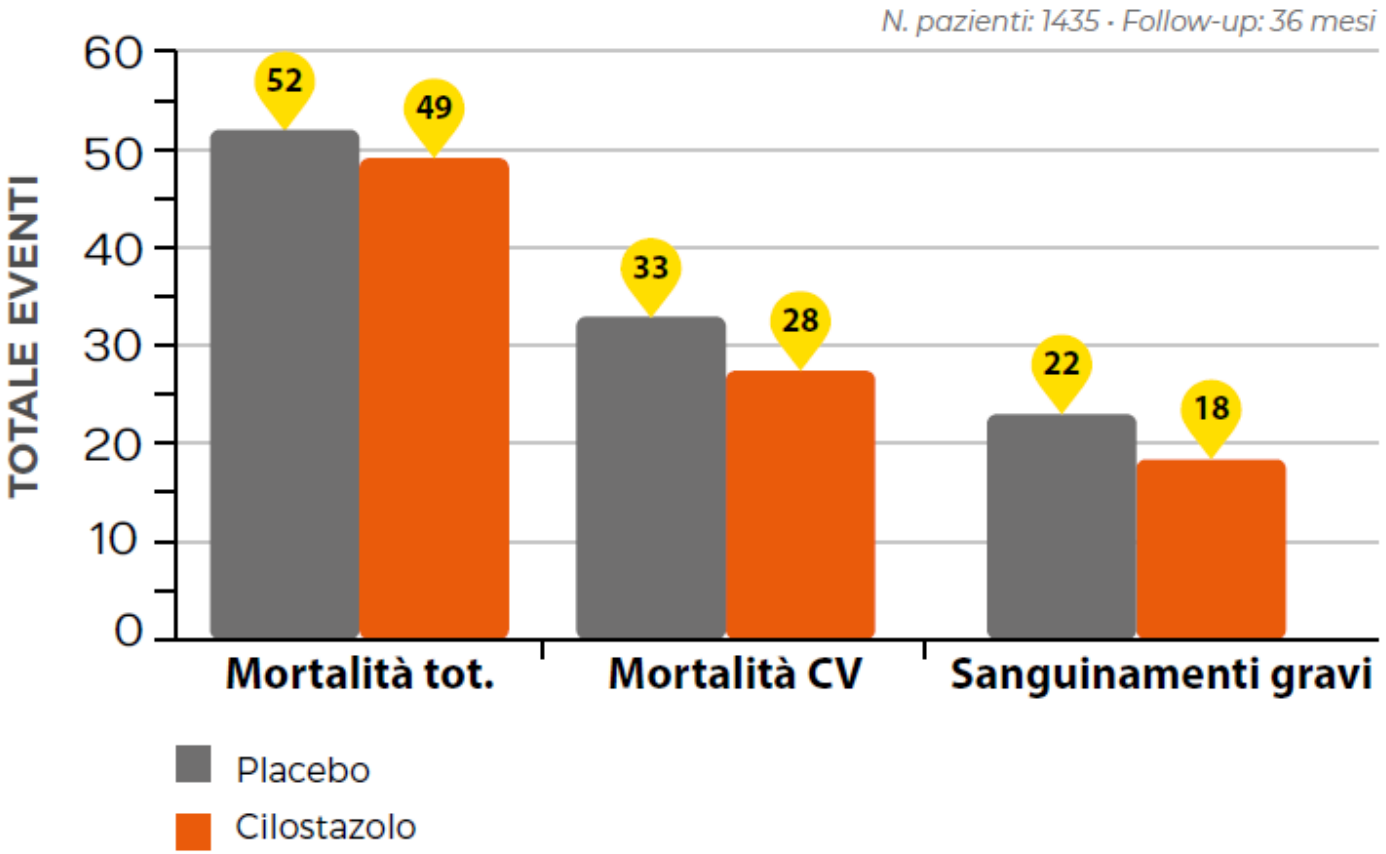
Test for overall effect: Z = 6.59 (P < 0.00001)

Test for subgroup differences: Not applicable



Cochrane 2014

Studio sulla sicurezza a lungo termine del cilostazolo



Cilostazolo non risulta associato a un incremento della mortalità o di sanguinamenti

Hiatt WR et al. Long-term safety of cilostazol in patients with peripheral artery disease: The CASTLE study. J Vasc Surg 2008;47:330-6.

Sicurezza Cilostazolo

Cochrane Library
Cochrane Database of Systematic Reviews

3718 oggetti studiati
Terapia da 6 a 26 settimane
Cilo 50 x 2, 100 x 2, 150 x 2
Costante miglioramento della distanza percorsa

Cilostazol for intermittent claudication (Review)

Bedenis R, Stewart M, Cleanthis M, Robless P, Mikhailidis DP, Stansby G

EFFETTI COLLATERALI: cefalea, diarrea, vertigini, palpitazioni

Authors' conclusions

Cilostazol has been shown to be of benefit in improving walking distance in people with intermittent claudication secondary to PAD. Although there is an increase in adverse side effects, they are generally mild and treatable. There is currently insufficient data on whether taking cilostazol results in a reduction of all-cause mortality and cardiovascular events or an improvement in quality of life. Future research into the effect of cilostazol on intermittent claudication should carefully consider comparability, sample size and homogeneity when designing a study.

Tali reazioni sono solitamente di intensità da lieve a moderata.

European Society for Vascular Medicine

GUIDELINE ON PERIPHERAL ARTERIAL DISEASE

Recommendation	Class of recommendation	Level of evidence
It is recommended that consideration be given to cilostazol and naftidrofuryl as they may be beneficial in improving walking distance in patients with claudication. They should be prescribed only if the patients' quality of life is substantially limited, and walking training is restricted, unfeasible or ineffective.	I	B
It is recommended that treatment with these agents is to be discontinued if symptoms fail to improve after 3 months.	I	B

VASA 2019

Review

Cilostazol for peripheral arterial disease – a position paper from the Italian Society for Angiology and Vascular Medicine

Romeo Martini[1], Walter Ageno[2], Corrado Amato[3], Elisabetta Favaretto[4], Angelo Porfidia[5], and Adriana Visonà[6]

Summary: Cilostazol is a quinolinone-derivative selective phosphodiesterase inhibitor and is a platelet-aggregation inhibitor and arterial vasodilator for the symptomatic treatment of intermittent claudication (IC). Cilostazol has been shown to improve walking distance for patients with moderate to severe disabling intermittent claudication who do not respond to exercise therapy and who are not candidates for vascular surgical or endovascular procedures. Several studies evaluated the pharmacological effects of cilostazol for restenosis prevention and indicated a possible effect on re-endothelialization mediated by hepatocyte growth factor and endothelial precursor cells, as well as inhibiting smooth muscle cell proliferation and leukocyte adhesion to endothelium, thereby exerting an anti-inflammatory effect. These effects may suggest a potential effectiveness of cilostazol in preventing restenosis and promoting the long-term outcome of revascularization interventions. This review aimed to point out the role of cilostazol in treating patients with peripheral arterial disease, particularly with IC, and to explore its possible role in restenosis after lower limb revascularization.

Vasa (2024), 1–11
https://doi.org/10.1024/0301-1526/a001114

Recommendations for lifestyle, physical activity, and patient education (1)

Recommendations	Class	Level
In patients with PAAD, cessation and abstinence from smoking of any kind is recommended to reduce the risk of AD, MI, death, and limb ischaemia.	I	A
A healthy diet rich in legumes, dietary fibre, nuts, fruits, and vegetables, with a high flavonoid intake (Mediterranean diet), is recommended for CV disease prevention in patients with PAAD.	I	A
Low- to moderate-intensity (or high if tolerated) aerobic activities are recommended in patients with PAD to increase overall and pain-free walking distance.	I	A
In patients with PAAD, behavioural counselling to promote healthy diet, smoking cessation, and physical activity is recommended to improve the CV risk profile.	I	B
It is recommended to promote patient and caregivers' education and empowerment through tailored guidance on lifestyle adjustments and the importance of regular physical activity.	I	C
In patients with PAAD, avoidance of exposure to second-hand smoke and air pollution should be considered.	IIa	C

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Recommendations for lifestyle, physical activity, and patient education (2)

Recommendations cont.	Class	Level
Physical exercise and sports activities should be considered in patients with aortic diseases based on prior risk stratification (based on the extent of the aneurysm, risk of dissection, and BP control).	IIa	C
Use of web- or app-based secondary prevention risk calculators should be considered in the shared decision-making to improve patient adherence to treatment and lifestyle changes.	IIa	C
E-cigarettes may be considered as an aid to quit tobacco smoking, but it is advisable to limit their use and avoid simultaneous use with conventional cigarettes due to unknown long-term effects.	IIb	C

Recommendations for exercise therapy in patients with peripheral arterial disease (1)

Recommendations	Class	Level
In patients with symptomatic PAD, SET is recommended.	I	A
In those patients undergoing endovascular revascularization, SET is recommended as an adjuvant therapy.	I	A
When SET is not available or feasible, a structured and monitored (calls, logbooks, connected devices) HBET programme should be considered.	IIa	A
Walking should be considered as a first-line training modality. When walking exercise is not an option, alternative exercise modes (strength training, arm cranking, cycling, and combinations of different training modes) should also be considered.	IIa	A
Walking training performed at high intensity (77%–95% of maximal heart rate or 14–17 self-perceived exertion on Borg's scale) should be considered to improve walking performance, and high-intensity exercise training (various aerobic training modes) should be considered to improve cardiorespiratory fitness.	IIa	A

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Recommendations for exercise therapy in patients with peripheral arterial disease (2)

Recommendations	Class	Level
Training frequency of at least three times per week, training session duration of at least 30 min, and training programme duration of at least 12 weeks should be considered.	IIa	B
In patients with PAD, exercise training to moderate-high claudication pain may be considered to improve walking performance. However, improvements are also achievable with lesser claudication pain severities (low-mild pain or pain-free).	IIb	B
Based on patient's tolerance, a progressive increase (every 1–2 weeks) in exercise training load may be considered.	IIb	C

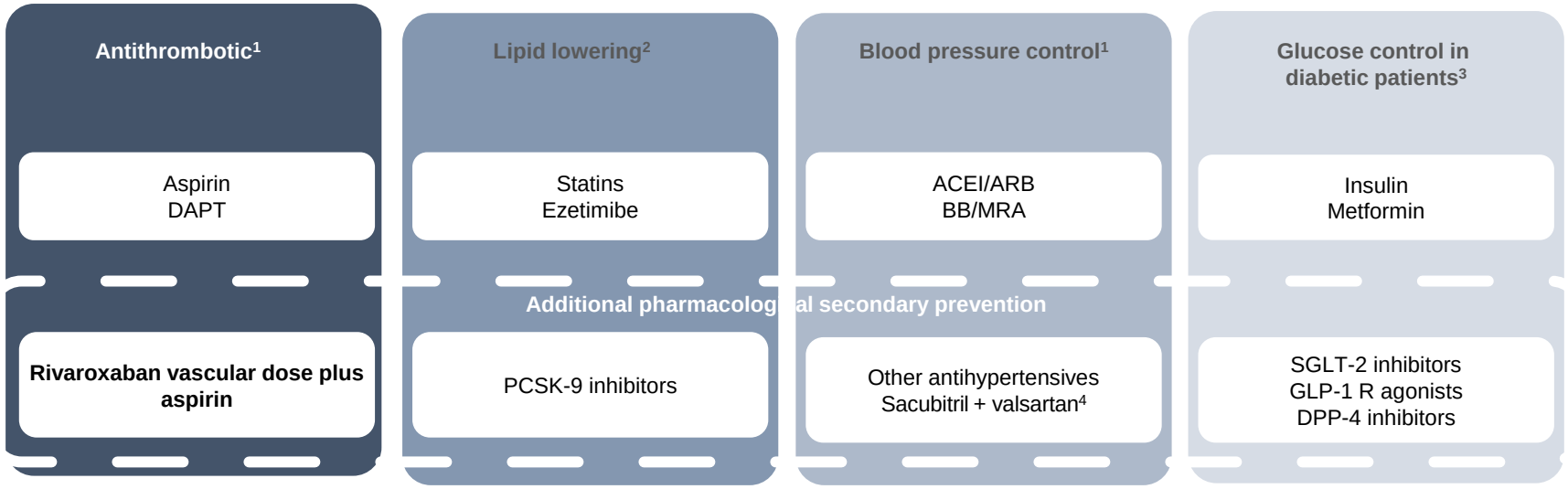
PAD
TERAPIA MEDICA
Nuovo paradigma di protezione vascolare

Vascular Protection

Standard pharmacological secondary prevention

Healthy lifestyle[1]

Healthy diet, physical activity/exercise, weight control, psychosocial support, etc



1. Cortés-Beringola A et al. *Eur J Prevent Cardiol.* 2017;24:22–28; 2. Catapano AL et al. *Eur Heart J* 2016;37:2999-3058; 3. American Diabetes Association. *Diabetes Care* 2018;41(1 Suppl):S1-S159; 4. Entresto SmPC, April 2018.

PAD e FDR

Terapia ipotensivante

Old 2018 ESC/ESH categories

ESC European Society of Cardiology
European Heart Journal (2018) 39, 3021–3104
doi:10.1093/eurheartj/ehy339

ESC/ESH GUIDELINES

2018 ESC/ESH Guidelines for the management of arterial hypertension

Table 3 Classification of office blood pressure[a] and definitions of hypertension grade[b]

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[b]	≥140	and	<90

2024 ESC Guidelines for the management of elevated blood pressure and hypertension (European Heart Journal: 2024 – doi: 10.1093/eurheartj/ehae178)

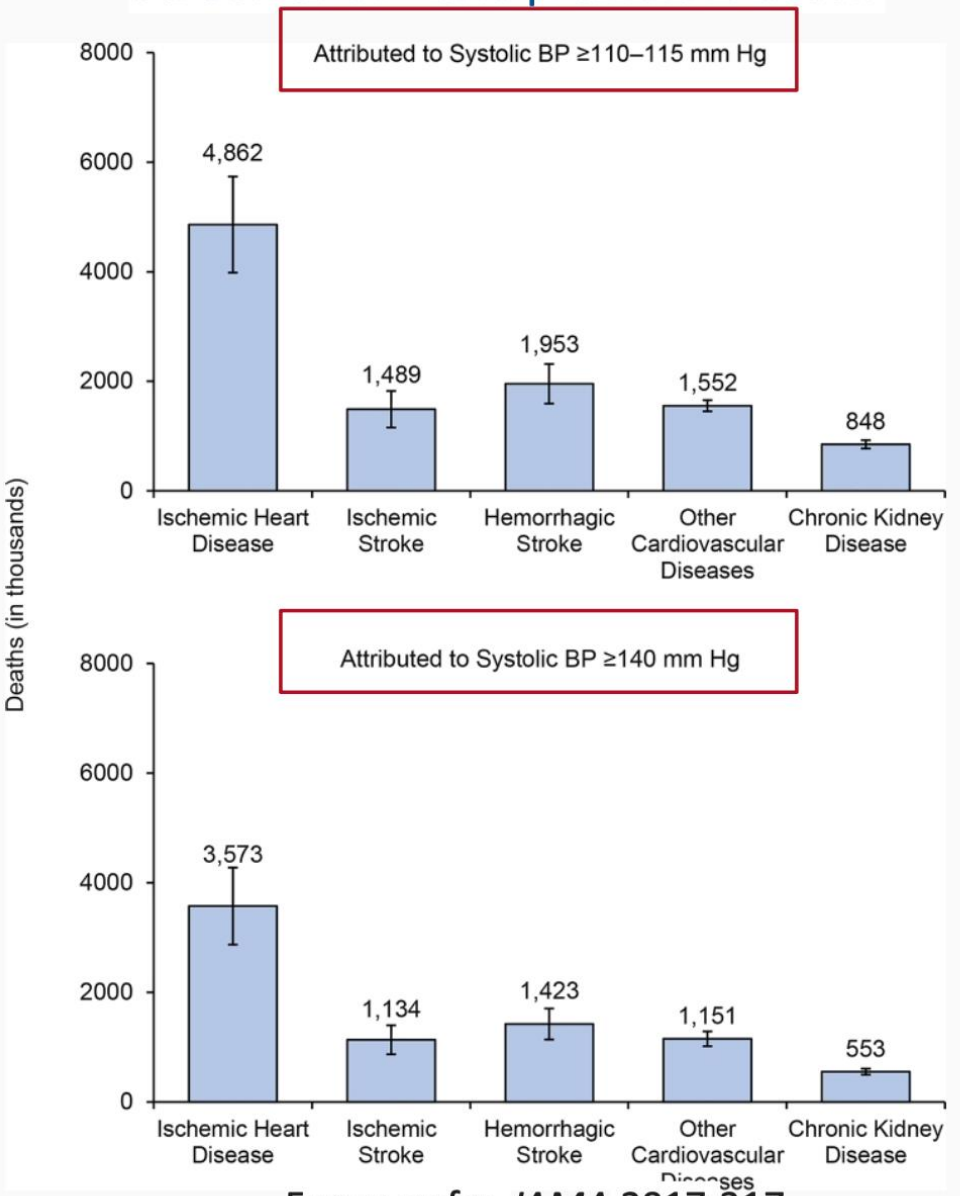
Some new concepts

- Title changed to “Guidelines on the management of **elevated blood pressure** and hypertension’

- A new BP category ‘**elevated BP**’ is introduced

Office SBP 120-139 mmHg or
Office DBP 70-89 mmHg

Elevated BP is associated with a large global burden of CVD and premature death



Forouzanfar. *JAMA* 2017:317

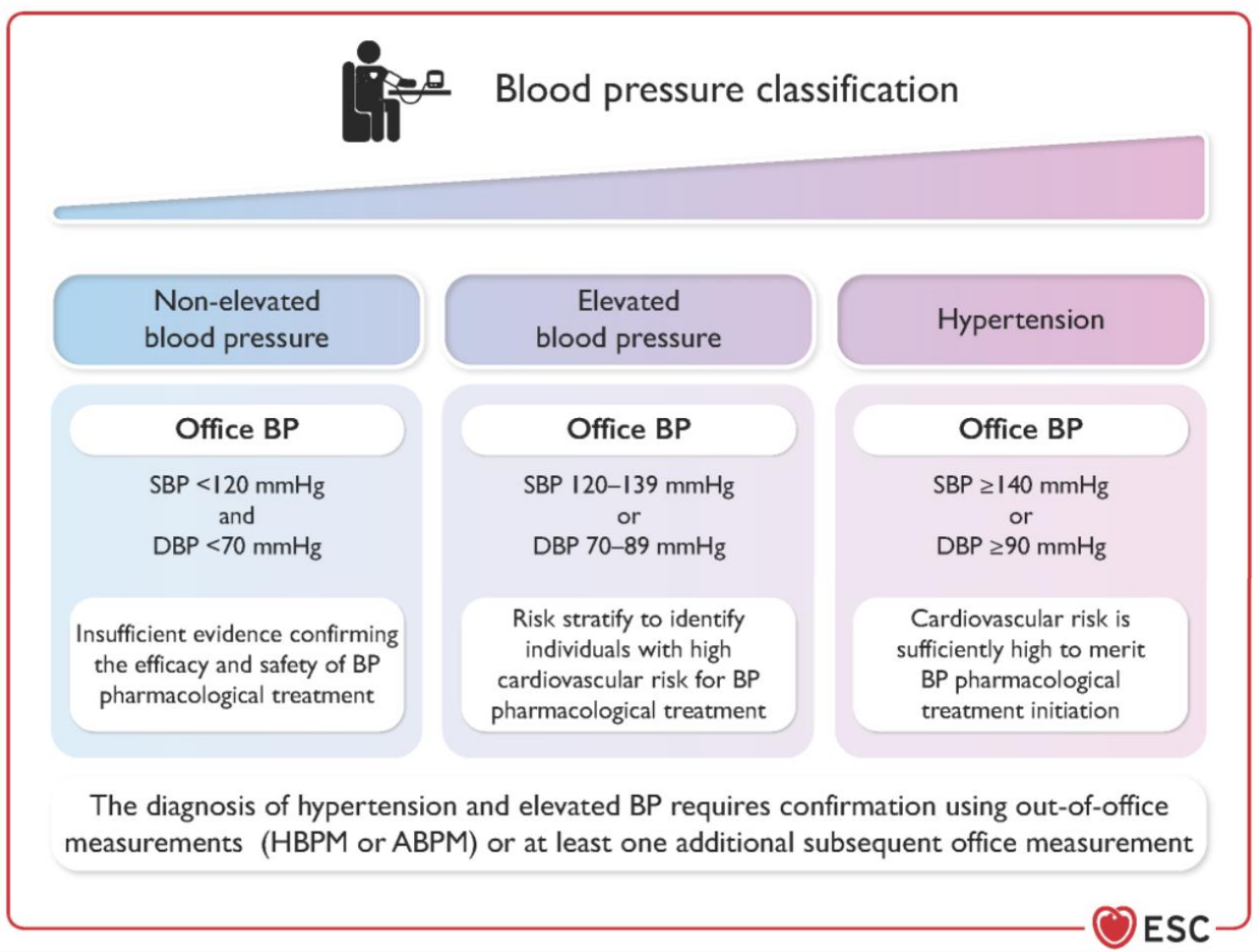
2024 ESC Guidelines for the management of elevated blood pressure and hypertension
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae178)

New 2024 ESC categories

-Non-elevated
<120/70 mmHg

-Elevated
120-139/70-89 mmHg

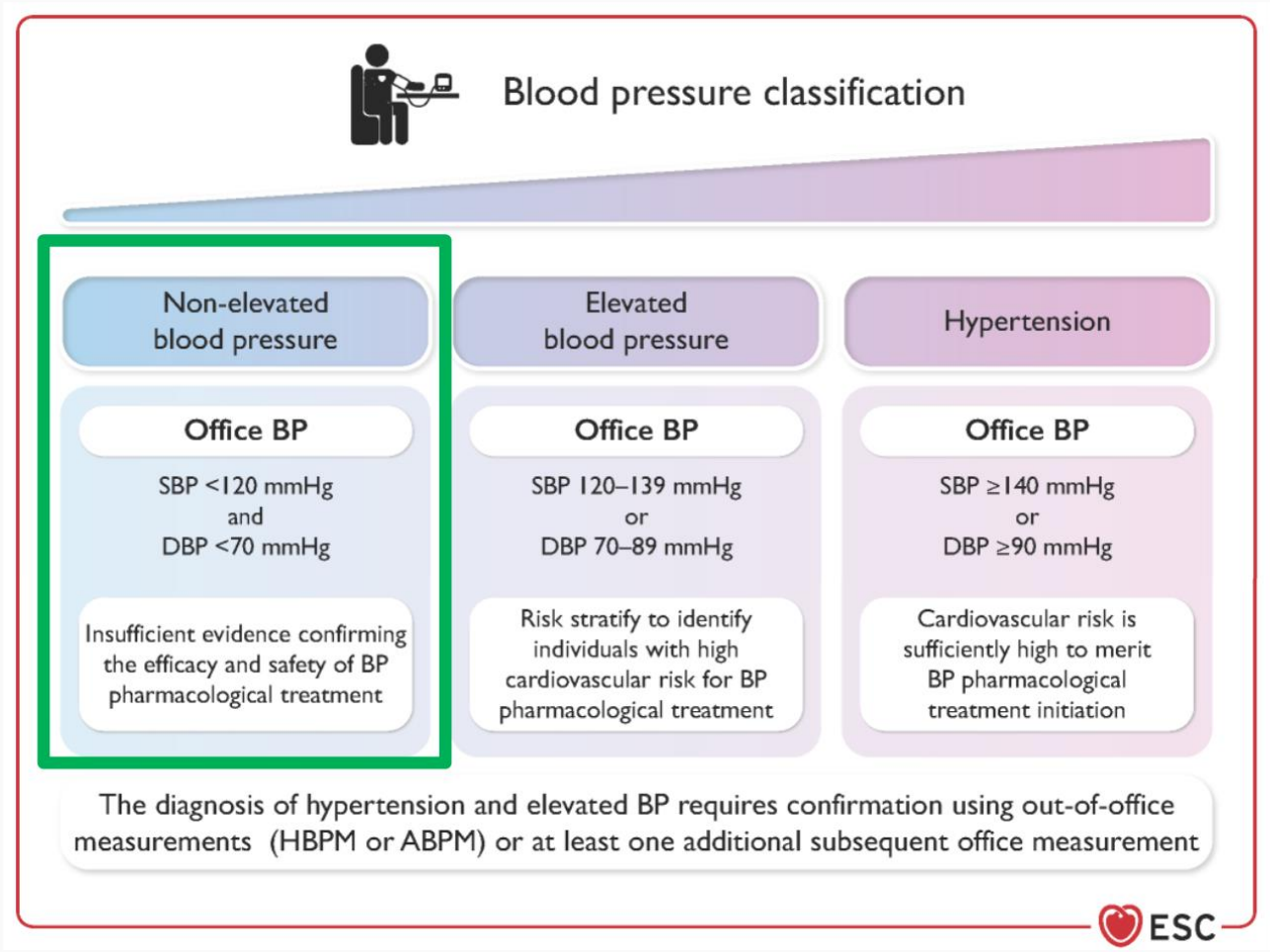
-Hypertension
≥140/90 mmHg



2024 ESC Guidelines for the management of elevated blood pressure and hypertension (European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae178)

New 2024 ESC categories

-Non-elevated
<120/70 mmHg

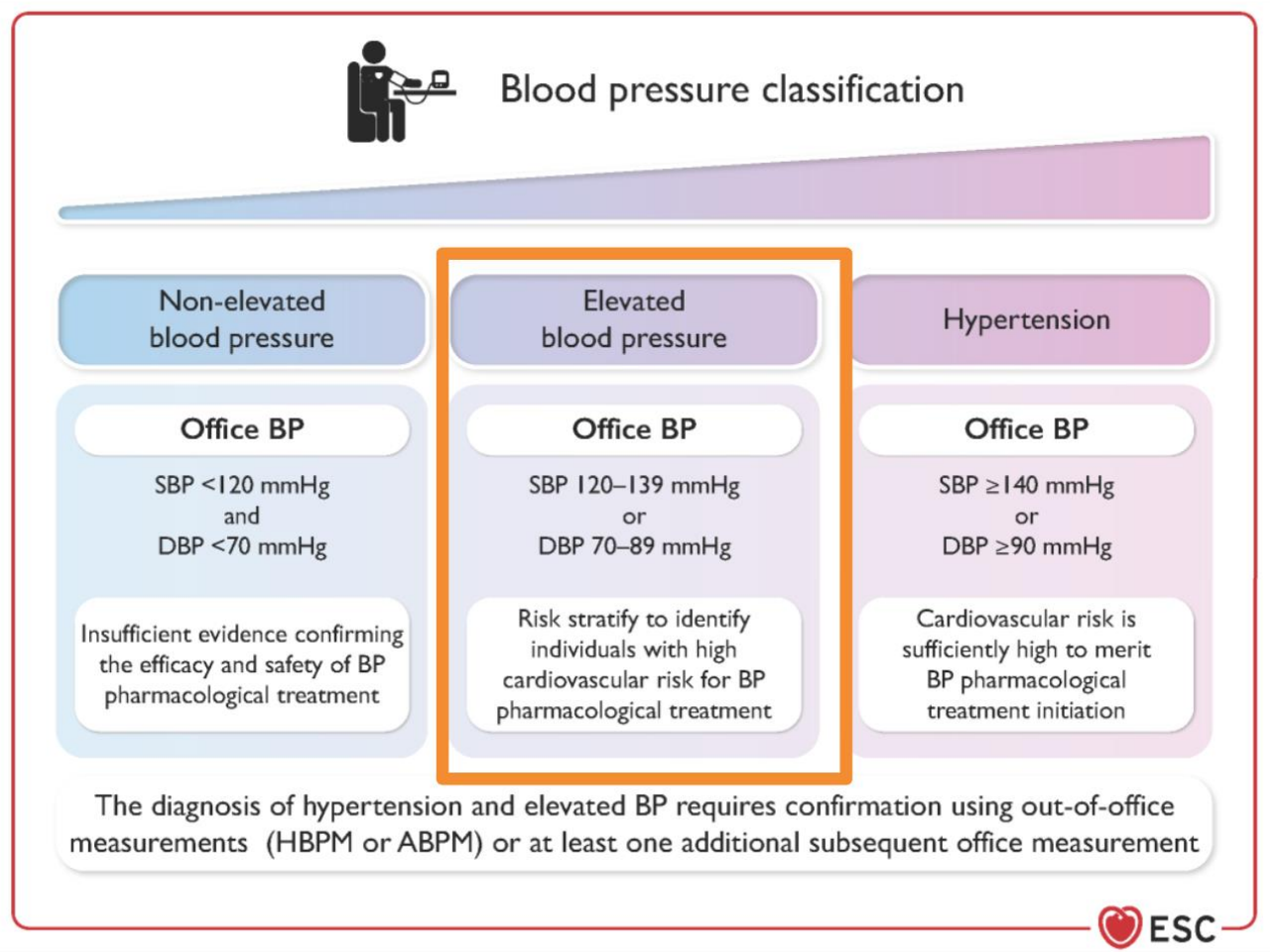


2024 ESC Guidelines for the management of elevated blood pressure and hypertension
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae178)

New 2024 ESC categories

-Elevated

120-139/70-89 mmHg



2024 ESC Guidelines for the management of elevated blood pressure and hypertension (European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae178)

Misurazioni Pressione Arteriosa

Tipo di Misurazione	Vantaggi principali	Svantaggi principali
Office BP (Ambulatorio)	Standardizzato, valutazione immediata dello stato di salute.	Possibile effetto "camice bianco", stress da visita.
Home BP (Domiciliare)	Misurazioni più naturali, senza l'effetto del camice bianco.	Affidabilità dipendente dal paziente.
ABPM (Monitoraggio Ambulatoriale 24h)	Visione completa della pressione durante il giorno e la notte.	Dispositivo scomodo, necessita di interpretazione medica.

8. Preventing and treating elevated blood pressure (blood pressure targets)					
It is recommended that the first objective of treatment should be to lower BP to <140/90 mmHg in all patients and, provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients.	I	A	To reduce CVD risk, it is recommended that treated systolic BP values in most adults be targeted to 120–129 mmHg, provided the treatment is well tolerated.	I	A

ESC 2024

Recommendations for antihypertensive therapy in patients with peripheral and aortic disease (1)

Recommendations	Class	Level
In patients with PAAD and hypertension an SBP target towards 120–129 mmHg, if tolerated, is recommended.	I	A
In unilateral RAS patients, it is recommended that antihypertensive medication include ACEIs/ARBs.	I	B
In patients with PAAD and hypertension, ACEIs or ARBs should be considered as first-line antihypertensive therapy.	IIa	B
In RAS-related hypertension, the combination of ACEIs/ARBs with diuretics and/or calcium channel blockers should be considered.	IIa	B
An individualized, more lenient BP goal (e.g. <140/90 mmHg) should be considered in: •Age ≥85 years •Residential care •Symptomatic orthostatic hypotension	IIa	C
An individualized, more lenient BP goal (e.g. <140/90 mmHg) may be considered in: •Clinically severe frailty at any age •Limited life expectancy (<3 years)	IIb	C

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

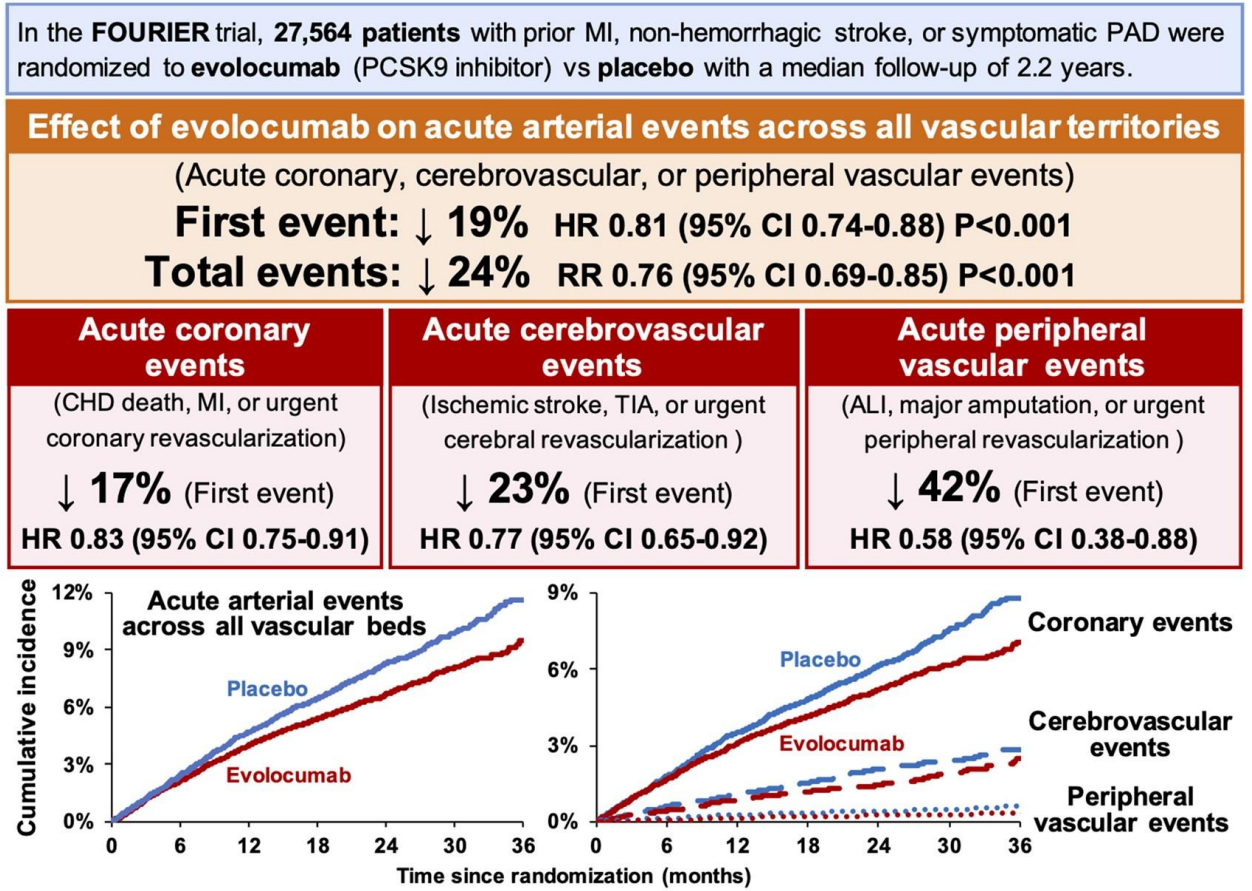
Recommendations for antihypertensive therapy in patients with peripheral and aortic disease (2)

Recommendations cont.	Class	Level
In patients with bilateral RAS, antihypertensive medication including ACEIs/ARBs may be considered if close patient monitoring (renal function) is feasible.	IIb	B
ACEIs/ARBs may be considered in all patients with PAD, regardless of BP levels, in the absence of contraindications.	IIb	B
In cases where on-treatment SBP is at or below target (120–129 mmHg) but DBP is not at target (≥80 mmHg), intensifying BP-lowering treatment to achieve an on-treatment DBP of 70–79 mmHg may be considered to reduce CVD risk.	IIb	C

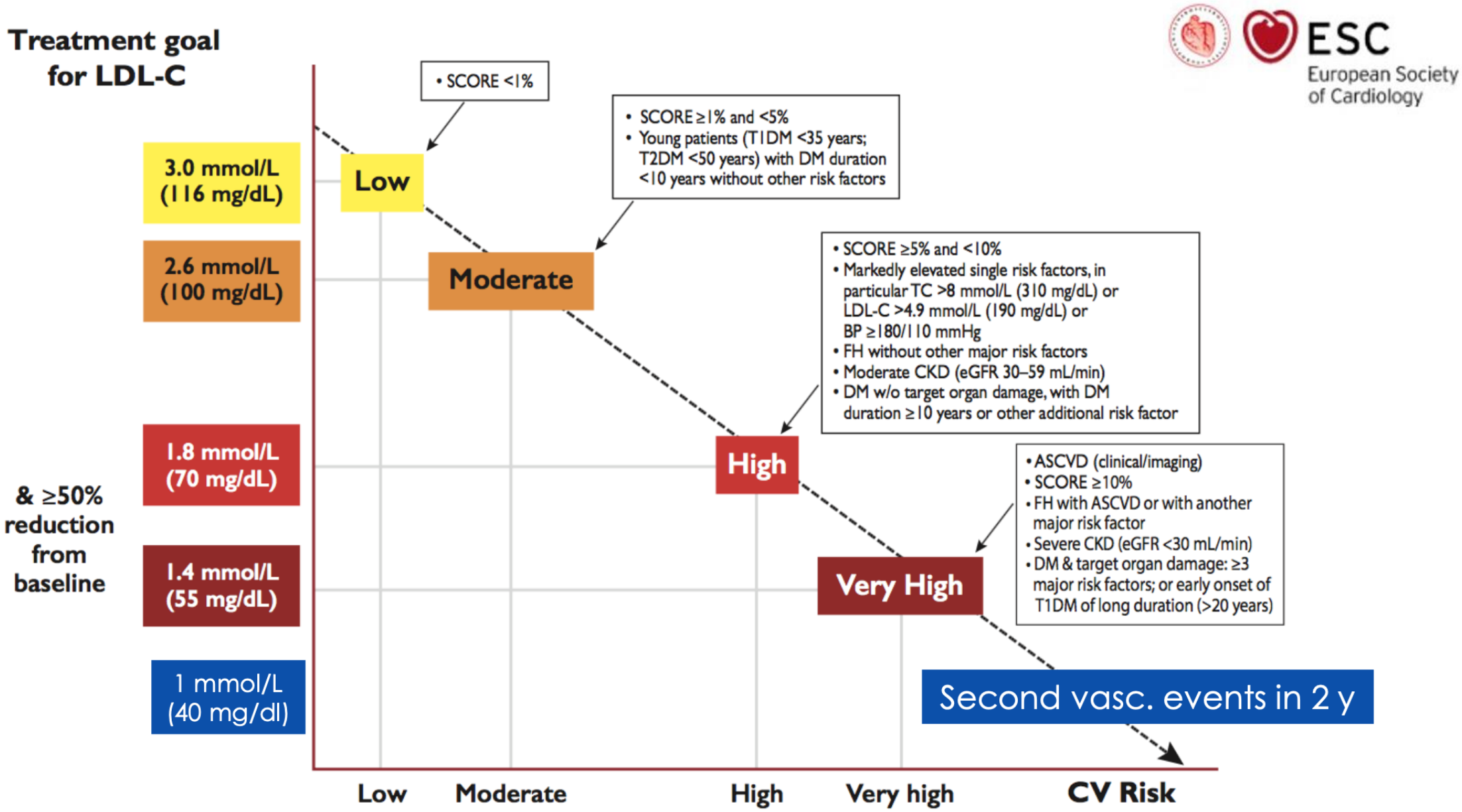
PAD e FDR

Terapia Ipolipemizzante

Effect of evolocumab on acute arterial events across all vascular territories. ALI, acute limb ischaemia; ...



Eur Heart J, Volume 42, Issue 47, 14 December 2021, Pages 4821–4829, https://doi.org/10.1093/eurheartj/ehab604


Treatment goal for LDL-C
ESC
European Society of Cardiology
• SCORE <1%
• SCORE ≥1% and <5%
• Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years without other risk factors
• SCORE ≥5% and <10%
• Markedly elevated single risk factors, in particular TC >8 mmol/L (310 mg/dL) or LDL-C >4.9 mmol/L (190 mg/dL) or BP ≥180/110 mmHg
• FH without other major risk factors
• Moderate CKD (eGFR 30–59 mL/min)
• DM w/o target organ damage, with DM duration ≥10 years or other additional risk factor
• ASCVD (clinical/imaging)
• SCORE ≥10%
• FH with ASCVD or with another major risk factor
• Severe CKD (eGFR <30 mL/min)
• DM & target organ damage: ≥3 major risk factors; or early onset of T1DM of long duration (>20 years)
Low
Moderate
High
Very High
3.0 mmol/L (116 mg/dL)
2.6 mmol/L (100 mg/dL)
1.8 mmol/L (70 mg/dL)
1.4 mmol/L (55 mg/dL)
1 mmol/L (40 mg/dl)
& ≥50% reduction from baseline
Second vasc. events in 2 y
Low
Moderate
High
Very high
CV Risk

Members of the guidelines committee

European Society of Vascular Medicine (ESVM): Guideline on peripheral arterial disease

PAD Guideline Writing Group
Ulrich Frank (Switzerland), Sigrid Nikol (Germany), and Jill Belch (UK) for the European Society of Vascular Medicine – all co-first authors

ESVM Board Authors
Vinko Boc* (Slovenia), Marianne Brodmann (Austria), Patrick H Carpentier (France), Ali Chraim* (Ukraine), Caitriona Canning (Ireland); Evangelos Dimakakos* (Greece), Anders Gottsäter (Sweden), Christian Heiss (Germany), Lucia Mazzolai (Switzerland), Juraj Madaric* (Slovakia), Dan Mircea Olinic* (Romania), Zsolt Pécsvárady* (Hungary), Pavel Poredoš* (Slovenia), Isabelle Quéré (France), Karel Roztocil (ESVM President, Czech Republic), Agata Stanek (Poland), Dragan Vasic* (Serbia), Adriana Visonà (Italy), and Jean-Claude Wautrecht* (Belgium)

ESVM Country Society Authors
Miroslav Bulvas (Czech Republic), Mary-Paula Colgan (Ireland), Walter Dorigo (Italy), Graeme Houston (UK), Thomas Kahan (Sweden), Holger Lawall (Germany), Isak Lindstedt (Sweden), Guillaume Mahe (France), Romeo Martini (Italy), Giles Pernod (France), Stanislaw Przywara (Poland). Marc Righini (Switzerland), Oliver Schlager (Austria), and Piotr Terlecki (Poland)

*Indicates ESVM Board members who were also nominated by their Country Society as reviewers.

European Society of Vascular Medicine

Recommendation	Class of recommendation	Level of evidence
A PCSK9 inhibitor may be considered in PAD patients on maximum tolerated statin therapy, plus ezetimibe, who do not reach a target LDL.	I	B
In view of the primary prevention studies with statins and the known risk profile in asymptomatic PAD disease, consideration should be given to also treating asymptomatic PAD patients.	IIb	C

Vasa, 2019

PAD e DISLIPIDEMIA: LG ESC 2019

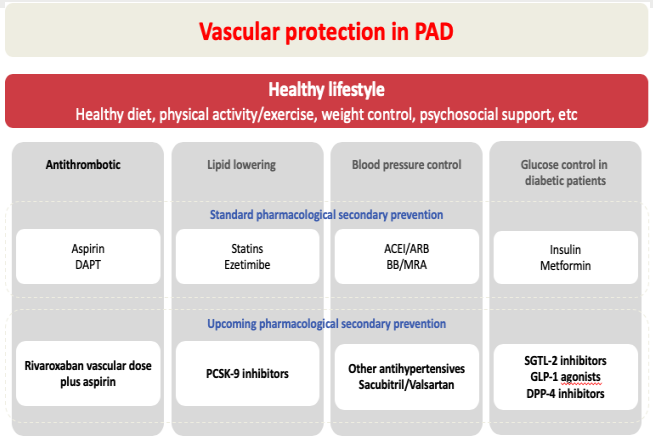
- **New/revised concepts**

More intensive reduction of LDL-C across CV risk categories

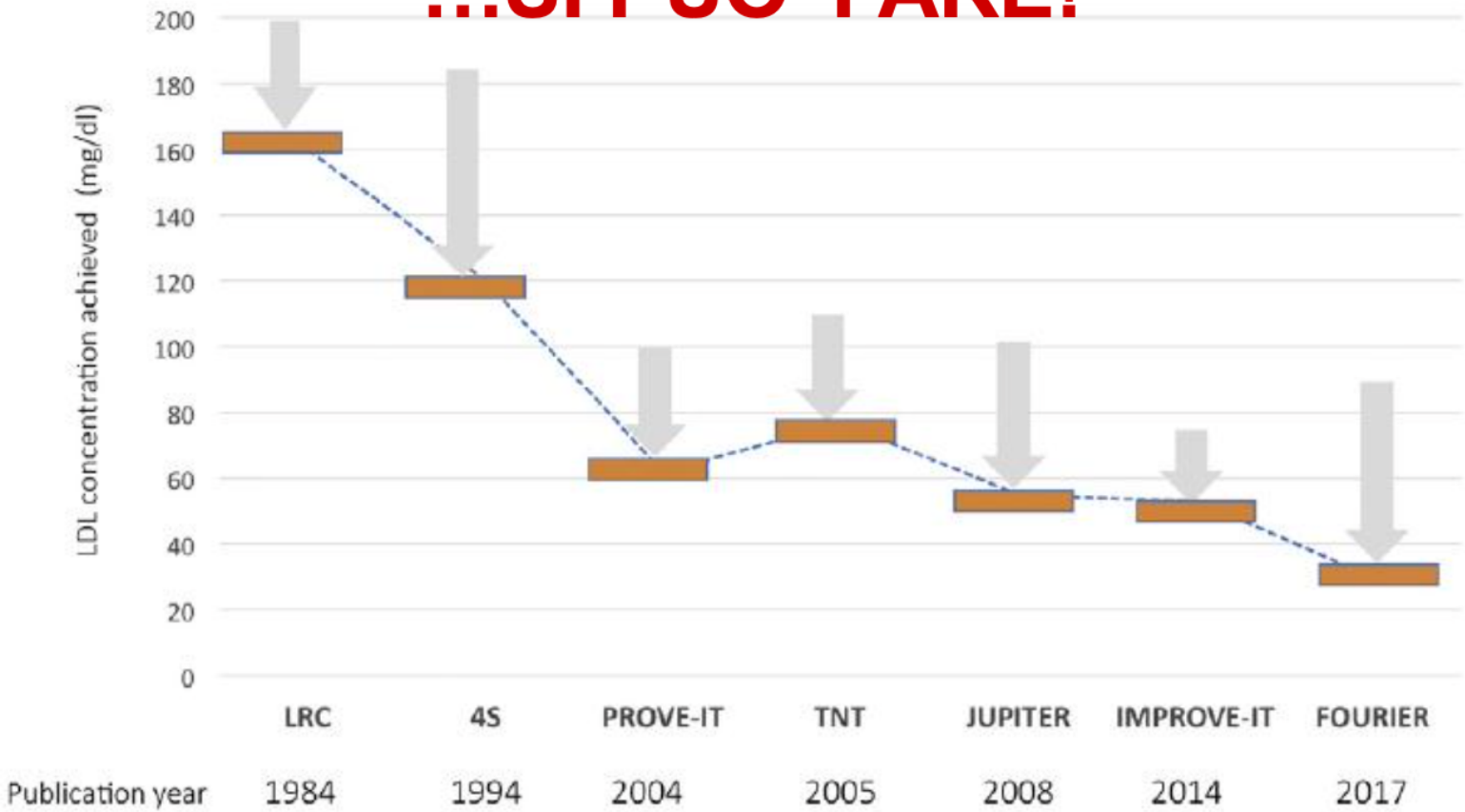
- For secondary prevention in very-high-risk patients, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.
  - For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.

Recommendations	Class[a]	Level[b]
In patients with PAD, lipid-lowering therapy, including a maximum tolerated dose of statin, plus ezetimibe or a combination with a PCSK9 inhibitor if needed, is recommended to reduce the risk of ASCVD events.[512,524]	I	A

© ESC 2019

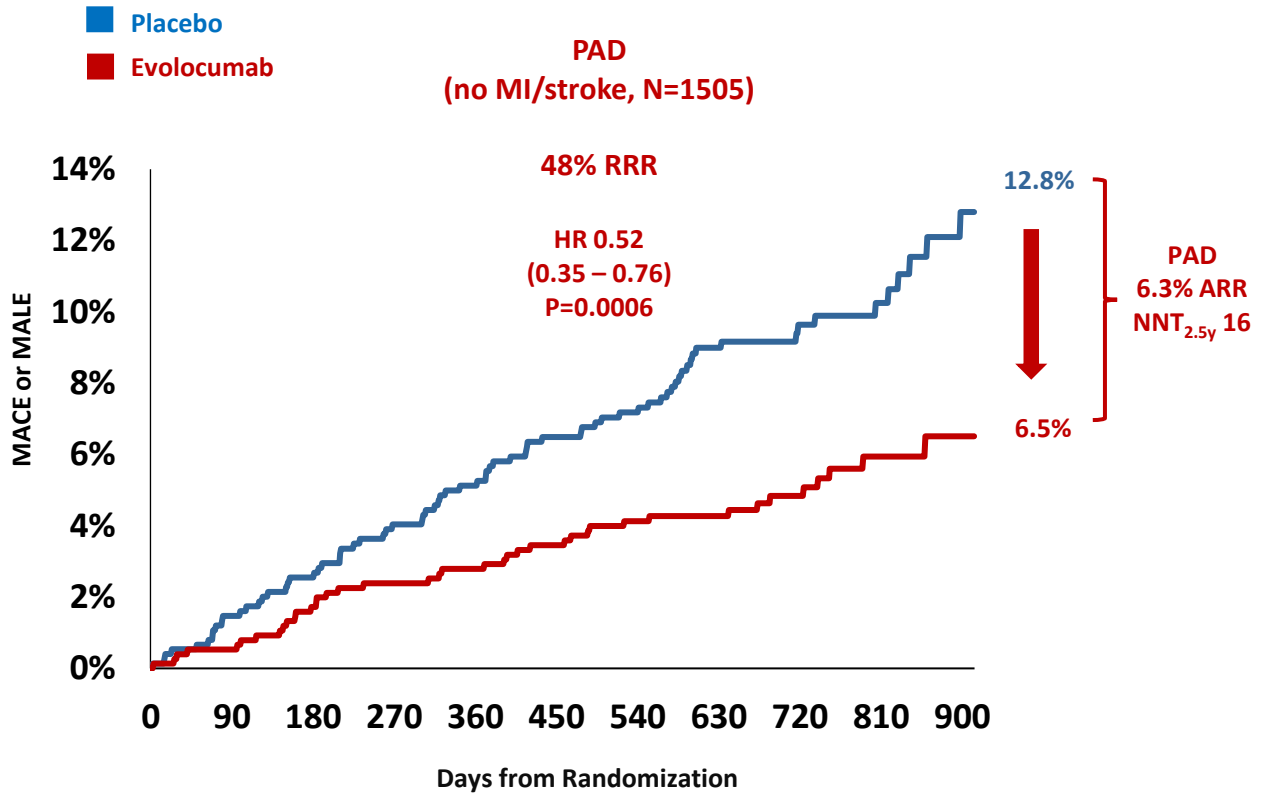


Ipotesi “zero colesterolo”…
…SI PUO’ FARE!



Masana L et al. J Clin Lipidol. 2018 Jan 8. pii: S1933-2874(18)30014-X.

MACE or MALE
In Patients with PAD and no MI or Stroke



M. Bonaca AHA 2017

Target non raggiunto (colesterolo LDL > 55 mg/dl)

Target non raggiunto (colesterolo non-HDL > 85 mg/dl)

Colesterolo LDL 97 mg/dl

Colesterolo non-HDL 125

In terapia con Rosuvastatina 20 mg/die + Ezetimibe 10 mg

Che fare?

Raccomandazioni	Classe	Livello
Si raccomanda una terapia di combinazione che includa un **inibitore del PCSK9** per i pazienti in prevenzione secondaria che non raggiungano i loro target alla massima dose tollerata di una statina ed ezetimibe	I	A

Inibitori del PCSK9- Criteri eleggibilità

Età 18-80 anni

PREVENZIONE PRIMARIA

Ipercolesterolemia familiare
DLCN > 8

PREVENZIONE SECONDARIA

Malattia cardiovascolare
- Cardiopatia ischemica
- CHD
- IMA
- Rivascolarizzazione (PTCA, stenting, bypass)

Malattia cerebrovascolare
- TIA, ictus
- Rivascolarizzazione carotidea

Arteriopatie periferiche

Diabete mellito con uno o più FdR CV (fumo, IPA) e/o markers di danno d'organo (retinopatia, nefropatia, ecc)

Almeno 6 mesi di terapia con atorvastatina o rosuvastatina alla massima dose tollerata + ezetimibe oppure ezetimibe in monoterapia con dimostrata intolleranza alle statine

LDL ≥ 130 mg/dl

LDL ≥ 100 mg/dl

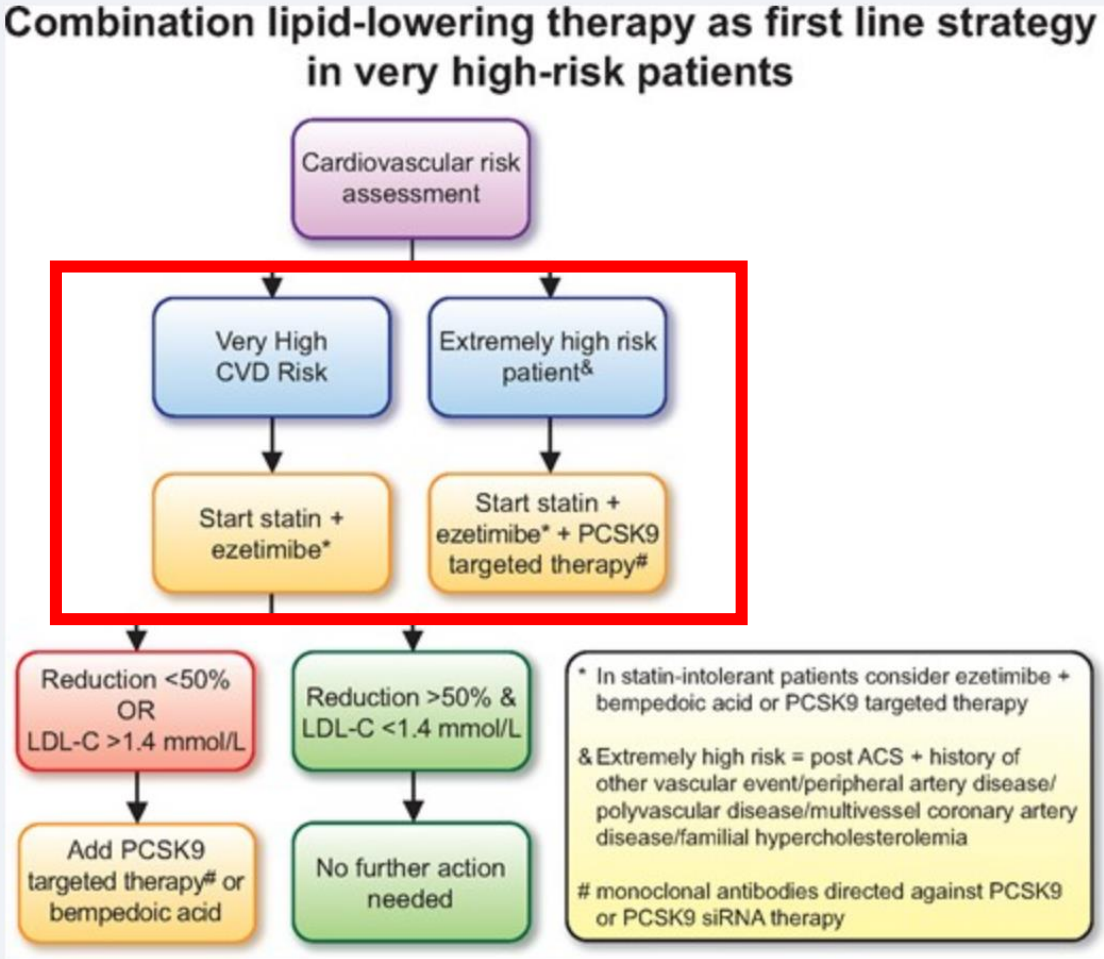
PAZIENTE ELEGGIBILE
(eccetto per funzione renale e/o epatica grave)

Intensità del trattamento ipolipemizzante

Trattamento	Riduzione media del colesterolo LDL
Statina a moderata intensità	≈ 10%
Statina ad alta intensità	≈ 50%
Statina ad alta intensità + ezetimibe	≈ 65%
Inibitore del PCSK9	≈ 60%
Inibitore del PCSK9 + statina ad alta intensità	≈ 75%
Inibitore del PCSK9 + statina ad alta intensità + ezetimibe	≈ 85%

Visseren FLJ et al. European Heart Journal 2021;00:1-111

Expected low-density lipoprotein cholesterol reductions for combination therapies. LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9. Adapted from Mach et al.3



Open in new tab Download slide

Combination lipid-lowering therapy as first line strategy in very high-risk patients.

Ray KK, EHJ 2022

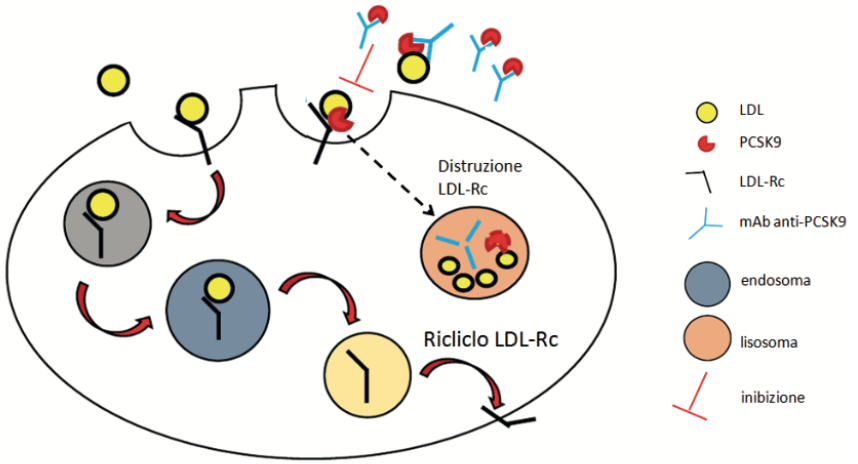


Figura 21. Il legame dell'anticorpo monoclonale (mAb) anti-PCSK9 alla molecola di PCSK9 impedisce il catabolismo del recettore delle LDL (LDL-Rc), favorendone al contempo il riciclo e l'espressione sulla superficie cellulare.

ACIDO BEMPEDOICO, INIBITORI DI PCSK9 E INCLISIRAN

- L'acido bempedoico contribuisce a ridurre il colesterolo LDL in sostituzione alla statina o in aggiunta a terapia ipolipemizzante in atto in un ampio spettro di pazienti ad alto rischio cardiovascolare.
- L'impiego di inibitori di PCSK9 fornisce un valido ausilio ipocolesterolemizzante nei pazienti a maggiore rischio cardiovascolare quando non sia stato raggiunto il target di colesterolo LDL con la massima dose tollerata di statina + ezetimibe.
- Inclisiran è risultato efficace nel ridurre significativamente i livelli di colesterolo LDL.

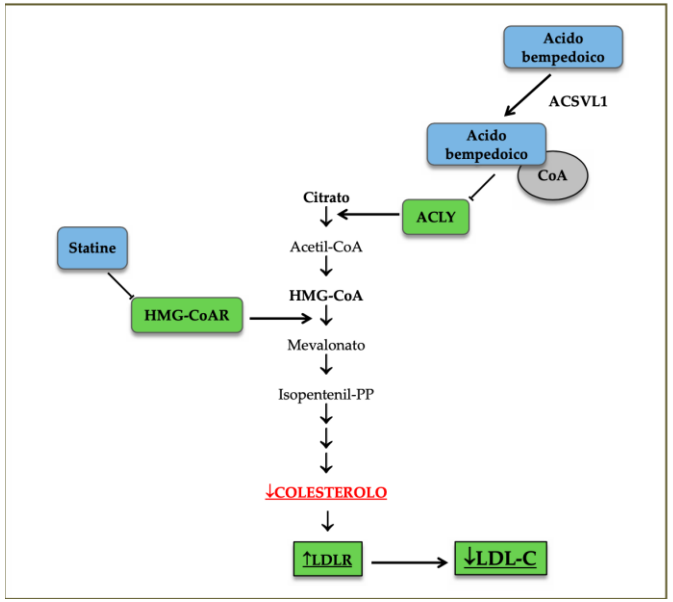


Figura 1 - Meccanismo d'azione dell'acido bempedoico, L'acido bempedoico inibisce l'attività dell'enzima ATP citrato liasi (ACLY), un enzima a monte dell'idrossimetilglutaril-CoA reduttasi, che è invece il target delle statine. Un enzima specifico, ACSVL1 (*very-long-chain acyl-CoA synthetase-1*), espresso nel fegato ma non in altri tessuti periferici, converte l'acido bempedoico nella forma attiva.

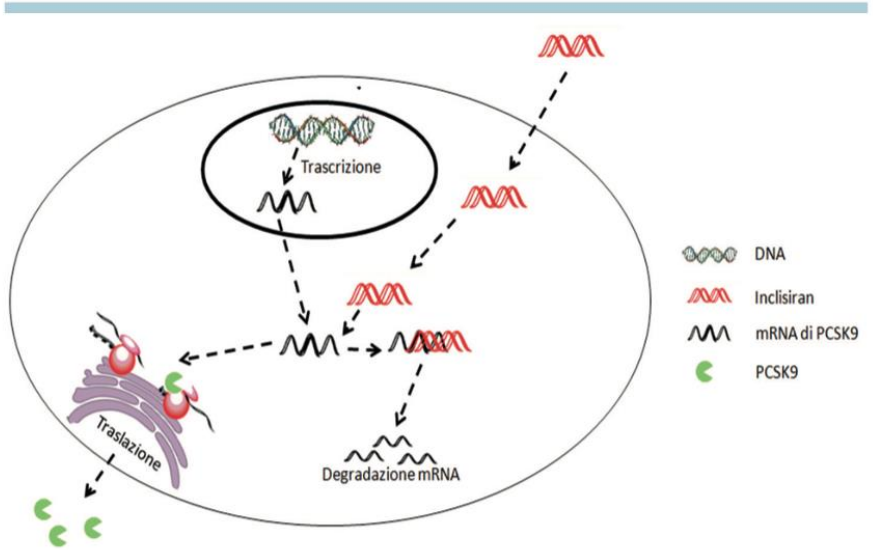


Figura 22. Inclisiran promuove la degradazione dell'mRNA di PCSK9, impedendone la traslazione e, quindi, la sintesi di PCSK9.

SIPREC, GIC 2021

SERIE GENERALE

Spediz. abb. post. - art. 1, comma 1
Legge 27-02-2004, n. 46 - Filiale di Roma

Anno 164° - Numero 22

GAZZETTA UFFICIALE

DELLA REPUBBLICA ITALIANA

PARTE PRIMA Roma - Venerdì, 27 gennaio 2023 SI PUBBLICA TUTTI I GIORNI NON FESTIVI

Visti gli atti d'ufficio;

Determina:

Art. 1.

Classificazione ai fini della rimborsabilità

Il medicinale NILEMDO (acido bempedoico) nelle confezioni sotto indicate è classificato come segue.

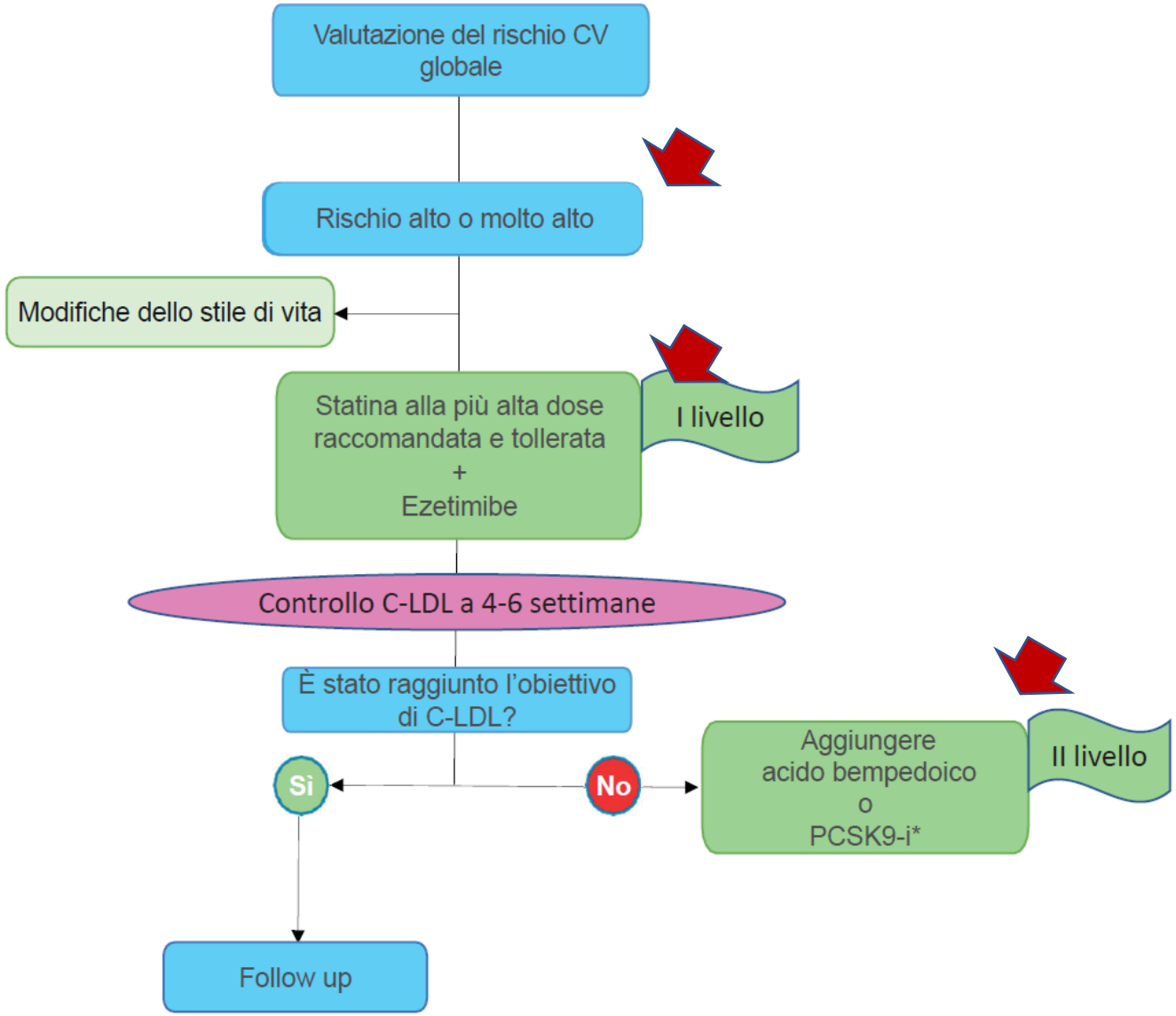
Indicazioni terapeutiche oggetto della negoziazione:

«Nilemdo» è indicato negli adulti affetti da ipercolesterolemia primaria (familiare eterozigote e non familiare) o dislipidemia mista, in aggiunta alla dieta:

in associazione a una statina o con una statina in associazione ad altre terapie ipolipemizzanti nei pazienti non in grado di raggiungere gli obiettivi di LDL-C con la dose massima tollerata di una statina (vedere paragrafi RCP 4.2, 4.3 e 4.4) oppure;

in monoterapia o in associazione ad altre terapie ipolipemizzanti in pazienti intolleranti alle statine o nei quali ne è controindicato l'uso.

Acido Bempedoico Position paper ANMCO



«Considerando che le ultime linee guida sulla gestione dei pazienti con dislipidemia hanno reso i target dei pazienti a rischio alto e molto alto ancora più difficili da raggiungere, in questi specifici contesti l'acido bempedoico, **terapia addizionale rispetto a statine ed ezetimibe**, maneggevole e ben tollerata, può facilitare il raggiungimento degli obiettivi terapeutici raccomandati.»

«L'acido bempedoico, da solo o in combinazione fissa con l'ezetimibe, per il **rapporto costo/efficacia più favorevole rispetto agli agenti anti-PCSK9**, rappresenta un'opzione terapeutica particolarmente utile nei pazienti che non riescono a raggiungere il target terapeutico con il trattamento statinico alla massima dose tollerata.

Di Fusco S.A et al, G Ital Cardiol 2023;24

Bempedoic Acid and Limb Outcomes in Statin-Intolerant Patients with Peripheral ArteryDisease: New insights from the Clear Outcomes Trial

(MP Bonaca **AHA, November2024**)

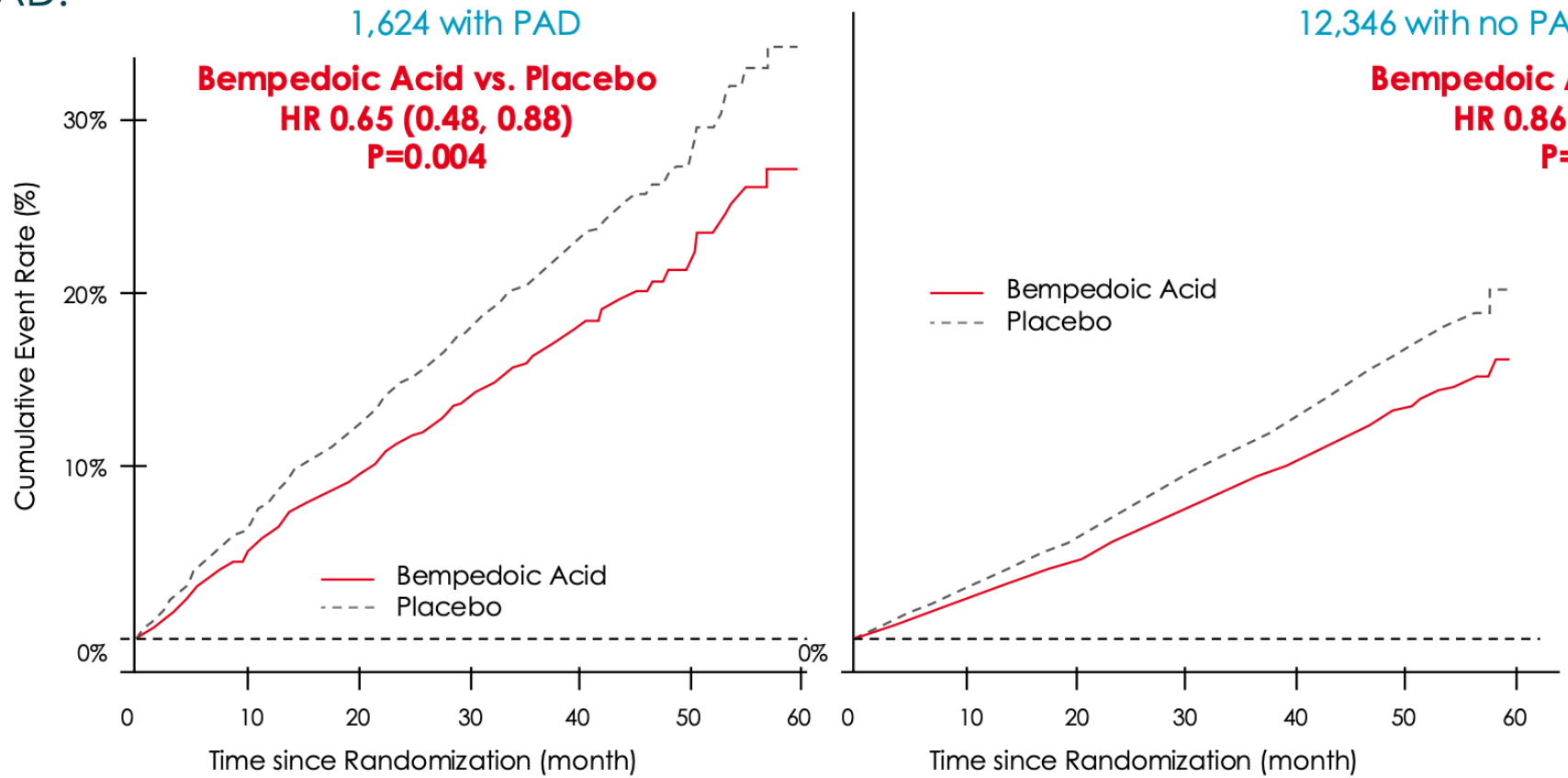
PREMESSE

- La maggior parte dei pazienti con arteriopatia periferica (PAD) non raggiunge il *target* desiderato di LDL-C (< 55 mg/dl) e circa i due terzi di questi richiedono terapia di associazione per raggiungere il *target*.
- La riduzione di LDL-C in questi pazienti, come dimostrato nello studio FOURIER, riduce significativamente il tasso di eventi e il rischio cardiovascolare.
- L'acido bempedoico, inibitore della citrato liasi, ha dimostrato, nello studio CLEAR OUTCOME, di poter ridurre gli eventi cardiovascolari se associato a ezetimibe o statina e ezetimibe, senza incrementare significativamente gli eventi muscolari correlati alle statine

SOTTOANALISI OUTOCOME CLEAR

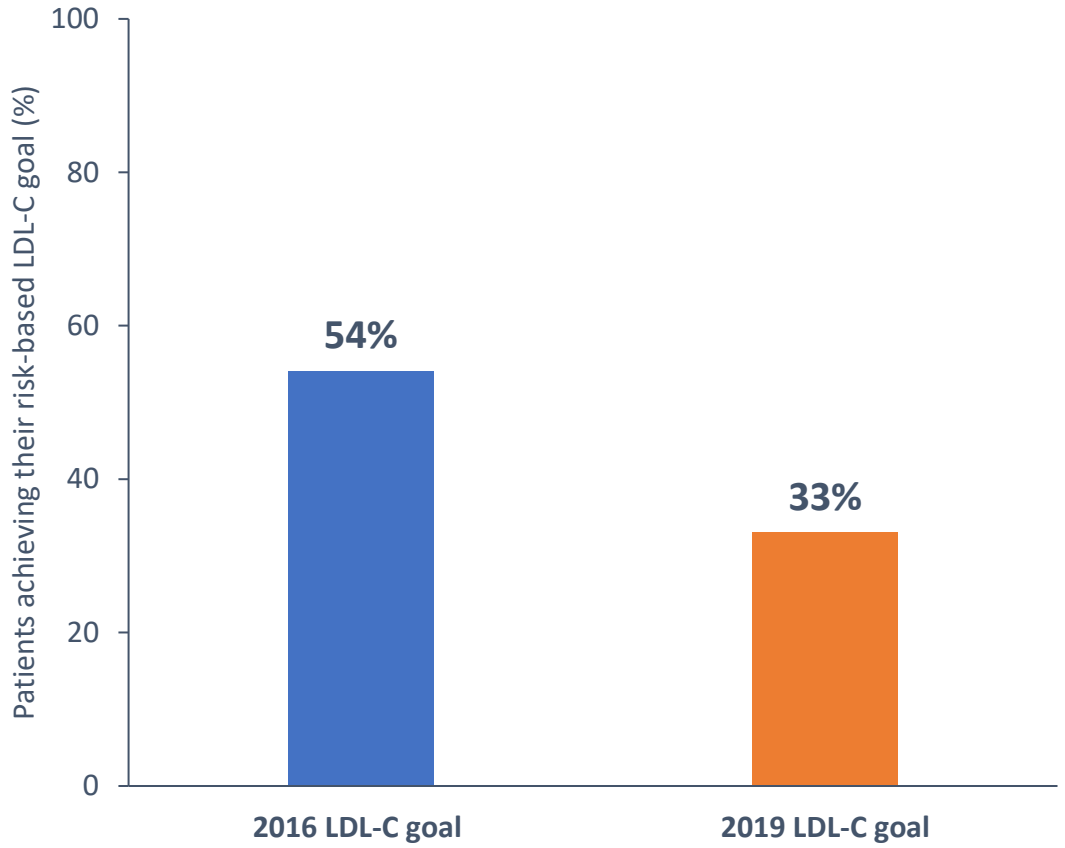
- Lo studio qui presentato è una sottoanalisi dello studio CLEAR OUTCOME, che ha riguardato i pazienti PAD e ha valutato l'efficacia dell'acido bempedoico sugli eventi cardiovascolari maggiori (MACE) ma anche e, soprattutto, sugli eventi vascolari a carico degli arti inferiori.
- È stato altresì confrontato l'effetto dell'acido bempedoico su pazienti con e senza PAD, in merito agli eventi vascolari periferici e in merito ai MACE.

- L'acido bempedoico ha ridotto significativamente i MACE3 o i MALE sia nei pazienti PAD che in quelli non PAD.



Studio DA VINCI: Raggiungimento degli obiettivi di C-LDL

- Circa metà dei pazienti non hanno raggiunto i loro obiettivi terapeutici di C-LDL secondo le Linee Guida ESC/EAS 2016 e circa due terzi non hanno raggiunto gli obiettivi raccomandati dalle Linee Guida 2019.
- Nelle singole categorie di rischio, gli obiettivi terapeutici raccomandati dalle LG 2016 sono stati raggiunti dalle seguenti percentuali di pazienti:
  - **Rischio basso: 63%** (95% CI 56–70)
  - **Rischio moderato: 75%** (95% CI 73–78);
  - **Rischio alto: 63%** (95% CI 59–67);
  - **Rischio molto alto: 39%** (95% CI 37–41)



Ray, KK et al. Eur. J. Prev. Cardiol. 2020

Treatment gaps in the implementation of LDL cholesterol control among high- and very high-risk patients in Europe between 2020 and 2021: the multinational observational SANTORINI study

Kausik K. Ray,[a,*] Inaam Haq,[b] Aikaterini Bilitou,[c] Marius C. Manu,[b] Annie Burden,[d] Carlos Aguiar,[e] Marcello Arca,[f] Derek L. Connolly,[g] Mats Eriksson,[h] Jean Ferrières,[i] Ulrich Laufs,[j] Jose M. Mostaza,[k] David Nanchen,[l] Ernst Rietzschel,[m] Timo Strandberg,[n,o] Hermann Toplak,[p] Frank L. J. Visseren,[q] and Alberico L. Catapano,[r,s] on behalf of the SANTORINI Study Investigators[t]

- I dati dello studio SANTORINI mostrano che, nonostante le linee guida ESC/EAS del 2019 sembrino essere ampiamente utilizzate in Europa per classificare i pazienti in base al loro livello di rischio CV, gli obiettivi non vengono sufficientemente implementati, con il risultato che una percentuale sostanziale di pazienti rimane ad alto rischio CV
- I fattori che contribuiscono a questo fenomeno possono essere l'inadeguata classificazione del rischio e il sottoutilizzo delle terapie combinate

Lancet Reg Health Eur. 2023 Apr 5;29:100624

European Atherosclerosis Journal
www.eathj.org

EAJ 2023;1:1-13
https://doi.org/10.56095/eaj.v2i1.26

Lipid-lowering treatment and LDL-C goal attainment in high and very high cardiovascular risk patients: Evidence from the

In base alle più recenti linee guida ESC/EAS del 2019, l'uso di terapie ipocolesterolemizzanti non è sempre ottimale per raggiungere gli obiettivi terapeutici anche nei pazienti con rischio CV molto elevato. Ciò significa che circa l'80% dei pazienti è lontano dagli obiettivi terapeutici raccomandati per la propria categoria di rischio.

[4]*Center for the Study of Atherosclerosis, E. Bassini Hospital, Cinisello Balsamo, Milan, Italy*
[5]*Medical Affairs at Daiichi Sankyo Italy, Rome, Italy*
[6]*Imperial Centre for Cardiovascular Disease Prevention, ICTU-Global, Imperial College London, London, United Kingdom*
[7]*Center for the Study of Dyslipidaemias, IRCCS Multimedica, Milan, Italy*
** A complete list of the SANTORINI Italian Group can be found in the Appendix at the end of the article.*

Revised recommendations (3)

2017 PAD and 2014 Aortic Guidelines	Class	Level	2024 PAAD Guidelines	Class	Level
Recommendations for lipid-lowering therapy for patients with peripheral arterial and aortic diseases					
In patients with PAD, it is recommended to reduce LDL-C to <1.8 mmol/L (70 mg/dL) or decrease it by >50% if baseline values are 1.8–3.5 mmol/L (70–135 mg/dL).	I	C	An ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and a >50% reduction in LDL-C vs. baseline are recommended in patients with atherosclerotic PAAD.	I	A
Recommendations for carotid artery stenosis assessment					
DUS (as first-line imaging), CTA, and/or MRA are recommended for evaluating the extent and severity of extracranial carotid stenosis.	I	B	It is recommended to use DUS as first-line imaging to diagnose ICA stenosis.	I	C

Recommendations for lipid-lowering therapy in patients with peripheral arterial and aortic diseases (1)

Recommendations	Class	Level
In patients with atherosclerotic PAAD, lipid-lowering therapy is recommended.	I	A
An ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and a >50% reduction in LDL-C vs. baseline are recommended in patients with atherosclerotic PAAD.	I	A
Statins are recommended in all patients with PAD.	I	A
If the target LDL-C level is not achieved on maximally tolerated statins and ezetimibe, treatment with a PCSK9 inhibitor is recommended in patients with atherosclerotic PAAD, to achieve target values.	I	A
If the target LDL-C level is not achieved, a combination of statins and ezetimibe is indicated in patients with atherosclerotic PAAD, to achieve the given target values.	I	B
For statin-intolerant patients with atherosclerotic PAAD, at high CV risk, who do not achieve their LDL-C goal on ezetimibe, it is recommended to add bempedoic acid either alone or in combination with a PCSK9 inhibitor.	I	B

Recommendations for lipid-lowering therapy in patients with peripheral arterial and aortic diseases (2)

Recommendations cont.	Class	Level
Statins for the reduction of growth and rupture of AAA should be considered.	IIa	B
Statins for the reduction of growth and rupture of TAA may be considered.	IIb	B
In high-risk patients with PAAD and triglycerides >1.5 mmol/L despite lifestyle measures and statin therapy, icosapent ethyl 2g b.i.d. may be considered in addition to a statin.	IIb	B
Fibrates are not recommended for cholesterol lowering.	III	B

PAD e FDR

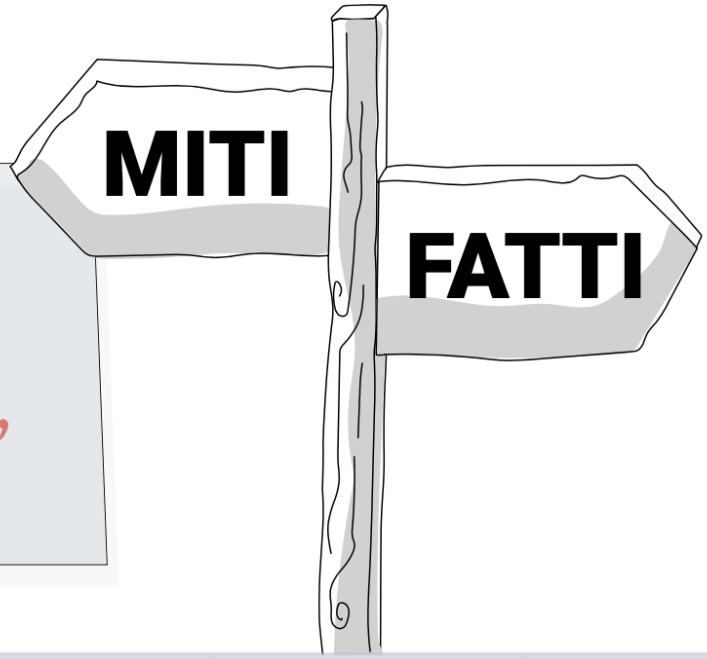
Terapia Diabete

Recommendations for the medical management of patients with peripheral arterial and aortic diseases and diabetes

Recommendations	Class	Level
It is recommended to apply tight glycaemic control (HbA1c <53 mmol/mol [7%]) to reduce microvascular complications in patients with PAAD.	I	A
SGLT2i with proven CV benefit are recommended in patients with T2DM and PAAD to reduce CV events, independent of baseline or target HbA1c and concomitant glucose-lowering medication.	I	A
GLP-1RAs with proven CV benefit are recommended in patients with T2DM and PAAD to reduce CV events, independent of baseline or target HbA1c and concomitant glucose-lowering medication.	I	A
It is recommended to avoid hypoglycaemia in patients with PAAD.	I	B
It is recommended to individualize HbA1c targets according to comorbidities, diabetes duration, and life expectancy.	I	C
It is recommended to prioritize the use of glucose-lowering agents with proven CV benefits, followed by agents with proven CV safety, over agents without proven CV benefit or safety.	I	C
If additional glucose control is needed, metformin should be considered in patients with T2DM and PAAD.	IIa	B

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

OBIETTIVI DI HbA1c NEL DIABETE TIPO 2



“**La parte più importante del mio lavoro è stabilire gli obiettivi di HbA1c** per i miei pazienti con diabete tipo 2. *”

Questo è un

FALSO MITO

Sfatare i miti

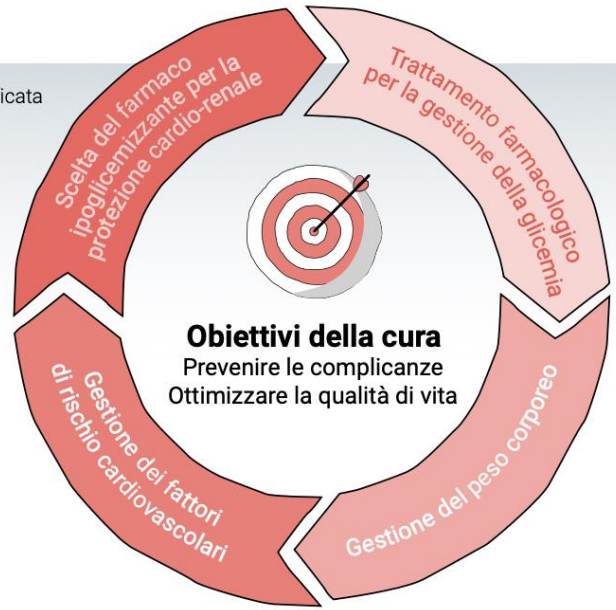
Sebbene il controllo glicemico precoce e rigoroso (HbA1c ≤7% (~ 53 mmol/mol)) sia una delle raccomandazioni ADA/EASD, **l'obiettivo primario del trattamento nel diabete tipo 2 è prevenire le complicanze e ottimizzare la qualità di vita**. [1]

Il diabete tipo 2 è una malattia cronica, sistemica e complessa con diverse disfunzioni che contribuiscono all'iperglicemia e, **pertanto, la gestione del diabete richiede anche un approccio multifattoriale e olistico**. [1,2]

Le linee guida ADA/EASD

per la gestione del diabete tipo 2 **raccomandano un approccio olistico e centrato** sulla persona che vada oltre i soli obiettivi di HbA1c. [1]

Figura modificata dal ref 1

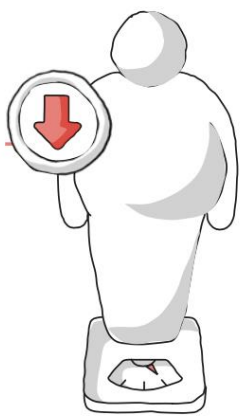


La gestione del peso corporeo è una componente essenziale della terapia del diabete tipo 2 che può impattare sugli esiti a lungo termine per il paziente. [1]

Riduzione del peso corporeo[1]

5-10%

Miglioramento metabolico



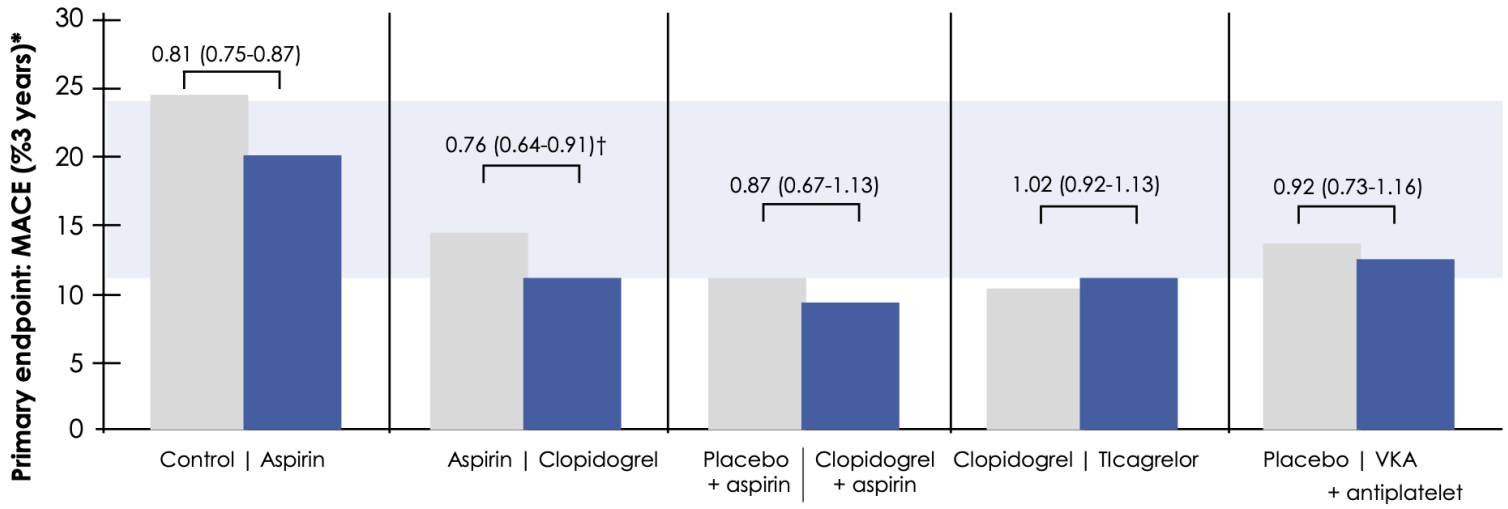
≥10-15%

Effetto modificante la malattia che porta alla remissione del diabete tipo 2

PAD

TERAPIA ANTITROMBOTICA

Even With Evidence-Based Therapies, PAD Patients are Faced with High Cumulative Risk for Atherothrombotic Events



% Use of key Therapies in Intervention arm	ATTC[1] Meta-analysis Secondary prevention	CAPRIE[2] Subgroup Symptomatic PAD	CHARISMA[3] Subgroup Prior ND stroke or Symptomate PAD	EUCLID[4] PAD	WAVE[5] PAD
ACEvARB			Up to 85.3	Up to 65.5	50.4
Statin	Meta-analysis of 16 trials	Not reported			
Lipid lowering			77.1-89.3	73.7	55.1

Xxxx calculated from annual rates (ATTC & CAPRIE), % across 28 months of median follow-up (CHARISMA), 3-year Kaplan-Meier event Rates(EUCLID), and % across 35 months of mean follow up (WAVE); †Calculated from relative risk reduction

1. ATT Collaboration Lancet 2009;373:1849-1860; 2. CAPRIE Steering Committee. Lancet 1996;348:1329-1339; 3. Bhatt DL et al. H Am Cott Cardiol 2007;49:1982-1988; 4 Hiatt WR et al. N Engl J Med 2017;376:32-40; 5. The Warfarin Antiplatelet Vascular Evaluation Trial Investigation N Engl J Med 2007;357:217-227

ESC Guidelines 2017 - Diagnosis and treatment of peripheral arterial diseases, in collaboration with the ESVS

Antithrombotic therapy for PAD

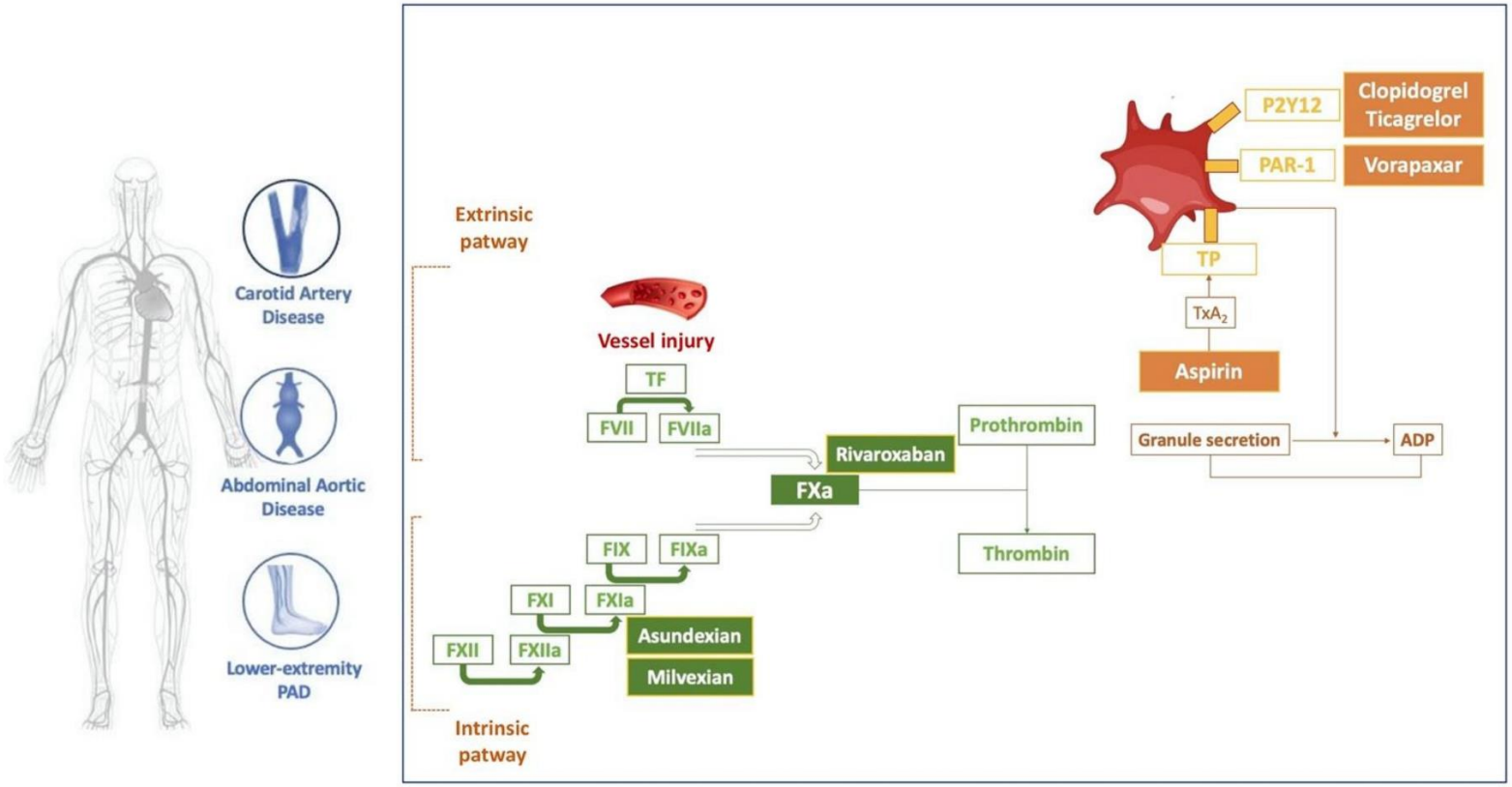
Clopidogrel preferito ad ASA in caso di pazienti con PAD degli arti inferiori (Classe IIb Livello B).

Recommendations	Class	Level
Lower extremity artery disease (continued)		
SAPT is recommended after infra-inguinal bypass surgery.	I	A
In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin.	IIb	B
Vitamin K antagonists may be considered after autologous vein infrainguinal baypass.	IIb	B
DAPT with aspirin and clopidogrel for at least one month should be considered after infra-inguinal stent implantation	IIa	C
DAPT with aspirin and clopidogrel may be considered in below-knee bypass with prosthetic graft.	IIb	B

European Society for Vascular Medicine (ESVM) Guideline on peripheral arterial disease

Recommendation	Class of recommendation	Level of evidence
In patients with symptomatic PAD, platelet aggregation inhibitors are indicated for the secondary prevention of cardiovascular events.	I	A
Clopidogrel may be preferred over aspirin.	IIb	B

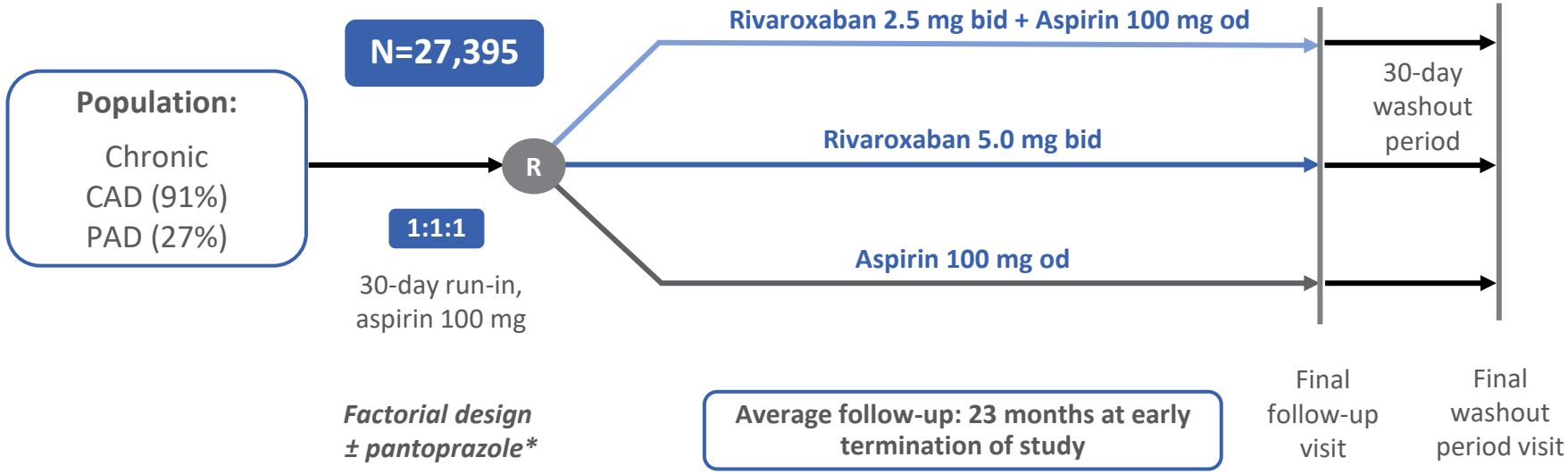
Pharmacodynamic targets of antithrombotic drugs in peripheral artery disease by thrombotic pathway



Canonico E et al, J. Cardiovasc. Dev. Dis. **2023**, *10*, 164

A Dual Pathway Approach Targeting Chronic Patients with CAD or PAD was Investigated in COMPASS

Objective: To determine the efficacy and safety of rivaroxaban, vascular dose of rivaroxaban plus aspirin or aspirin alone for reducing the risk of MI, stroke and cardiovascular death in CAD or PAD



Antithrombotic investigations were stopped 1 year ahead of expectations in Feb 2017 due to overwhelming efficacy in the rivaroxaban 2.5 mg bid + aspirin arm

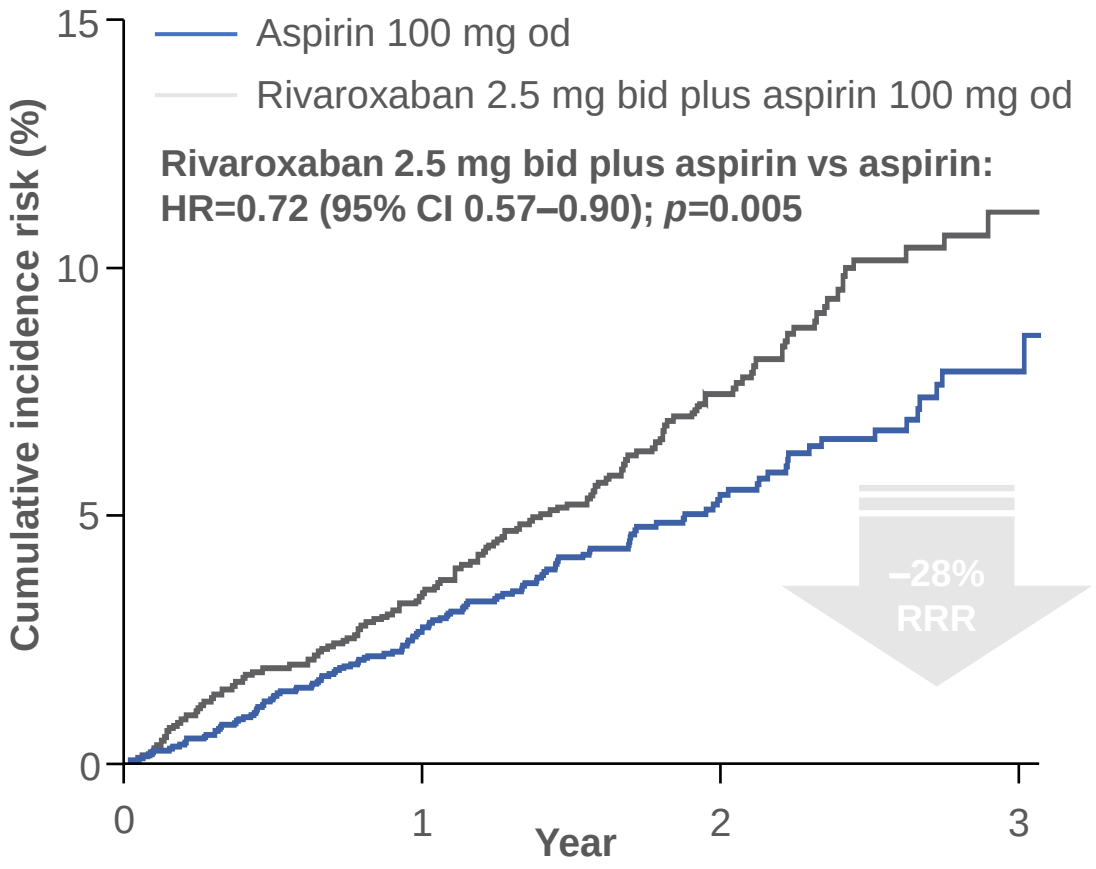
*Patients who were not receiving a proton pump inhibitor (PPI) were randomized to pantoprazole or placebo (partial factorial design); the PPI pantoprazole component of the study is continuing; data will be communicated once complete

1. Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118;
2. Bosch J *et al. Can J Cardiol* 2017;33(8):1027–1035

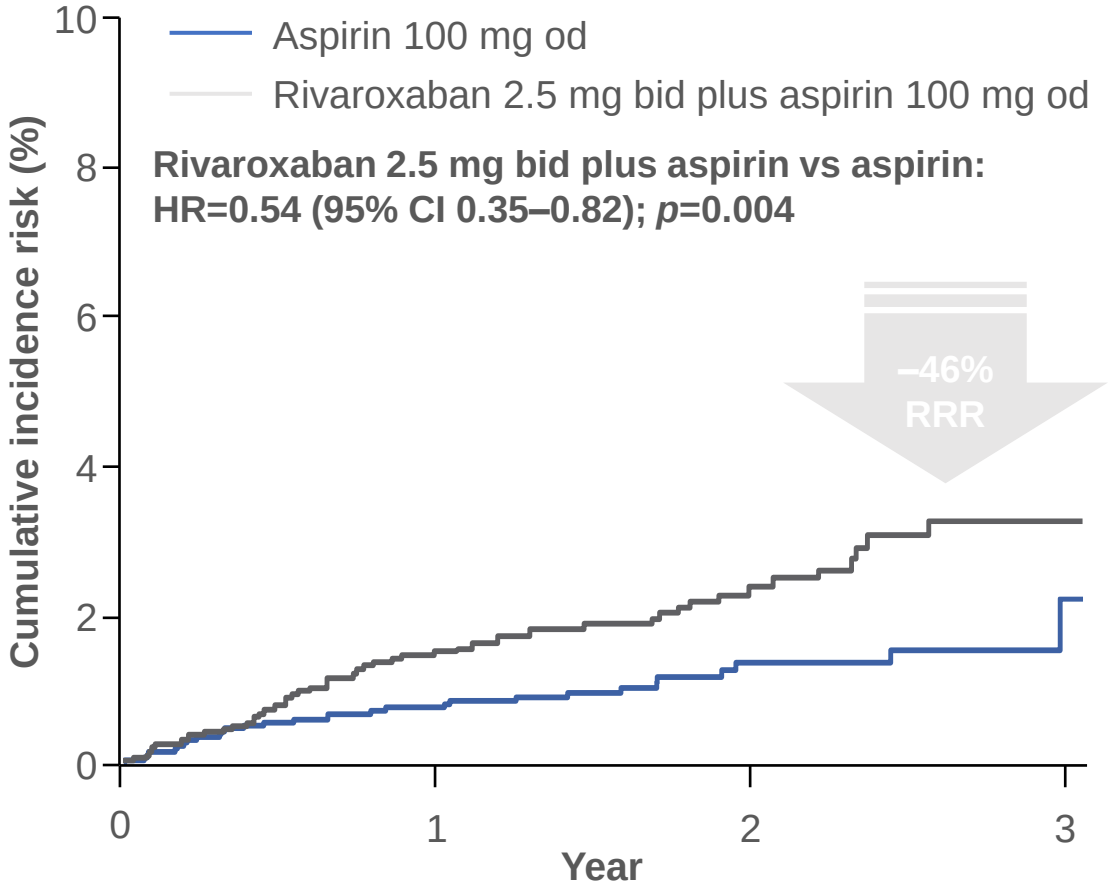
COMPASS

Rivaroxaban 2.5 mg bid plus Aspirin Significantly Reduced MACE and MALE Versus Aspirin Alone in Patients with Chronic PAD in COMPASS

Stroke/MI/CV death



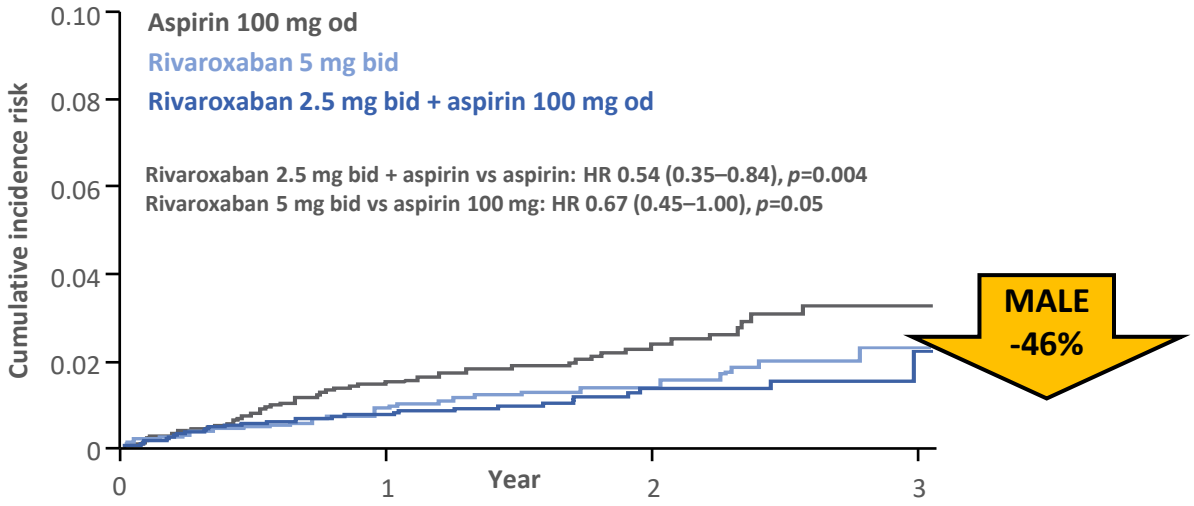
MALE* including major amputation



*Defined in COMPASS as ALI or CLI.

Anand SS *et al*. *Lancet* 2018;391:219–229.

Cumulative incidence of individual components of major adverse limb events including major amputation



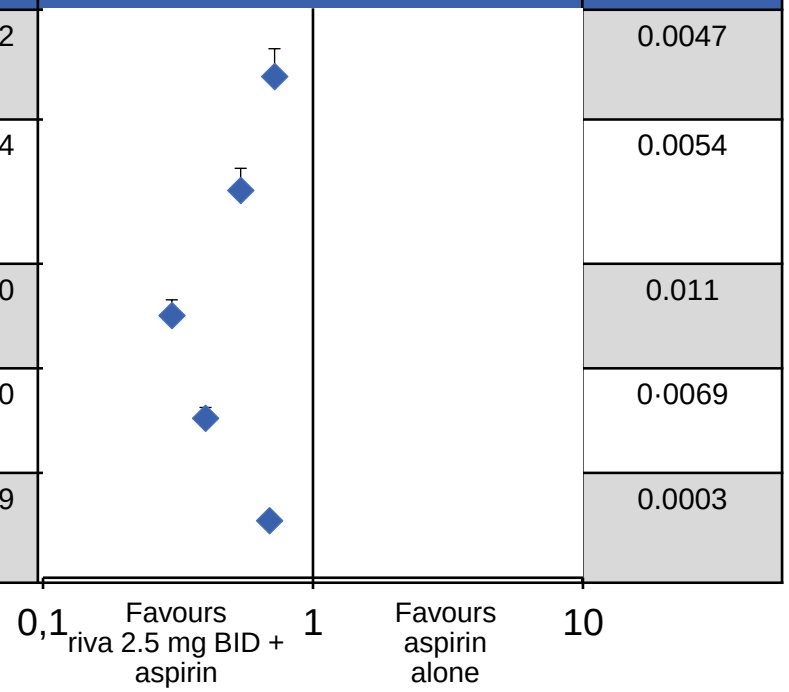
Number at risk				
Rivaroxaban + aspirin	2492	2099	919	129
Rivaroxaban	2474	2071	902	151
Aspirin	2504	2072	951	120

COMPASS

Anand SS *et al*, *Lancet* 2017: doi:10.1016/S0140-6736(17)32757-5

Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Significantly ↓ Both CV & Limb Events Incl. Amputations vs Aspirin in PAD

Pre-specified PAD outcomes*	Riva 2.5 mg bid + aspirin n (%)	Aspirin n (%)	HR	HR (95% CI)	*p*-value
CV death, stroke, MI (MACE: major adverse cardiac events)	126 (5)	174 (7)	0.72		0.0047
Acute limb ischaemia or chronic limb ischaemia (MALE: major adverse limb events)	30 (1)	56 (2)	0.54		0.0054
Major amputation	5 (0.2)	17 (0.7)	0.30		0.011
All vascular amputations	11 (0.4)	28 (1)	0.40		0·0069
MACE or MALE, or major amputation	157 (6)	225 (9)	0.69		0.0003



*Crude incidence over mean follow-up of 23 months

Anand SS et al. *Lancet* 2017;doi:10.1016/S0140-6736(17)32409-1.

COMPASS

Modified ISTH Major Bleeding Definition

ISTH major bleeding[1]	Modified ISTH major bleeding (COMPASS)
• Fatal bleeding, *and/or*	• Fatal bleeding, *and/or*
• Symptomatic bleeding in a critical area or organ (such as intracranial), *and/or*	• Symptomatic bleeding in a critical area or organ (such as intracranial), *or*
• ***Bleeding causing a drop in haemoglobin level of ≥20 g/l, or leading to transfusion of ≥2 units of whole blood or red cells***	• ***Bleeding into the surgical site requiring re-operation, and/or*** • ***Bleeding leading to hospitalization***

Unlike the standard ISTH criteria, all bleeding that led to presentation to an acute care facility or hospitalization were considered as major compared with the standard ISTH major bleeding definition

1. Schulman S *et al*, *J Thromb Haemost* 2005;3:692–694

COMPASS

Bleeding Rates

Rates at mean follow-up of 23 months	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Aspirin 100 mg N=9126	HR (95% CI)	p value
Modified major ISTH bleeding	288 (3.1%)	170 (1.9%)	1.70 (1.40–2.05)	<0.001
Fatal	15 (0.2%)	10 (0.1%)	1.49 (0.67–3.33)	0.32
Non-fatal ICH*	21 (0.2%)	19 (0.2%)	1.10 (0.59–2.04)	0.77
Non-fatal other critical organ*	42 (0.5%)	29 (0.3%)	1.43 (0.89–2.29)	0.14

Each event is counted in the most severe hierarchical category (fatal; critical organ bleeding; bleeding into surgical site requiring re-operation; bleeding leading to hospitalization) only. For each outcome, the first event experienced per patient is considered. Subsequent events of the same type are not shown. Therefore subcategories do not necessarily sum up to overall category.
*Symptomatic

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

COMPASS

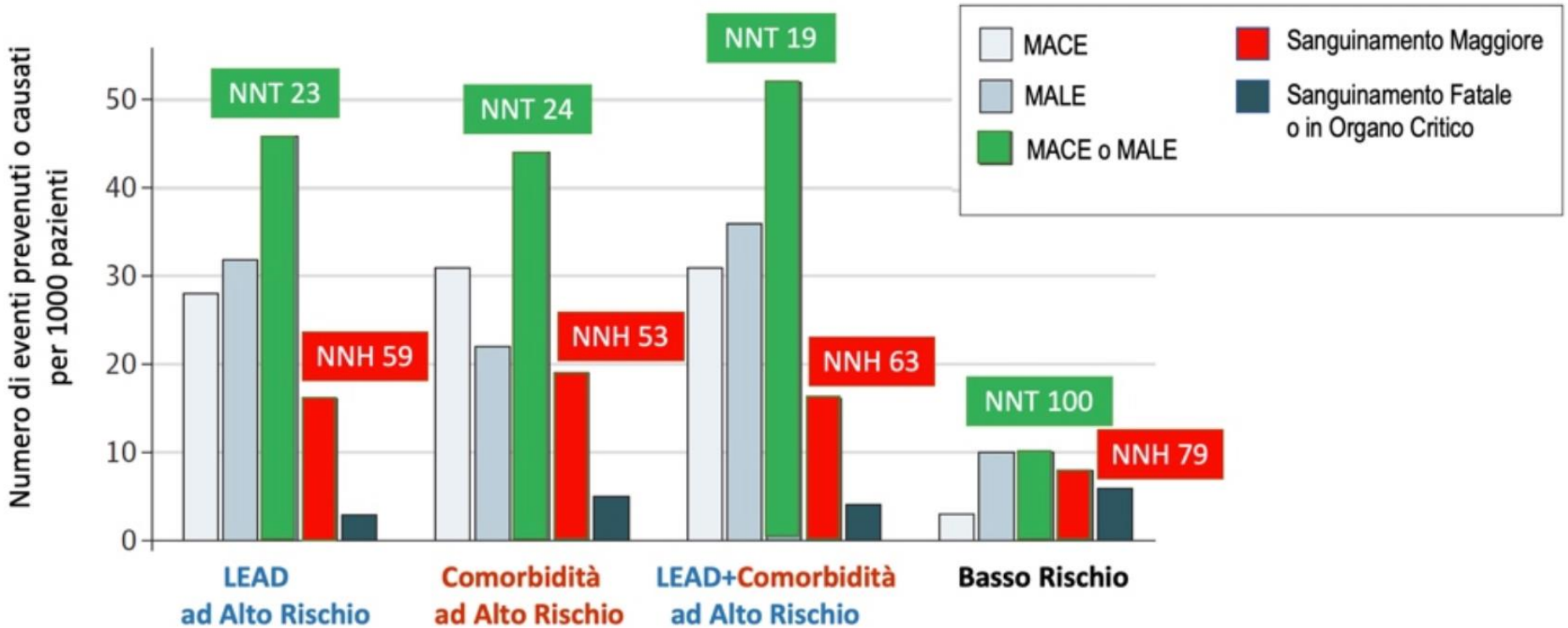
Net Clinical Benefit

- **Definition:** composite of CV death, stroke, MI, fatal bleeding or symptomatic bleeding into a critical organ
  - **In other words, net clinical benefit represented the composite of fatal and non-fatal events of irreversible harm**

Outcome	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Aspirin 100 mg N=9126	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg	
			HR (95% CI)	*p*-value
Net clinical benefit	431 (4.7%)	534 (5.9%)	0.80 (0.70–0.91)	<0.001

COMPASS

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

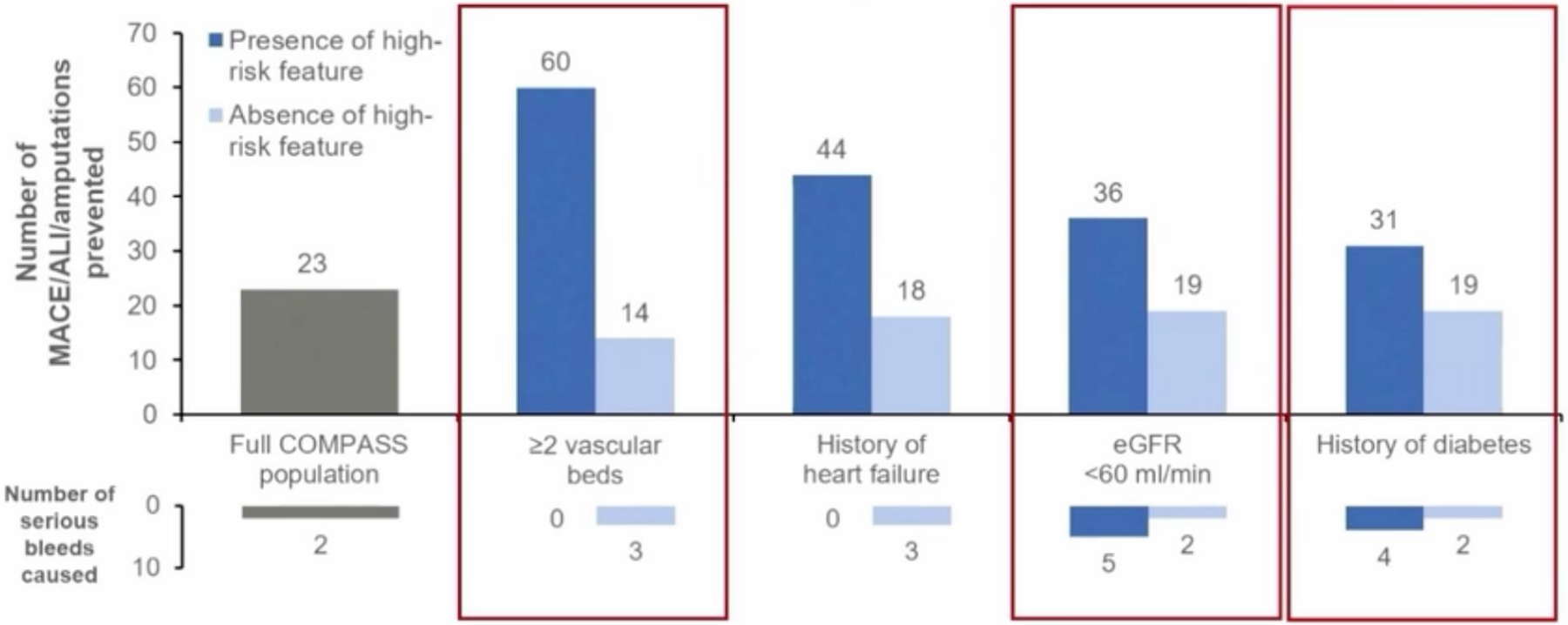


Comorbidità ad Alto Rischio: polivasculopatia, scompenso cardiaco, diabete, insufficienza renale
LEAD ad Alto Rischio: storia di amputazione, storia di rivascolarizzazione, Fontaine stadio III o IV

Modified from Kaplovitch E. JAMA Cardiol. 2021;6(1):21–29

Absolute Benefit of Rivaroxaban Vascular Dose Plus Aspirin Was Highest in High-Risk Patient Groups

Ischaemic events prevented and bleeding events caused per 1000 patients over 30 months with addition of rivaroxaban 2.5 mg bid to aspirin in high-risk groups



Anand SS *et al. J Am Coll Cardiol* 2019;73:3271–3280

Members of the guidelines committee

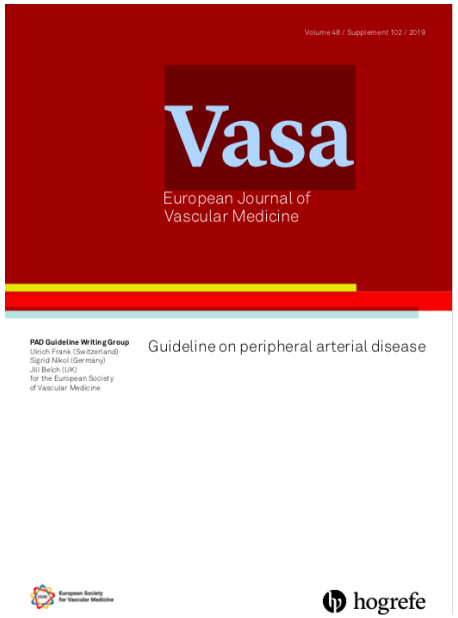
European Society of Vascular Medicine (ESVM): Guideline on peripheral arterial disease

PAD Guideline Writing Group
Ulrich Frank (Switzerland), Sigrid Nikol (Germany), and Jill Belch (UK) for the European Society of Vascular Medicine – all co-first authors

ESVM Board Authors
Vinko Boc* (Slovenia), Marianne Brodmann (Austria), Patrick H Carpentier (France), Ali Chraim* (Ukraine), Caitriona Canning (Ireland); Evangelos Dimakakos* (Greece), Anders Gottsäter (Sweden), Christian Heiss (Germany), Lucia Mazzolai (Switzerland), Juraj Madaric* (Slovakia), Dan Mircea Olinic* (Romania), Zsolt Pécsvárady* (Hungary), Pavel Poredoš* (Slovenia), Isabelle Quéré (France), Karel Roztocil (ESVM President, Czech Republic), Agata Stanek (Poland), Dragan Vasic* (Serbia), Adriana Visonà (Italy), and Jean-Claude Wautrecht* (Belgium)

ESVM Country Society Authors
Miroslav Bulvas (Czech Republic), Mary-Paula Colgan (Ireland), Walter Dorigo (Italy), Graeme Houston (UK), Thomas Kahan (Sweden), Holger Lawall (Germany), Isak Lindstedt (Sweden), Guillaume Mahe (France), Romeo Martini (Italy), Giles Pernod (France), Stanislaw Przywara (Poland). Marc Righini (Switzerland), Oliver Schlager (Austria), and Piotr Terlecki (Poland)

*Indicates ESVM Board members who were also nominated by their Country Society as reviewers.

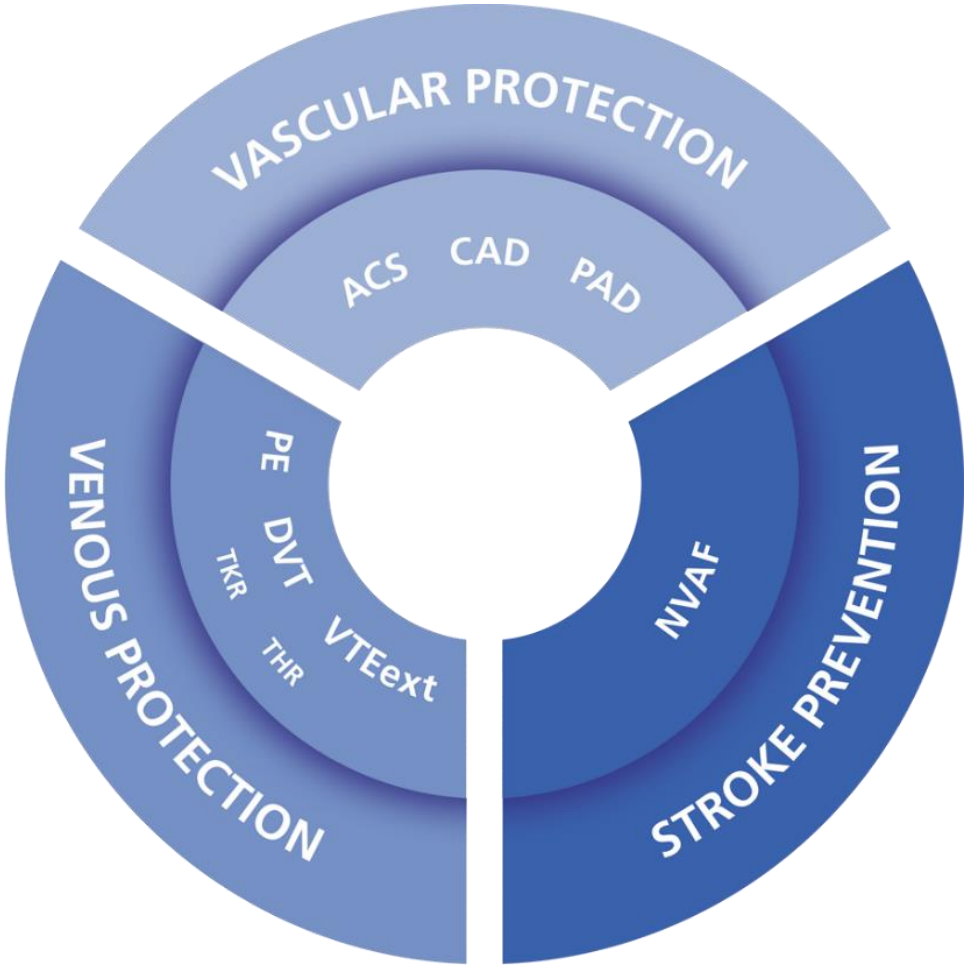


Recommendation	Class of recommendation	Level of evidence
Based on the results of the COMPASS trial, the combined therapy of ASA 100 mg/d and rivaroxaban 2 × 2.5 mg/d should be considered in PAD patients without a high risk of bleeding, or other contraindications.	IIa	B

Raccomandazioni europee per l'utilizzo di rivaroxaban 2,5 mg

		Evidenza Classe	Livello
ESC European Society of Cardiology	**2019 ESC guidelines on the management of CCS** Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischaemic events* and without high bleeding risk **(e.g: rivaroxaban 2.5 mg bid)**	IIa	A
ESC European Society of Cardiology EASD	**2019 ESC–EASD guidelines on diabetes, pre-diabetes and CVD** In patients with diabetes and chronic symptomatic LEAD without high bleeding risk, a combination of low-dose **rivaroxaban 2.5 mg bid** and aspirin (100 mg od) should be considered	IIa	B
GLOBAL VASCULAR GUIDELINES ESVS, SVS, WFVS Working Together to Improve Patient Care	**2019 Global Vascular Guidelines on the management of CLTI** Consider low-dose aspirin and **rivaroxaban 2.5 mg bid** to reduce adverse cardiovascular events and lower-extremity ischaemic events in patients with CLTI	2	B
ESVM	**2019 ESVM guidelines on the management of PAD** The combined therapy of aspirin 100 mg od and **rivaroxaban 2.5 mg bid** should be considered in PAD patients without a high risk of bleeding, or other contraindications	IIa	B

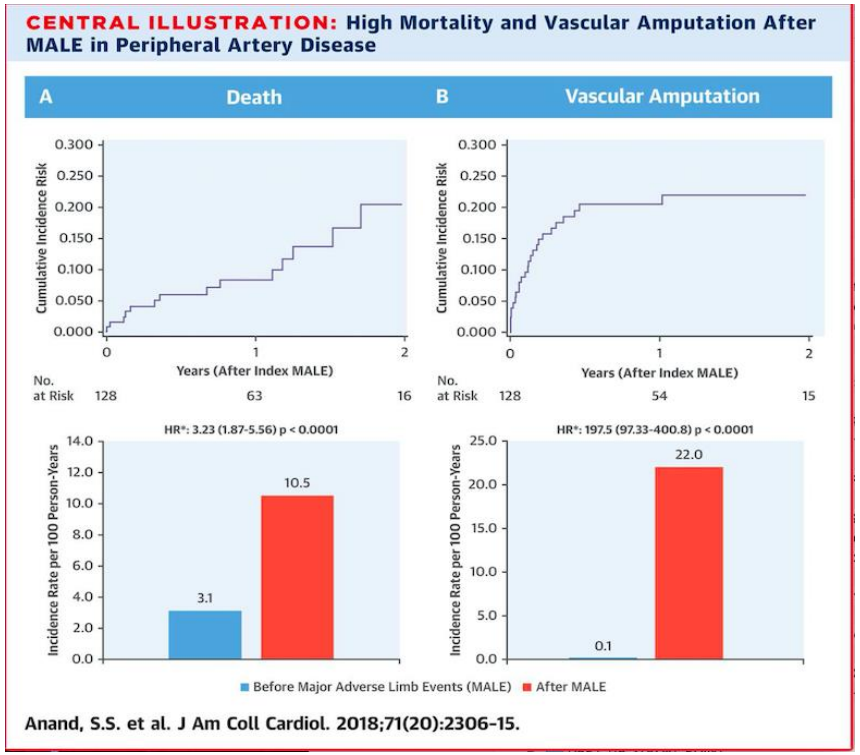
VOYAGER PAD

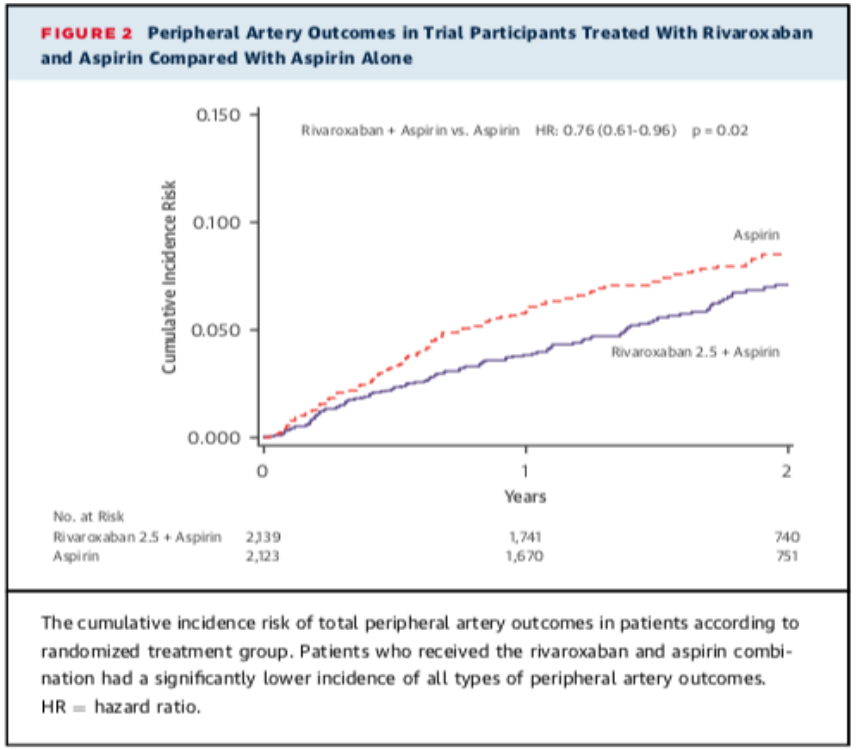

VASCULAR PROTECTION
ACS
CAD
PAD
VENOUS PROTECTION
PE
DVT
VTEext
TKR
THR
STROKE PREVENTION
NVAF

Le ragioni della scelta

- I pazienti con malattia vascolare periferica (PAD) sottoposti a rivascolarizzazione degli arti inferiori hanno un rischio aumentato di eventi ischemici cardiaci e vascolari.
- Sebbene il potenziamento della terapia antitrombotica dopo rivascolarizzazione abbia dimostrato benefici nei pazienti coronarici, questo approccio non ha dati solidi nella PAD.
- Recenti *trial* hanno dimostrato come una una terapia con rivaroxaban a basso dosaggio aggiunto alla terapia antipiastrinica abbia ridotto il rischio ischemico nei pazienti con recente SCA, nonché nei pazienti con malattia vascolare aterosclerotica stabile.
- Indagare se questi benefici si estendano alla popolazione di pazienti con PAD sintomatica degli arti inferiori che vengono sottoposti a rivascolarizzazione è l'obiettivo dello studio VOYAGER PAD.

Mortality and vascular Amputation after MALE in PAD

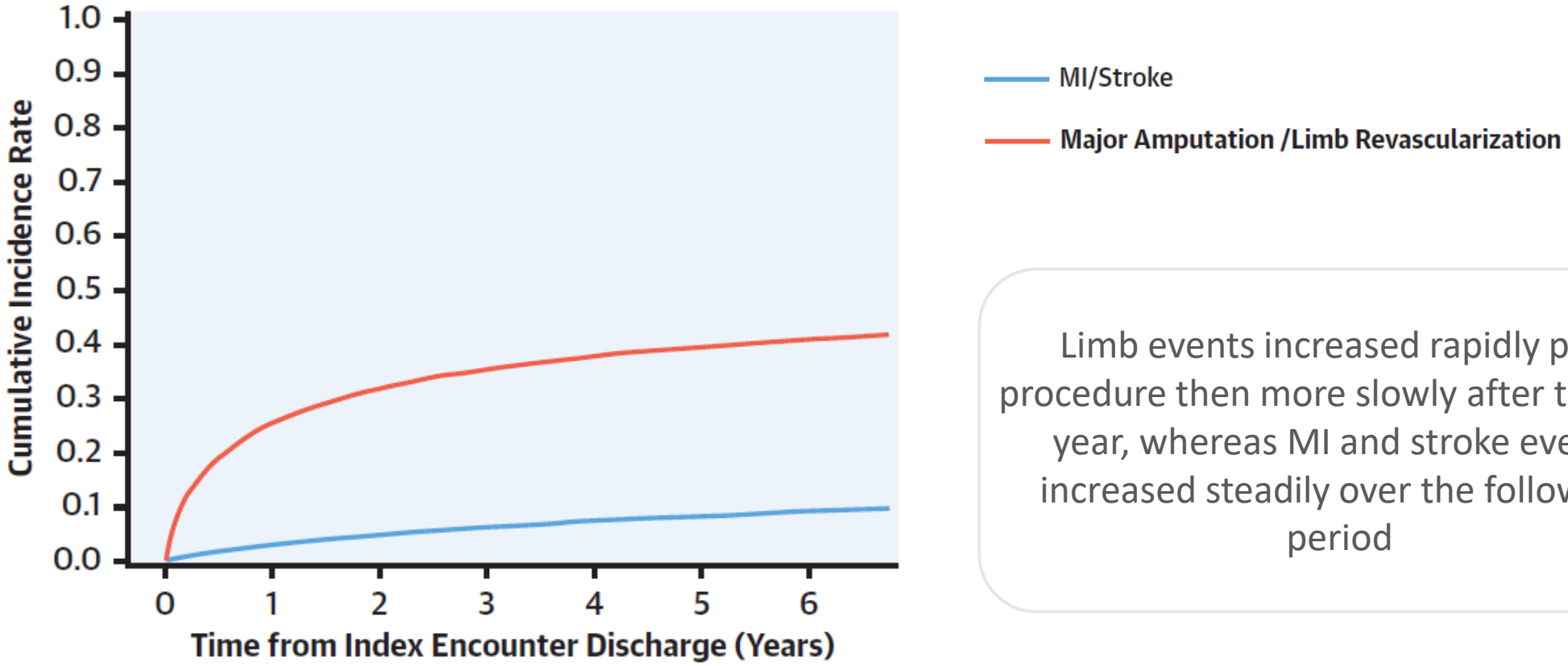




Anand et al, JACC 2018; 71:2306-15

Risk of MALE Is Substantially Increased After Peripheral Revascularization

Analysis of patients in the Premier Healthcare Database who underwent peripheral revascularization (N=393,017)



Limb events increased rapidly post procedure then more slowly after the first year, whereas MI and stroke events increased steadily over the follow-up period

Median follow-up 2.7 years.

Hess CN *et al*. *J Am Coll Cardiol* 2020;75:498–508.

ORIGINAL ARTICLE

Rivaroxaban in Peripheral Artery Disease after Revascularization

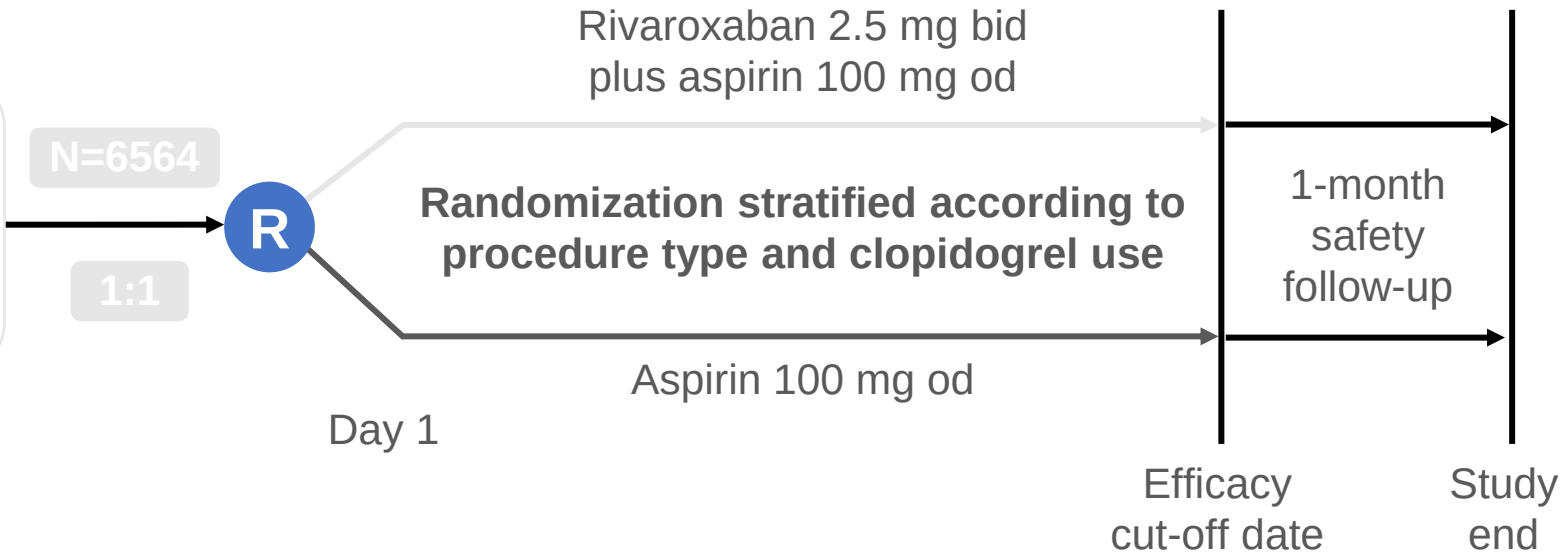
Marc P. Bonaca, M.D., M.P.H., Rupert M. Bauersachs, M.D., Sonia S. Anand, M.D., E. Sebastian Debus, M.D., Ph.D., Mark R. Nehler, M.D., Manesh R. Patel, M.D., Fabrizio Fanelli, M.D., Warren H. Capell, M.D., Lihong Diao, M.D., Nicole Jaeger, M.S., Connie N. Hess, M.D., M.H.S., Akos F. Pap, M.Sc., John M. Kittelson, Ph.D., Ivan Gudz, M.D., Ph.D., Lajos Mátyás, M.D., Dainis K. Krievins, M.D., Rafael Diaz, M.D., Marianne Brodmann, M.D., Eva Muehlhofer, M.D., Lloyd P. Haskell, M.D., Scott D. Berkowitz, M.D., and William R. Hiatt, M.D.

NEJM 2020,May 21

VOYAGER PAD: Study Design

Objective: To evaluate the efficacy and safety of rivaroxaban 2.5 mg bid plus aspirin compared with aspirin to reduce the risk of thrombotic vascular events in patients with PAD undergoing peripheral (lower extremity) revascularization procedures

Population:
Patients with symptomatic PAD with a recent peripheral revascularization (≤10 days previously)



Short design: Randomized, double-blind, phase III, controlled trial

Indication:
Symptomatic PAD

Completion date:
December 2019

Mean treatment duration per patient: ~30 months.

Capell WH *et al*. *Am Heart J* 2018;199:83–91. Bayer 2019. www.clinicaltrials.gov/ct2/show/NCT02504216 [accessed Dec 2019].

VOYAGER PAD

Baseline Demographics Were Well Balanced Between Randomized Treatment Groups

	Rivaroxaban 2.5 mg bid plus aspirin (n=3286)	Aspirin (n=3278)
Median age (IQR), years	67.0 (61.0–73.0)	67.0 (61.0–73.0)
Female sex, n (%)	847 (25.8)	857 (26.1)
Median BMI (IQR), kg/m^2	26.0 (23.3–29.1)	26.0 (23.2–29.1)
Race, n (%)		
White	2647 (80.6)	2656 (81.0)
Asian	484 (14.7)	482 (14.7)
Black	84 (2.6)	71 (2.2)
Other	71 (2.2)	69 (2.1)

Bonaca MP *et al. N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

Risk Factors and Co-morbidities Were Similar Between Randomized Treatment Groups

	Rivaroxaban 2.5 mg bid plus aspirin (n=3286)	Aspirin (n=3278)
Hypertension	2684 (81.7)	2658 (81.1)
Hyperlipidaemia	1971 (60.0)	1968 (60.0)
Current smoker	1147 (34.9)	1132 (34.5)
Diabetes mellitus	1313 (40.0)	1316 (40.1)
eGFR <60 ml/min/1.73 m^2	661 (20.1)	666 (20.3)
Symptomatic CAD	1052 (32.0)	1015 (31.0)
MI	365 (11.1)	349 (10.6)
Carotid artery disease	282 (8.6)	293 (8.9)

Bonaca MP *et al. N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

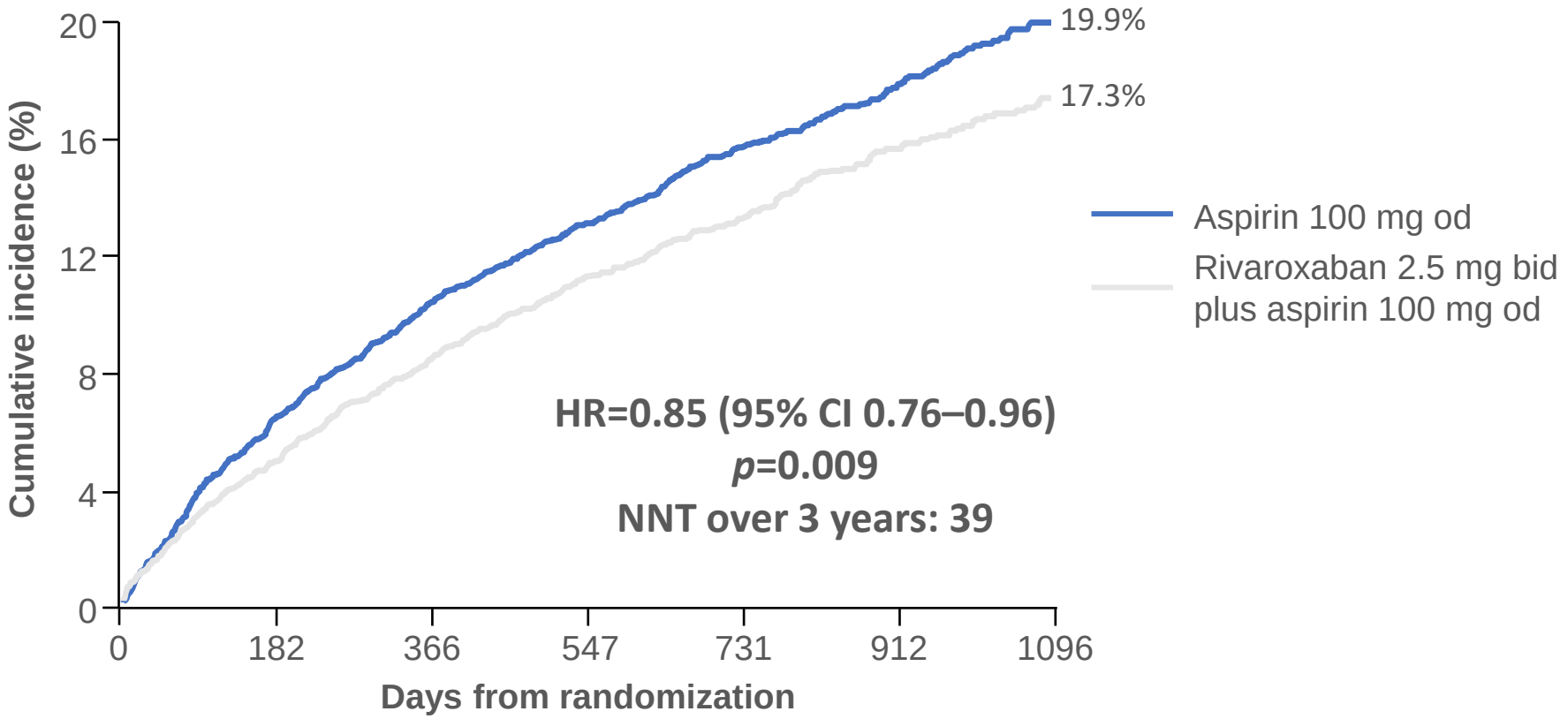
Other Clinical Characteristics Were Well Balanced Between Randomized Treatment Groups

	Rivaroxaban 2.5 mg bid plus aspirin (n=3286)	Aspirin (n=3278)
PAD history		
Median ABI (IQR)	0.56 (0.42–0.67)	0.56 (0.42–0.67)
Prior amputation, n (%)	194 (5.9)	196 (6.0)
Qualifying revascularization, n (%)		
Endovascular	2153 (65.5)	2140 (65.3)
Surgical	1133 (34.5)	1138 (34.7)
Performed for CLI	762 (23.2)	771 (23.5)
Medications, n (%)		
Statin	2608 (79.4)	2641 (80.6)
ACE inhibitor or ARB	2096 (63.8)	2063 (62.9)
Clopidogrel at randomization	1658 (50.5)	1655 (50.5)

Bonaca MP *et al. N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

Rivaroxaban Vascular Dose plus Aspirin Significantly Reduced Risk of the Composite Primary Endpoint by 15% Versus Aspirin

Cumulative incidence of ALI, major amputation of vascular aetiology, MI, ischaemic stroke or CV death



Number at risk							
Rivaroxaban plus aspirin	3286	3082	2938	2834	2219	1415	684
Aspirin	3278	3030	2881	2773	2151	1351	642

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

Reduction in the Primary Endpoint Was Driven by a 33% Reduction in Risk of ALI with DPI Versus Aspirin

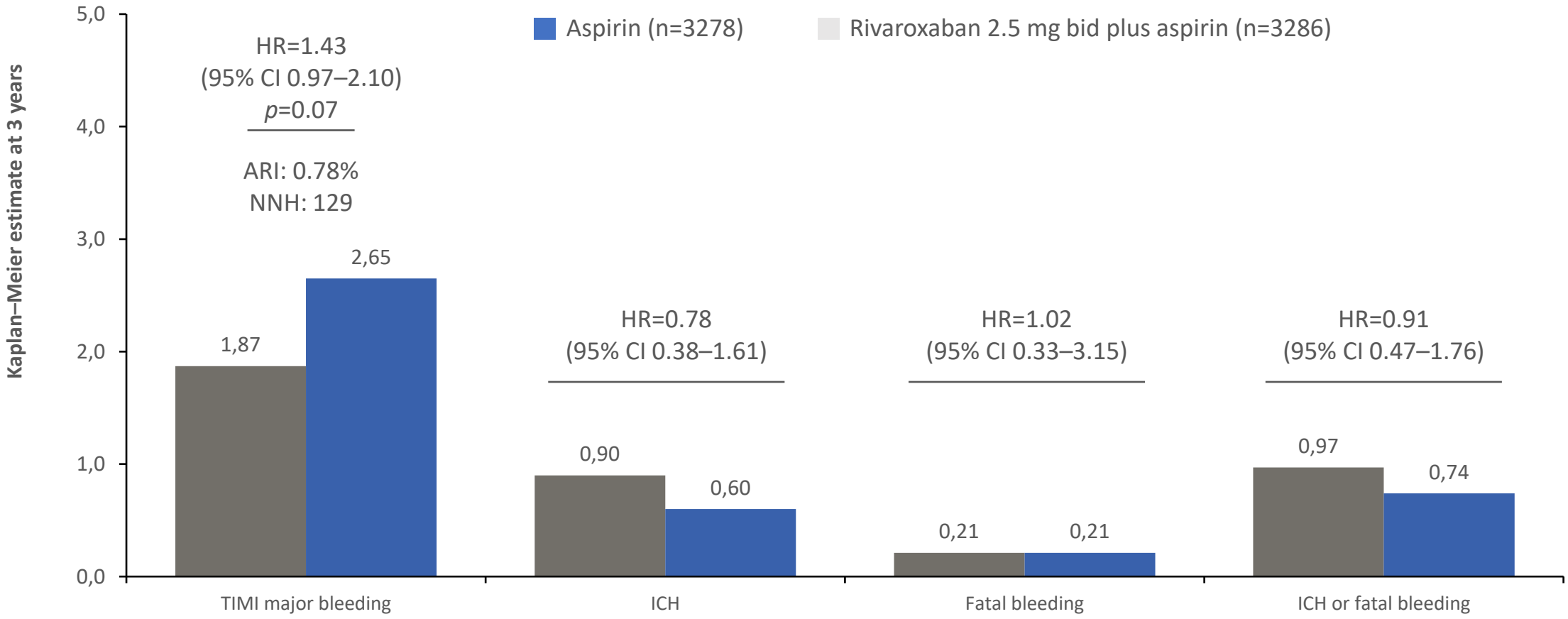
Endpoint	Rivaroxaban 2.5 mg bid + aspirin (N=3286)		Aspirin (N=3278)		HR (95% CI)	*p*-value
	Patients with event n (%)	K-M Estimate at 3 years	Patients with event n (%)	K-M Estimate at 3 years		
ALI, major amputation of vascular aetiology, MI, ischaemic stroke or CV death	508 (15.5)	17.3	584 (17.8)	19.9	0.85 (0.76–0.96)	0.009
ALI	155 (4.7)	5.2	227 (6.9)	7.8	0.67 (0.55–0.82)	
Major amputation of vascular aetiology	103 (3.1)	3.4	115 (3.5)	3.9	0.89 (0.68–1.16)	
MI	131 (4.0)	4.6	148 (4.5)	5.2	0.88 (0.70–1.12)	
Ischaemic stroke	71 (2.2)	2.7	82 (2.5)	3.0	0.87 (0.63–1.19)	
CV death	199 (6.1)	7.1	174 (5.3)	6.4	1.14 (0.93–1.40)	

The study was not powered to test for significance in the individual components of the primary endpoint.

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

No Significant Excess in the Primary Safety Outcome of TIMI Major Bleeding with DPI Versus Aspirin

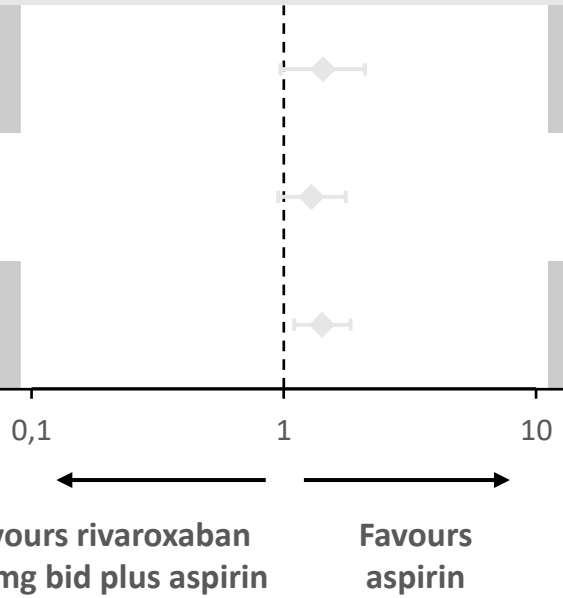


Bonaca MP *et al. N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

Rates of TIMI Major and BARC Major Bleeding Were Not Significantly Increased with DPI Versus Aspirin

Outcome	Rivaroxaban 2.5 mg bid plus aspirin (n=3256)		Aspirin (n=3248)		HR (95% CI)	HR (95% CI)	*p*-value
	Patients with event n (%)	K-M estimate at 3 years	Patients with event n (%)	K-M estimate at 3 years			
TIMI major bleeding	62 (1.90)	2.65	44 (1.35)	1.87		1.43 (0.97–2.10)	0.07
BARC major bleeding*	93 (2.86)	3.86	73 (2.25)	2.92		1.29 (0.95–1.76)	0.10
ISTH major bleeding	140 (4.30)	5.94	100 (3.08)	4.06		1.42 (1.10–1.84)	0.007



*Grade 3b or higher.

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

VOYAGER PAD and COMPASS Studied Complementary Patient Populations

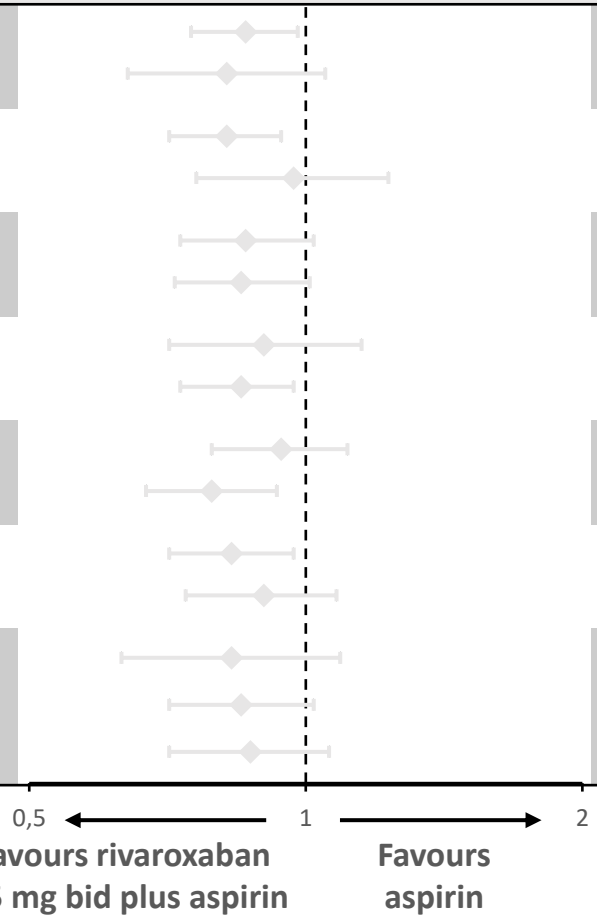
	VOYAGER[1,2]	COMPASS[3,4]
PAD patient characteristics	◆ Symptomatic PAD only ◆ Undergoing peripheral revascularization ◆ Carotid disease not included	◆ Symptomatic or asymptomatic ◆ Chronic ◆ Carotid disease included as PAD
Allowance for clopidogrel	Allowed up to 6 months after qualifying revascularization	Not allowed at randomization
Primary endpoint	MACE*, ALI or major amputation of a vascular cause	MACE#
Efficacy results in patients with PAD	◆ 15% reduction in primary endpoint ◆ 33% reduction in ALI	◆ 28% reduction in primary endpoint ◆ 44% reduction in ALI‡
Safety results in patients with PAD	◆ No significant increase in TIMI major bleeding ◆ No increase in ICH or fatal bleeding	◆ 61% increase in modified ISTH major bleeding ◆ No increase in ICH or fatal bleeding

*MI, ischaemic stroke or CV death; #MI, stroke or CV death; ‡ALI was a prespecified outcome for patients with PAD.

1. Capell WH *et al. Am Heart J* 2018;199:83–91. 2. Bonaca MP *et al. N Engl J Med* 2020; doi:10.1056/NEJMoa2000052. 3. Bosch J *et al. Can J Cardiol* 2017;33:1027–1035.
4. Anand SS *et al. Lancet* 2018;391:219–229.

Primary Efficacy Outcomes Were Consistent Across Subgroups

Subgroup		Rivaroxaban 2.5 mg bid plus aspirin n/N (%)	Aspirin n/N (%)	HR (95% CI)	HR (95% CI)
Age (years)	<75	391/2613 (14.96)	446/2621 (17.02)		0.86 (0.75–0.98)
	≥75	117/673 (17.38)	138/657 (21.00)		0.82 (0.64–1.05)
Sex	Male	375/2439 (15.38)	445/2421 (18.38)		0.82 (0.71–0.94)
	Female	133/847 (15.70)	139/857 (16.22)		0.97 (0.76–1.23)
BMI group	< Median	262/1610 (16.27)	301/1631 (18.45)		0.86 (0.73–1.02)
	≥ Median	241/1637 (14.72)	276/1613 (17.11)		0.85 (0.72–1.01)
eGFR (ml/min/1.73 m^2)	<60	130/661 (19.67)	146/666 (21.92)		0.90 (0.71–1.15)
	≥60	360/2499 (14.41)	413/2493 (16.57)		0.85 (0.73–0.97)
Diabetes	Yes	248/1313 (18.89)	261/1316 (19.83)		0.94 (0.79–1.11)
	No	260/1972 (13.18)	323/1961 (16.47)		0.79 (0.67–0.93)
Hyperlipidaemia	Yes	294/1971 (14.92)	348/1968 (17.68)		0.83 (0.71–0.97)
	No	214/1313 (16.30)	236/1310 (18.02)		0.90 (0.74–1.08)
Smoking status	Never	95/662 (14.35)	119/689 (17.27)		0.83 (0.63–1.09)
	Former	229/1475 (15.53)	263/1456 (18.06)		0.85 (0.71–1.02)
	Current	184/1147 (16.04)	202/1132 (17.84)		0.87 (0.71–1.06)



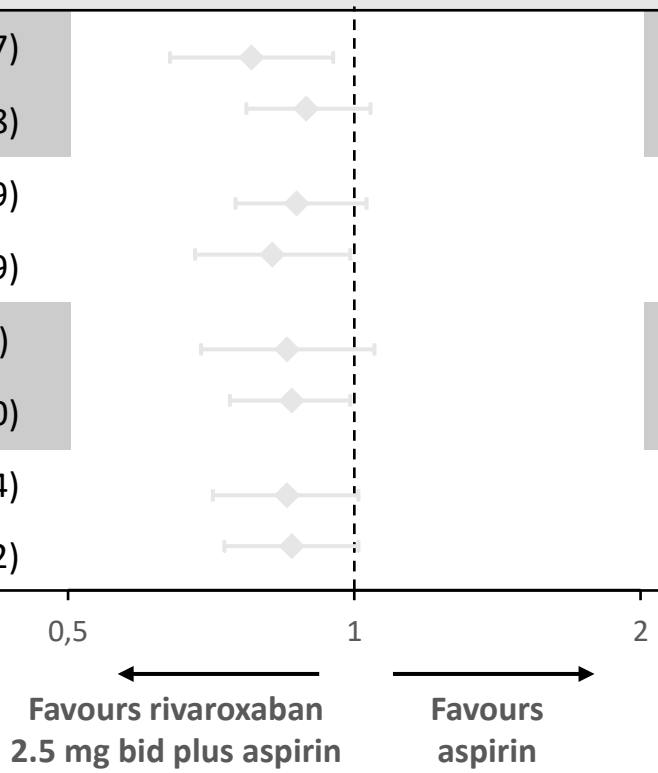
Hazard ratios show comparison of rivaroxaban plus aspirin versus aspirin alone for the primary efficacy outcome of ALI, major amputation of vascular aetiology, MI, ischaemic stroke or CV death.

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052

VOYAGER PAD

Primary Efficacy Outcomes Were Consistent Irrespective of PAD Characteristics

Subgroup		Rivaroxaban 2.5 mg bid plus aspirin n/N (%)	Aspirin n/N (%)	HR (95% CI)
CAD	Yes	183/1052 (17.40)	220/1015 (21.67)	0.78 (0.64–0.95)
	No	325/2233 (14.55)	364/2263 (16.08)	0.89 (0.77–1.04)
Index ABI	< Median	284/1588 (17.88)	321/1582 (20.29)	0.87 (0.75–1.03)
	≥ Median	201/1588 (12.66)	239/1594 (14.99)	0.82 (0.68–0.99)
Critical limb ischaemia	Yes	159/762 (20.87)	188/771 (24.38)	0.85 (0.69–1.05)
	No	349/2524 (13.83)	396/2507 (15.80)	0.86 (0.74–0.99)
Concomitant clopidogrel use	Yes	235/1658 (14.17)	272/1655 (16.44)	0.85 (0.71–1.01)
	No	272/1621 (16.78)	310/1613 (19.22)	0.86 (0.73–1.01)



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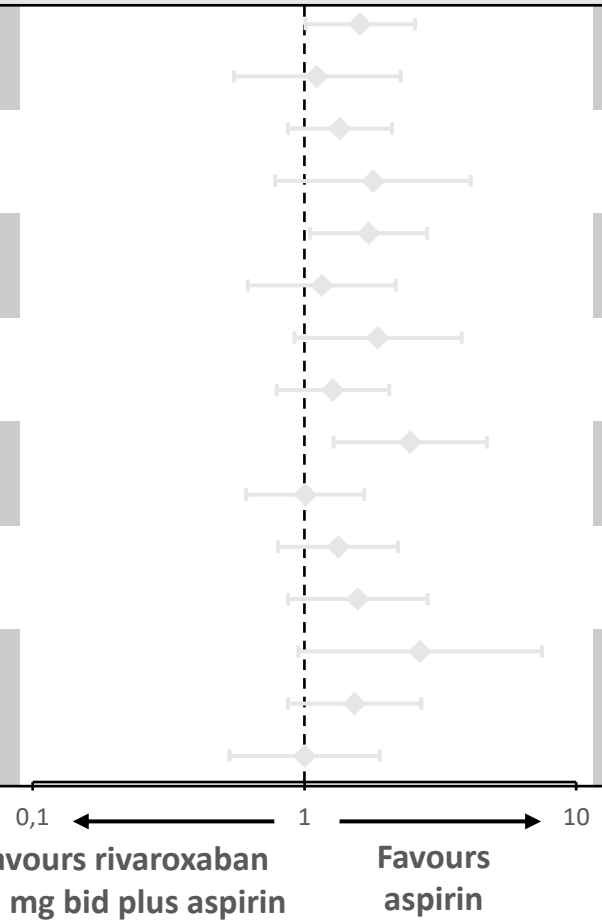
Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

Primary Safety Outcomes Were Consistent Across Subgroups

Subgroup		Rivaroxaban 2.5 mg bid plus aspirin n/N (%)	Aspirin n/N (%)	HR (95% CI)
Age (years)	<75	46/2595 (1.77)	29/2598 (1.12)	1.60 (1.01–2.55)
	≥75	16/661 (2.42)	15/650 (2.31)	1.11 (0.55–2.26)
Sex	Male	47/2417 (1.94)	35/2400 (1.46)	1.35 (0.87–2.10)
	Female	15/839 (1.79)	9/848 (1.06)	1.79 (0.78–4.09)
BMI group	< Median	41/1593 (2.57)	25/1615 (1.55)	1.72 (1.05–2.83)
	≥ Median	21/1626 (1.29)	18/1601 (1.12)	1.16 (0.62–2.17)
eGFR (ml/min/1.73 m^2)	<60	21/649 (3.24)	12/657 (1.83)	1.86 (0.92–3.79)
	≥60	38/2483 (1.53)	30/2474 (1.21)	1.27 (0.79–2.05)
Diabetes	Yes	31/1298 (2.39)	13/1305 (1.00)	2.45 (1.28–4.69)
	No	31/1958 (1.58)	31/1942 (1.60)	1.01 (0.61–1.66)
Hyperlipidaemia	Yes	34/1950 (1.74)	26/1953 (1.33)	1.33 (0.80–2.21)
	No	28/1305 (2.15)	18/1295 (1.39)	1.57 (0.87–2.84)
Smoking status	Never	13/653 (1.99)	5/686 (0.73)	2.66 (0.95–7.48)
	Former	30/1466 (2.05)	20/1440 (1.39)	1.53 (0.87–2.69)
	Current	19/1136 (1.67)	19/1122 (1.69)	1.00 (0.53–1.89)



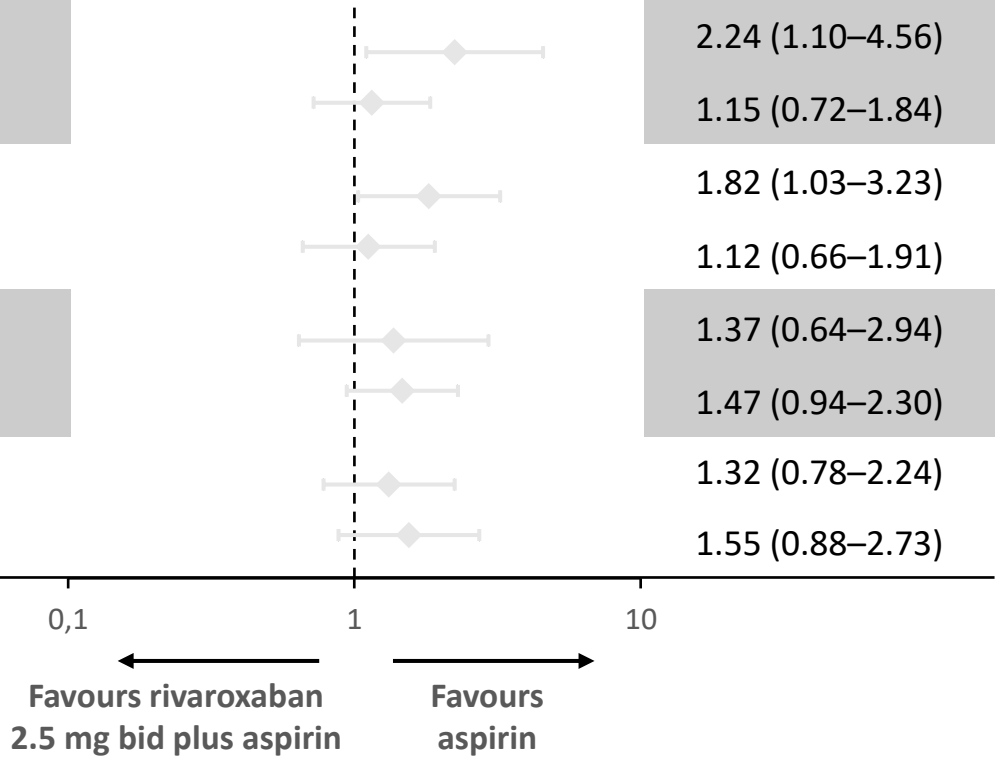
Hazard ratios show comparison of rivaroxaban plus aspirin versus aspirin alone for the primary safety outcome of TIMI major bleeding

Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

VOYAGER PAD

Primary Safety Outcomes Were Consistent Irrespective of PAD Characteristics

Subgroup		Rivaroxaban 2.5 mg bid plus aspirin n/N (%)	Aspirin n/N (%)	HR (95% CI)	HR (95% CI)
CAD	Yes	25/1041 (2.40)	11/1006 (1.09)		2.24 (1.10–4.56)
	No	37/2215 (1.67)	33/2242 (1.47)		1.15 (0.72–1.84)
Index ABI	< Median	33/1575 (2.10)	18/1569 (1.15)		1.82 (1.03–3.23)
	≥ Median	28/1573 (1.78)	26/1578 (1.65)		1.12 (0.66–1.91)
Critical limb ischaemia	Yes	15/754 (1.99)	12/767 (1.56)		1.37 (0.64–2.94)
	No	47/2502 (1.88)	32/2481 (1.29)		1.47 (0.94–2.30)
Concomitant clopidogrel use	Yes	32/1646 (1.94)	24/1637 (1.47)		1.32 (0.78–2.24)
	No	30/1603 (1.87)	20/1601 (1.25)		1.55 (0.88–2.73)



Hazard ratios show comparison of rivaroxaban plus aspirin versus aspirin alone for the primary safety outcome of TIMI major bleeding

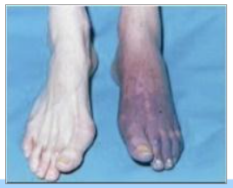
Bonaca MP *et al*. *N Engl J Med* 2020; doi:10.1056/NEJMoa2000052.

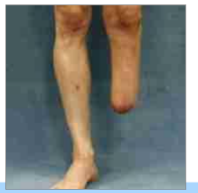
VOYAGER PAD

Rivaroxaban Vascular Dose 2.5 mg BID + ASA Could Help to Save Lives and Limbs in Vascular Disease

Asymptomatic PAD*[1,3] → Intermittent Claudication[3] → Symptom Deterioration[3] → Minor Amputation[3] → Major Amputation[3]

Elective Revascularisation[3]
Emergency Revascularisation[3]





Rivaroxaban 2.5 mg BID + ASA (vs ASA)[2]

−33% (n.s.)
Chronic limb ischaemia
HR: 0.67 (95% CI 0.35–1.26) p=0.21[2]

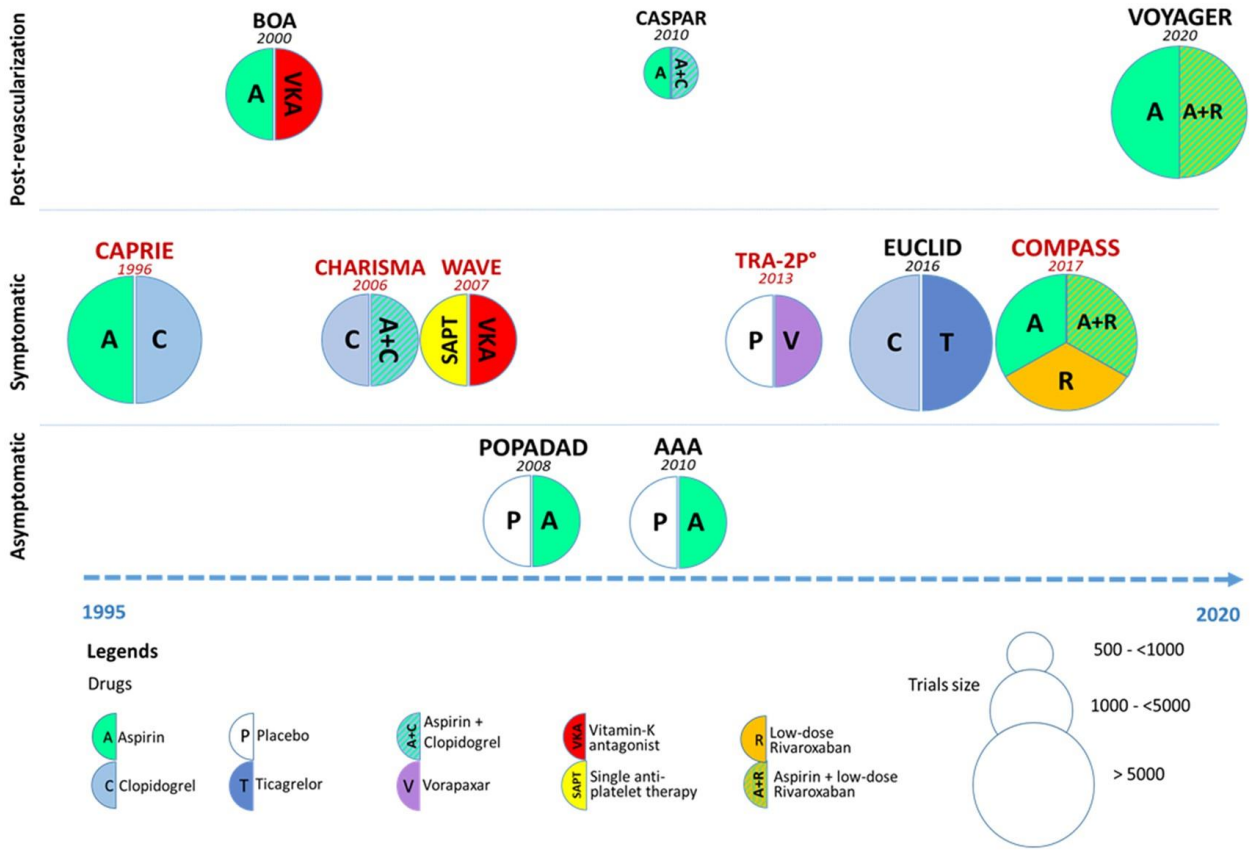
−44%
Acute limb ischaemia
HR: 0.56 (95% CI 0.32–0.99) p=0.042[2]

−60%
All vascular amputations
HR: 0.40 (95% CI 0.20–0.79) p=0.0069[2]

−70%
Major amputation
HR: 0.30 (95% CI 0.11–0.80) p=0.011[2]

−28%
MACE
HR: 0.72 (95% CI 0.57–0.90) p=0.0047[2]

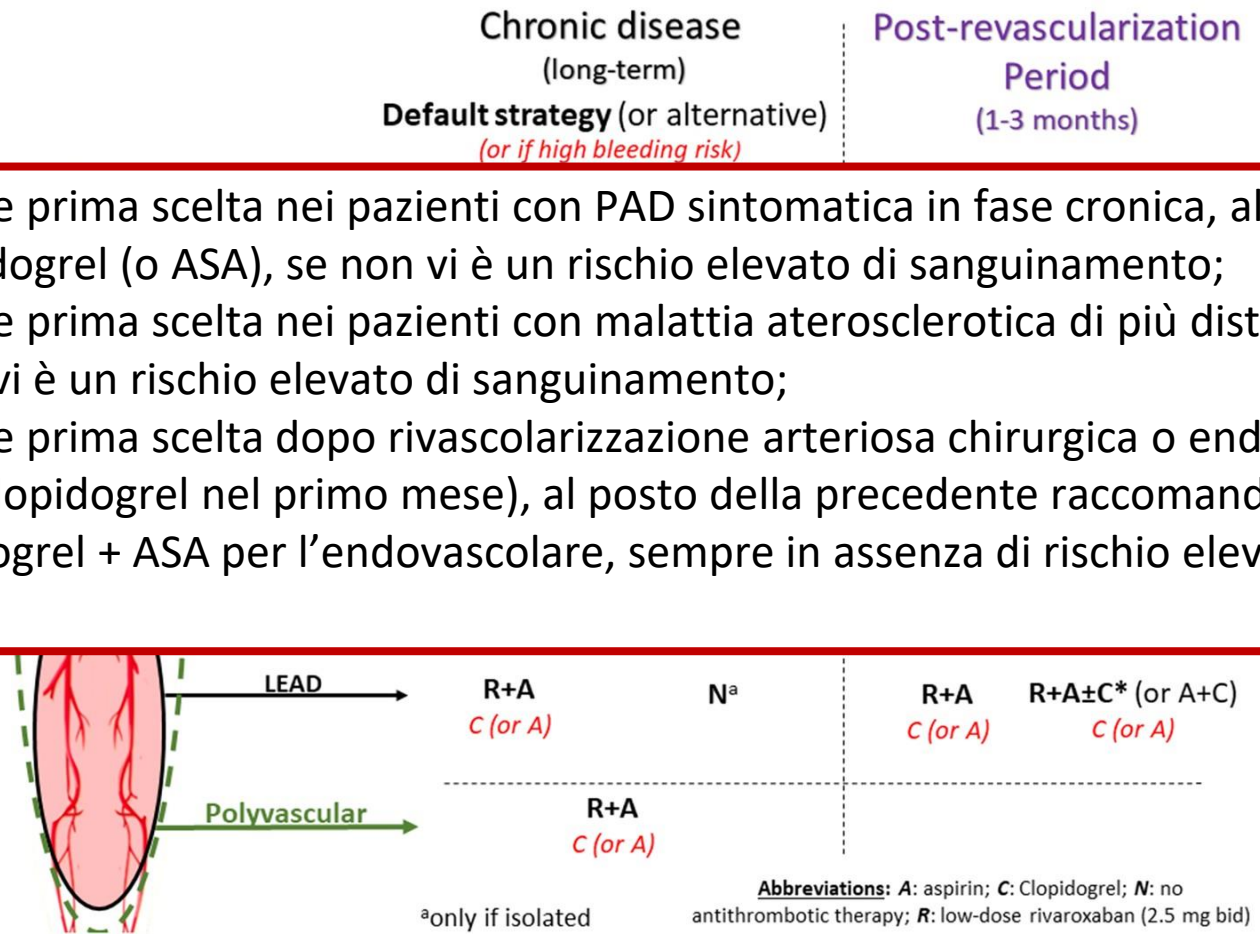
Figure 1 Major trials on antithrombotic therapies in lower-extremities artery disease including >500 patients. Trial ...



Eur Heart J, ehab390, https://doi.org/10.1093/eurheartj/ehab390

Graphical Abstract Summary of optimal and alternative antithrombotic strategies in patients with peripheral arterial disease.

...



- la DPI viene proposta come prima scelta nei pazienti con PAD sintomatica in fase cronica, al posto della precedente raccomandazione di clopidogrel (o ASA), se non vi è un rischio elevato di sanguinamento;
- la DPI viene proposta come prima scelta nei pazienti con malattia aterosclerotica di più distretti vascolari (sia sintomatica che asintomatica), se non vi è un rischio elevato di sanguinamento;
- la DPI viene proposta come prima scelta dopo rivascolarizzazione arteriosa chirurgica o endovascolare (in questo caso con possibile aggiunta di clopidogrel nel primo mese), al posto della precedente raccomandazione di clopidogrel (o ASA) per la chirurgia e di clopidogrel + ASA per l'endovascolare, sempre in assenza di rischio elevato di sanguinamento.

Eur Heart J, ehab390, https://doi.org/10.1093/eurheartj/ehab390

PAD
TERAPIA
ANTITROMBOTICA

DPI
COMPASS VOYAGER
Mondo Reale

ESC European Society of Cardiology

European Heart Journal (2021) **00**, 1–9
doi:10.1093/eurheartj/ehab408

FASTTRACK CLINICAL RESEARCH
Thrombosis and antithrombotic treatment

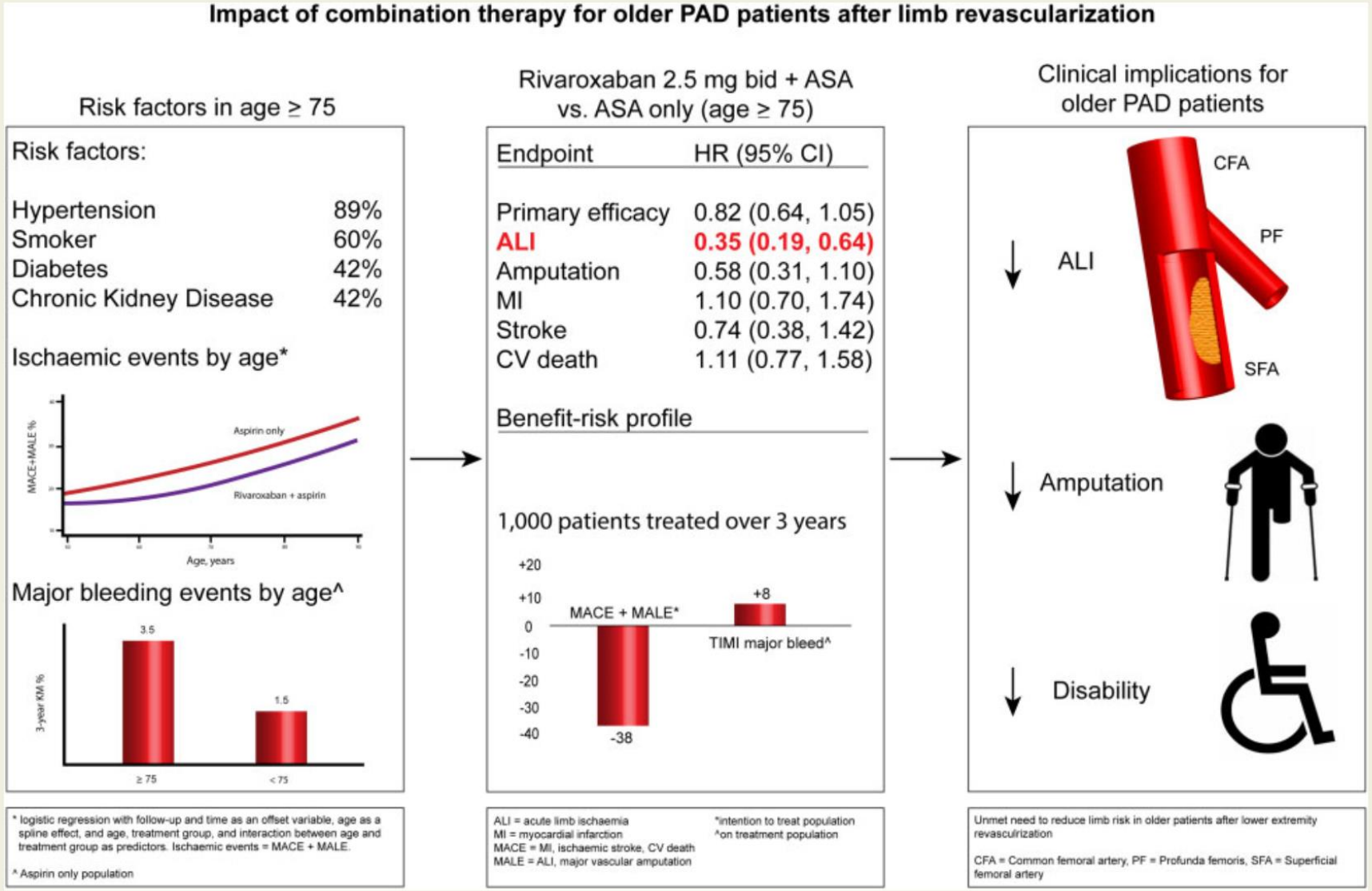
Low-dose rivaroxaban plus aspirin in older patients with peripheral artery disease undergoing acute limb revascularization: insights from the VOYAGER PAD trial

Mori J. Krantz[1,2]*, Sebastian E. Debus [3], Judith Hsia [1], Manesh R. Patel[4], Sonia S. Anand[5], Mark R. Nehler [1,6], Connie N. Hess [1,2], Warren H. Capell [1,2], Taylor Bracken[1], Michael Szarek [1,7], Lajos Mátyás[8], Dainis K. Krievins[9,10], Patrice Nault [11], Stefan Stefanov[12], Lloyd P. Haskell[13], Scott D. Berkowitz [14], Eva Muehlhofer[15], William R. Hiatt[1,2], Rupert M. Bauersachs [16,17], and Marc P. Bonaca [1,2]

NNT 26

NNH 125

Graphical Abstract



M.J. Krantz et al. European Heart Journal (2021) 42, 4040–4048

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 84, NO. 9, 2024

Low-Dose Rivaroxaban Plus Aspirin in Fragile Patients After Lower Extremity Revascularization

Mario Enrico Canonico, MD, PhD,[a,b] Cecilia C. Low Wang, MD,[a,c] Judith Hsia, MD,[a,b] E. Sebastian Debus, MD, PhD,[d] Mark R. Nehler, MD,[a,e] Manesh R. Patel, MD,[f] Sonia S. Anand, MD,[g] Joseph Ycas, PhD,[h] Warren H. Capell, MD,[a,c] Eva Muehlhofer, MD,[h] Lloyd P. Haskell, MD, MRA,[i] Scott D. Berkowitz, MD,[a,b,j] Rupert Bauersachs, MD,[k,l] Marc P. Bonaca, MD, MPH[a,b]

ABSTRACT

BACKGROUND Rivaroxaban 2.5 mg plus aspirin reduced limb and cardiovascular events and increased bleeding in patients with symptomatic peripheral artery disease (PAD) after lower extremity revascularization in the VOYAGER PAD (Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects With Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremities) study. Fragile patients are at heightened risk for ischemic and bleeding events.

OBJECTIVES The purpose of this study was to investigate the safety and efficacy of rivaroxaban 2.5 mg in fragile patients from VOYAGER PAD.

METHODS Patients were categorized as fragile based on prespecified criteria (age >75 years, weight ≤50 kg, or baseline estimated glomerular filtration rate <50 mL/min/1.73 m^2). The primary efficacy outcome was the composite of acute limb ischemia, major amputation of a vascular etiology, myocardial infarction, ischemic stroke, or cardiovascular death. The principal safety outcome was TIMI major bleeding.

RESULTS Of 6,564 randomized patients, a total of 1,674 subjects were categorized as fragile at baseline. In the placebo arm, fragile patients were at higher risk of the primary outcome (HR: 1.34; 95% CI: 1.12-1.61) and TIMI major bleeding (HR: 1.57; 95% CI: 0.83-2.96), compared with nonfragile patients. The effect of rivaroxaban on the primary endpoint was not modified by frailty status (fragile HR: 0.93; 95% CI: 0.75-1.15; nonfragile HR: 0.83; 95% CI: 0.72-0.97; *P* interaction = 0.37). Rivaroxaban increased TIMI major bleeding in fragile (HR: 1.54; 95% CI: 0.82-2.91) and nonfragile patients (HR: 1.37; 95% CI: 0.84-2.23; *P* interaction = 0.65).

CONCLUSIONS Patients with PAD after lower extremity revascularization meeting fragile criteria are at higher risk of ischemic complications and bleeding. Rivaroxaban reduces ischemic risk and increases bleeding regardless of frailty status. These data may assist in personalization of antithrombotic therapy in fragile population.
(J Am Coll Cardiol 2024;84:801-811)

From the [a]CPC Clinical Research, Aurora, Colorado, USA; [b]Division of Cardiology, Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado, USA; [c]Division of Endocrinology, Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado, USA; [d]Department of Vascular Medicine, Vascular Surgery - Angiology - Endovascular Therapy, University of Hamburg-Eppendorf, Hamburg, Germany; [e]Department of Surgery, University of Colorado School of Medicine, Aurora, Colorado, USA; [f]Duke Clinical Research Institute, Division of Cardiology, Duke University Medical Center, Durham, North Carolina, USA; [g]Population Health Research Institute, Hamilton Health Sciences, Department of Medicine, McMaster University, Hamilton, Ontario, Canada; [h]Bayer AG Research and Development, Pharmaceuticals, Wuppertal, Germany; [i]Janssen Research and Development, Raritan, New Jersey, USA; [j]Division of Hematology, Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado, USA; [k]Cardioangiologic Center, Agaplesion Bethanien Hospital, Frankfurt am Main, Germany; and the [l]Center for Thrombosis and Hemostasis, University of Mainz, Mainz, Germany
Review and acceptance occurred under Dr Valentin Fuster's term as Editor-in-Chief.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2024.05.060

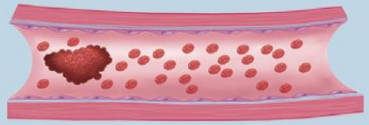
CENTRAL ILLUSTRATION Fragile Patients Affected by Peripheral Artery Disease Who Underwent Lower Extremity Revascularization From the VOYAGER PAD Trial

Fragile Patients
- Age >75 years
- CKD
- Low BMI

Very High CV Risk
- 88% Arterial hypertension
- 59% Hyperlipidemia
- 45% Diabetes mellitus
- 36% CAD
- 34% Prior LER
- 7% Prior limb amputation

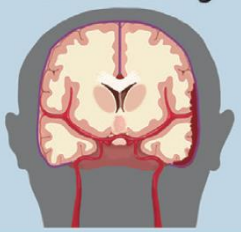
Risk of MACE plus MALE 23.6% at 3 years in fragile, 34% higher comparing fragile vs not fragile

- ↓42% of MALE
- ↓19% of total vascular events
- ↓35% of CAD/PAD hospitalization



Rivaroxaban
+ low-dose aspirin
vs
Placebo
+ low-dose aspirin

Bleeding risk consistent regardless of fragile status and no increase in intracranial or fatal bleeding



Canonico ME, et al. J Am Coll Cardiol. 2024;84(9):801-811.

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2022) **0**, 1–10
https://doi.org/10.1093/ehjcvp/pvac023

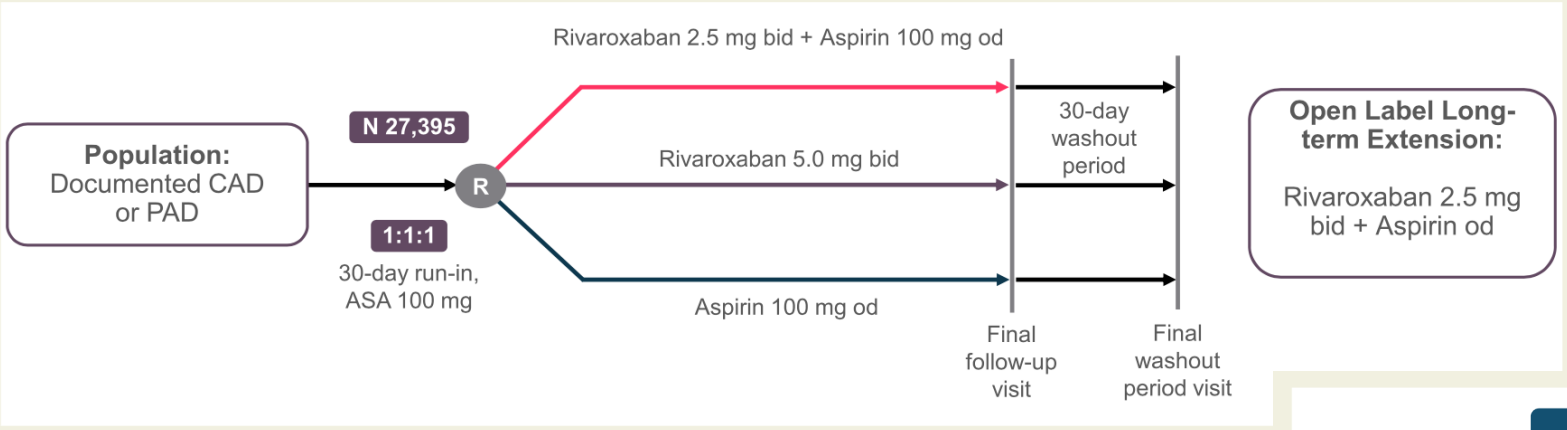
ORIGINAL ARTICLE
Coronary artery disease

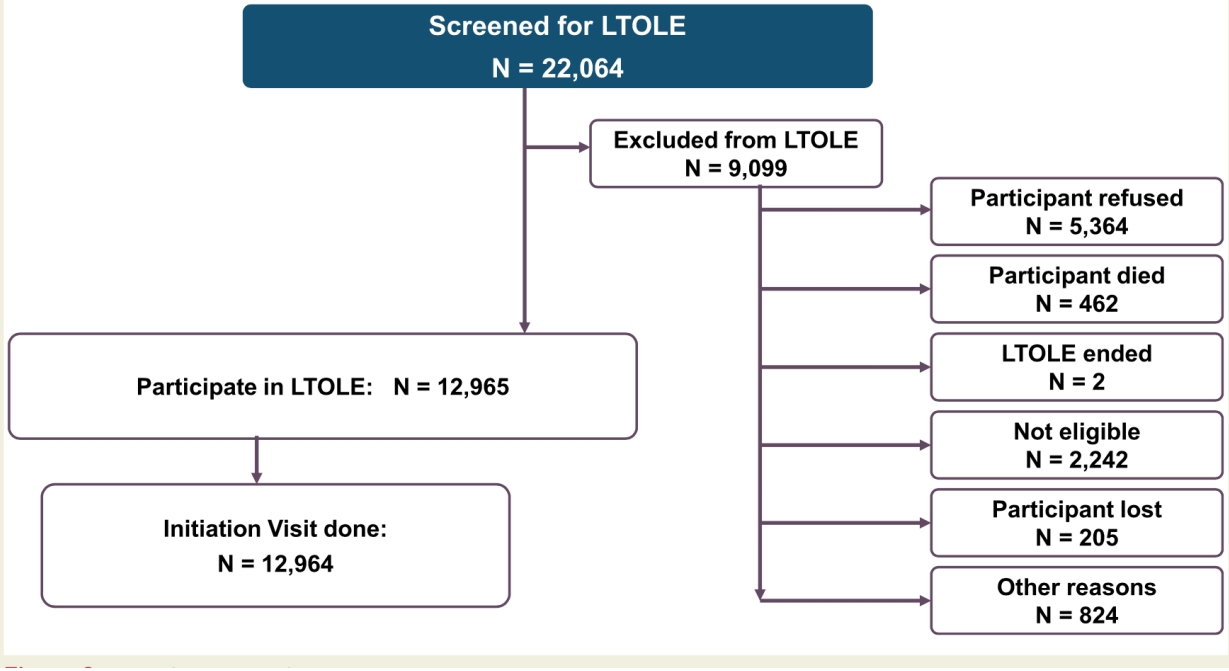
Long-Term Treatment with the Combination of Rivaroxaban and Aspirin in Patients with Chronic Coronary or Peripheral Artery Disease: Outcomes During the Open Label Extension of the COMPASS trial

John W. Eikelboom[1,*], Jacqueline Bosch[1,2], Stuart J. Connolly[1], Jessica Tyrwitt[1], Keith A.A. Fox[3], Eva Muehlhofer[4], Christoph Neumann[4], Christoph Tasto[4], Shrikant I. Bangdiwala[1], Rafael Diaz[5], Marco Alings[6], Gilles R. Dagenais[7], Darryl P. Leong[1], Eva M. Lonn[1], Alvaro Avezum[8], Leopoldo S. Piegas[9], Petr Widimsky[10], Alexander N. Parkhomenko[11], Deepak L. Bhatt[12], Kelley R.H. Branch[13], Jeffrey L. Probstfield[14], Patricio Lopez-Jaramillo[15], Lars Rydén[16], Nana Pogosova[17], Katalin Keltai[18], Matyas Keltai[18], Georg Ertl[19], Stefan Stoerk[19], Antonio L. Dans[20], Fernando Lanas[21], Yan Liang[22], Jun Zhu[23], Christian Torp-Pedersen[23], Aldo P. Maggioni[24], Patrick J. Commerford[25], Tomasz J. Guzik[26,27], Thomas Vanassche[28], Peter Verhamme[28], Martin O'Donnell[29], Andrew M. Tonkin[30], John D. Varigos[30], Dragos Vinereanu[31], Camillo Felix[32], Jae-Hyung Kim[33], Khairul S. Ibrahim[34], Basil S. Lewis[35], Kaj P. Metsarinne[36], Victor Aboyans[37], Phillippe Gabriel Steg[38], Masatsugu Hori[39], Ajay Kakkar[40], Sonia S Anand[1], Andre Lamy[1], Mukul Sharma[1] and Salim Yusuf[1]

Overall study design and flow diagram for LTOLE

(Long Term Open Labeled Extension)

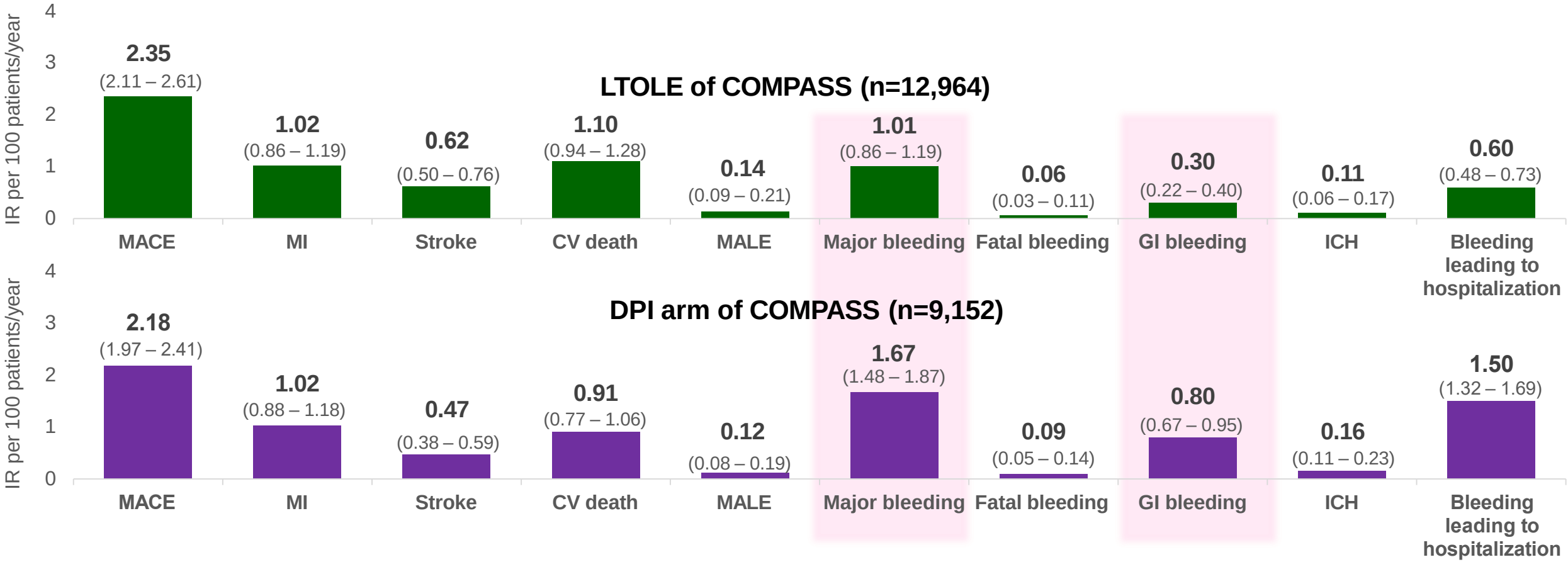




J. W. Eikelboom *et al.* European Heart Journal - Cardiovascular Pharmacotherapy (2022)

Consistent Efficacy and Lower Bleeding Risk was Seen in COMPASS LTOLE

- **MACE were similar** to those seen during the randomized phase trial
- **Lower major bleeding** rate, including GI and ICH



*LTOLE: long term open label extension

Eur Heart J Cardiovasc Pharmacother. 2022 Apr 6;pvac023

COMPASS LTOLE- Conclusions

- COMPASS LTOLE demonstrated that among patients who agreed to participate after successfully completing follow-up during the randomized phase, **treatment with the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily for up to a further 3 years** was associated with incidence rates for CV death, stroke, or MI that were **similar to those seen during the randomized phase**
- COMPASS LTOLE showed **similar or lower incidence rates for bleeding**, including gastrointestinal and intracranial bleeding
- These data provide further **support for guideline recommendations for the long-term use** of the combination of rivaroxaban and aspirin in high-risk patients with chronic CAD and/or PAD

ESC European Society of Cardiology

J. W. Eikelboom *et al.* European Heart Journal - Cardiovascular Pharmacotherapy (2022)

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2022) **8**, 825–836
https://doi.org/10.1093/ehjcvp/pvac028

ORIGINAL ARTICLE
Thrombosis and antithrombotic therapy

Patients selected for dual pathway inhibition in clinical practice have similar characteristics and outcomes to those included in the COMPASS randomized trial: The XATOA Registry

Keith A.A. Fox[1,*], Victor Aboyans[2], E. Sebastian Debus[3], Uwe Zeymer[4], Martin R. Cowie[5], Manesh Patel[6], Robert C. Welsh[7], Jackie Bosch[8], Alain Gay[9], Kai Vogtländer[10] and Sonia S. Anand[8,11]

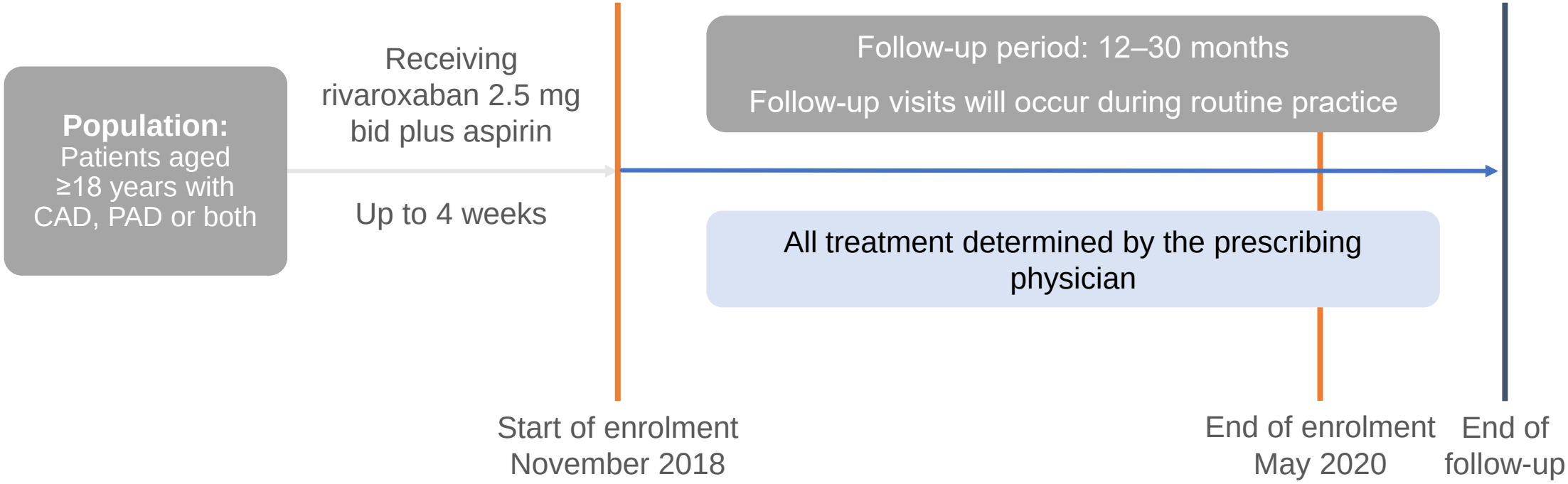
[1]Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK; [2]Department of Cardiology, Dupuytren University Hospital, and Inserm U1094, Limoges, France; [3]Department of Vascular Medicine, Vascular Surgery, Angiology, Endovascular Therapy, University of Hamburg-Eppendorf, Hamburg, Germany; [4]Klinikum der Stadt Ludwigshafen, Medizinische Klinik B, and Institut für Herzinfarktforschung, Ludwigshafen am Rhein, Germany; [5]Royal Brompton Hospital and King's College London, London, UK; [6]Division of Cardiology, Duke Clinical Research Institute, Duke University, Durham NC; [7]Mazankowski Alberta Heart Institute and University of Alberta, Edmonton, Alberta, Canada; [8]School of Rehabilitation Science, Chanchlani Research Centre and the Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada; [9]Bayer AG, Berlin, Germany; [10]Bayer AG, Wuppertal, Germany; and [11]Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Received 28 January 2022; revised 24 March 2022 online publish-ahead-of-print 4 July 2022

XATOA Study Design

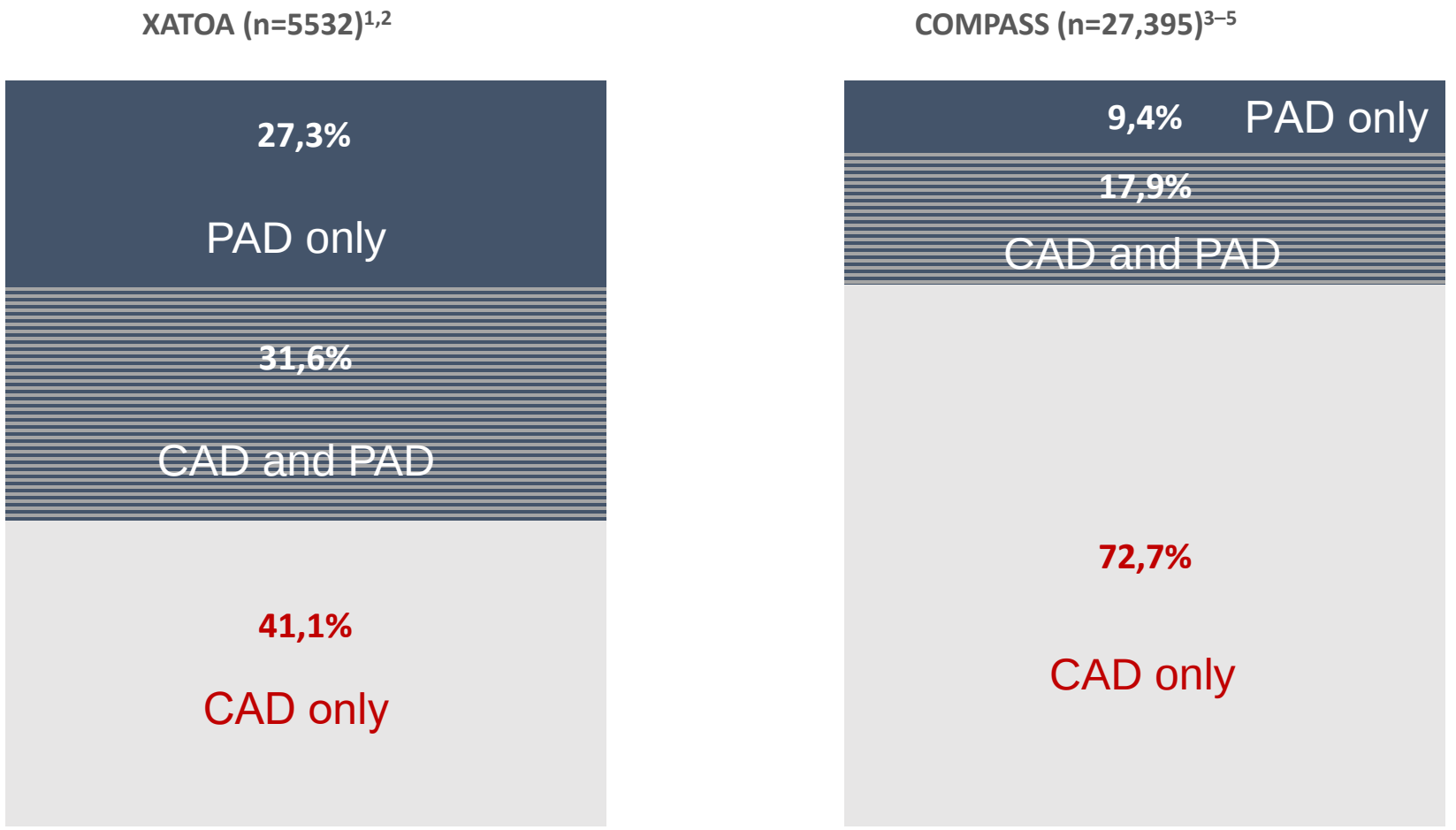
Design: International, multicentre, prospective single-arm registry study enrolled and prospectively followed patients receiving DPI in routine clinical practice

Objectives: To assess the characteristics as well as ischaemic and bleeding outcomes in patients with CAD, PAD or both receiving DPI therapy with rivaroxaban 2.5 mg bid plus aspirin in clinical practice



Fox KAA *et al*. *Am Heart J* 2020;222:166–173.

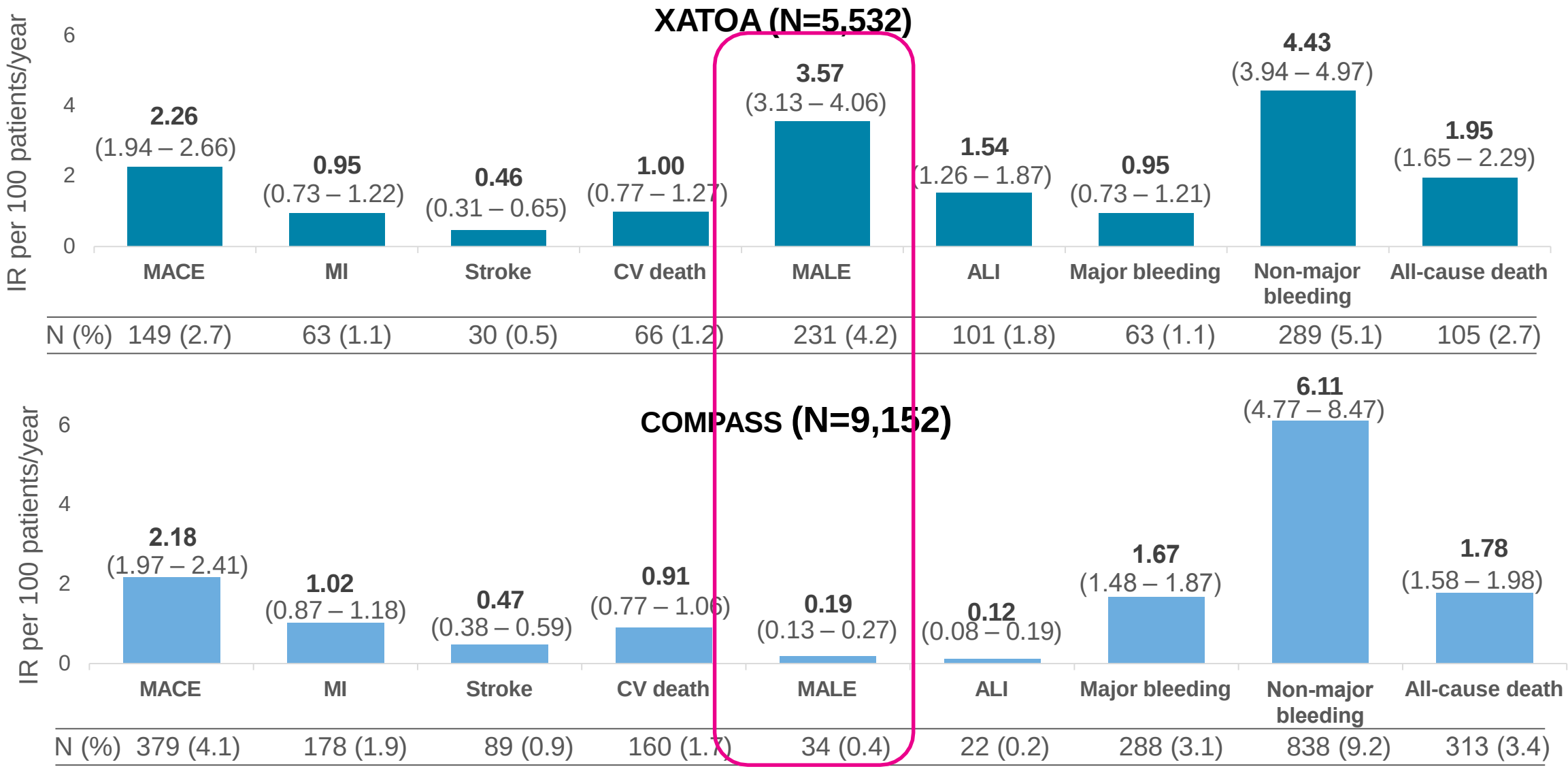
Patients Subgroups in XATOA and COMPASS



1. Fox KAA *et al*. *Eur Heart J Cardiovasc Pharmacother* 2022:doi:10.1093/ehjcvp/pvac028. 2. Zeymer U e*t al*. ACC. Washington DC, USA, 2–4 April 2022. Poster 10610. https://www.jacc.org/doi/abs/10.1016/S0735-1097(22)02737-1 [accessed 8 April 2022]; 3. Eikelboom JW *et al. N Engl J Med* 2017;377:1319–1330. 4. Anand SS *et al. Lancet* 2017;391:219–229. 5. Connolly SJ *et al. Lancet* 2018;391:205–218.

DPI Demonstrate Consistent MACE Effectiveness with Low BLEEDING Risk in Real World Practice

Higher MALE rates are consistent with the greater proportion of PAD patients



Zeymerl et al, poster number 10610, ACC 2022 poster presentation

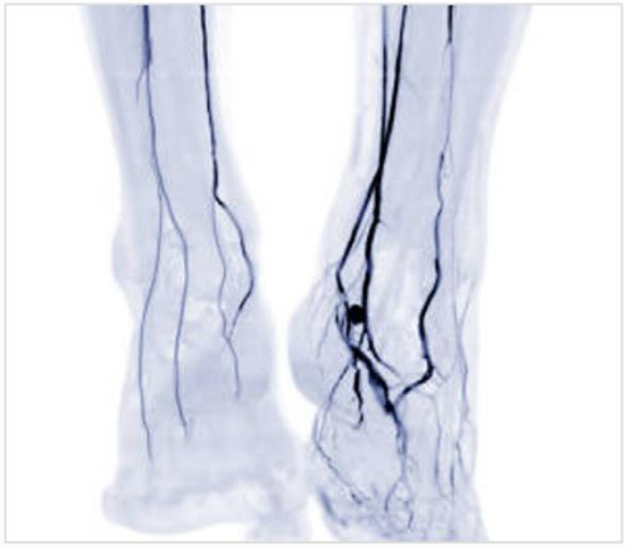
XATOA: CONCLUSIONS

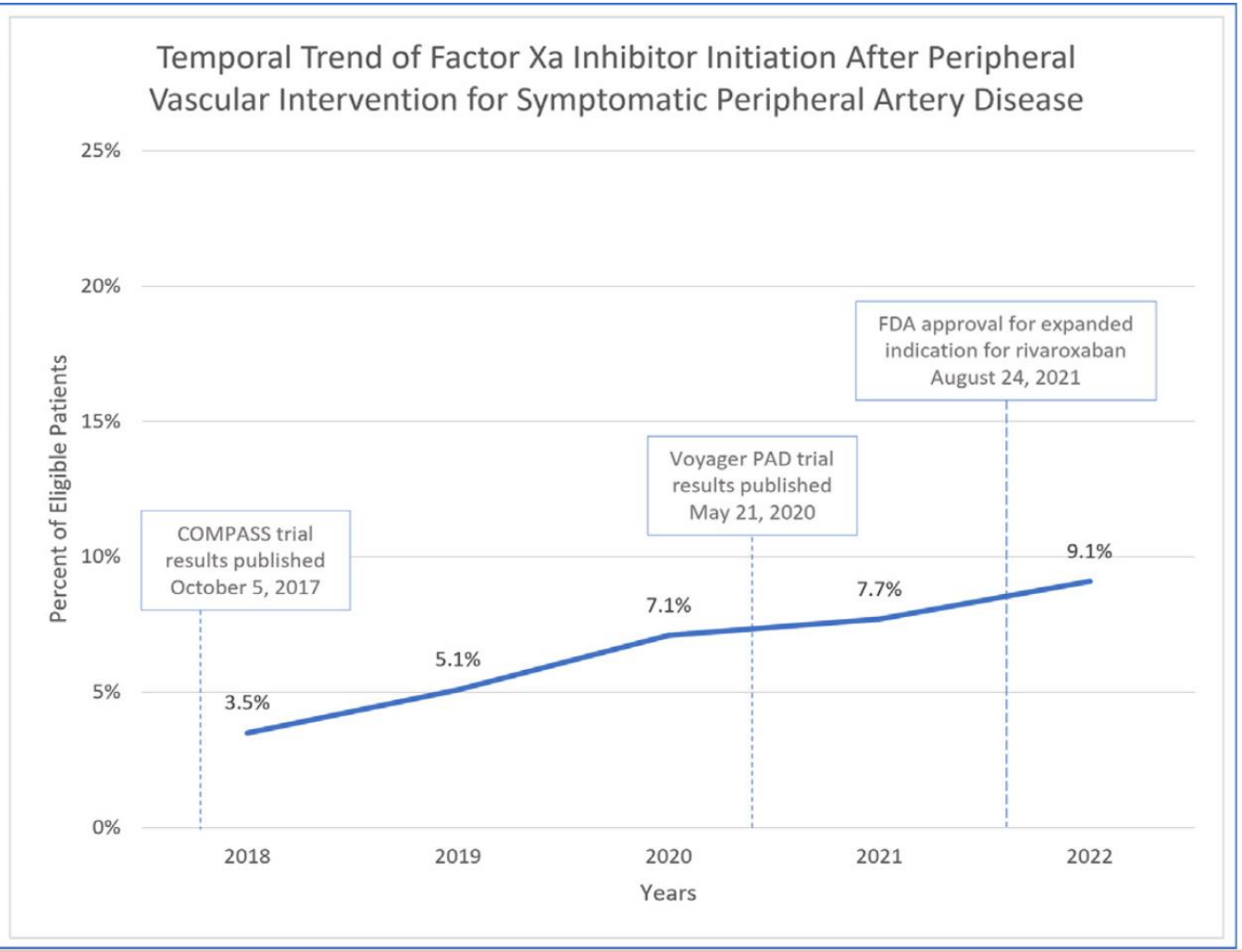
- The baseline characteristics of patients in the XATOA cohort were broadly comparable with those of patients included in the COMPASS trial and represent **real-world data**
- The rates of **MACE were similar in XATOA** and COMPASS, whereas the rates of **MALE were higher in XATOA** which is consistent with the **enrolment of a higher proportion of patients with PAD in XATOA**
- Although the studies cannot be compared directly, the annualized rate of acute limb ischaemia in patients with PAD from XATOA was higher than in COMPASS; however, the annualized rates of MACE, CV death and major bleeding events were lower

Fox KAA *et al*. *Eur Heart J Cardiovasc Pharmacother* 2022:doi:10.1093/ehjcvp/pvac028.

Oral factor Xa inhibitor underutilization following lower extremity peripheral vascular intervention

Sapan I
Parveer



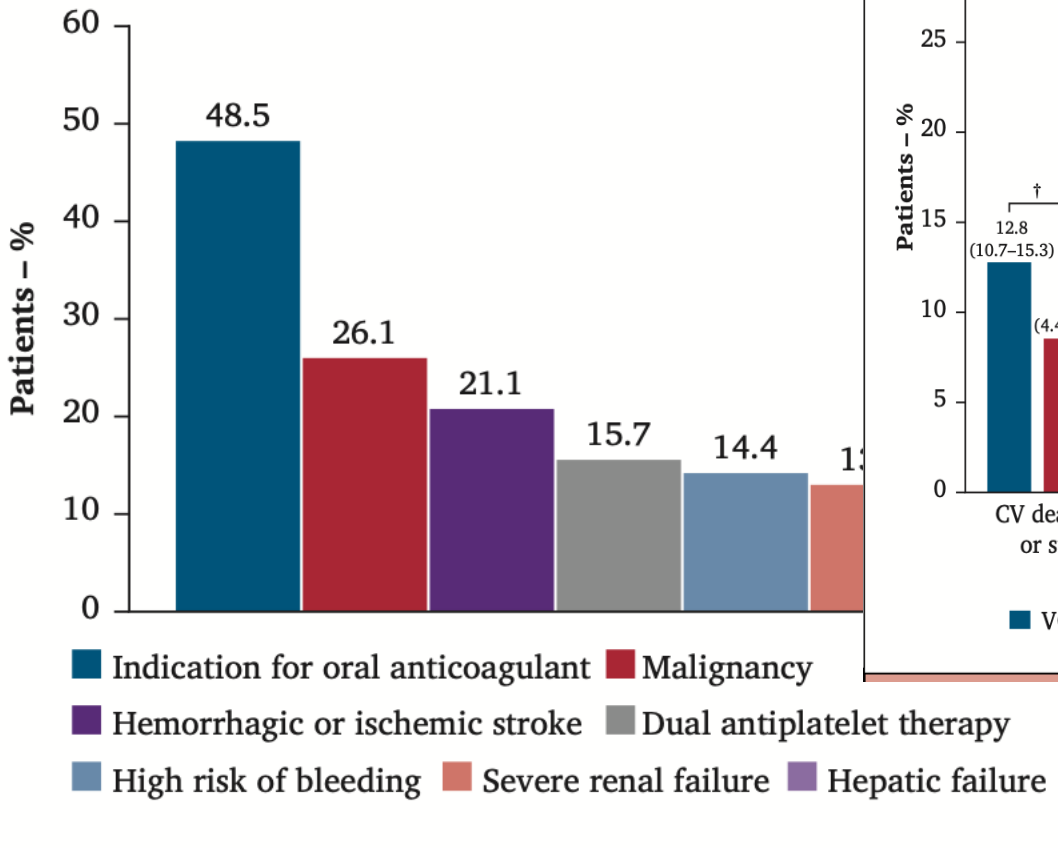


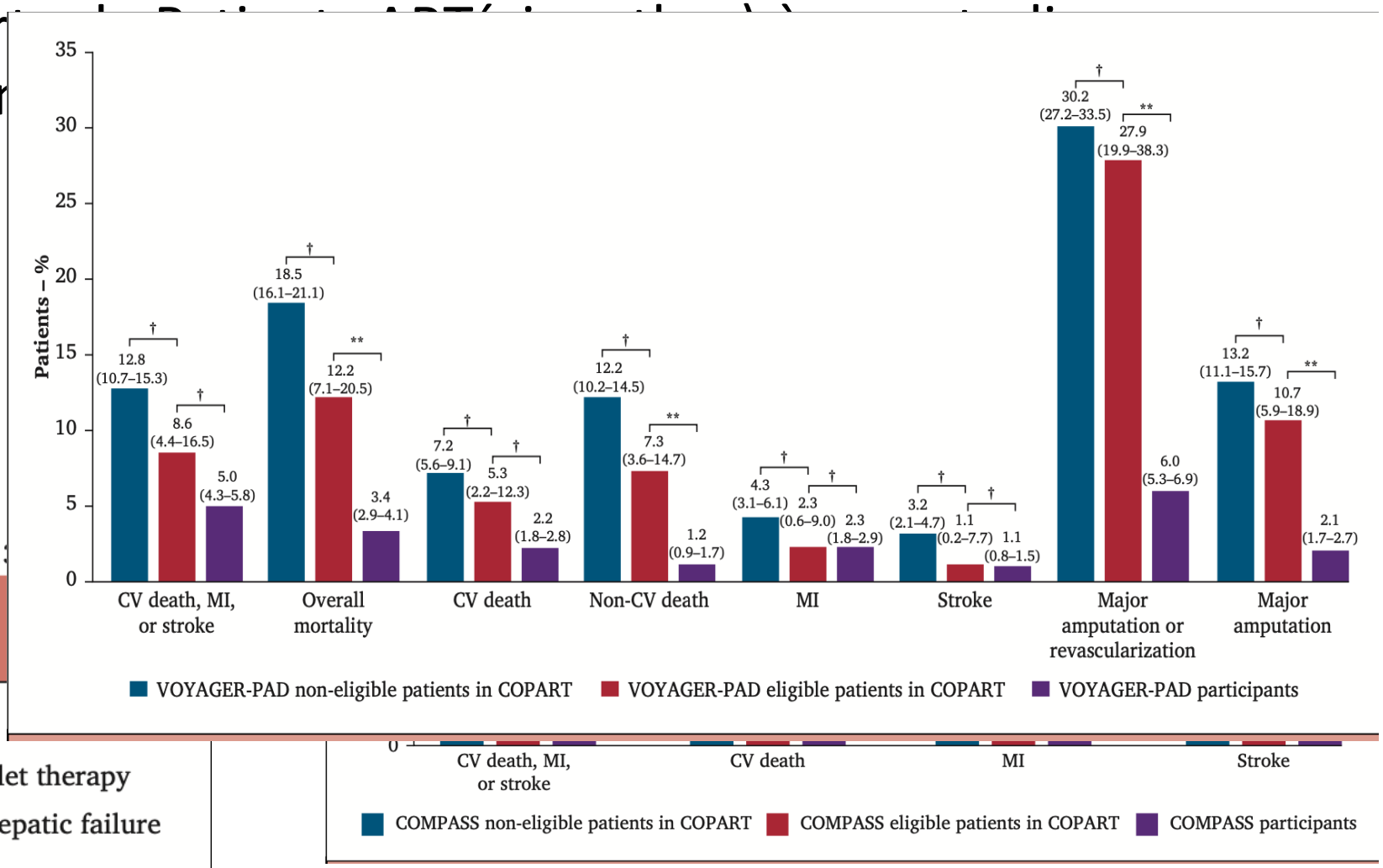
Bhuta et al, Journal of Vascular Surgery 2023

Editor's Choice – External Applicability of the COMPASS and VOYAGER-PAD Trials on Patients with Symptomatic Lower Extremity Artery Disease in France: The COPART Registry

François-Xavier Lapébie [a,b,*], Victor Aboyans [c,d], Philippe Lacroix [d,e], Joël Constans [f,g], Carine Boulon [f], Emmanuel Messas [h,i], Jean Ferrières [b,j,k], Vanina Bongard [b,j,k], Alessandra Bura-Rivière [a,l]

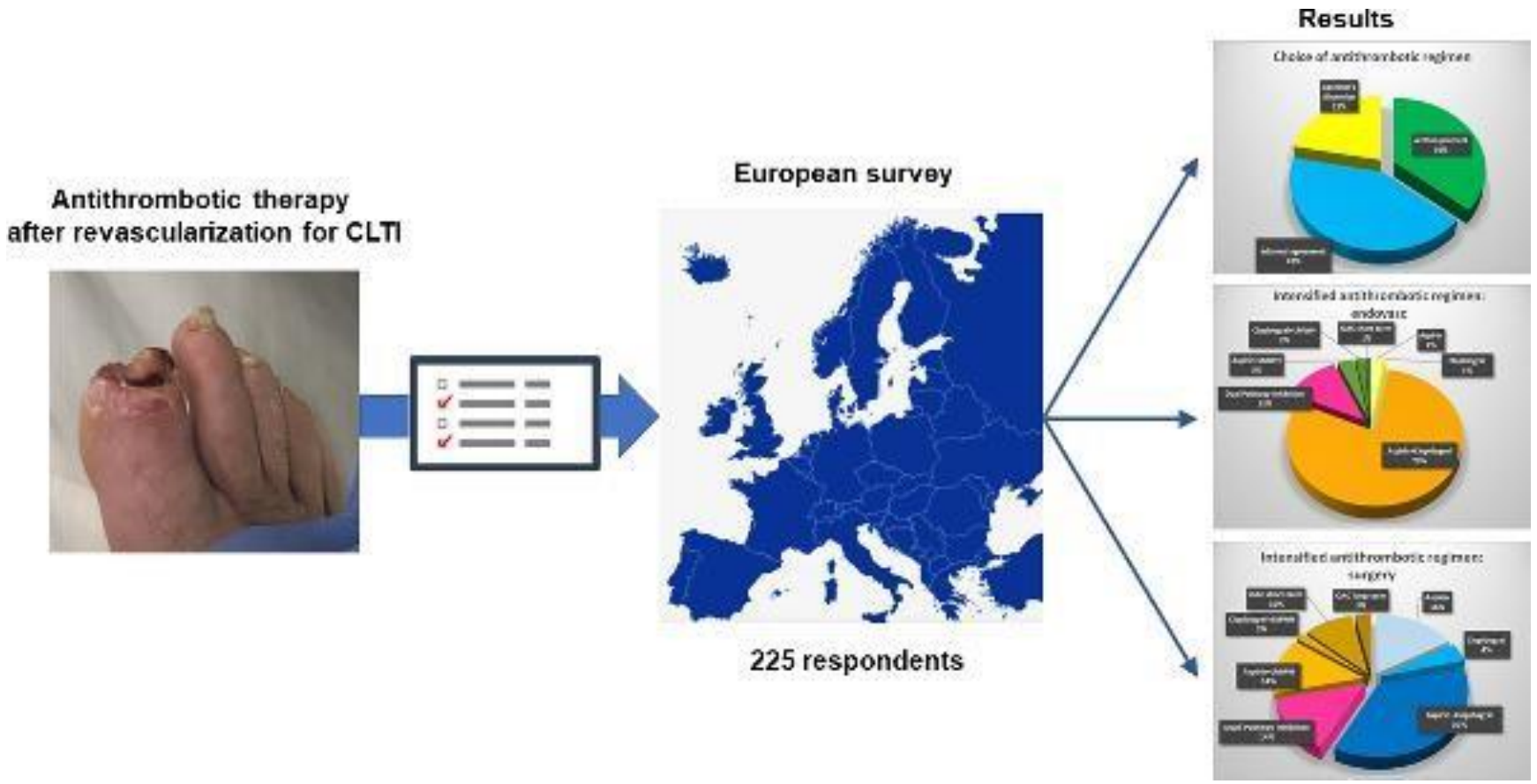
- Il registro COPART (COhor
multicentrico, osservazior





Eur J Vasc Endovasc Surg (2021) 62, 439e449

Graphical Abstract Abbiamo condotto un'indagine europea per **valutare l'uso attuale delle terapie antitrombotiche dopo la rivascolarizzazione per l'ischemia critica degli ari inferiori.** Un totale di 225 centri ha risposto a un **questionario basato sul web** che documentava la scelta dei regimi terapeutici antitrombotici e l'uso di **terapie antitrombotiche intensificate dopo la rivascolarizzazione, sia endovascolare che chirurgica**. I risultati di questa indagine documentano l'eterogeneità degli approcci antitrombotici e mettono in evidenza le numerose esigenze non soddisfatte in questo settore.



Eur Heart J Cardiovasc Pharmacother, Volume 9, Issue 3, April 2023, Pages 201–207, https://doi.org/10.1093/ehjcvp/pvac055

PAD

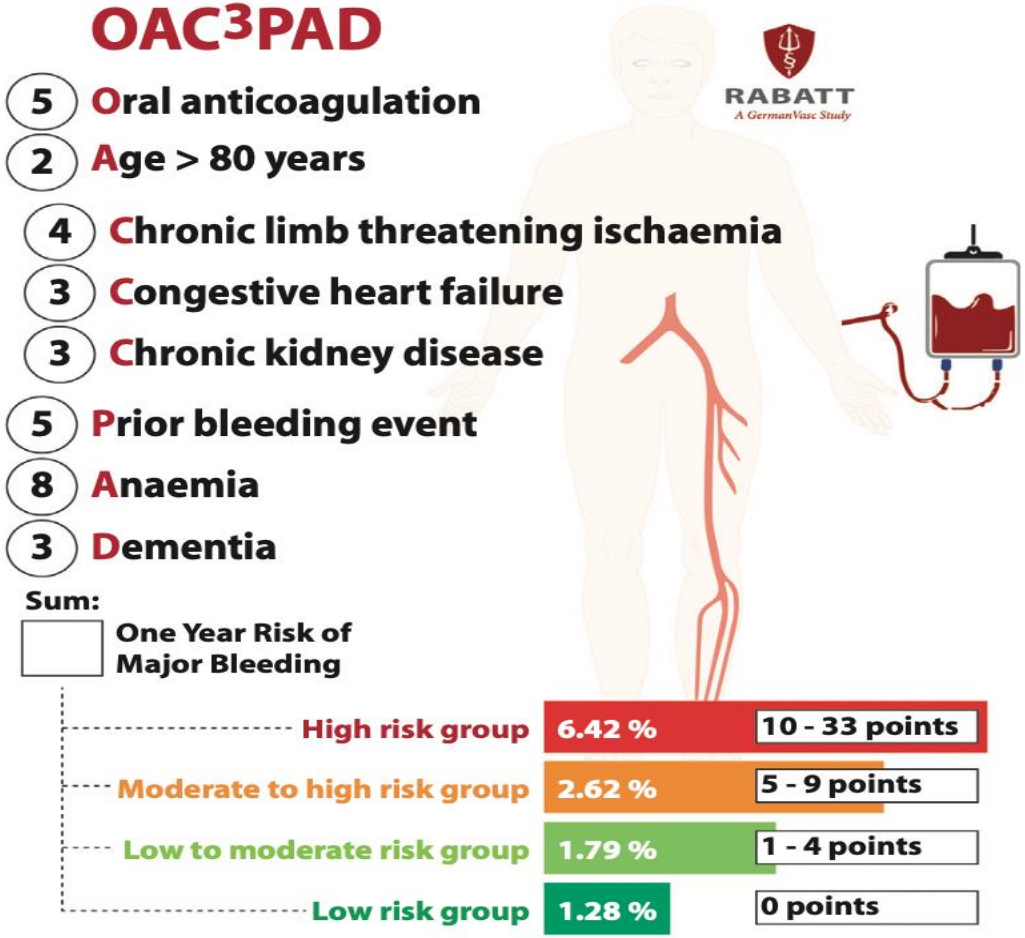
TERPIA ANTITROMBOTICA DPI COMPASS VOYAGER

Il rischio emorragico

OAC [3] - PAD BLEEDING SCORE

WHAT THIS PAPER ADDS

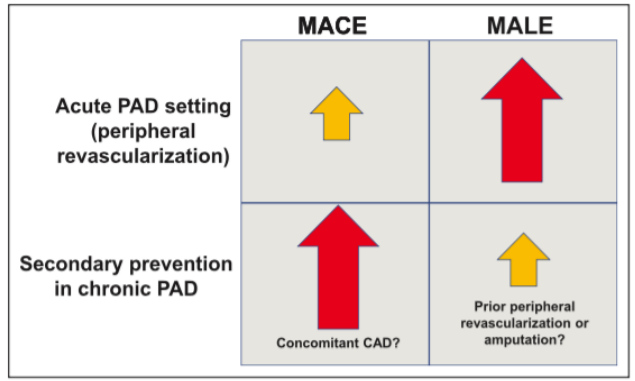
While available risk prediction scores for major bleeding events were developed primarily for patients treated for cardiac disease, there is a paucity of evidence concerning the mid term bleeding risk after treatment of patients with peripheral artery disease. Taking advantage of unselected data from the second largest insurance fund in Germany, a total of 81 930 patients were included in the current retrospective analysis. For the first time, a pragmatic risk score was developed to predict the individual bleeding risk classifying a fifth of the cohort as high risk patients. In total 2.2% of all patients had a major bleeding event after one year.



«Oral anticoagulation: prior use of direct *thrombin* inhibitors, *vitamin K* antagonists or direct *factor Xa* inhibitors. **Chronic limb threatening ischaemia**: peripheral artery disease at Fontaine *stage III* (ischaemic rest pain) *and IV* (ischaemic wound healing disor- ders, ulcer, gangrene). **Prior bleeding event**: *transfusion* during index hospitalisation or a prior diagnosis of *coagulopathy* or a prior primary diagnosis of *major bleeding*. **Anaemia**: presence of blood loss anaemia or deficiency anaemia or antianaemic medication. **Dementia**: presence of vascular or unspecified dementia or antidementia medication.»

Behrendt AC et al. Eur J Vasc Endovasc Surg 2022

PAD and Bleeding RISK



- **Peripheral Artery Disease***
  - **Acute setting of peripheral revascularization**
    - Low-dose rivaroxaban + low-dose aspirin
    - If on clopidogrel, use shortest duration possible
  - **Secondary prevention for chronic disease**
    - **Bleeding risk assessment**
      - **High bleeding risk** → **Monotherapy with aspirin or clopidogrel**
      - **Low bleeding risk**
        - **MACE risk assessment**
          - **High MACE risk**
            Known CAD or prior MI
            Other (diabetes?, smoking?)
            - Low-dose rivaroxaban plus low-dose aspirin
            - Continue DAPT if on for another indication (e.g. ACS, PCI)**
          - **Low MACE risk**
        - **MALE risk assessment**
          - **Low MALE risk**
          - **High MALE risk**
            Prior revascularization or amputation
            Other (procedure type?, anatomy?)
            - Low-dose rivaroxaban plus low-dose aspirin
            - Continue DAPT if on for another indication (e.g. ACS, PCI)**

*Use therapeutic anticoagulation if indicated
**Data support use of ticagrelor over other $P2Y_{12}$ inhibitors

HESS CN. Circ. Cardiovasc. Interv. 2020

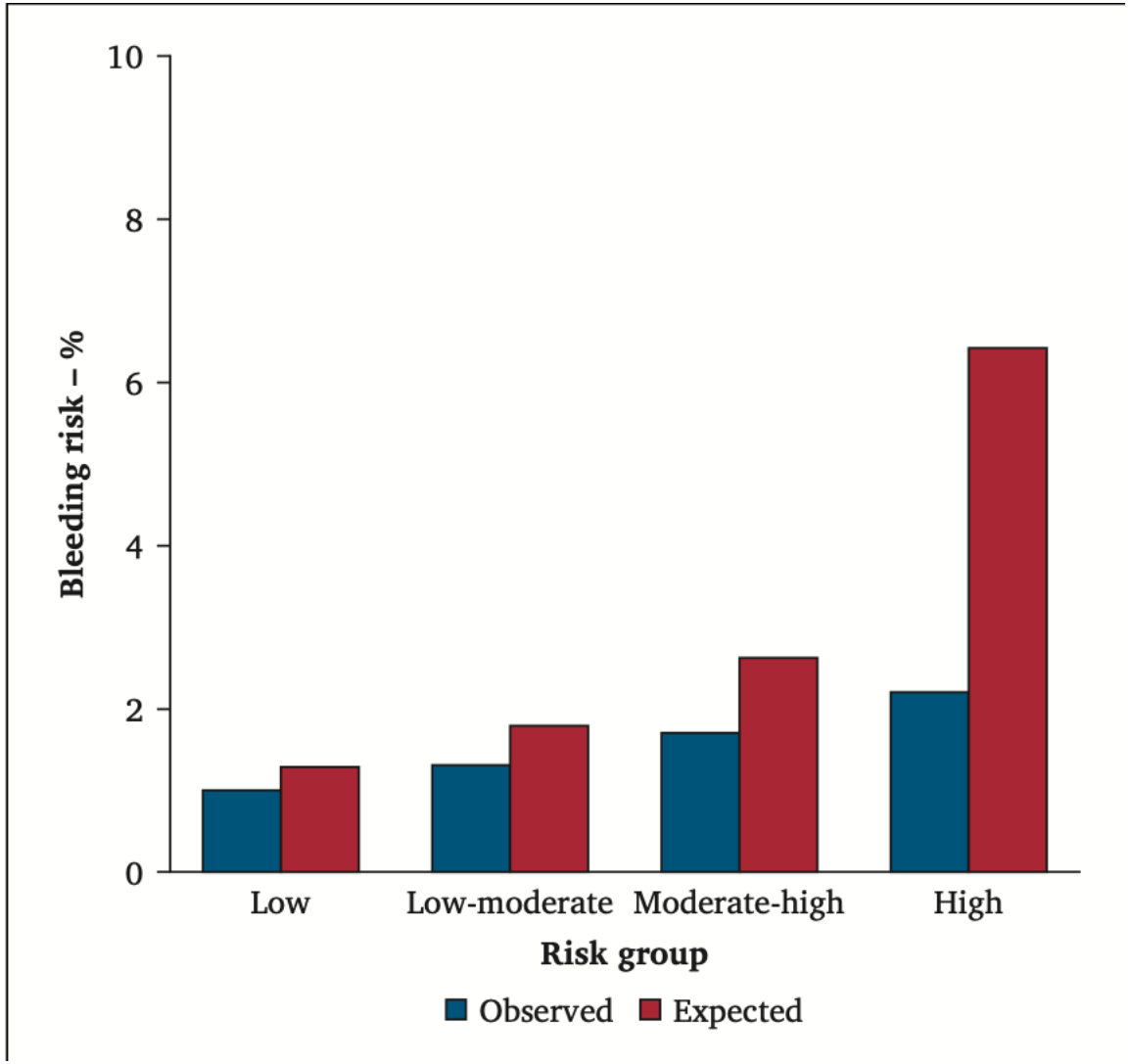
RESEARCH LETTER

External Validation of the OAC3-PAD Risk Score to Predict Major Bleeding Events Using the Prospective GermanVasc Cohort Study

Frederik Peters, Christian-Alexander Behrendt *

[a] Department of Vascular Medicine, Research Group GermanVasc, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

Model calibration comparing the observed risk of major bleeding from the GermanVasc study cohort with the expected risk of major bleeding from the development cohort for each of the four risk groups of the OAC3-PAD bleeding risk score. The observed probability of major bleeding was estimated via a parametric Cox proportional hazards model for interval censored data with Weibull baseline distribution.



Eur J Vasc Endovasc Surg (2022) 64, 429e430

Peripheral Arteries

Eur J Vasc Endovasc Surg (2023) 66, 213–219

Nationwide Study in France To Predict One Year Major Bleeding and Validate the OAC3-PAD Score in Patients Undergoing Revascularisation for Lower Extremity Arterial Disease

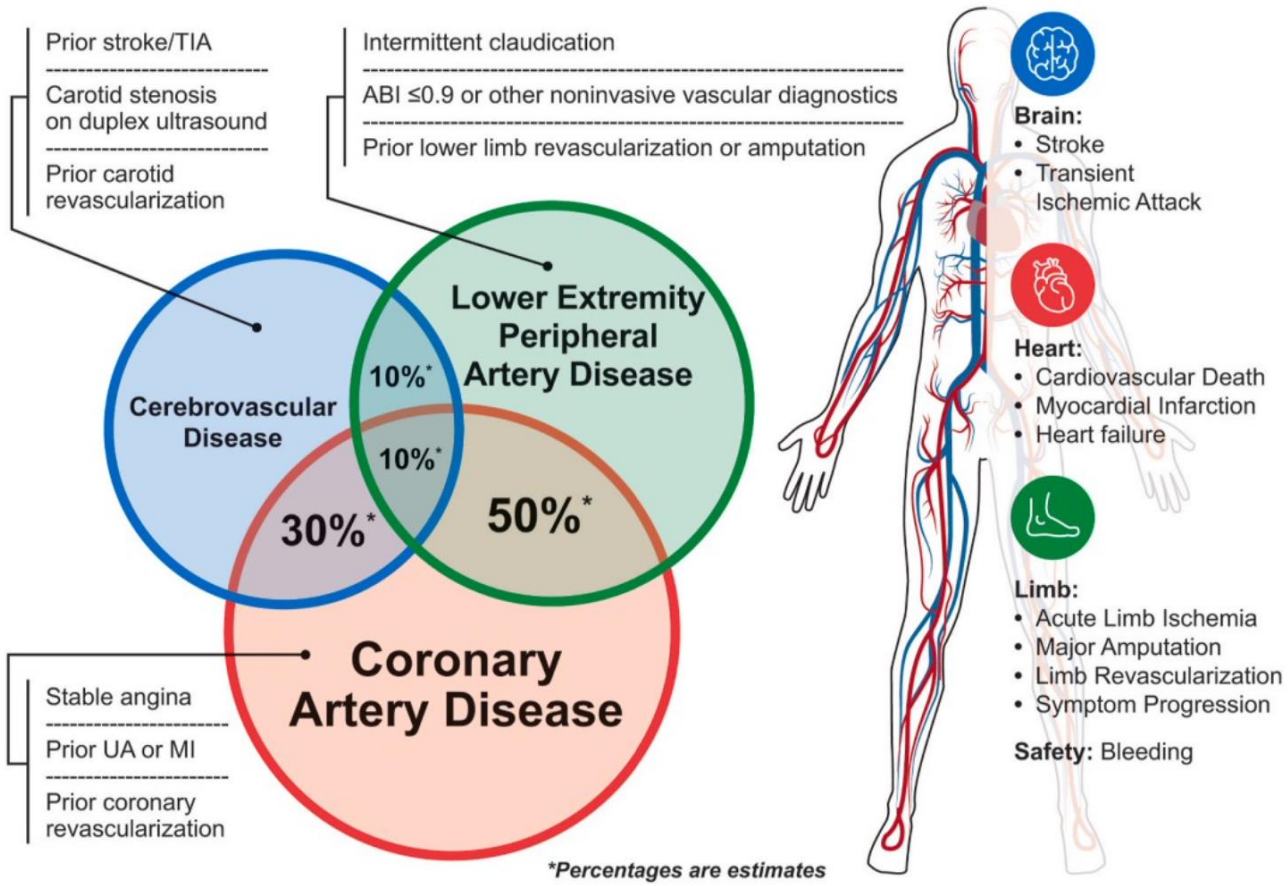
Fabien Lareyre [a,b,*,‡], Christian-Alexander Behrendt [c,d,‡], Christian Pradier [e,k], Nicla Settembre [f], Arindam Chaudhuri [g], Roxane Fabre [e,h], Juliette Raffort [b,i,j,†], Laurent Bailly [e,k,†]

- Questo studio multicentrico retrospettivo su scala nazionale, durato 10 anni e basato su dati sanitari elettronici nazionali francesi, è servito come validazione esterna del punteggio OAC3-PAD per la previsione di un'emorragia maggiore a un anno nei pazienti ricoverati per la rivascolarizzazione della malattia arteriosa degli arti inferiori (PAD).
- Serve come base per costruire ulteriori raccomandazioni e generalizzare l'uso del punteggio OAC3-PAD per la gestione del rischio di sanguinamento nei pazienti con PAD.

PAD e CAD
Malattia polivascolare

TERAPIA ANTITROMBOTICA
DPI
COMPASS VOYAGER

Relative frequencies of polyvascular disease subtypes for each disease territory and ischemic outcomes related to disease in that territory



Weissler et al, Athrosclerosis 2020

ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–71
doi:10.1093/eurheartj/ehz425

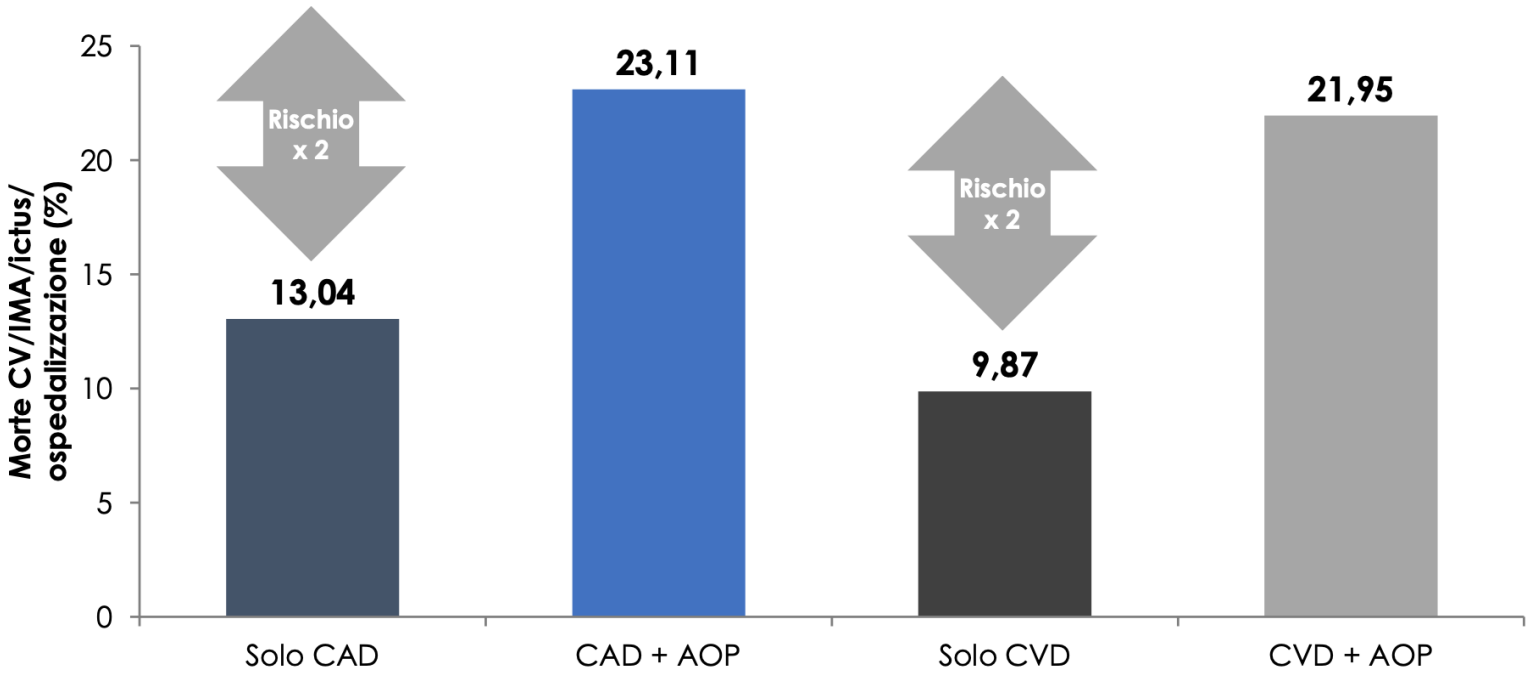
ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)

The most recent European guidelines on chronic coronary syndrome (CCS) indicate that patients with concomitant PAD are among the highest-risk categories compared to patients without PAD

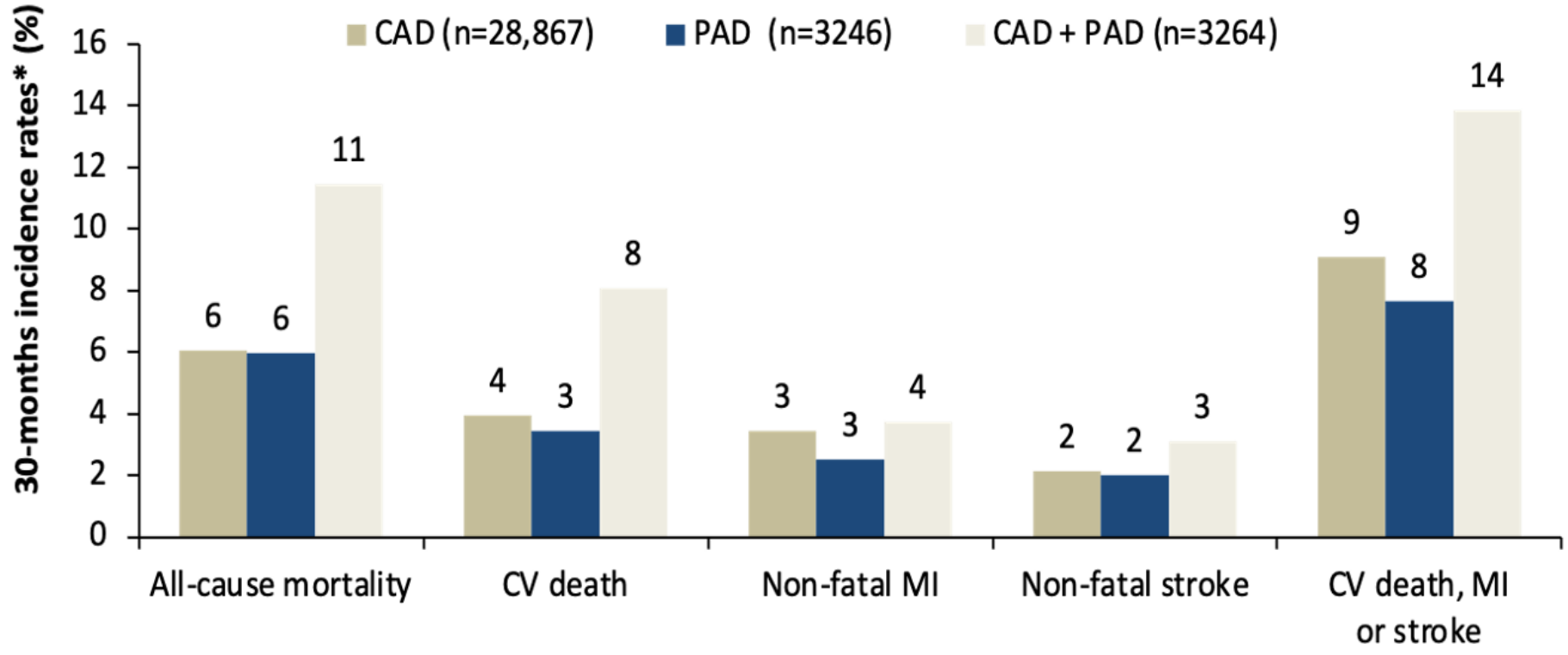
Registro REACH



Bhatt DL et al. JAMA 2006

Patients with polyvascular disease need to be protected from the risk of a life-threatening CV event

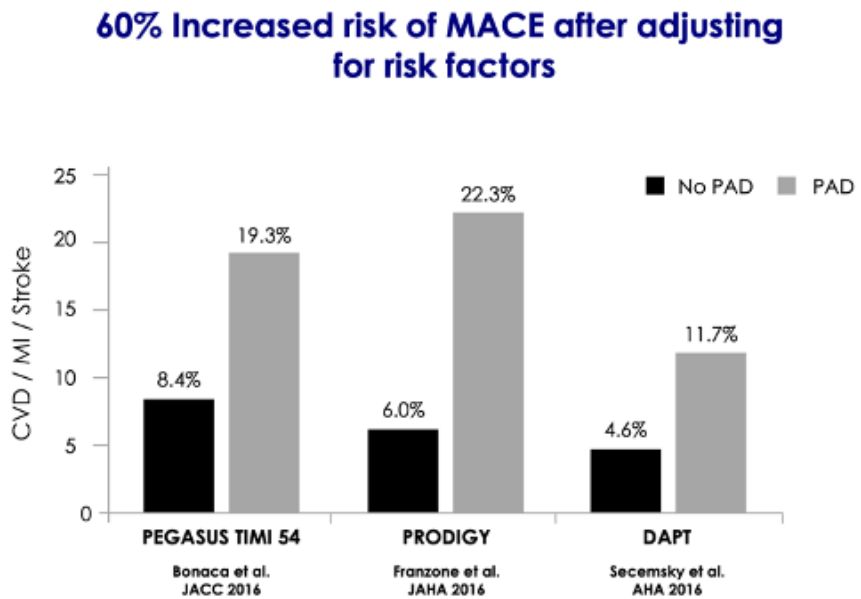
Outcomes in patients with CAD, PAD or CAD + PAD in the REACH registry



*Estimated from 1-year incidence rates.

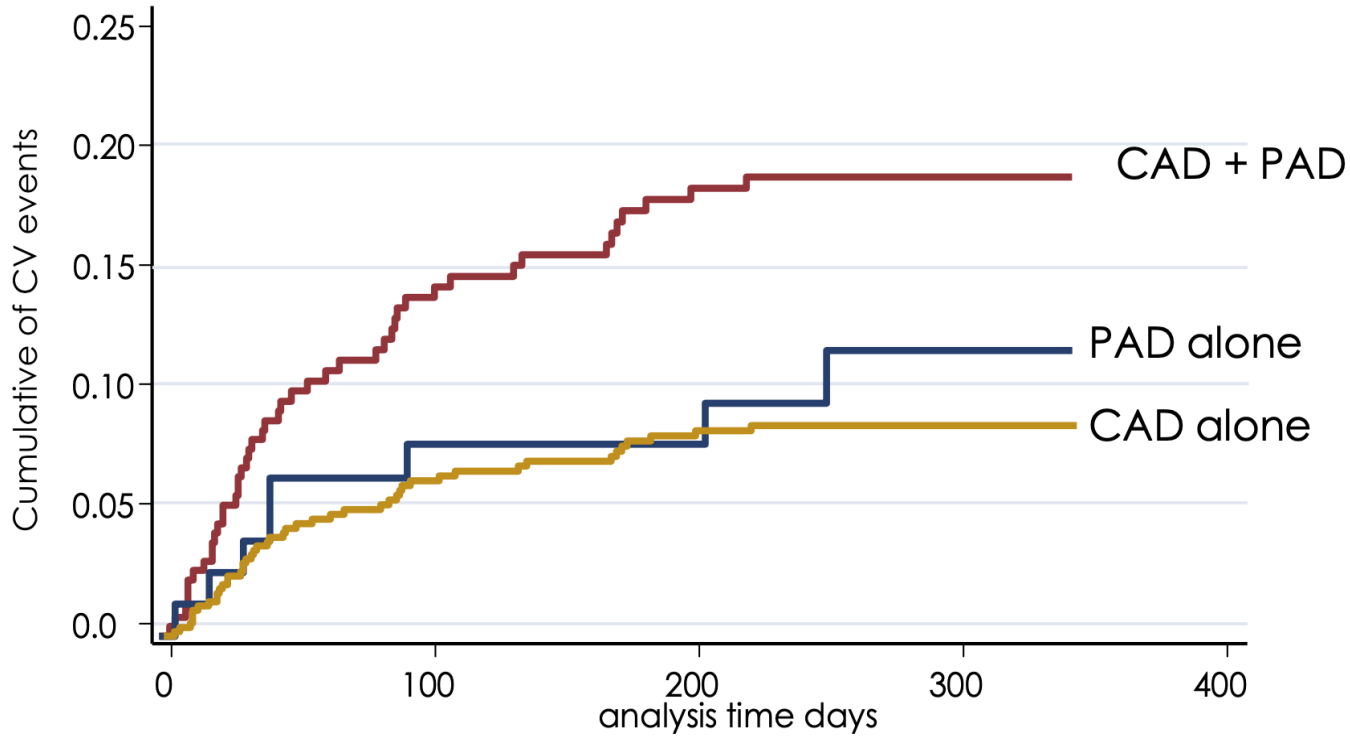
Steg P et al. *JAMA* 2007;297:1197–1206.

Is PAD + CAD the Same as CAD only?



PAD e CAD

Prognostic impact of the coexistence of CAD and PAD: analysis of the COMPASS study



ANAND SS JACC 2019

Il GRACE score per la valutazione a breve e medio termine nel paziente con SCA: i predittori indipendenti del rischio

Modello GRACE
Età, per aumento di 10 anni
Storia di infarto del miocardio
Aumento iniziale degli enzimi cardiaci
No PCI in ospedale
Pressione sistolica per decremento di 20 mmHg
Depressione del segmento ST

E la PAD?

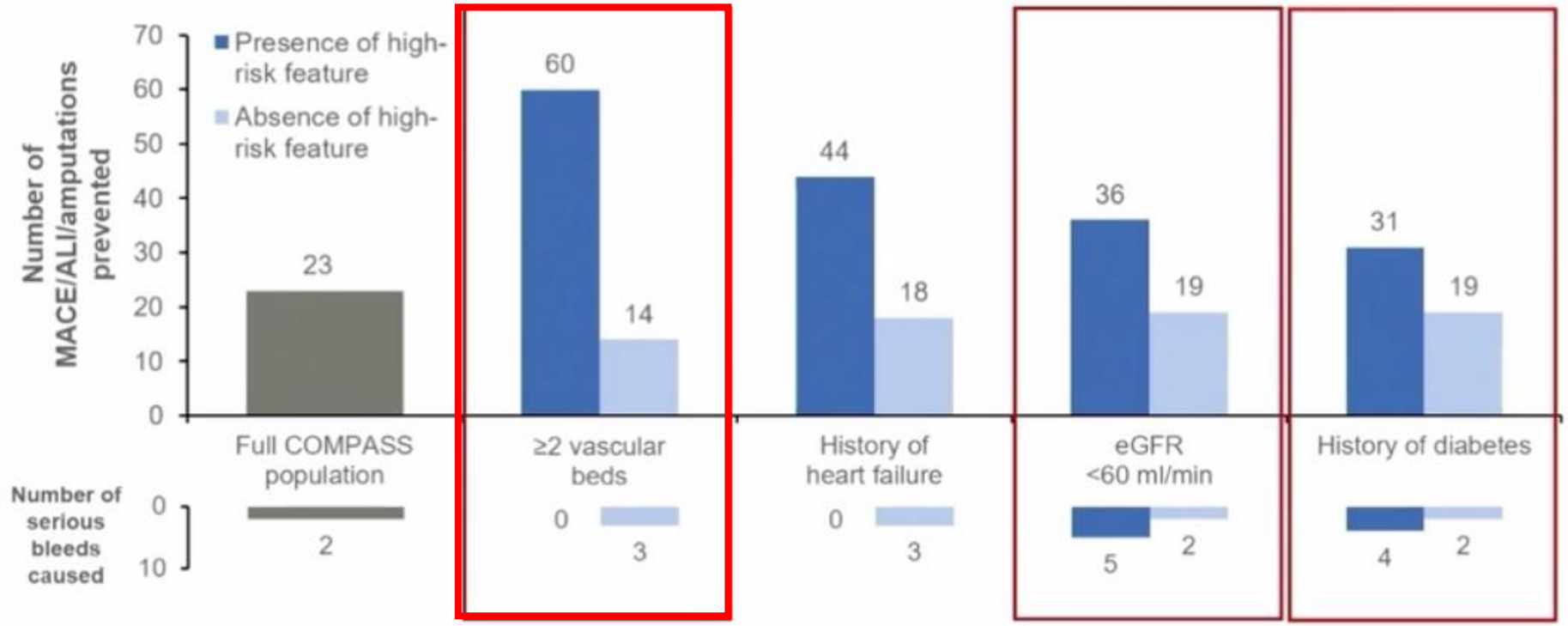
PAD E CAD

Predittori indipendenti di morte e morte/IMA/ictus a sei mesi. Il registro GRACE

Precedenti ictus e PAD	1,79 (1,34-2,39)	1,95 (1,50-2,53)
Età (per aumento di 10 anni)	1,78 (1,69-1,88)	1,45 (1,39-1,51)
Storia di scompenso cardiaco	1,72 (1,49-1,98)	1,45 (1,27-1,65)
Positività biomarker	1,54 (1,37-1,74)	1,49 (1,35-1,64)
Solo precedente PAD	1,49 (1,25-1,77)	1,46 (1,26-1,70)
Solo precedente ictus	1,41 (1,17-1,70)	1,62 (1,38-1,89)
Scompenso cardiaco all'ammissione	1,40 (1,23-1,60)	1,29 (1,14-1,45)
Pulsazioni (per aumento di 30 battiti)	1,27 (1,19-1,37)	1,16 (1,09-1,24)
Depressione del tratto ST all'ammissione	1,24 (1,10-1,39)	1,16 (1,05-1,28)

Absolute Benefit of Rivaroxaban Vascular Dose Plus Aspirin Was Highest in High-Risk Patient Groups

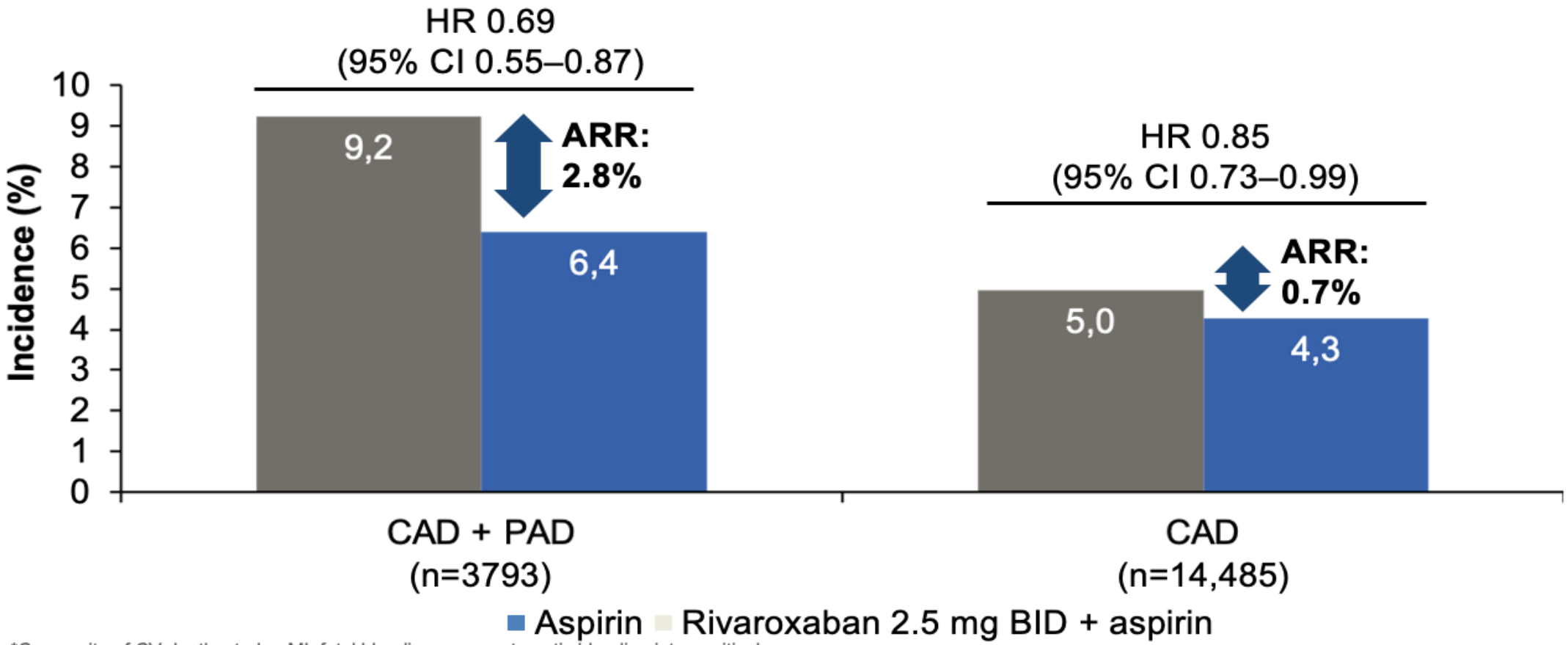
Ischaemic events prevented and bleeding events caused per 1000 patients over 30 months with addition of rivaroxaban 2.5 mg bid to aspirin in high-risk groups



Anand SS *et al. J Am Coll Cardiol* 2019;73:3271–3280

Patients with polyvascular disease can benefit from enhanced overall protection with rivaroxaban vascular dose plus aspirin

Net clinical benefit* in CAD patients with and without PAD



*Composite of CV death, stroke, MI, fatal bleeding, or symptomatic bleeding into a critical organ.

Steffel J et al. *Circulation* 2020;142:40–48.

Patients with polyvascular disease can be offered enhanced vascular protection in line with the 2019 ESC CCS Guidelines

Recommendations	Class	Evidence level
ESC Adding a **second antithrombotic drug** to aspirin for long-term secondary prevention should be considered in patients with a **high risk of ischaemic events** and without high bleeding risk	IIa	A
ESC Adding a **second antithrombotic drug** to aspirin for long-term secondary prevention may be considered in patients with at least a **moderately increased risk of ischaemic events** and without high bleeding risk	IIb	A

High ischaemic risk defined as:

- Diffuse multivessel CAD with **at least 1** of the following:
  - Diabetes mellitus requiring medication
  - Recurrent MI
  - **PAD**
  - CKD with eGFR 15–59 mL/min/1.73 m^2

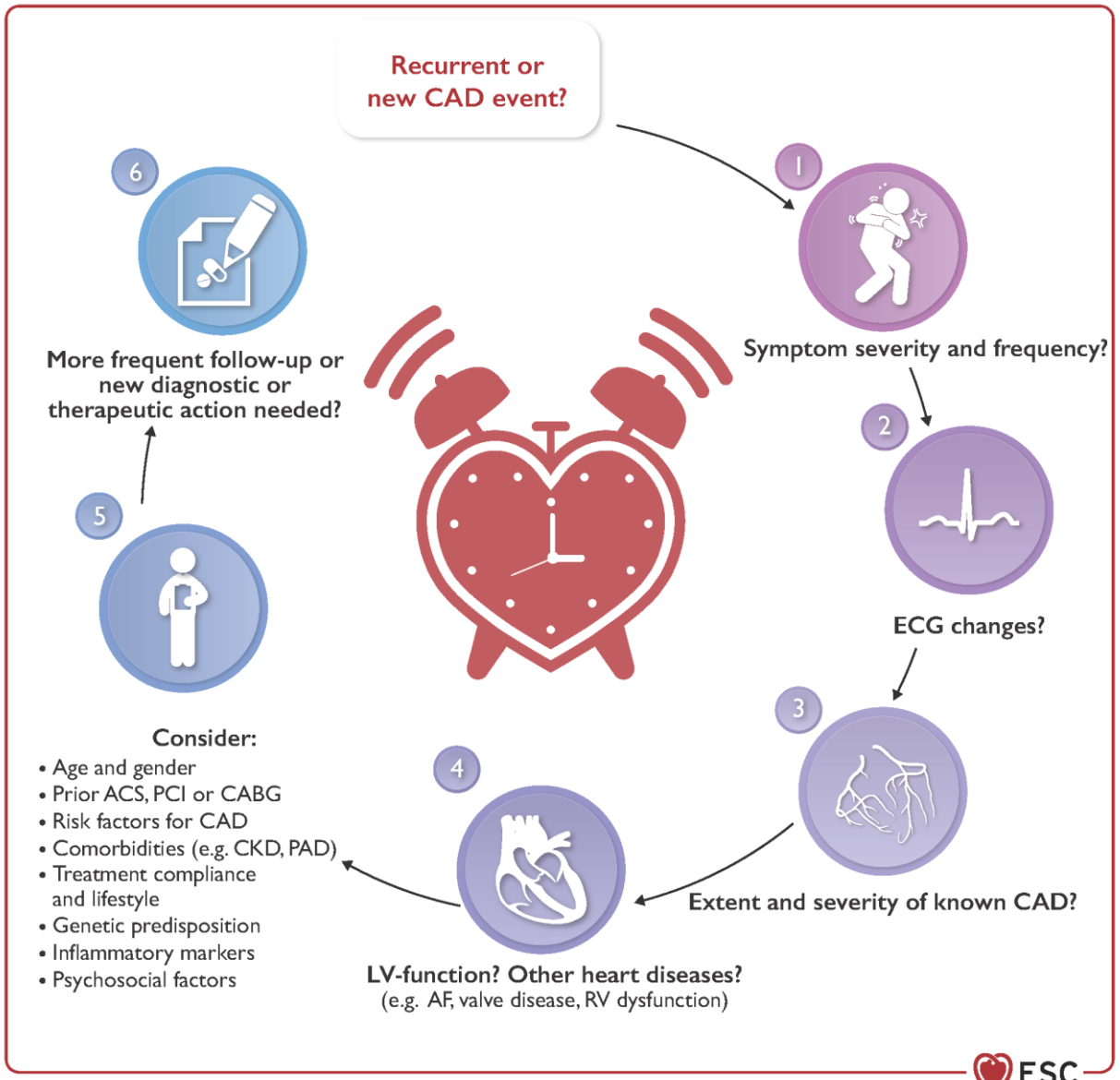
Moderate ischaemic risk defined as:

- **At least 1** of the following:
  - Multivessel/diffuse CAD
  - Diabetes mellitus requiring medication
  - Recurrent MI
  - **PAD**
  - HF
  - CKD with eGFR 15–59 mL/min/1.73 m^2

Knuuti J et al. *Eur Heart J* 2019;41:407–477.

Figure 18

Approach for the follow-up of patients with established CCS



2024 ESC Guidelines for the management of chronic coronary syndromes
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

Recommendations for screening and management of PVD and PAD with cardiac diseases

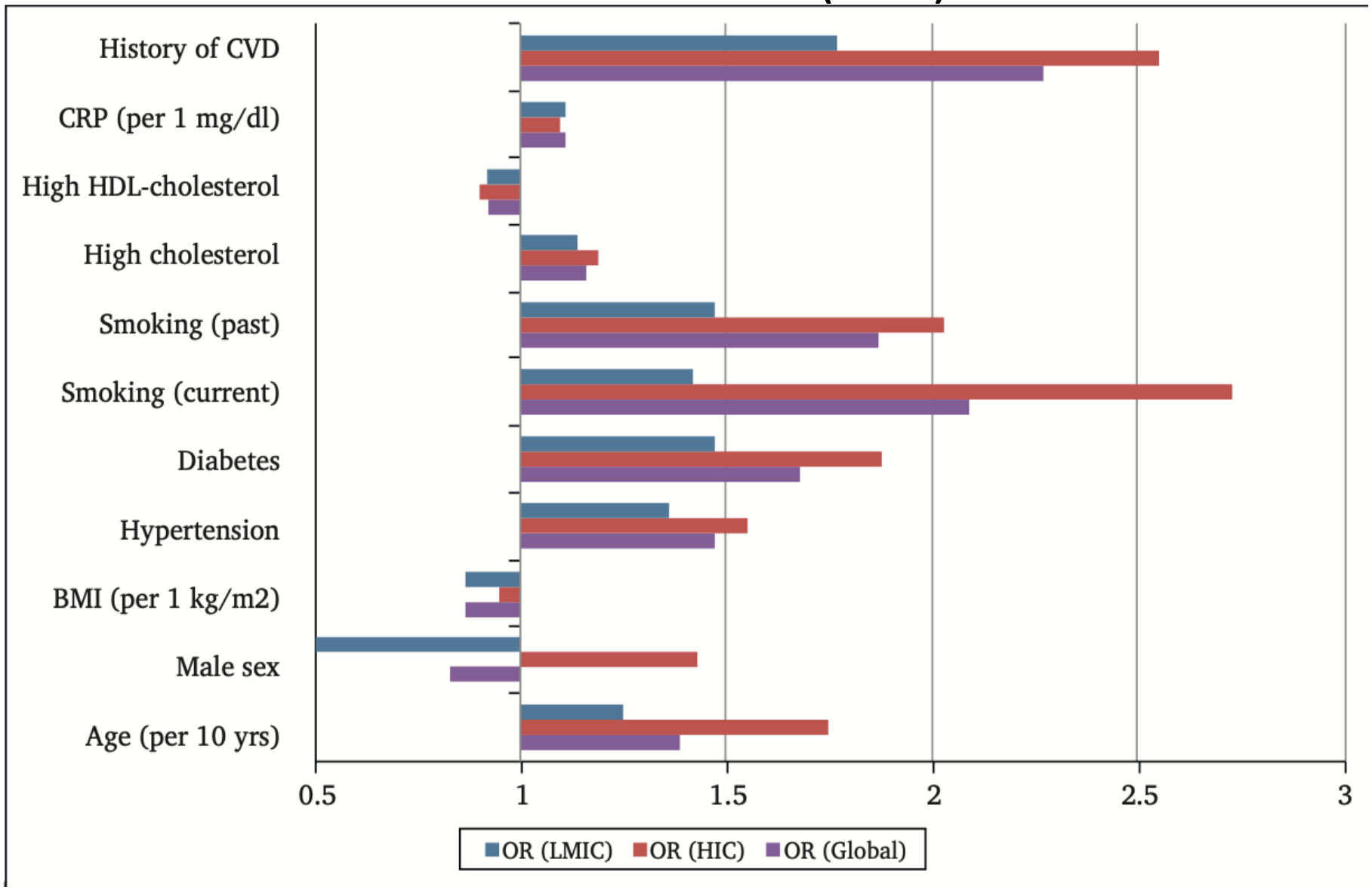
Recommendations	Class	Level
In patients with PVD, an LDL-C reduction by ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.	I	A
In patients with PAD and newly diagnosed AF with a CHA_2DS_2-VASc score ≥2, full oral anticoagulation is recommended.	I	C
Screening for ilio-femoral PAD is recommended in patients undergoing TAVI.	I	B
Carotid DUS should be considered for stable patients scheduled for CABG with TIA/stroke within the past 6 months without carotid revascularization.	IIa	B
In patients with stable PVD who are symptomatic in at least one territory and without high bleeding risk, treatment with a combination of rivaroxaban (2.5 mg b.i.d.) and aspirin (100 mg o.d.) should be considered.	IIa	A
Carotid DUS may be considered for stable patients scheduled for CABG without TIA/stroke within the past 6 months.	IIb	C

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

PAD e DIABETE

TERAPIA ANTITROMBOTICA
DPI
COMPASS VOYAGER

Odds ratios (ORs) for peripheral artery disease (PAD) in high-income countries (HICs) and low- and middle-income countries (LMICs)



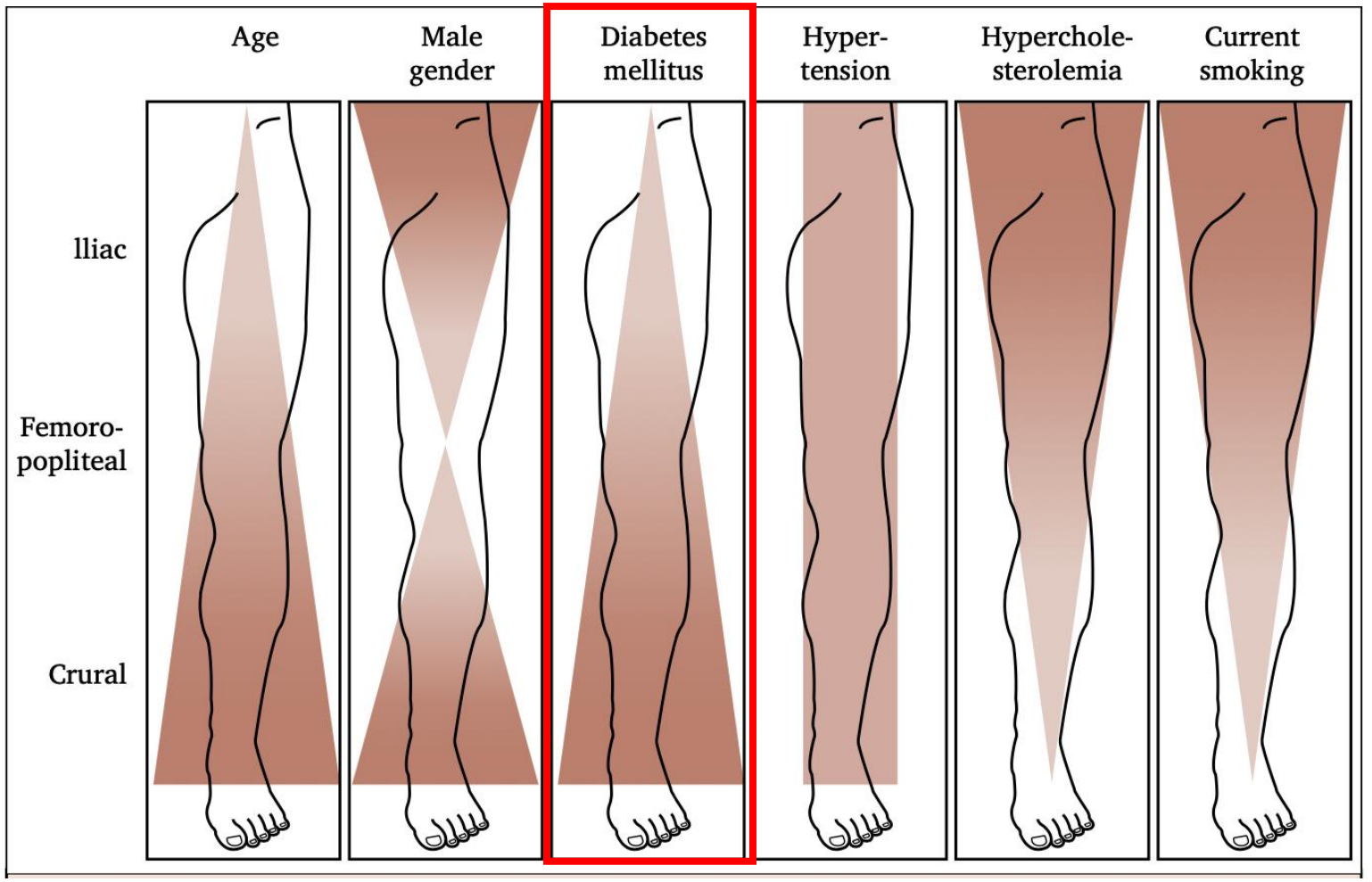
Criqui MH, Circ Res 2015

PAD e DIABETE: FDR per PAD nel paziente Diabetico

- MICROANGIOPATIA: **la macroalbuminuria e la retinopatia diabetica**, sono fattori di rischio indipendenti per la **PAD**
- Basso tasso di **filtrazione glomerulare e l'albuminuria** patologica sono associati in modo indipendente a un eccesso di rischio di **PAD**: associazione tra albuminuria e PAD in pazienti con diabete
- Relazione dose-risposta indipendente tra gli **stadi della retinopatia** diabetica e la **PAD**
- **Amputazione correlata a < GFR e albuminuria**
- La presenza di **diabete** è stata associata a un tasso più elevato di **amputazione** e l'uso di statine a un rischio inferiore
- La **MICROANGIOPATIA** da sola è stata associata a un rischio di **amputazione** aumentato di 4 volte, mentre la combinazione di **PAD e MICROANGIOPATIA** è associata a un rischio aumentato di 20 volte
- Inoltre, è stata riportata una relazione dose-risposta indipendente tra gli stadi della **retinopatia diabetica e la AMPUTAZIONE**

Foussard, L. Dari, E. Ducasse et al. Presse Med 52 (2023) 104164

Association of risk factors with the level of atherosclerotic target lesions. The red overlay on the anatomic cartoon illustrates the association of risk factor with patterns of atherosclerotic disease



Diehm N, Eur J Vasc Endovasc Surg 2006

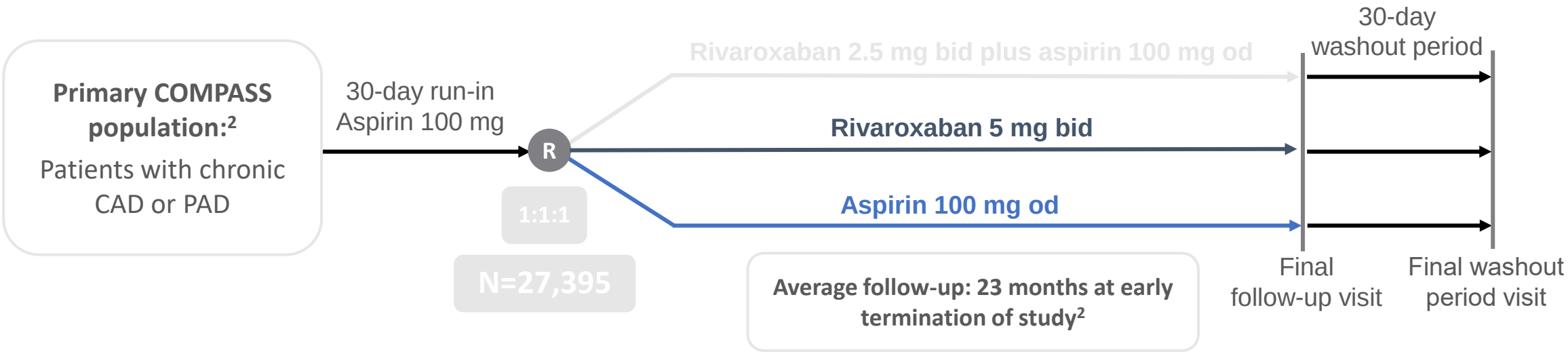
Background

- Patients with established CAD or PAD often have diabetes mellitus
- Diabetes contributes to a pro-thrombotic state; therefore, these patients are at high risk of coronary, cerebral and peripheral ischaemic events
- Dual antiplatelet therapy does not directly address the higher rates of thrombin generation in this patient group
- The COMPASS trial demonstrated that the combination of rivaroxaban 2.5 mg bid plus aspirin was superior to aspirin alone for the reduction of ischaemic events in patients with chronic CAD and/or PAD[8]
- Diabetes was independently identified as one of four predictors of thrombotic risk in a post-hoc analysis of the COMPASS data, alongside polyvascular disease, moderate renal dysfunction and chronic heart failure

1. Bhatt DL *et al*. *JAMA* 2006;295:180–189. 2. Steg PG *et al*. *JAMA* 2007;297:1197–1206. 3. Bhatt DL *et al*. *JAMA* 2010;304:1350–1357.
4. Cavender MA *et al*. *Circulation* 2015;132:923–931. 5. Bhatt DL. *JAMA* 2012;308:921–922. 6. Alberts MJ *et al*. *Eur Heart J* 2009;30:2318–2326.
7. Gutierrez JA *et al*. *Am J Cardiol* 2019;123:145–152. 8. Eikelboom JW *et al*. *N Engl J Med* 2017;377:1319–1330. 9. Anand SS *et al. J Am Coll Cardiol*;73:3271–3280

Prespecified Subgroup Analysis of COMPASS Patients with Diabetes and Chronic CAD or PAD

Objective: To evaluate the efficacy and safety of rivaroxaban 2.5 mg bid plus aspirin compared with aspirin alone in patients with chronic vascular disease with or without diabetes[1]



Primary endpoints of subgroup analysis[1]

- Efficacy: Composite of CV death, MI or stroke
- Safety: Major bleeding events (modified ISTH criteria)

Secondary endpoints of subgroup analysis[1]

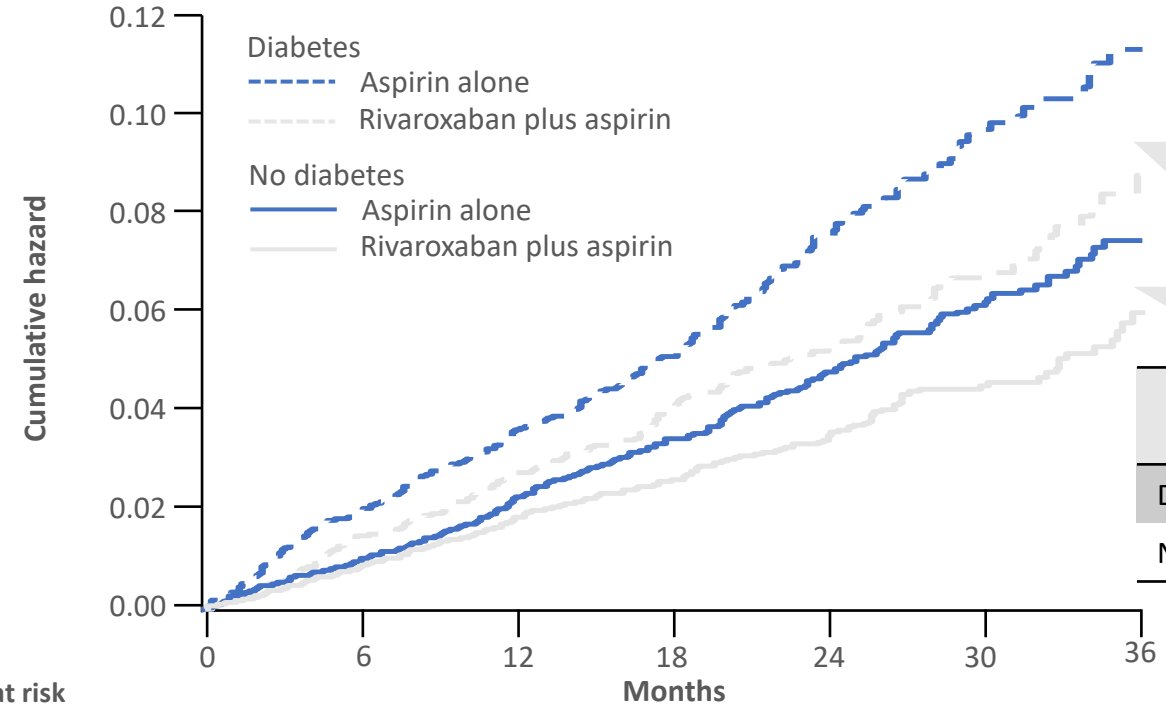
- All-cause mortality
- MALE
- Major vascular events (CV death, MI, stroke, and MALE*)

*Including amputation

1. Bhatt DL *et al*. *Circulation* 2020 doi:10.1161/CIRCULATIONAHA.120.046448; 2. Eikelboom JW *et al*. *N Engl J Med* 2017:377:1319–1330.

Benefits of Rivaroxaban 2.5 mg bid Plus Aspirin Versus Aspirin Alone Were Greater in Patients With Versus Without Diabetes

MI, stroke or CV death



ARR: 2.3%

ARR: 1.4%

Absolute risk
p_{int}<0.0001

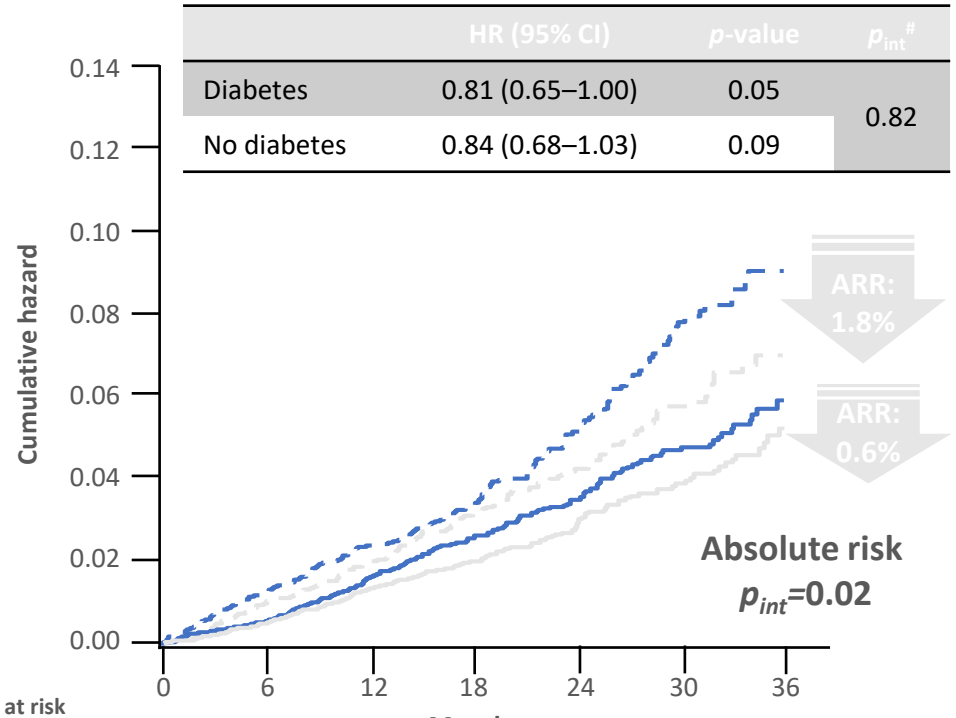
	HR (95% CI)	*p*-value	Relative risk p_{int}
Diabetes	0.74 (0.61–0.90)	0.002	0.77
No diabetes	0.77 (0.64–0.93)	0.005	

Number of patients at risk							
Diabetes							
Aspirin alone	3474	3394	2964	2319	1436	781	222
Rivaroxaban plus aspirin	3448	3384	2955	2372	1491	831	244
No diabetes							
Aspirin alone	5652	5587	4834	3838	2424	1386	446
Rivaroxaban plus aspirin	5704	5641	4943	3917	2420	1379	414

Bhatt DL *et al*. *Circulation* 2020 doi:10.1161/CIRCULATIONAHA.120.046448.

Benefits of Rivaroxaban 2.5 mg bid Plus Aspirin Versus Aspirin Alone Were Greater in Patients With Versus Without Diabetes

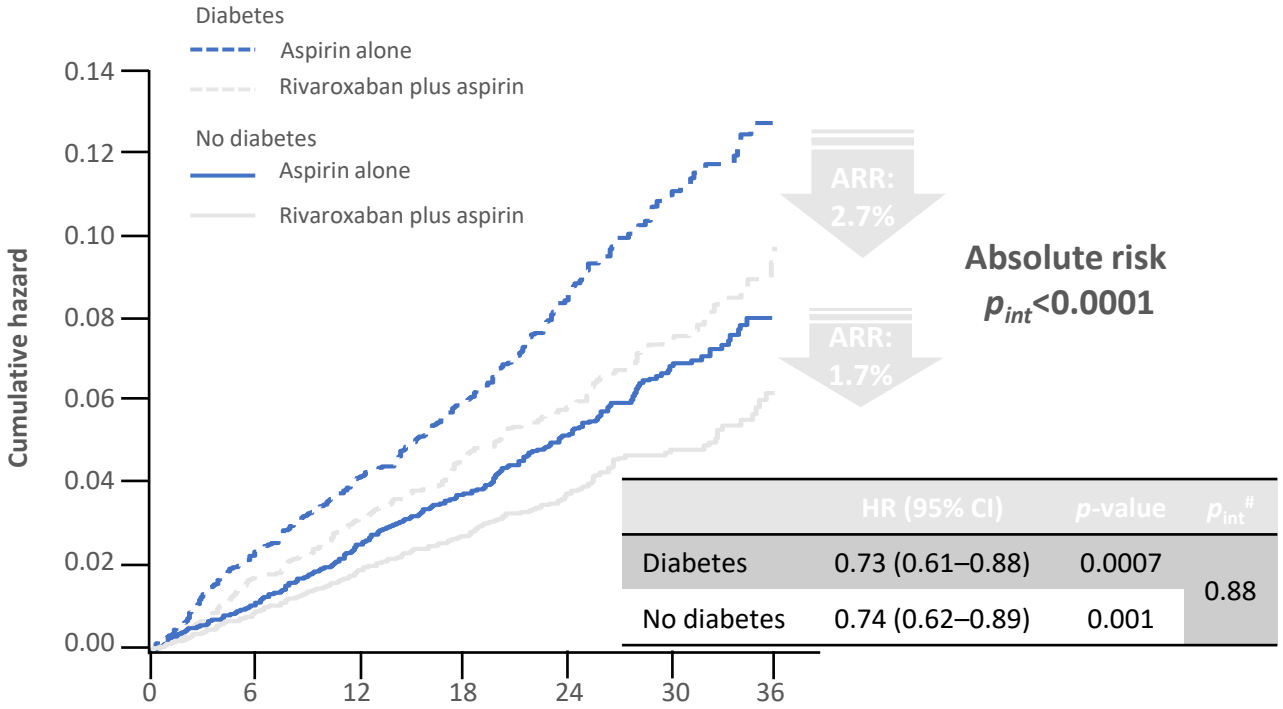
All-cause mortality



	HR (95% CI)	*p*-value	p_{int}#
Diabetes	0.81 (0.65–1.00)	0.05	0.82
No diabetes	0.84 (0.68–1.03)	0.09	

Number of patients at risk							
Diabetes							
Aspirin alone	3474	3432	3027	2398	1511	837	240
Rivaroxaban plus aspirin	3448	3413	3000	2428	1537	864	254
No diabetes							
Aspirin alone	5652	5618	4899	3911	2497	1439	465
Rivaroxaban plus aspirin	5704	5671	5000	3981	2466	1418	425

CV death, stroke, MI or MALE*



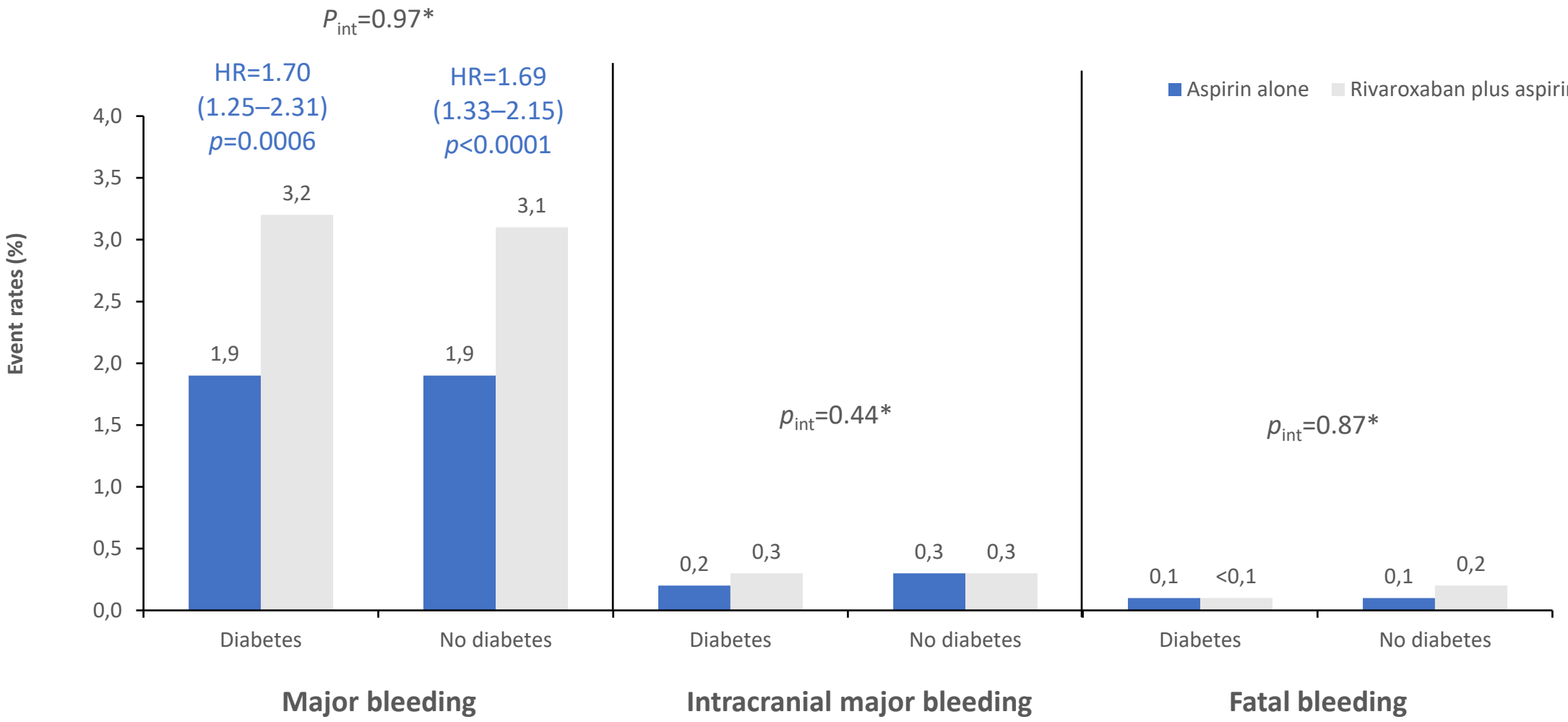
	HR (95% CI)	*p*-value	p_{int}#
Diabetes	0.73 (0.61–0.88)	0.0007	0.88
No diabetes	0.74 (0.62–0.89)	0.001	

3474	3382	2947	2301	1422	771	219
3448	3372	2941	2359	1484	824	241
5652	5579	4820	3825	2416	1381	442
5704	5638	4939	3911	2413	1375	414

*Including amputation; #*p*-interactions in tables relate to relative risk reductions.

Bhatt DL *et al*. *Circulation* 2020 doi:10.1161/CIRCULATIONAHA.120.046448.

Safety Data In Patients with Diabetes Are Consistent with Overall Data



HR (95% CI) are from the stratified Cox proportional hazards regression models fit in the respective subgroup.
**p*-value for the test of interaction of relative risk reduction (Cox regression)
Bhatt DL *et al*. *Circulation* 2020 doi:10.1161/CIRCULATIONAHA.120.046448.

Conclusions

- Rivaroxaban vascular dose plus aspirin reduced the risk of MACE versus aspirin alone in patients with atherosclerosis, irrespective of the presence or absence of diabetes
- Absolute reductions in the risk of MACE were significantly larger in patients with diabetes compared with those without
- Thus, in patients with acceptable bleeding risk, addition of rivaroxaban vascular dose to aspirin should be considered in the secondary prevention regimen of patients with atherosclerosis and diabetes

Bhatt DL *et al*. *Circulation* 2020 doi:10.1161/CIRCULATIONAHA.120.046448.

PAD e Diabete: LG ESC 2019

LEAD management		
In patients with DM and symptomatic LEAD, antiplatelet therapy is recommended.[541]	I	A
As patients with DM and LEAD are at very high CV risk,[d] an LDL-C target of <1.4 mmol/L (<55 mg/dL), or an LDL-C reduction of al least 50% is recommended.[200,201,210]	I	B
In patients with DM with CLTI, the assessment of the risk of amputation is recommended; the WIfI score[e] is useful for this purpose.[494,522]	I	B
In case of CLTI, revascularization is indicated whenever feasible for limb salvage.[542]	I	C
In patients with DM with CLTI, optimal glycaemic control should be considered to improve foot outcome.	IIa	C
In patients with DM and chronic symptomatic LEAD without high bleeding risk, a combination of low-dose rivaroxaban (2.5 mg b.i.d.) and aspirin (100 mg o.d.) should be considered.[f 531]	IIa	B

PAD

TERAPIA MEDICA
CONCLUSIONI ESC 2024

New recommendations (2)

Recommendations	Class	Level
Recommendations for lifestyle, physical activity, and patient education		
Use of web- or app-based secondary prevention risk calculators should be considered in the shared decision-making to improve patient adherence to treatment and lifestyle changes.	IIa	C
E-cigarettes may be considered as an aid to quitting tobacco smoking, but it is advisable to limit their use and avoid simultaneous use with conventional cigarettes due to unknown long-term effects.	IIb	C
Recommendations for lipid-lowering therapy in patients with peripheral arterial and aortic diseases		
In patients with atherosclerotic PAAD, lipid-lowering therapy is recommended.	I	A
An ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and a >50% reduction in LDL-C vs. baseline are recommended in patients with atherosclerotic PAAD.	I	A
If the target LDL-C level is not achieved on maximally tolerated statins and ezetimibe, treatment with a PCSK9 inhibitor is recommended in patients with atherosclerotic PAAD, to achieve target values.	I	A

New recommendations (3)

Recommendations	Class	Level
Recommendations for lipid-lowering therapy in patients with peripheral arterial and aortic diseases		
If the target LDL-C level is not achieved, a combination of statins and ezetimibe is indicated in patients with atherosclerotic PAAD, to achieve the given target values.	I	B
For statin-intolerant patients with atherosclerotic PAAD, at high CV risk, who do not achieve their LDL-C goal on ezetimibe, it is recommended to add bempedoic acid either alone or in combination with a PCSK9 inhibitor.	I	B
Statins for the reduction of growth and rupture of AAA should be considered.	IIa	B
Statins for the reduction of growth and rupture of TAA may be considered.	IIb	B
In high-risk patients with PAAD and triglycerides >1.5 mmol/L despite lifestyle measures and statin therapy, icosapent ethyl 2g b.i.d. may be considered in addition to a statin.	IIb	B
Fibrates are not recommended for cholesterol lowering.	III	B

New recommendations (4)

Recommendations	Class	Level
Recommendations for exercise therapy in patients with peripheral arterial disease		
In patients with symptomatic PAD, SET is recommended.	I	A
In those patients undergoing endovascular revascularization, SET is recommended as an adjuvant therapy.	I	A
When SET is not available or feasible, a structured and monitored (calls, logbooks, connected devices) HBET programme should be considered.	IIa	A
Walking should be considered as the first-line training modality. When walking exercise is not an option, alternative exercise modes (strength training, arm cranking, cycling, and combinations of different training modes) should also be considered.	IIa	A
Walking training performed at high intensity (77%–95% of maximal heart rate or 14–17 self-perceived exertion on Borg's scale) should be considered to improve walking performance, and high-intensity exercise training (various aerobic training modes) should be considered to improve cardiorespiratory fitness.	IIa	A

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

New recommendations (5)

Recommendations	Class	Level
Recommendations for exercise therapy in patients with peripheral arterial disease cont.		
Training frequency of at least three times per week, training session duration of at least 30 min, and training programme duration of at least 12 weeks should be considered.	IIa	B
In patients with PAD, exercise training to moderate-severe claudication pain may be considered to improve walking performance. However, improvements are also achievable with lesser claudication pain severities (low-mild pain or pain-free).	IIb	B
Based on patient's tolerance, a progressive increase (every 1–2 weeks) in exercise training load may be considered.	IIb	C
Recommendations for antithrombotic therapy in patients with peripheral arterial disease		
Treatment with combination rivaroxaban (2.5 mg b.i.d.) and aspirin (100 mg o.d.) should be considered for patients with PAD and high ischaemic risk, and non-high bleeding risk.	IIa	A
Treatment with combination rivaroxaban (2.5 mg b.i.d.) and aspirin (100 mg o.d.) should be considered for patients with PAD and non-high bleeding risk following lower-limb revascularization.	IIa	B
Aspirin (75–100 mg) for primary prevention may be considered in patients with asymptomatic PAD and DM, in the absence of contraindications.	IIb	A

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

New recommendations (6)

Recommendations	Class	Level
Recommendations for interventional treatment of asymptomatic and symptomatic peripheral arterial disease (general)		
In patients with symptomatic PAD, after a 3-month period of OMT and exercise therapy, PAD-related QoL assessment is recommended.	I	B
It is recommended to adapt the mode and type of revascularization options to anatomical lesion location, lesion morphology, and general patient condition.	I	C
In patients with symptomatic PAD and impaired PAD-related QoL after a 3-month period of OMT and exercise therapy, revascularization may be considered.	IIb	B
In patients with PAD, revascularization is not recommended if the reason is to solely prevent progression to CLTI.	III	B
In patients with asymptomatic PAD, revascularization is not recommended.	III	C

New recommendations (7)

Recommendations	Class	Level
Recommendations for interventional treatment of patients with symptomatic peripheral arterial disease (per arterial bed)		
In femoro-popliteal lesions, drug-eluting treatment should be considered as the first-choice strategy.	**IIa**	**A**
In femoro-popliteal lesions, if revascularization is indicated, an open surgical approach should be considered when an autologous vein (e.g. GSV) is available in patients with low surgical risk.	**IIa**	**C**
In patients with severe IC undergoing endovascular femoro-popliteal revascularization, treatment of BTK arteries may be considered in the same intervention.	**IIb**	**C**

New recommendations (8)

Recommendations	Class	Level
Recommendations in patients with peripheral arterial disease: follow-up of patients with peripheral arterial disease		
It is recommended to regularly, at least once a year, follow up patients with PAD, assessing clinical and functional status, medication adherence, limb symptoms, and CVRFs, with DUS assessment as needed.	I	C
Recommendations for the management of chronic limb-threatening ischaemia		
Early recognition of CLTI and referral to the vascular team are recommended for limb salvage.	I	C
Recommendations for medical treatment in patients with chronic limb-threatening ischaemia		
It is recommended that patients with CLTI are managed by a vascular team.	I	C
In patients with CLTI and ulcers, offloading mechanical tissue stress is indicated to allow wound healing.	I	C
Lower-limb exercise training is not recommended in patients with CLTI and wounds.	III	C

New recommendations (9)

Recommendations	Class	Level
Recommendations for interventional treatment of chronic limb-threatening ischaemia		
In CLTI patients, it is recommended to perform revascularization as soon as possible.	I	B
In CLTI, it is recommended to use autologous veins as the preferred conduit for infra-inguinal bypass surgery.	I	B
In multilevel vascular disease, it is recommended to eliminate inflow obstructions when treating downstream lesions.	I	C
In CLTI patients with good autologous veins and low surgical risk (<5% peri-operative mortality, >50% 2-year survival), infra-inguinal bypass may be considered.	IIb	B
In CLTI patients, endovascular treatment may be considered as first-line therapy, especially in patients with increased surgical risk or inadequate autologous veins.	IIb	B
Recommendations for follow-up in patients with chronic limb-threatening ischaemia		
In patients with CLTI, following revascularization it is recommended to follow up patients on a regular basis.	I	C
At follow-up, it is recommended to assess clinical, haemodynamic and functional status, limb symptoms, treatment adherence, and CVRFs.	I	C

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Recommendations for antithrombotic therapy in patients with peripheral arterial disease (1)

Recommendations	Class	Level
Use of antiplatelet therapy with aspirin alone (range 75–160 mg o.d.) or clopidogrel alone (75 mg o.d.) is recommended for the reduction of MACE in patients with symptomatic PAD.	I	A
Treatment with combination rivaroxaban (2.5 mg b.i.d.) and aspirin (100 mg o.d.) should be considered for patients with PAD, high ischaemic risk, and non-high bleeding risk.	IIa	A
Treatment with combination rivaroxaban (2.5 mg b.i.d.) and aspirin (100 mg o.d.) should be considered for patients with PAD and non-high bleeding risk following lower-limb revascularization.	IIa	B
Use of antiplatelet therapy with clopidogrel alone (75 mg o.d.) may be considered over aspirin to reduce MI, stroke, and vascular death.	IIb	B
Aspirin (75–100 mg) for primary prevention may be considered in patients with asymptomatic PAD and DM, in the absence of contraindications.	IIb	A
DAPT for at least 1 month after revascularization may be considered to reduce limb events.	IIb	B

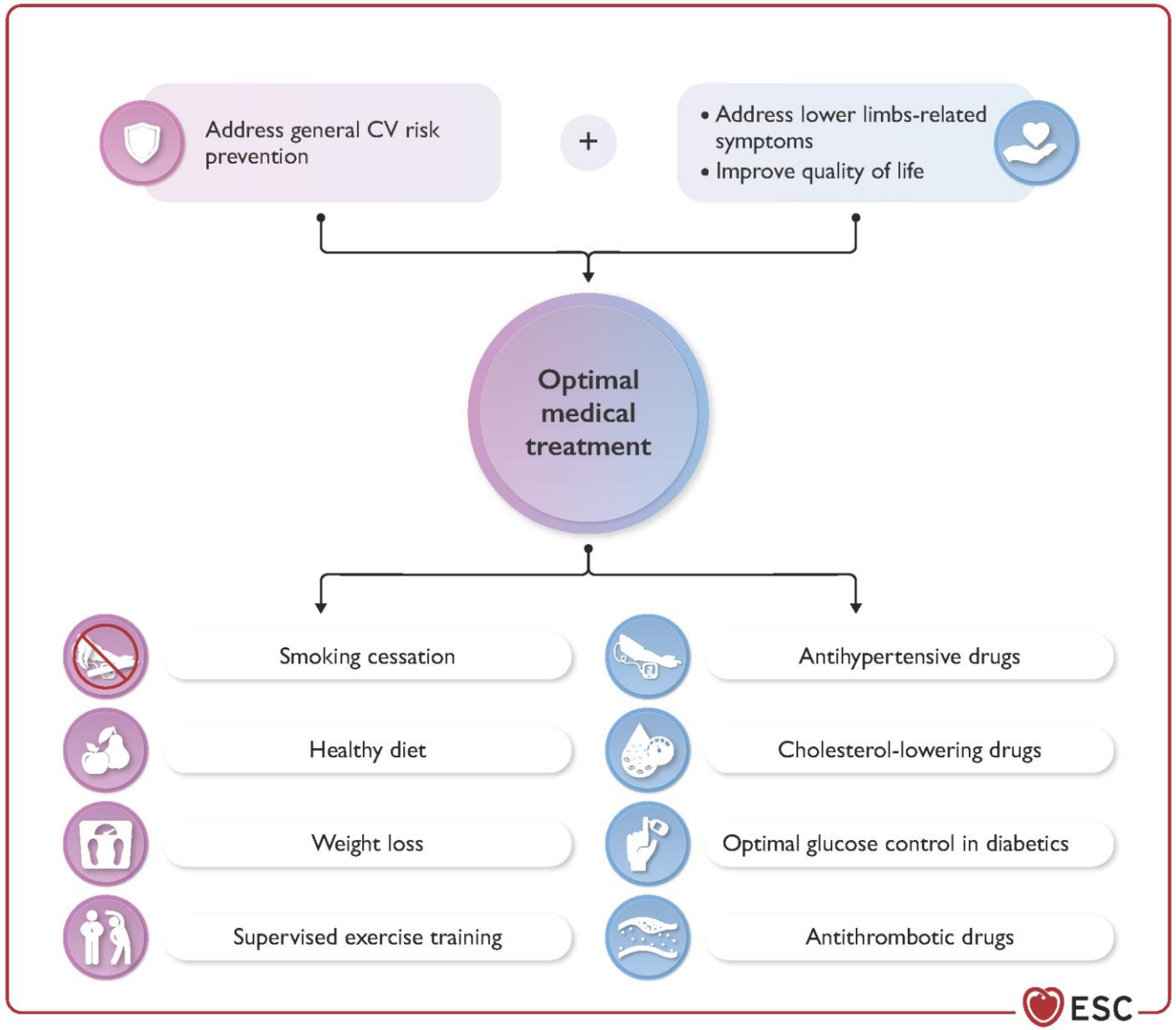
2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Recommendations for antithrombotic therapy in patients with peripheral arterial disease (2)

Recommendations cont.	Class	Level
Long-term DAPT in patients with PAD is not recommended.	III	A
Oral anticoagulant monotherapy for PAD (unless for another indication) is not recommended.	III	A
The routine use of ticagrelor in patients with PAD is not recommended.	III	A
It is not recommended to systematically treat patients with asymptomatic PAD without any sign of clinically relevant ASCVD with antiplatelet drugs.	III	B

Figure 10

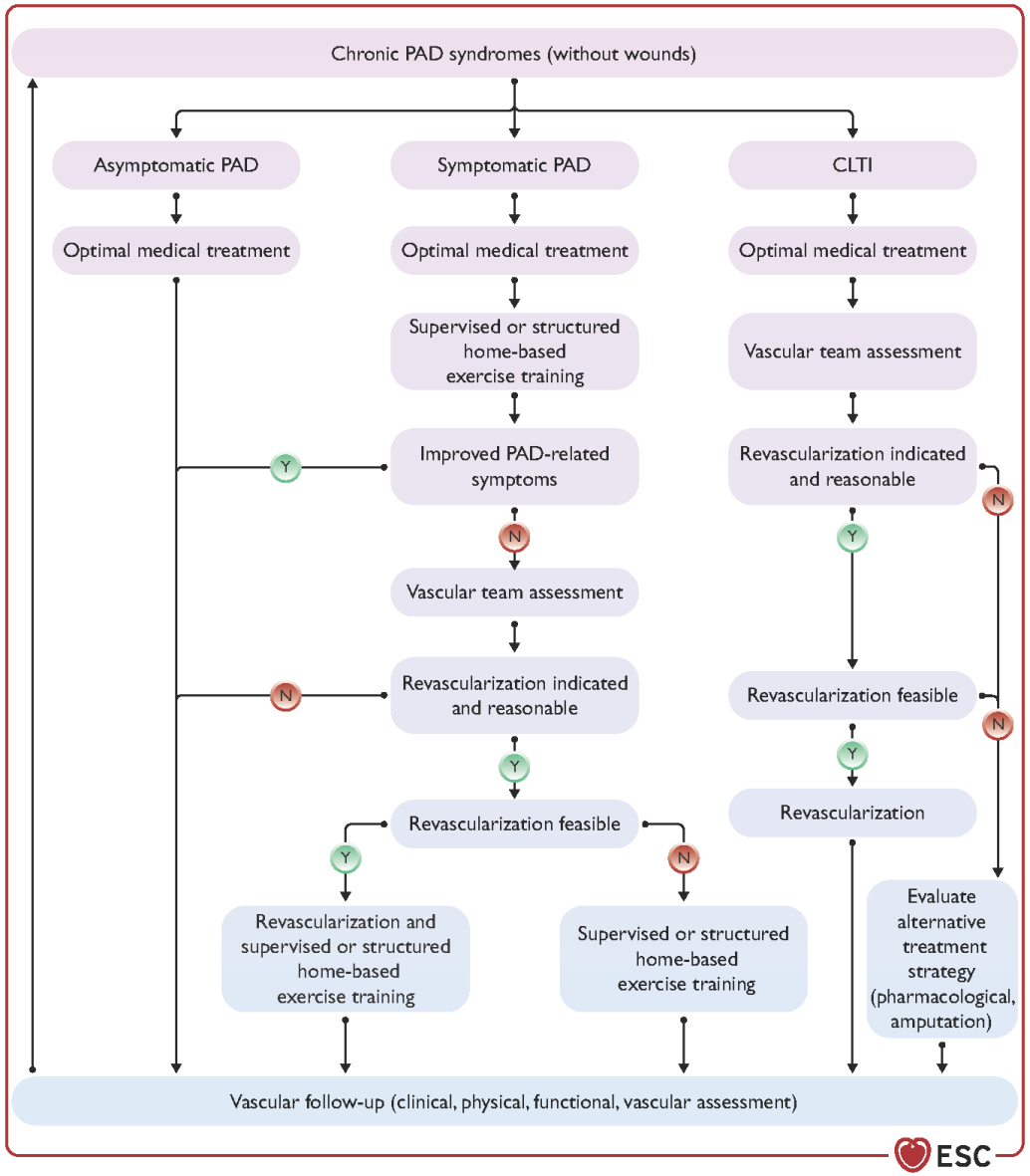
Optimal medical treatment in patients with peripheral arterial disease



2024 ESC Guidelines for the management peripheral arterial and aortic diseases (European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Figure 11

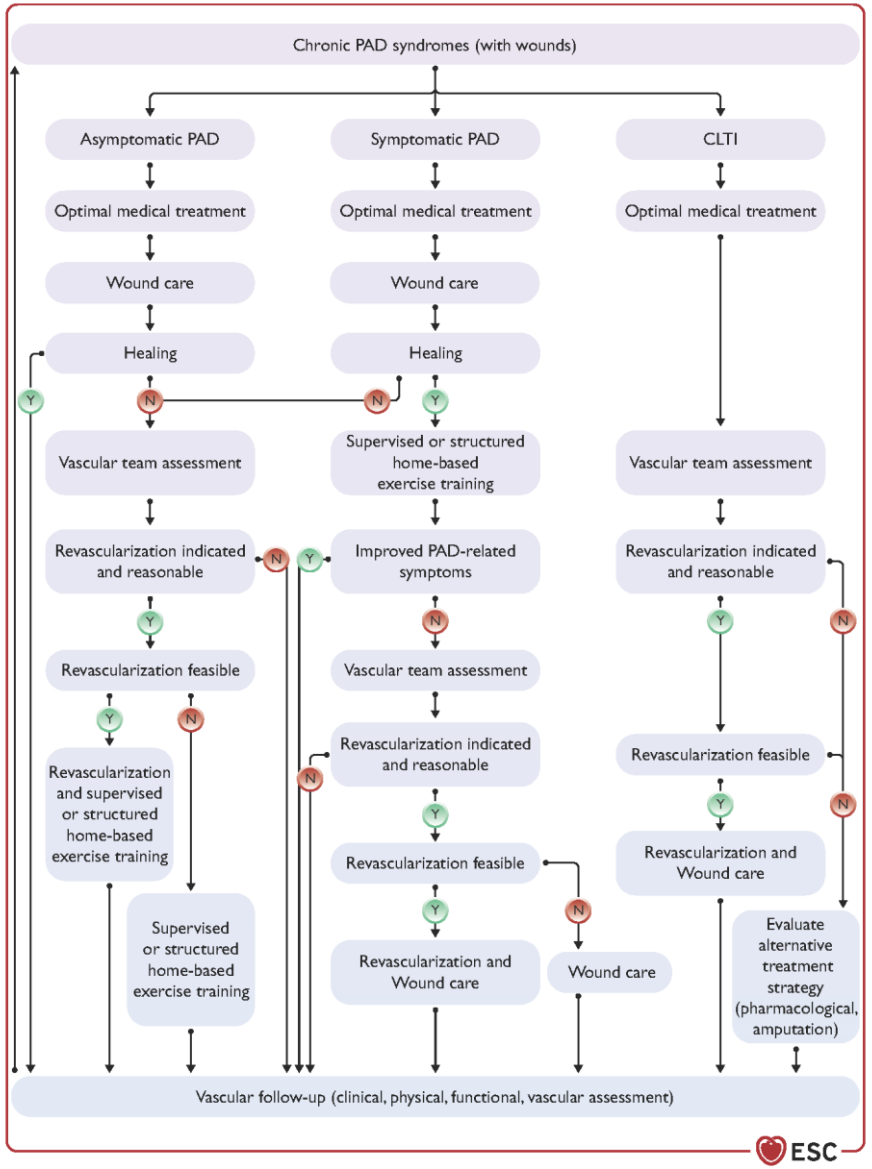
Treatment algorithm in peripheral arterial disease without wounds



2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Figure 12

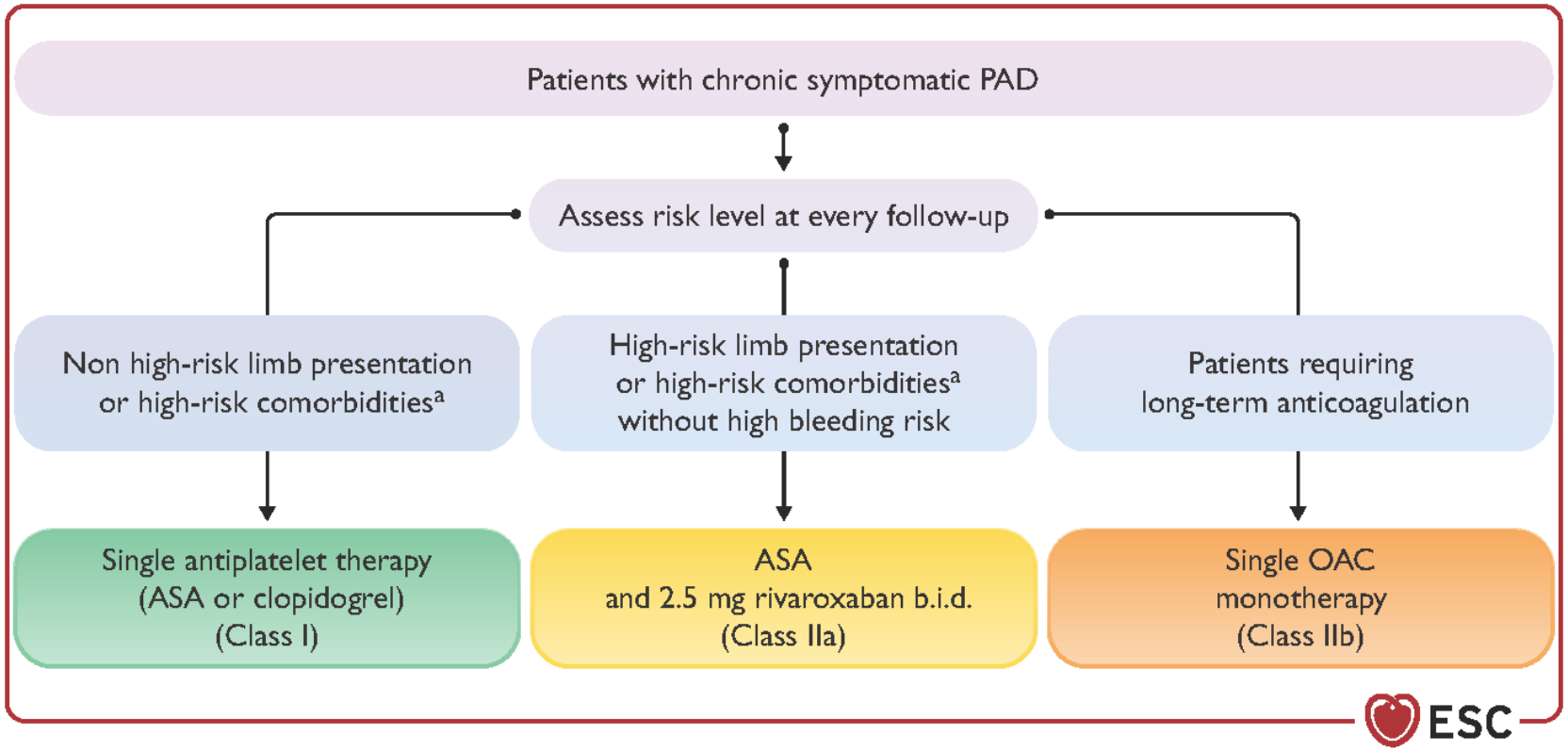
Treatment algorithm in peripheral arterial disease with wounds



2024 ESC Guidelines for the management peripheral arterial and aortic diseases (European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Figure 14

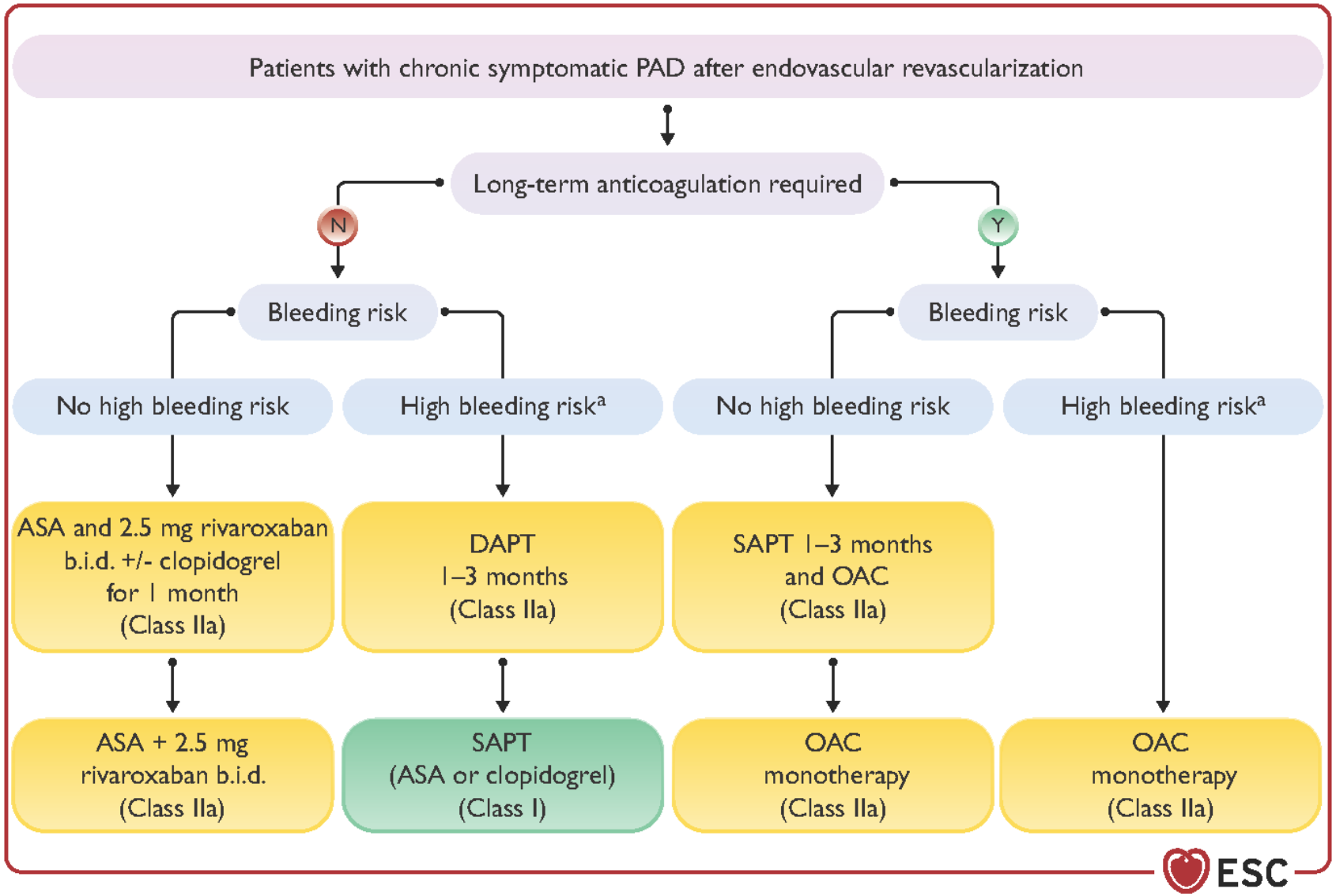
Long-term antithrombotic therapy in patients with symptomatic peripheral arterial disease



2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Figure 15

Patients with chronic symptomatic PAD after endovascular revascularization



2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Recommendations for interventional treatment of asymptomatic and symptomatic PAD (general)

Recommendations	Class	Level
In patients with symptomatic PAD, after a 3-month period of OMT and exercise therapy, PAD-related QoL assessment is recommended.	I	B
It is recommended to adapt the mode and type of revascularization options to anatomical lesion location, lesion morphology, and general patient condition.	I	C
In patients with symptomatic PAD and impaired PAD-related quality of life after a 3-month period of OMT and exercise therapy, revascularization may be considered.	IIb	B
In patients with PAD, revascularization is not recommended if the reason is to solely prevent progression to CLTI.	III	B
In patients with asymptomatic PAD, revascularization is not recommended.	III	C

Recommendations for interventional treatment of patients with symptomatic peripheral arterial disease (per arterial bed)

Recommendations	Class	Level
In femoro-popliteal lesions, drug-eluting treatment should be considered as the first-choice strategy.	IIa	A
In iliac lesions, balloon angioplasty with or without stenting in external iliac arteries, or primary stenting in common iliac arteries, should be considered.	IIa	B
In femoro-popliteal lesions, if revascularization is indicated, endovascular therapy should be considered.	IIa	B
In femoro-popliteal lesions, if revascularization is indicated, an open surgical approach should be considered when an autologous vein (e.g. GSV) is available in patients with low surgical risk.	IIa	C
In patients with severe IC undergoing endovascular femoro-popliteal revascularization, treatment of BTK arteries may be considered in the same intervention.	IIb	C

Recommendations for the management of chronic limb-threatening ischaemia

Recommendations	Class	Level
For limb salvage in patients with CLTI, revascularization is recommended.	I	B
Early recognition of CLTI and referral to the vascular team are recommended for limb salvage.	I	C
In patients with CLTI, imaging of the entire affected limb should be considered.	IIa	C

Recommendations for medical treatment in patients with chronic limb-threatening ischaemia

Recommendations	Class	Level
It is recommended that patients with CLTI are managed by a vascular team.	I	C
In patients with CLTI and ulcers, offloading mechanical tissue stress is recommended to allow wound healing.	I	C
It is recommended to treat infection with antibiotics.	I	C
Lower-limb exercise training is not recommended in patients with CLTI and wounds.	III	C

Recommendations for interventional treatment of chronic limb-threatening ischaemia

Recommendations	Class	Level
In CLTI patients, it is recommended to perform revascularization as soon as possible.	I	B
In CLTI, it is recommended to use autologous veins as the preferred conduit for infra-inguinal bypass surgery.	I	B
In multilevel vascular disease, it is recommended to eliminate inflow obstructions when treating downstream lesions.	I	C
An individual risk assessment (weighing the patient's individual procedural risk of endovascular vs. surgical revascularization) by a multidisciplinary vascular team is recommended.	I	C
In CLTI patients with good autologous veins and low surgical risk (<5% peri-operative mortality, >50% 2-year survival), infra-inguinal bypass may be considered.	IIb	B
In CLTI patients, endovascular treatment may be considered as first-line therapy, especially in patients with increased surgical risk or inadequate autologous veins.	IIb	B

2024 ESC Guidelines for the management peripheral arterial and aortic diseases
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae179)

Recommendation	Class of recommendation	Level of evidence
Prostanoids may be considered to provide a modest benefit in CLI patients.	IIb	B
Prostanoids may be considered as a medical treatment for patients with CLI who are not eligible for revascularization or where revascularization has failed.	IIb	B
This treatment is not recommended as an alternative to revascularization.	III	B

PROSTANOIDS

HBOT

Recommendation	Class of recommendation	Level of evidence
Currently, there is no clear evidence regarding the effectiveness of hyperbaric oxygen therapy as an adjunctive therapy for the treatment of wounds linked with severe lowering of distal perfusion of the lower limbs. Thus, it cannot be recommended as a treatment.	III	A

Recommendation	Class of recommendation	Level of evidence
Regenerative treatments outside clinical trials is not recommended in CLI on the basis of current evidence.	III	B

REGENERATIVE

Recommendation	Class of recommendation	Level of evidence
Due to its costs and spectrum of side effects, use of this treatment requires interdisciplinary agreement and may only be recommended once all methods of revascularization have been exhausted.	IIb	B

SCS

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TREATMENT of ULCERS and INFECTIONS

Recommendation	Class of recommendation	Level of evidence
It is recommended that • Any chronic lesion (not healed after 6 weeks) should be swabbed at first presentation of the patient. • Optimally swabs should also be taken from nose and groin to exclude the presence of multi-resistant bacteria. • After transfer from another hospital or care homes, patients should be isolated until the results of the swabs are available. • Patients with similar types of multi-resistant germs can be isolated in the same room. • The hospital's infection control plan should be implemented in all CLI patients. • The WIFI or PEDIS classification systems should be used to classify infection.	I	B/C

Recommendation	Class of recommendation	Level of evidence
Only patients with CLI and systemic infections are recommended to receive systemic antibiotic treatment, although exceptions may occur in patients with diabetes.	I	B

Recommendation	Class of recommendation	Level of evidence
Concomitant bone infection should be ruled out in the presence of soft-tissue infections, as therapeutic regime (duration of antibiotics, partial resection of bone) may change once such infections have been detected.	I	C

VASA 2019

‘What to do’ and ‘What not to do’ messages from the guidelines

Fibrates are not recommended for cholesterol lowering.	III	B
Long-term DAPT in patients with PAD is not recommended.	III	A
Oral anticoagulant monotherapy for PAD (unless for another indication) is not recommended.	III	A
The routine use of ticagrelor in patients with PAD is not recommended.	III	A
It is not recommended to systematically treat patients with asymptomatic PAD without any sign of clinically relevant ASCVD with antiplatelet drugs.	III	B
In patients with PAD, revascularization is not recommended if the reason is to solely prevent progression to CLTI.	III	B
In patients with asymptomatic PAD, revascularization is not recommended.	III	C
Lower-limb exercise training is not recommended in patients with CLTI and wounds.	III	C

GAPS in evidence

- 1) **Epidemiology and risk factors in PAAD**:
  - Improve PAAD risk definition.
  - Provide contemporary data on PAAD prevalence in Europe
  - Inflammation biomarkers, metabolomics, and proteomics have prognostic value in PAAD.
- (2) **Evaluation of peripheral arteries and aorta:**
  - Follow-up algorithms can assist PAAD patient management

  but have limitations and evidence on cost-effectiveness is needed.

GAPS in evidence

- (3) **Screening for carotid, peripheral arterial, and aortic diseases:**
  - Screening in specific populations: research is needed to understand the nuances of screening in particular populations and whether modifications to current guidelines are necessary.

  - Patient outcomes and benefits of screening: impact of screening on patient outcome should be assessed.

GAPS in evidence

(4)OMT and PAAD:

- (a) Research needed on QoL and workability
- (b) Research needed for optimal preventive strategies
- (c) Exercise therapy and rehabilitation for PAAD should be more accessible and employed
- (d) Anti-inflammatory therapy should be investigated
- (e) Antithrombotic therapies in specific risk groups of PAAD and patients undergoing revascularization should be addressed.

PAD

FOLLOW UP

Consensus document

European Journal of Preventive Cardiology

ESC European Society of Cardiology

European Journal of Preventive Cardiology
2019, Vol. 26(18) 1971–1984

DOI: 10.1177/2047487319846999
journals.sagepub.com/home/cpr

SAGE

Follow-up of patients after revascularisation for peripheral arterial diseases: a consensus document from the European Society of Cardiology Working Group on Aorta and Peripheral Vascular Diseases and the European Society for Vascular Surgery

Maarit Venermo[1,*], Muriel Sprynger[2,*], Ileana Desormais[3], Martin Björck[4], Marianne Brodmann[5], Tina Cohnert[6], Marco De Carlo[7], Christine Espinola-Klein[8], Serge Kownator[9], Lucia Mazzolai[10], Ross Naylor[11], Charalambos Vlachopoulos[12], Jean-Baptiste Ricco[13] and Victor Aboyans[14]

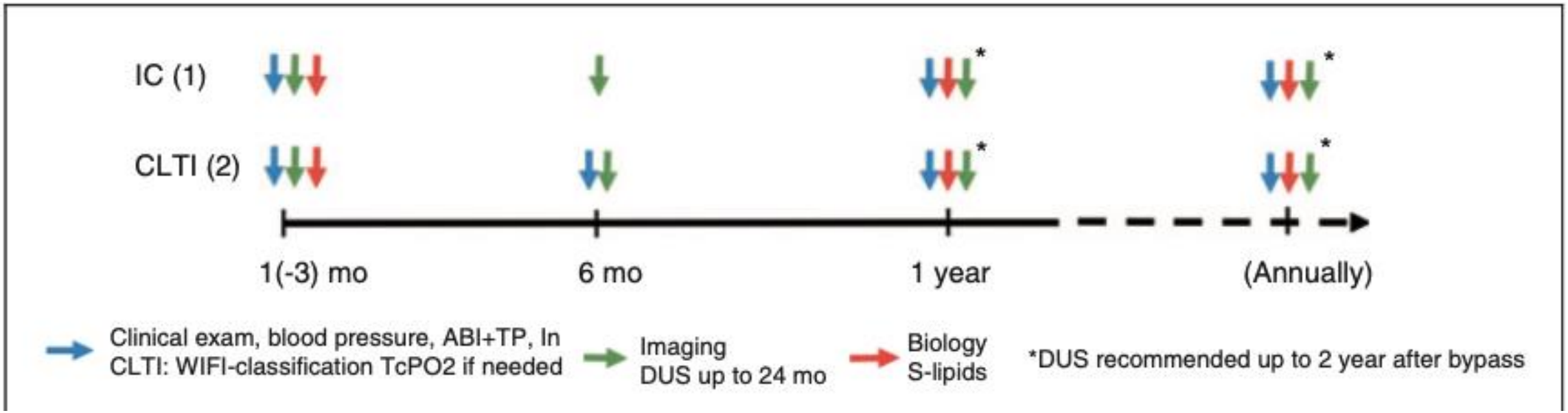
Cardiovascular prevention
- Tobacco smoking status
  - If smoking history: is cessation achieved?
    If yes: be supportive
    If not: propose specific intervention and follow-up, refer to
  smoking cessation programmes if available
- Hypertension
  - Check brachial blood pressure bilaterally, at least annually: blood pressure should be <140/90 mmHg with the target of 130/80 mmHg if tolerated
  - If treated hypertension:
    Check diet and drug adherence
    Check for other target organ damage (e.g. renal disease)
  - If high blood pressure during a visit:
    Reassess (ambulatory)
    Refer to hypertension specialists
- Diabetes
  - Check fasting glucose at least annually
  - If diabetes: check glycated haemoglobin (optimally HbA1c < 7%)
  - Check treatment and diet adherence
  - If newly detected or poorly controlled diabetes: refer to diabetes specialist
- Cholesterol
  - Check lipid levels at least annually: low-density lipoprotein cholesterol should be <1.8 mmol/l (70 mg/dL) or decreased at least by 50% compared to the baseline levels
  - Assess statin tolerance and compliance
  - In the case of significant statin intolerance and/or failure to reach target levels, refer to lipid specialist (consider ezetemibe and PCSK9 inhibitors)
- Other
  - Check for adherence to antithrombotic drugs
  - Check renal function (urea, creatinine, electrolytes, estimated glomerular filtration rate)
  - Record body mass index, advise optimal body weight
  - Re-enforce the importance of regular physical exercise

Symptoms and physical signs related to the revascularisation site (and contralateral if applicable)

Other cardiovascular conditions
- Assess for cardiovascular symptoms
- Full clinical cardiovascular examination (including 12-lead ECG)
- Screening for AAA

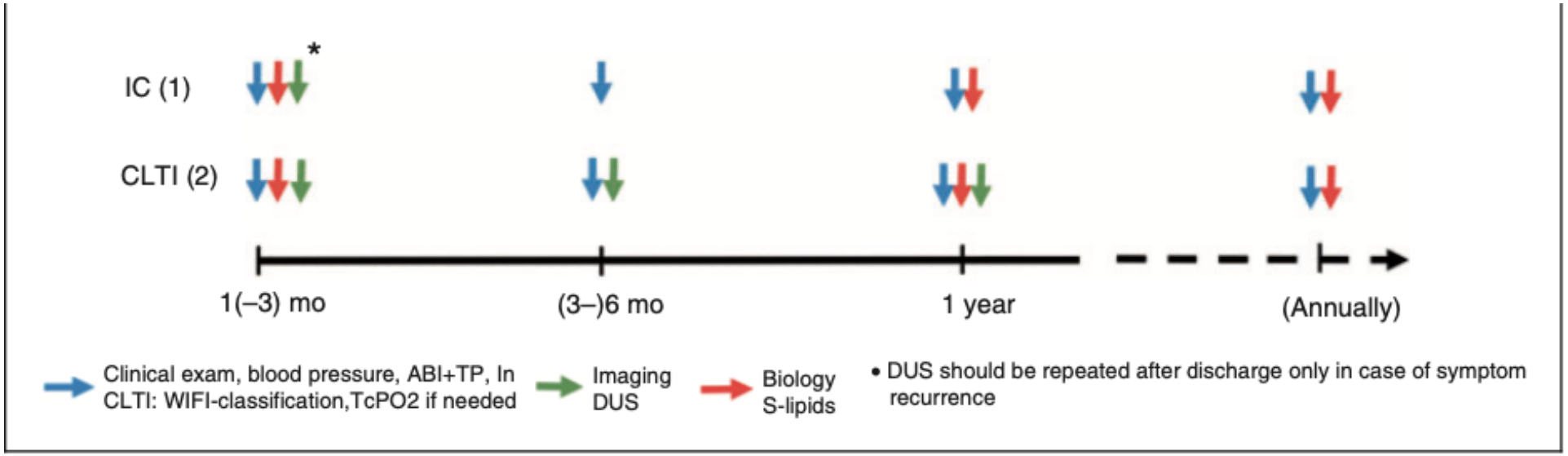
Raccomandazione di sorveglianza dopo bypass venoso per la PAD .

-La sorveglianza comprende **l'esame clinico, la misurazione dell'indice brachiale della caviglia (ABI) (o della pressione del piede/indice brachiale del piede (TBI)) e l'ecografia duplex (DUS).** Sebbene manchino prove scientifiche solide, c'è consenso sul fatto che il primo test dopo la dimissione dovrebbe essere eseguito entro 4-6 settimane, quindi a 3 mesi, 6 mesi, 12 e 24 mesi dopo l'intervento di bypass.
-Se viene eseguito un nuovo intervento per stenosi o occlusione dell'innesto, il programma di sorveglianza viene reiniziato dall'inizio.
-La sorveglianza clinica dura tutta la vita ed è di fondamentale importanza soprattutto per i pazienti con ischemia cronica minacciosa per gli arti (CLTI)
-In caso di sospetto di restenosi, si raccomanda un' angiografia.

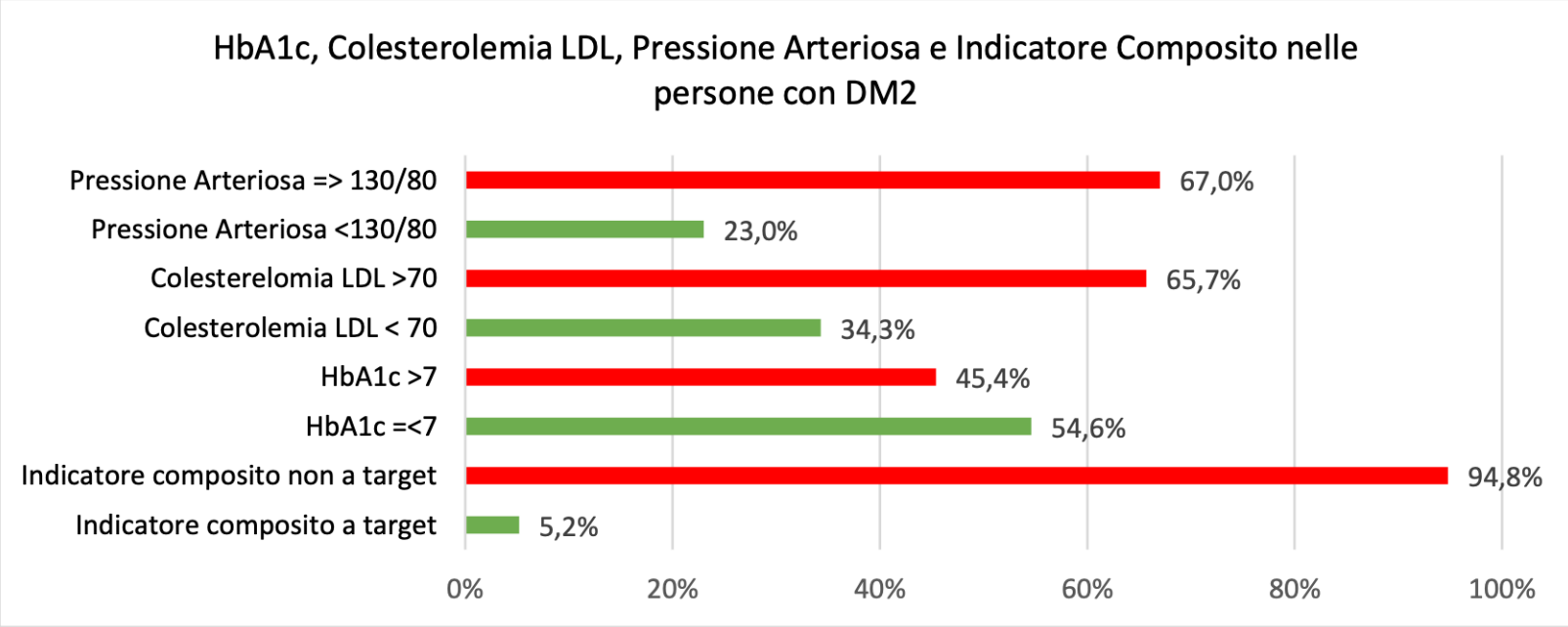


Raccomandazione di sorveglianza dopo il trattamento endovascolare (EVT) per la PAD.

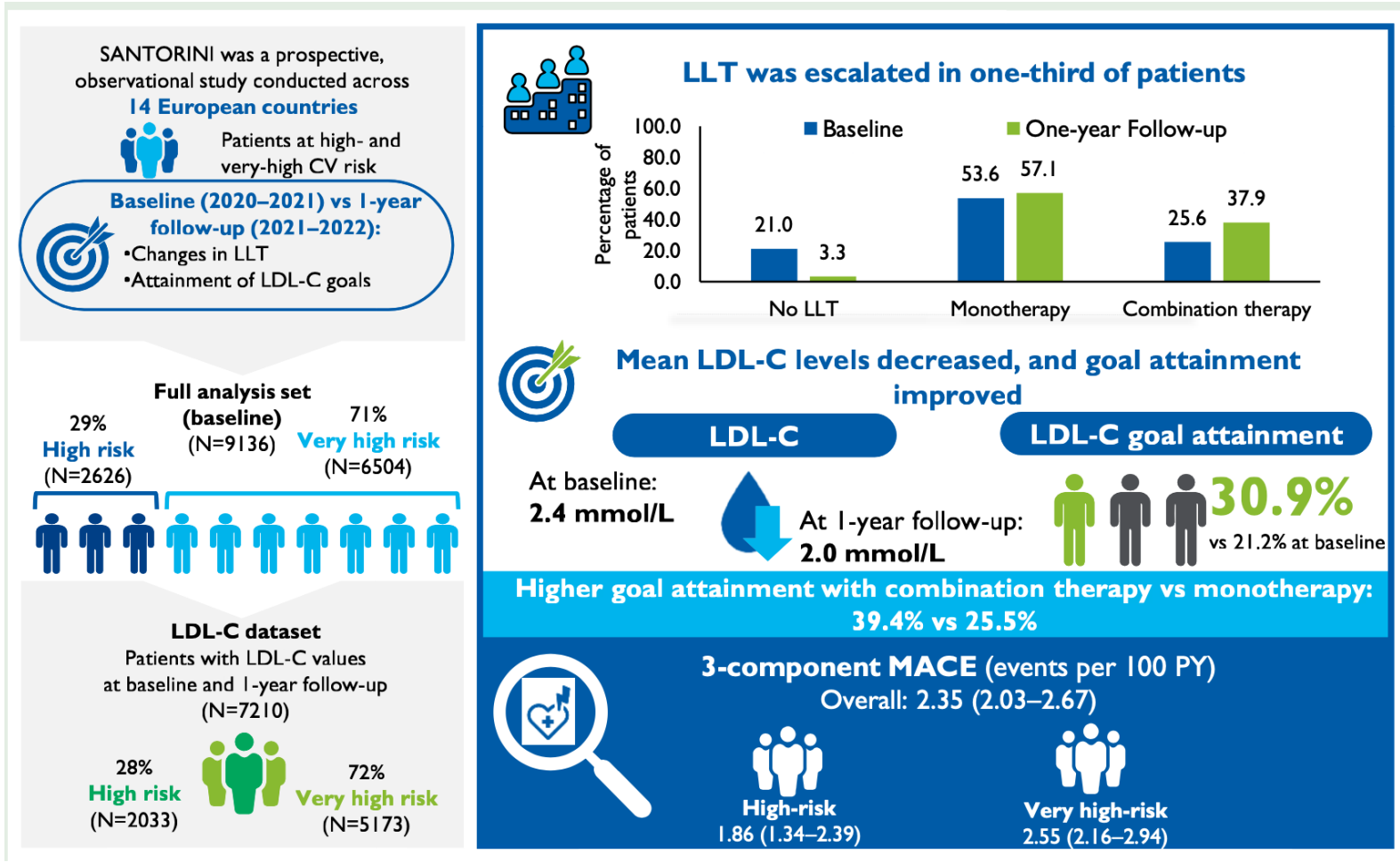
-La sorveglianza comprende **la valutazione clinica alla ricerca di sintomi o segni ricorrenti, la misurazione dell'indice brachiale della caviglia (ABI) e l'ecografia duplex (DUS). In caso di ischemia cronica minacciosa per gli arti (CLTI) possono essere necessari ulteriori esami, come la pressione all'alluce e/o la tensione transcutanea di ossigeno (TcPO2).**
-Si raccomanda la sorveglianza della DUS dopo la EVT mediante un esame iniziale eseguito tra la dimissione e un mese; se i risultati sono normali, gli esami successivi devono essere eseguiti a 6 e 12 mesi; mentre se la DUS iniziale è anormale, il reintervento o il follow-up DUS più ravvicinato devono essere decisi caso per caso.
-**L'utilità di una DUS annuale oltre i 12 mesi nei pazienti rivascolarizzati che rimangono asintomatici non è mai stata dimostrata e non può essere raccomandata come sorveglianza di routine**; tuttavia, questi pazienti richiedono una sorveglianza cardiovascolare completa incentrata sulla gestione dei fattori di rischio, sull'allenamento all'esercizio fisico e sulla terapia medica su base annuale.
-La sorveglianza clinica è permanente e di fondamentale importanza soprattutto per i pazienti con CLTI (
-Se c'è il sospetto di una restenosi che richiede un trattamento, si raccomanda un angiogramma.



Aderenza Terapeutica



Use of combination therapy is associated with improved LDL cholesterol management: 1-year follow-up results from the European observational SANTORINI study



K.K. Ray et al. European Journal of Preventive Cardiology (2024) 00, 1–12

Recommendations in patients with peripheral arterial disease: follow-up of patients with peripheral arterial disease

Recommendations	Class	Level
It is recommended to regularly, at least once a year, follow up patients with PAD, assessing clinical and functional status, medication adherence, limb symptoms, and CVRFs, with DUS assessment as needed.	I	C

Recommendations for follow-up in patients with chronic limb-threatening ischaemia

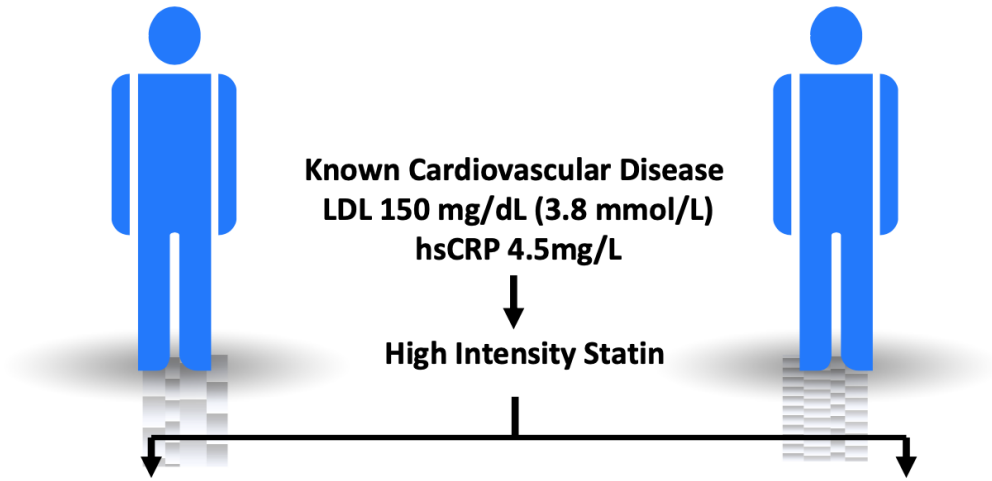
Recommendations	Class	Level
In patients with CLTI, following revascularization it is recommended to follow up patients on a regular basis.	I	C
At follow-up, it is recommended to assess clinical, haemodynamic and functional status, limb symptoms, treatment adherence, and CVRFs.	I	C

PAD

RISCHIO RESIDUO

Residual Inflammatory Risk:
Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Ridker PM. Eur Heart J 2016;37:1720-22



"Residual Cholesterol Risk"

LDL 110 mg/dL (2.8 mmol/L)
hsCRP 1.8 mg/L

Additional
LDL Reduction

IMPROVE-IT : Ezetimibe 6% RRR
FOURIER/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR

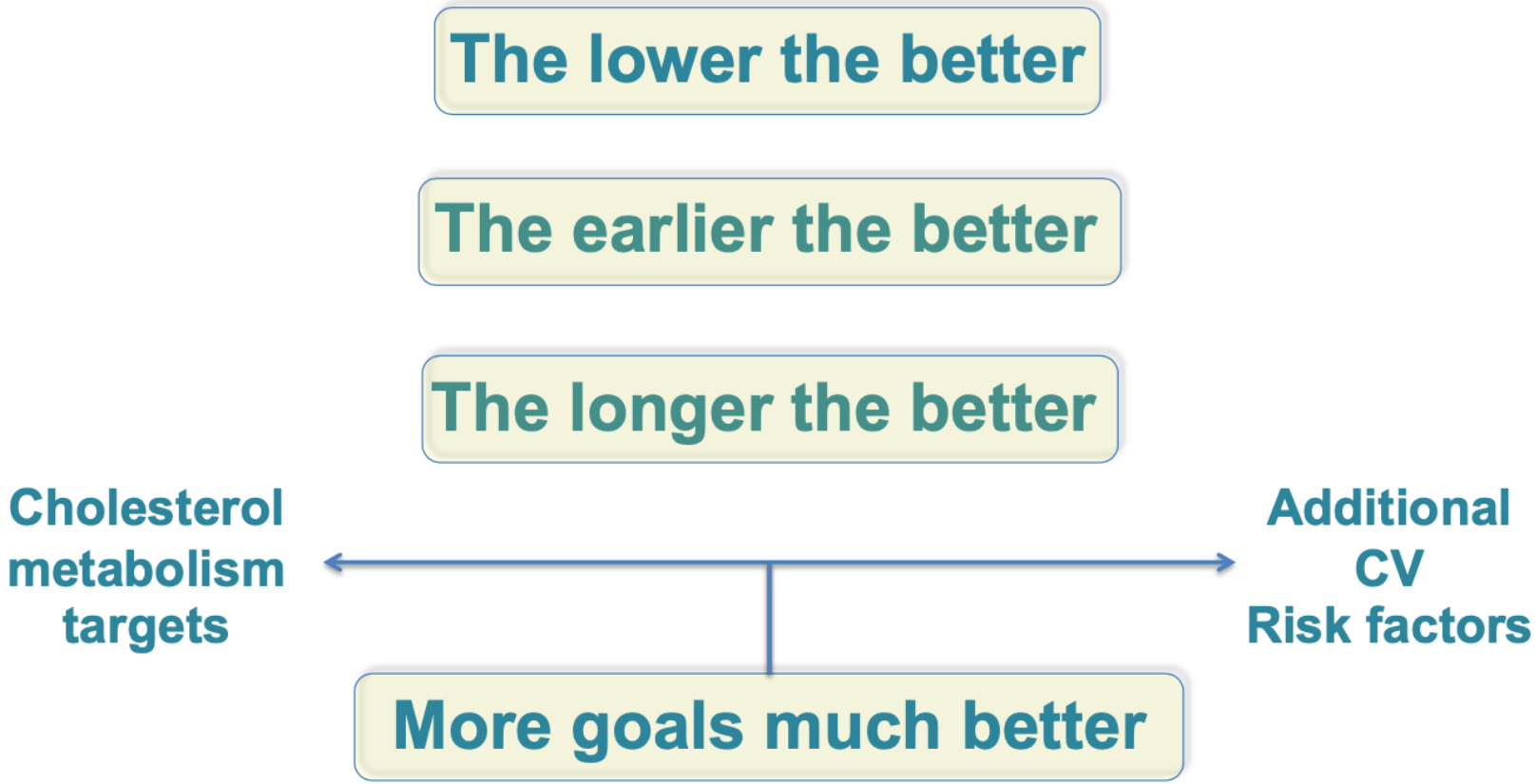
"Residual Inflammatory Risk"

LDL 70 mg/dL (1.8 mmol/L)
hsCRP 3.8 mg/L

Additional
Inflammation Reduction

No Prior Proof of Concept

Il rischio residuo esisterà fintanto che non si concretizzano questi assiomi…



Clinical Impact of Inflammation on Atherosclerosis

- **Plasma levels of inflammatory biomarkers including hsCRP and IL-6 robustly predict first and recurrent cardiovascular events, independent of lipid levels.**
- **Statins are both lipid lowering and anti-inflammatory, and the greatest benefits of statin therapy accrue to those who not only lower LDLC, but who also lower hsCRP.**
- **In primary prevention, the JUPITER trial demonstrated that those with elevated hsCRP but low levels of LDLC markedly benefit from statin therapy.**
- **In secondary prevention, clinicians now distinguish between those with "residual cholesterol risk" and those with "residual inflammatory risk"**

Ridker PM. JACC 2016;67:712-23

REDEFINING RESIDUAL CARDIOVASCULAR RISK

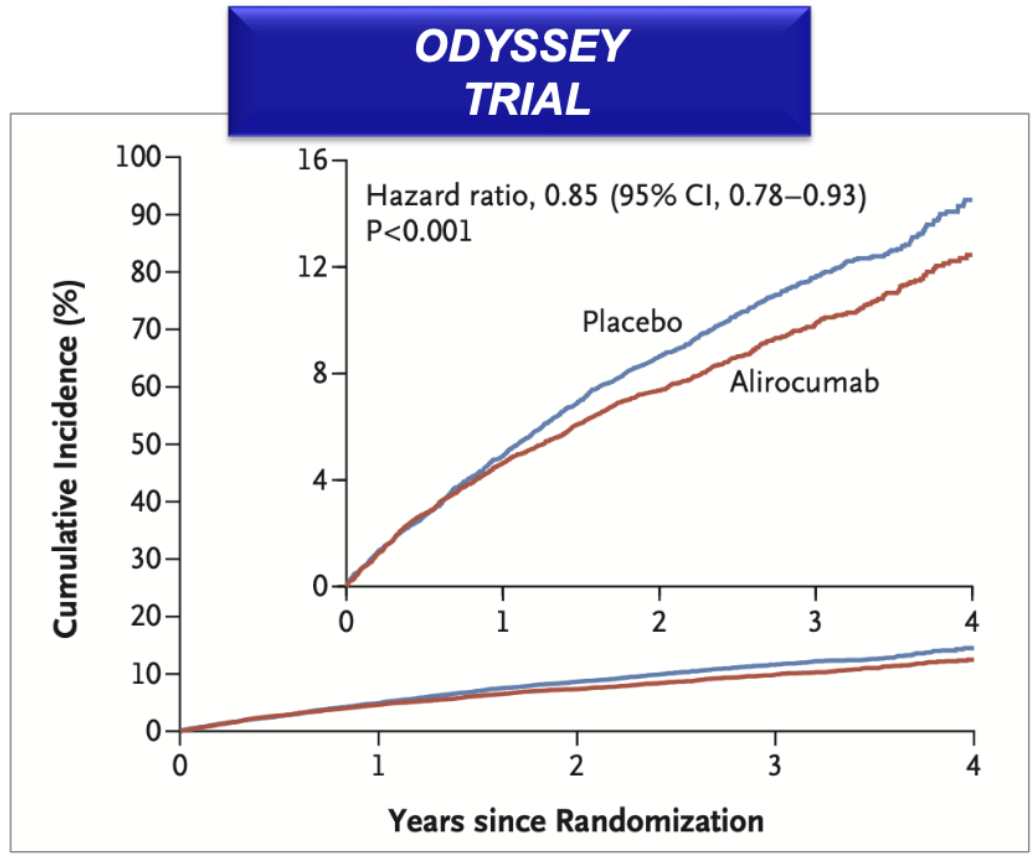
Ridker, P.M. J Am Coll Cardiol. 2018;72(25):3320–31.

Biological Issue	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk
Critical Biomarker	LDL-C >100 mg/dl	hsCRP >2 mg/l	No simple biomarker	TG >200 mg/dl HDL <40 mg/dl	Lp(a) >50 mg/dl
Potential Intervention	Targeted LDL/ Apo B Reduction	Targeted Inflammation Reduction	Targeted Antithrombotic Reduction	Targeted Triglyceride Reduction	Targeted Lp(a) Reduction
Randomized Trial Evidence	IMPROVE-IT FOURIER, SPIRE ODYSSEY	CANTOS *LoDoCo2*	COMPASS DAPT	REDUCE-IT STRENGTH PROMINENT	

RESIDUAL CHOLESTEROL RISK

18,924 patients who had an ACS 1 to 12 months earlier were randomly assigned to receive alirocumab subcutaneously at a dose of 75 mg (9462 patients) or matching placebo (9462 patients) every 2 weeks.

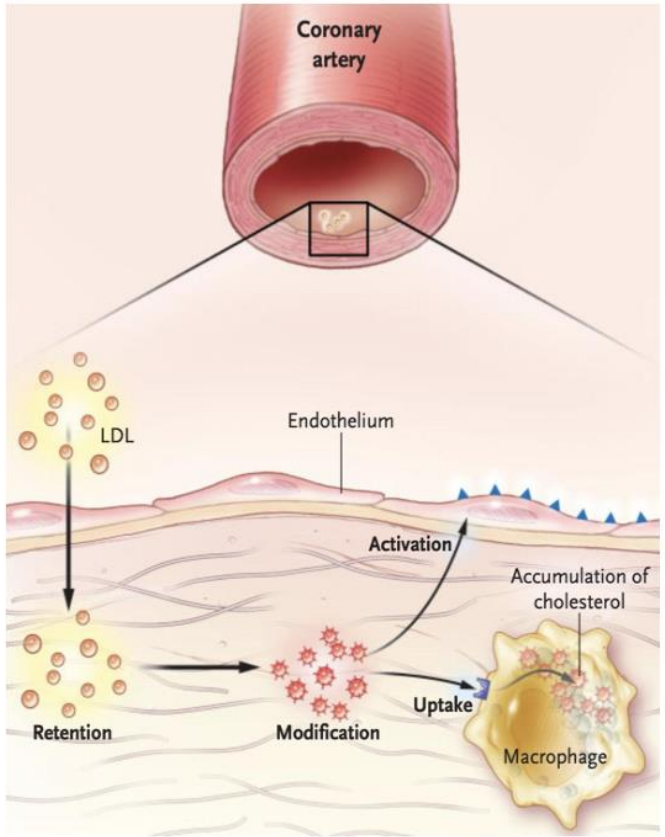
PRIMARY ENDPOINT: composite of death from coronary heart disease, nonfatal MI, ischemic stroke, or unstable angina

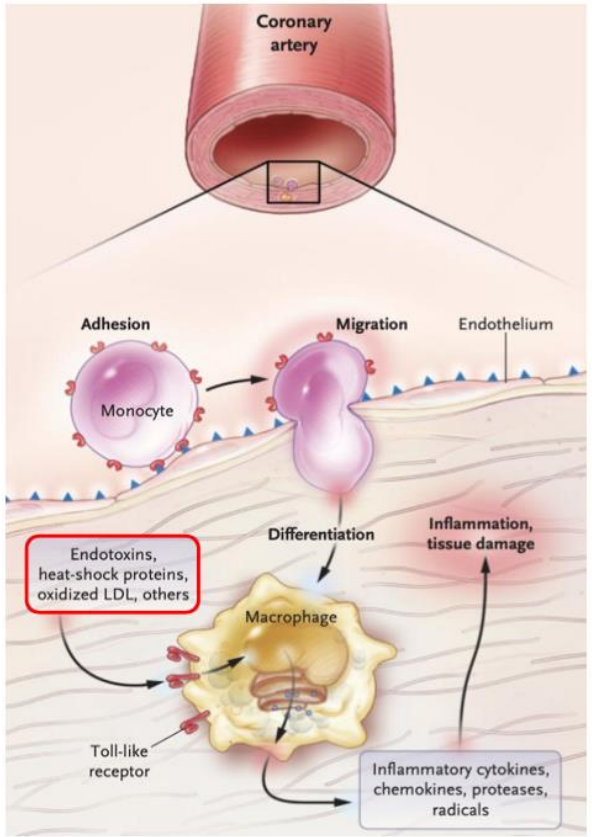


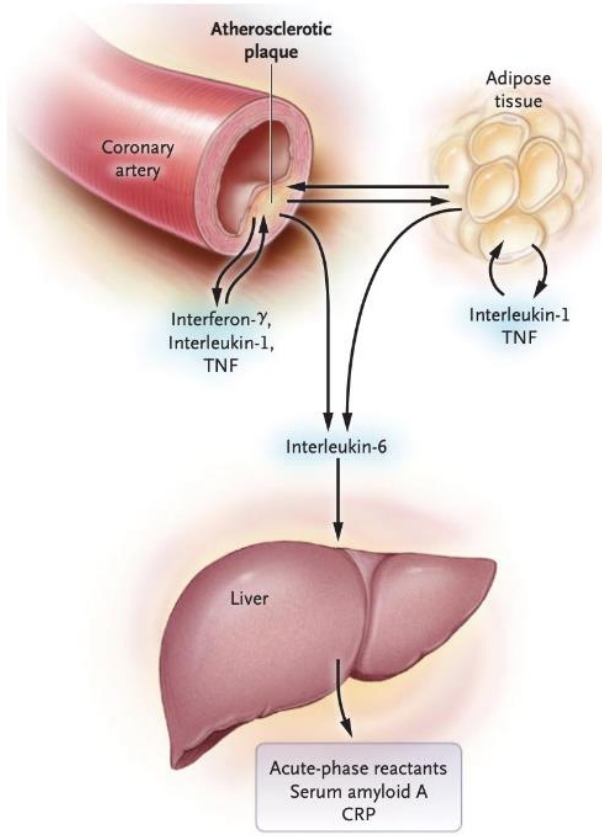
N Engl J Med 2018;379:2097-107.

INFLAMMATION AND cLDL
TWO SIDES OF THE SAME COIN

N Engl J Med 2005;352:1685-95.





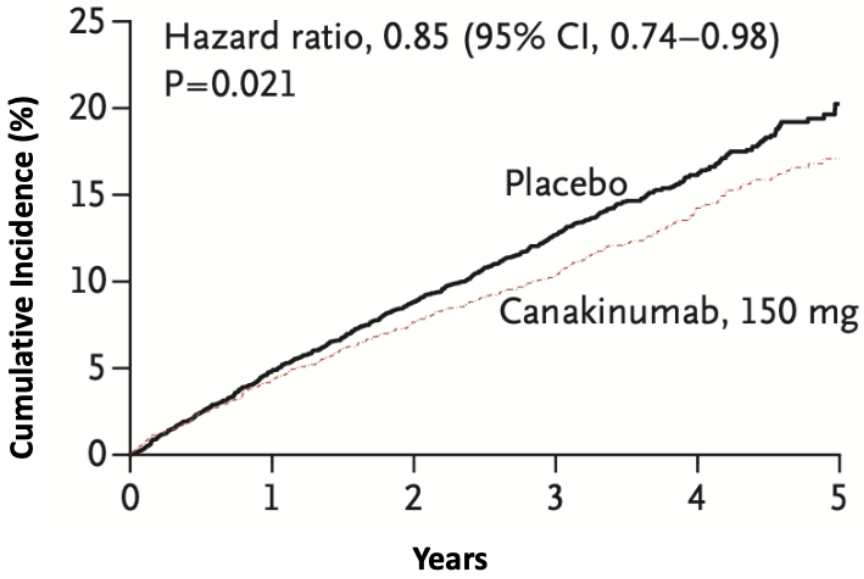


Residual Inflammatory Risk

CANTOS TRIAL
Canakinubab in Patients with Chronic Coronary Disease

10,061 patients with previous MI and a high-sensitivity C-PCR ≥ 2 mg/L were randomized to receive three doses of CANAKINUMAB (50 mg, 150 mg, and 300 mg, administered every 3 months) or placebo.

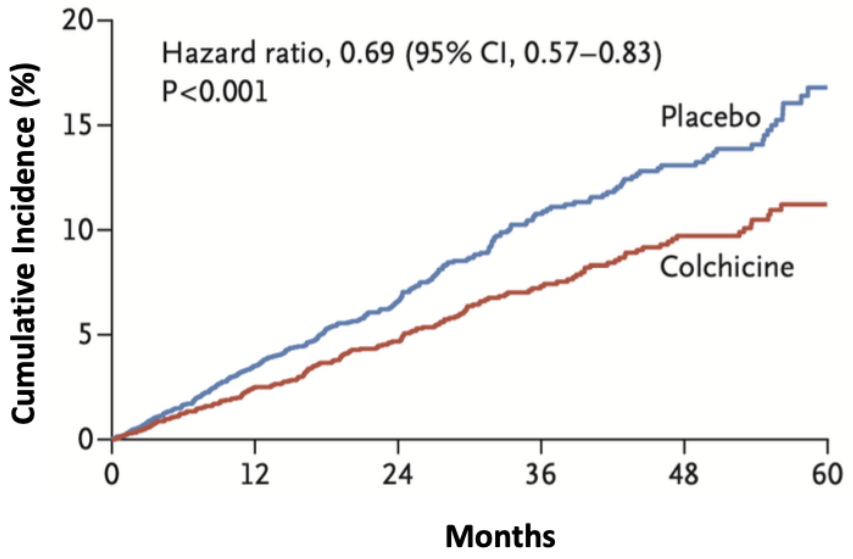
PRIMARY ENDPOINT: nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.



LoDoCo2 TRIAL
Colchicine in Patients with Chronic Coronary Disease

5522 patients with CCS were randomized to receive 0.5 mg of colchicine (2762) OD or placebo (2760).

PRIMARY ENDPOINT: composite of cardiovascular death, spontaneous MI, ischemic stroke, or coronary revascularization



Recommendation for anti-inflammatory therapy

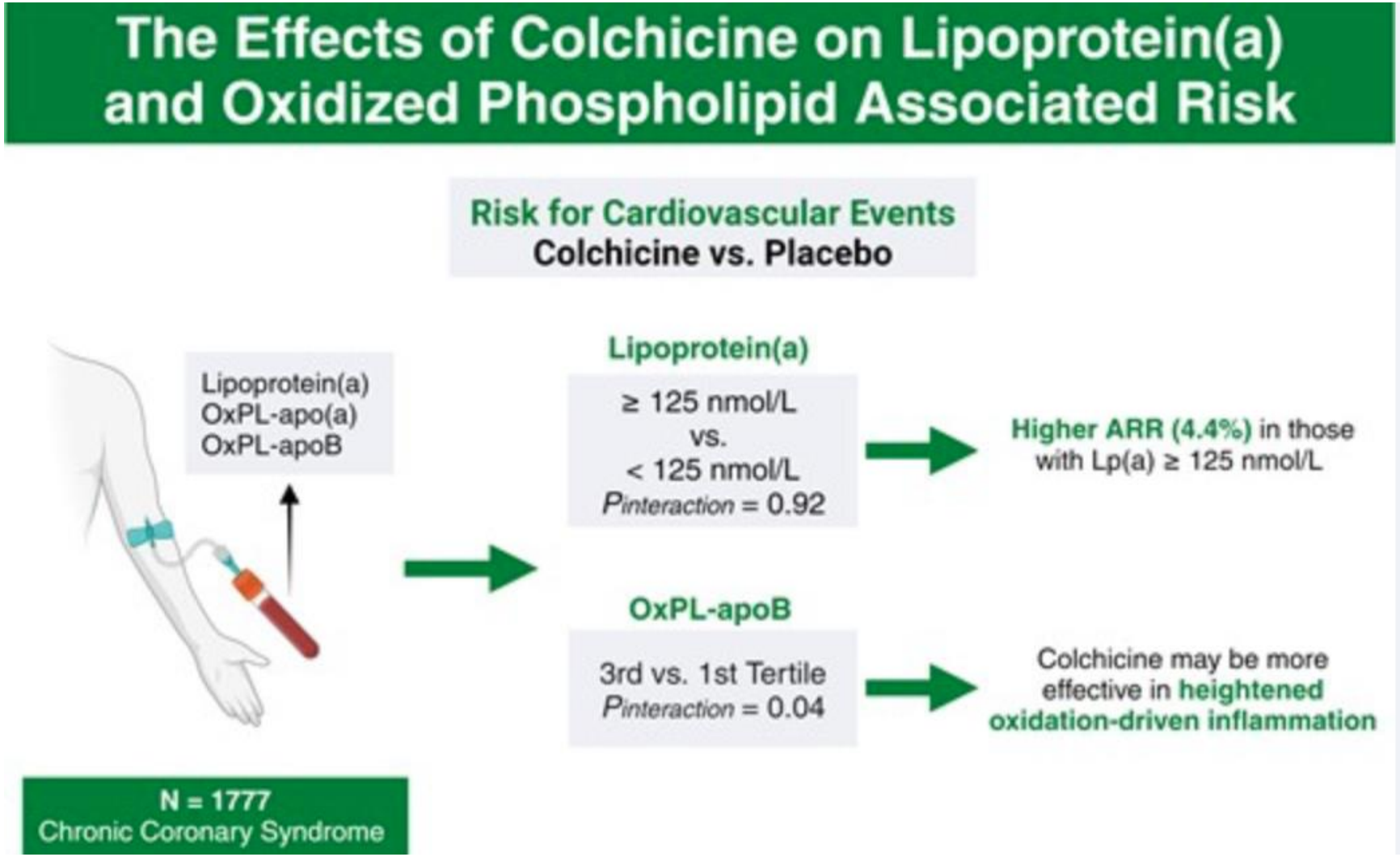
Recommendation	Class[a]	Level[b]
Low-dose colchicine (0.5 mg *o.d.*) may be considered in secondary prevention of CVD, particularly if other risk factors are insufficiently controlled or if recurrent CVD events occur under optimal therapy.[85,86]	IIb	A

CVD = cardiovascular; *o.d.* = *omni die* (once a day).

[a]Class of recommendation.

[b]Level of evidence.

Graphical Abstract



Eur. J. Prev. Cardiol., zwae355, https://doi.org/10.1093/eurjpc/zwae355

Original Research Article

VASCULAR MEDICINE

Vascular Medicine
2024, Vol. 29(6) 687–699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Sage

Neutrophil-to-lymphocyte ratio as a prognostic biomarker in patients with peripheral artery disease: A systematic review and meta-analysis

Roy B Kurniawan[1*], Paulus P Siahaan[1*], Pandit BT Saputra[2,3*], Jannatin N Arnindita[2,3], Cornelia G Savitri[2,3], Novia N Faizah[4], Luqman H Andira[2], Mario D'Oria[5], J Nugroho Eko Putranto[2,3] and Firas F Alkaff[6,7]

PREMESSA

Questa revisione sistematica e meta-analisi si proponeva di esplorare l'associazione tra NLR ed esiti della PAD, valutando al contempo la sua capacità di predire tali esiti, ovvero mortalità per tutte le cause, MACE e MALE tra i pazienti con PAD

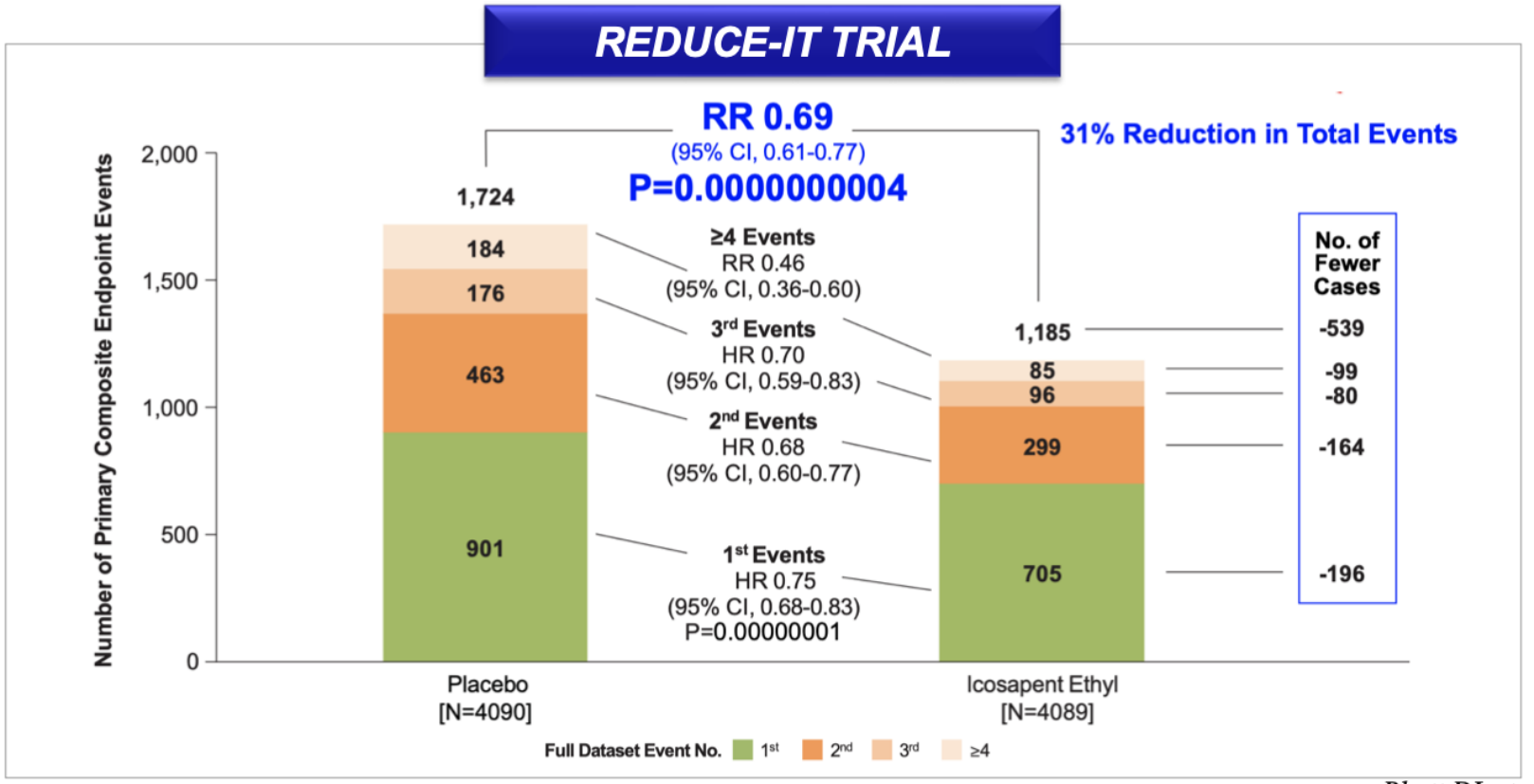
CONCLUSIONI

L'identificazione precoce dei pazienti ad alto rischio con PAD riveste un'importanza fondamentale per migliorare gli esiti attraverso una gestione aggressiva e tempestiva. Questa meta-analisi ha rivelato che la NLR è in grado di fornire previsioni decenti sull'insorgenza di ACM e MALE tra i pazienti con PAD, in particolare per gli esiti a breve termine. Pertanto, l'NLR emerge come un biomarcatore prognostico economico, fattibile e ampiamente applicabile per identificare i pazienti ad alto rischio con PAD.

RESIDUAL RESIDUAL TRIGLYCERIDE RISK

*8179 patients with cardiovascular disease or with diabetes and other risk factors with fasting triglyceride level of 135 to 499 mg/dl were randomly assigned to receive 2 g of **icosapent ethyl** twice daily **(total daily dose, 4 g)** or placebo*

PRIMARY ENDPOINT: composite of cardiovascular death,non fatal MI, stroke, coronary revascularization, or unstable angina.



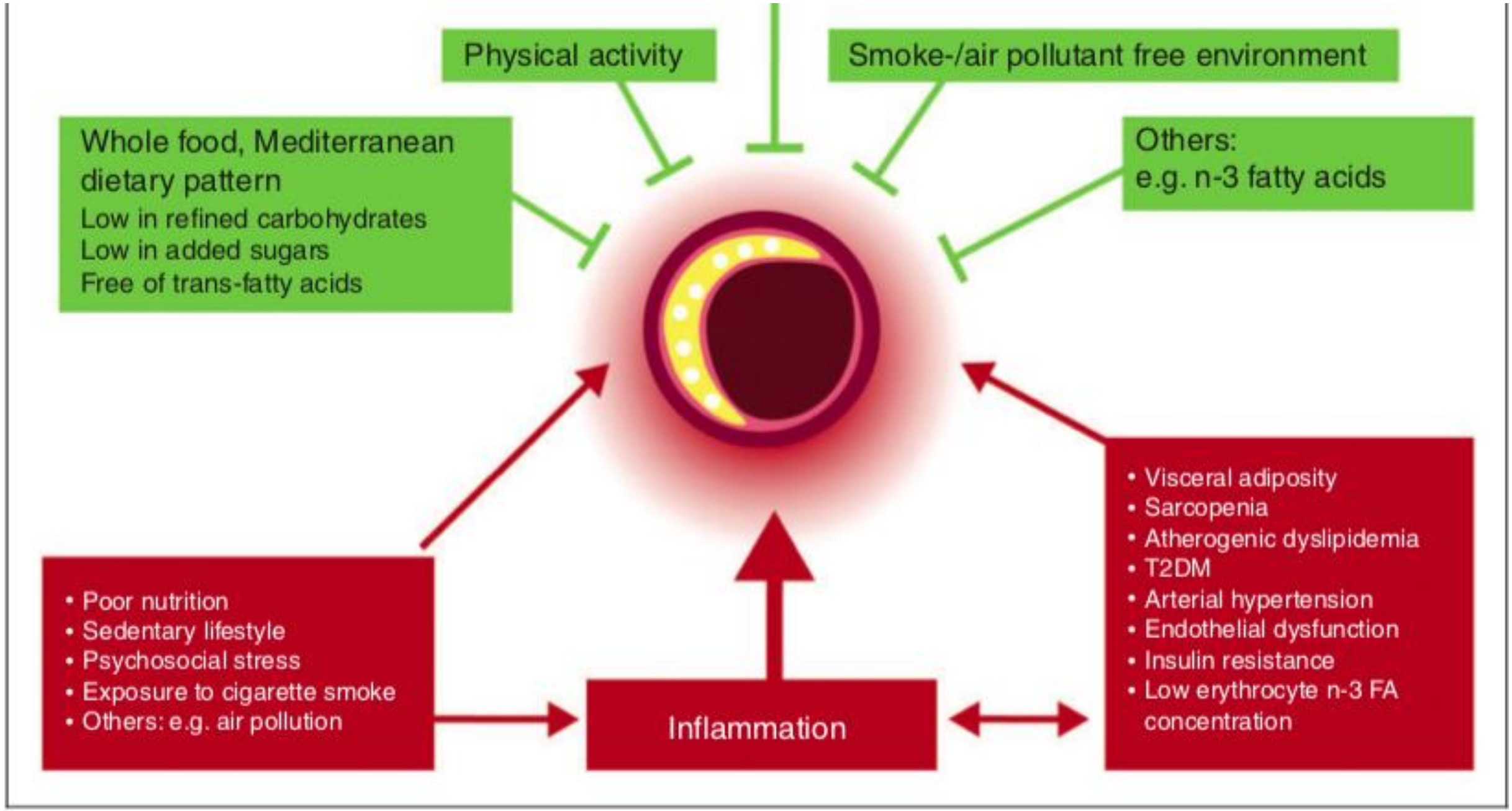
Bhatt DL et al, NEJM 2019

In high-risk patients with PAAD and triglycerides >1.5 mmol/L despite lifestyle measures and statin therapy, icosapent ethyl 2 g b.i.d. may be considered in addition to a statin.[368]	IIb	B

PAAD Guidelines, ESC ESVM 2024

PAD

riduzione del rischio e «guarigione» della placca aterosclerotica


Physical activity
Smoke-/air pollutant free environment
Whole food, Mediterranean dietary pattern
Low in refined carbohydrates
Low in added sugars
Free of trans-fatty acids
Others:
e.g. n-3 fatty acids
• Poor nutrition
• Sedentary lifestyle
• Psychosocial stress
• Exposure to cigarette smoke
• Others: e.g. air pollution
Inflammation
• Visceral adiposity
• Sarcopenia
• Atherogenic dyslipidemia
• T2DM
• Arterial hypertension
• Endothelial dysfunction
• Insulin resistance
• Low erythrocyte n-3 FA concentration

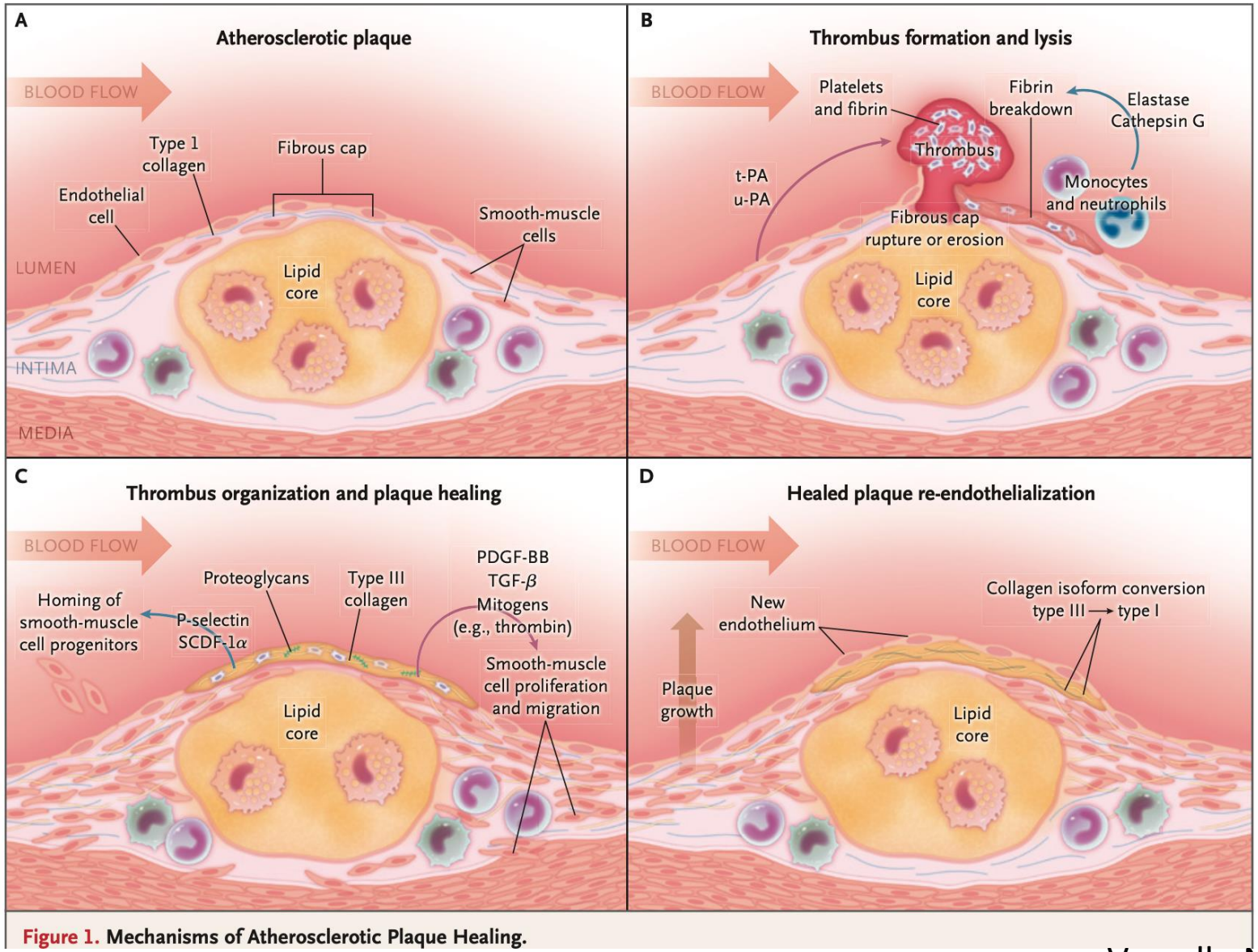
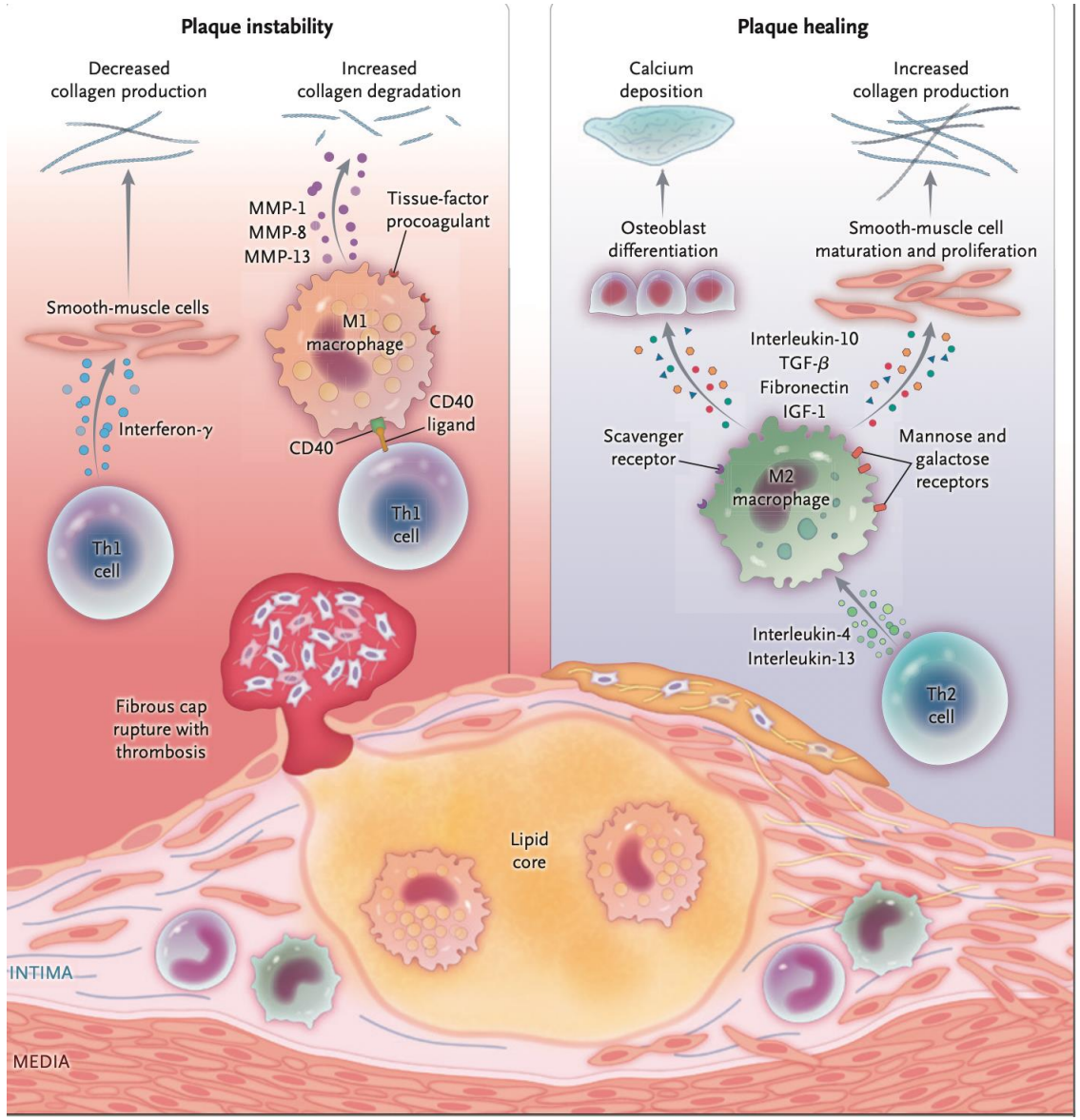


Figure 1. Mechanisms of Atherosclerotic Plaque Healing.

Vergallo NEJM 2020



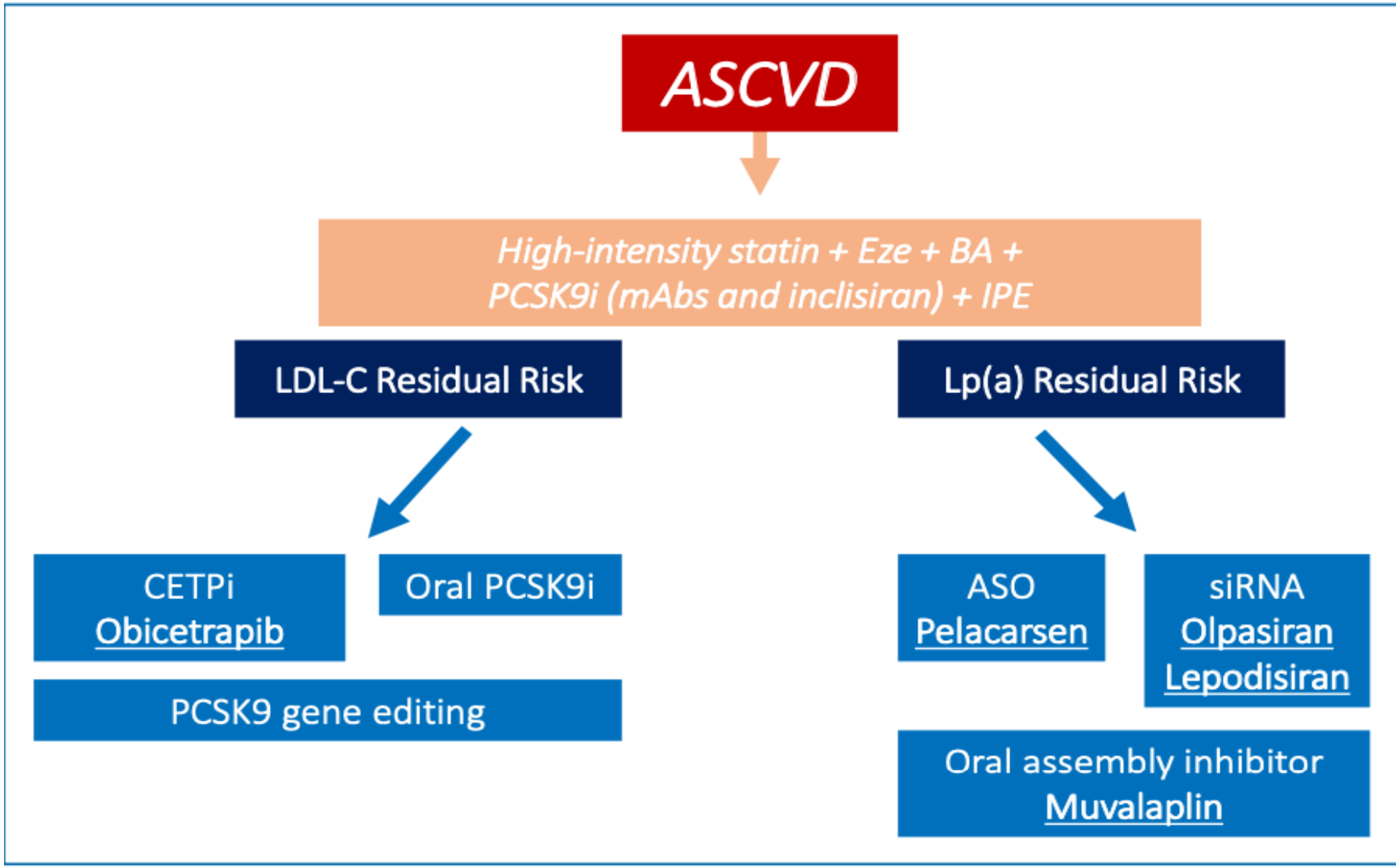
Vergallo, NEJM 2020

Table 1. Therapeutic Interventions That Might Enhance Atherosclerotic Plaque Healing.*

Therapy	Potential Favorable Effects on Plaque Healing
Lipid-lowering diet (e.g., low-cholesterol, low-fat diet)	Reduces expression and proteolytic activity of interstitial collagenase (MMP-1) Increases interstitial collagen content within fibrous cap
methylation, histone modifications, miRNAs, lnc-RNAs)	
PI3Kc–CXCL10 axis inhibitors	Increase re-endothelialization after vascular injury

Una migliore comprensione della fisiopatologia della guarigione delle placche potrebbe consentire l'implementazione di strategie per trasformare una scarsa guarigione in una buona guarigione, riducendo così ulteriormente il carico residuo della malattia cardiovascolare.

Vergallo, NEJM 2020



Averna M, EAJ 2024;2:51-53

PAD
Malattie infettive

Journal of Epidemiology and Global Health (2022) 12:219–223
https://doi.org/10.1007/s44197-022-00049-1

COMMENTARY

The Global Epidemiological Transition in Cardiovascular Diseases: Unrecognised Impact of Endemic Infections on Peripheral Artery Disease

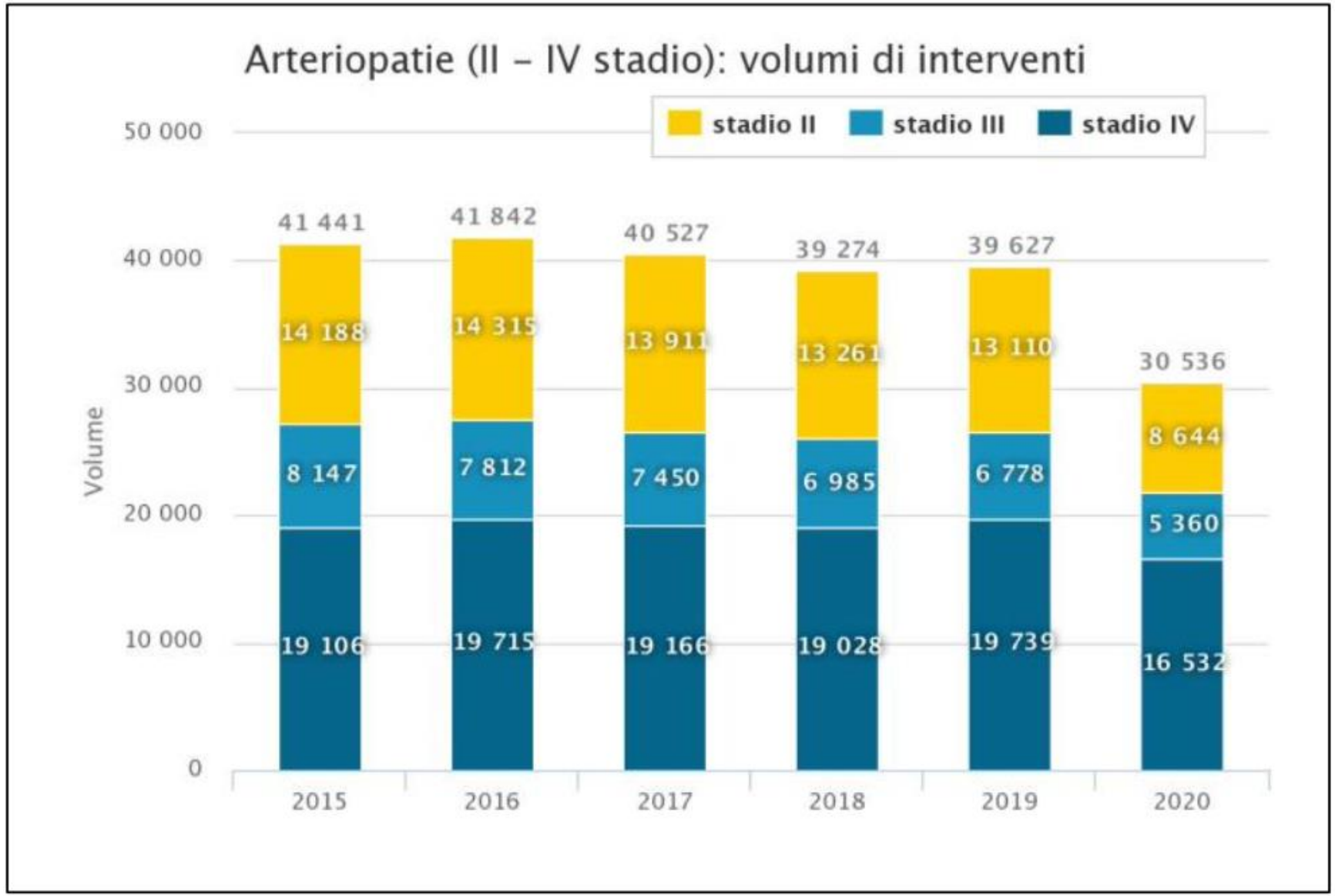
Paul A. Agius[1,2,3] · Julia C. Cutts[1,4] · Peige Song[5,6] · Igor Rudan[5] · Diana Rudan[7] · Victor Aboyans[8] · Mary M. McDermott[9] · Michael H. Criqui[10] · F. Gerald R. Fowkes[5] · Freya J. I. Fowkes[1,2,3]

È in atto una transizione epidemiologica nella prevalenza della malattia arteriosa periferica (PAD), soprattutto nei Paesi a basso e medio reddito (LMIC), dove l'invecchiamento della popolazione e l'adozione di stili di vita occidentali sono associati a un aumento della PAD. Pur limitate, vi sono evidenze che suggeriscono che le infezioni, potenzialmente mediate dall'infiammazione, possano essere un fattore di rischio per la PAD.
Gli Autori mostrano che la prevalenza a livello nazionale delle principali infezioni endemiche di HIV, tubercolosi e malaria è associata alla prevalenza della PAD. Sebbene siano necessarie ulteriori ricerche, propongono che gli scienziati e le autorità sanitarie prestino **maggiore attenzione all'interazione tra malattie trasmissibili e non trasmissibili e suggeriamo che limitare la presenza di infezioni endemiche potrebbe avere un certo effetto sul rallentamento della transizione epidemiologica della PAD.**

Rapporto sul coordinamento della finanza pubblica per il 2021 redatto dalla Corte Dei Conti" e dal **"Piano Nazionale Esiti (PNE) 2021**

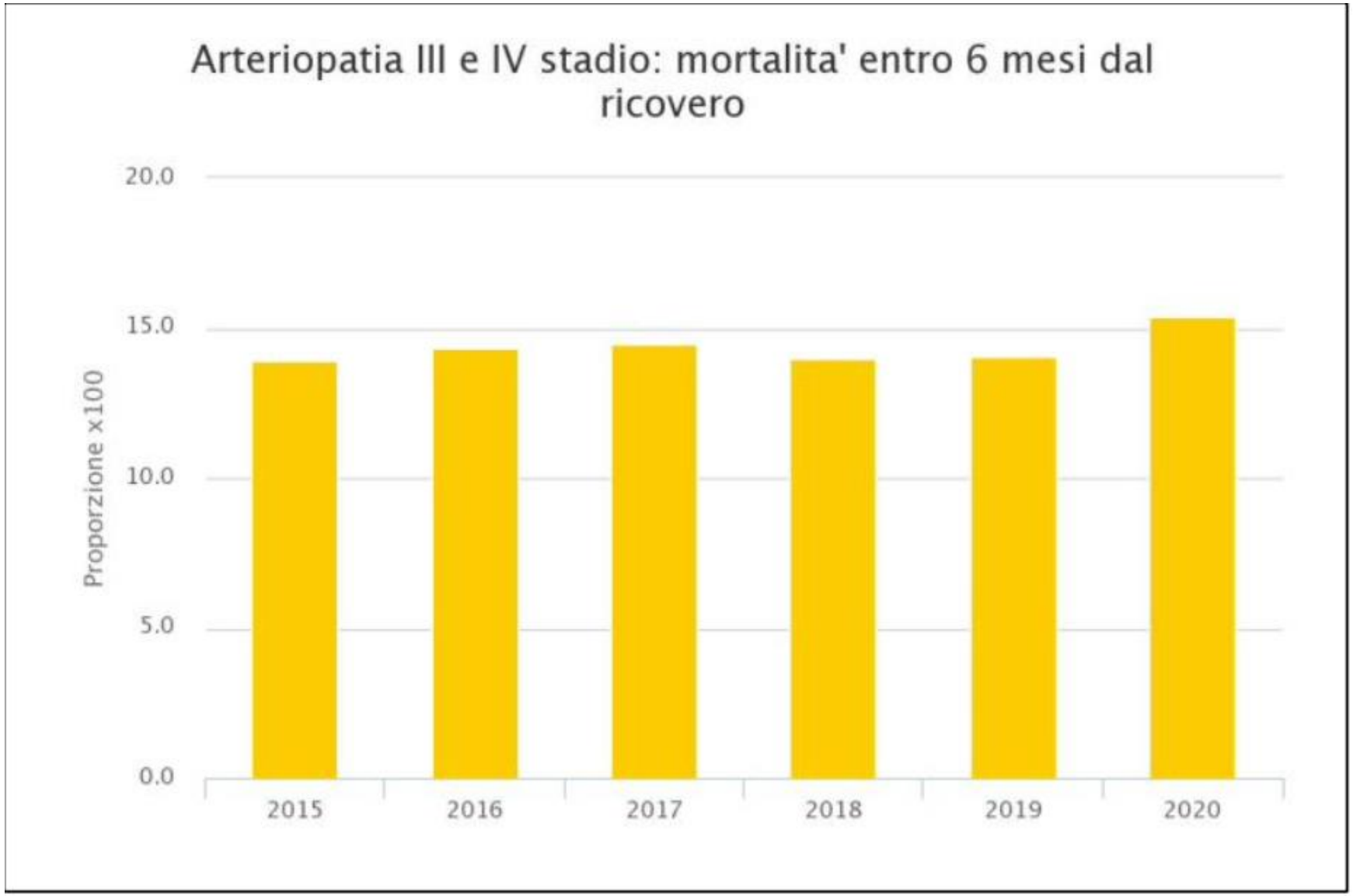
- Il "**Rapporto sul coordinamento della finanza pubblica per il 2021**" evidenzia che nel 2020, in seguito alla riduzione dell'attività ambulatoriale di elezione, in seguito alla Pandemia da Covid-19, vi sono state **144 milioni di prestazioni ambulatoriali in meno** di cui il 14%, circa 20 milioni, sono state quelle di diagnostica
- I dati del **PNE 2021** evidenziano come nonostante una riduzione del volume dei ricoveri per arteriopatia periferica, circa 10.000 in meno rispetto all'anno precedente (fig 1), nei pazienti arteriopatici periferici si sia evidenziato **un aumento delle amputazioni degli arti inferiori** passando dal 4.7% nel 2019 al 5.2% nel 2020 (fig 2) insieme ad un significativo **incremento della mortalità** che è passata dal 14% nel 2019, al 15.5% nel 2020 (fig 3)

PNE 2021Figurea 1



PNE 2021 Figura 2

PNE 2021 Figura 3



GRAZIE per ATTENZIONE Discussione

Quotation of the Week

"The pessimist sees difficulty in every opportunity.
The optimist sees opportunity in every difficulty."

Winston Churchill