

Arteriopatia periferica degli arti inferiori (PAD): caratteristiche e progressione di malattia nel diabetico e nuovi trattamenti

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La sottoscritta dott. ADRIANA VISONA'

dichiara che negli ultimi due anni

ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

- Bayer, Boehringer Ingelheim, Daiichi Sankyo, Neopharmed Gentili, Pfizer, Servier,

Il sottoscritto dichiara altresì che detti rapporti non sono tali da poter influenzare l'attività di docenza espletata nell'ambito di codesto evento pregiudicando la finalità esclusiva di educazione/formazione di professionisti.

La dott. ADRIANA VISONA' non si trova pertanto in una situazione di conflitto di interessi rispetto all'evento ai sensi e per gli effetti dell'Accordo Stato-Regioni del 2/02/2017

PAD e DIABETE

- PAD e DM2 sono due problemi di salute prevalenti che sono associati a un aumento della morbilità e della mortalità
- Questi pazienti continuano ad avere un rischio significativamente maggiore di complicanze CV e di morte, nonostante i grandi progressi nella terapia medica degli ultimi due decenni
- Epidemie del 21[^] secolo anche nei paesi in via di sviluppo

Prevalenza stimata di PAD nel mondo

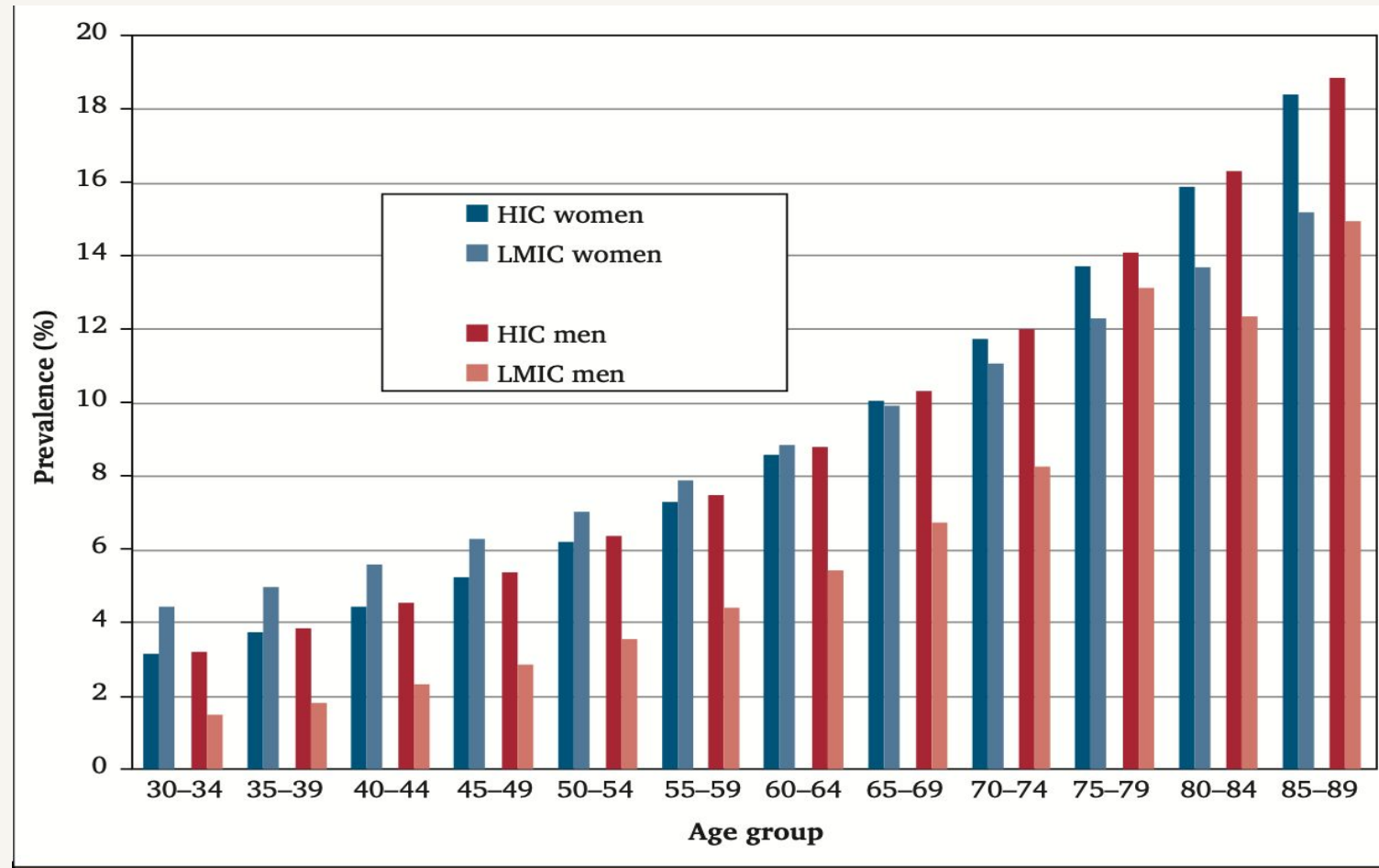
Pazienti con PAD → 202.000.000 nel mondo (2010)
236.000.000 nel mondo (5,56%) (2015)



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

↓
Più di 2/3 dei casi

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)



International Diabetes Federation global diabetes projections



IDF DIABETES ATLAS

2015
Seventh edition

Worldwide 2015 415 million people with diabetes
2040 642 million people with diabetes

North America & Caribbean
2015 44.3million
2040 60.5million

Europe
2015 59.8million
2040 71.1million

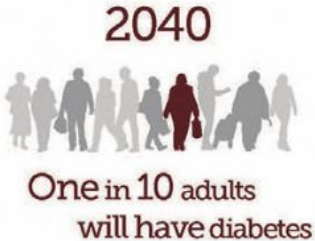
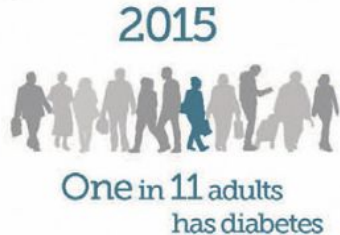
Middle east & North Africa
2015 35.4million
2040 72.1million

Western Pacific
2015 153.2million
2040 214.8million

South East Asia
2015 78.3million
2040 140.2million

South & Central America
2015 29.6million
2040 48.8million

Africa
2015 14.2million
2040 34.2million





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

Le lacune nella conoscenza dei pazienti a rischio di PAD, così come le lacune nella pratica tra i medici che trattano pazienti con PAD, sono state riscontrate nella popolazione canadese e altrove.

Pertanto, gli autori voluto valutare la consapevolezza della PAD tra i laureati in medicina per determinare se queste lacune di conoscenza esistono nei primi anni di formazione medica.

La conoscenza della PAD e della CAD è scarsa tra gli studenti di medicina, con una consapevolezza della PAD inferiore a quella della CAD.

Il tempo molto limitato in classe e le difficoltà nel programmare opportunità cliniche o di ricerca con specialisti vascolari potrebbero essere una ragione importante di questo gap di conoscenza.

EDUCATION CORNER

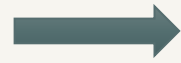
From the Canadian Society for Vascular Surgery

Knowledge gap of peripheral artery disease starts in medical school



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Toronto and London, Ontario, and Winnipeg, Manitoba, Canada; and Riyadh, Saudi Arabia

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

Lower-Limb peripheral arterial disease and amputations in people with diabetes: risk Factors, prognostic value and management.

LOWER-LIMB PERIPHERAL ARTERIAL DISEASE (PAD)



3th manifestation of atherosclerosis associated with cardiovascular (CV) risk factors



major endemic disease alarming increased prevalence



advances in medical, surgical, endovascular techniques,



but still lead to poor prognosis, including amputation



disabilities, reduced functional performances impaired mental health and quality of life



PAD associated : with CV and non CV disease and mortality

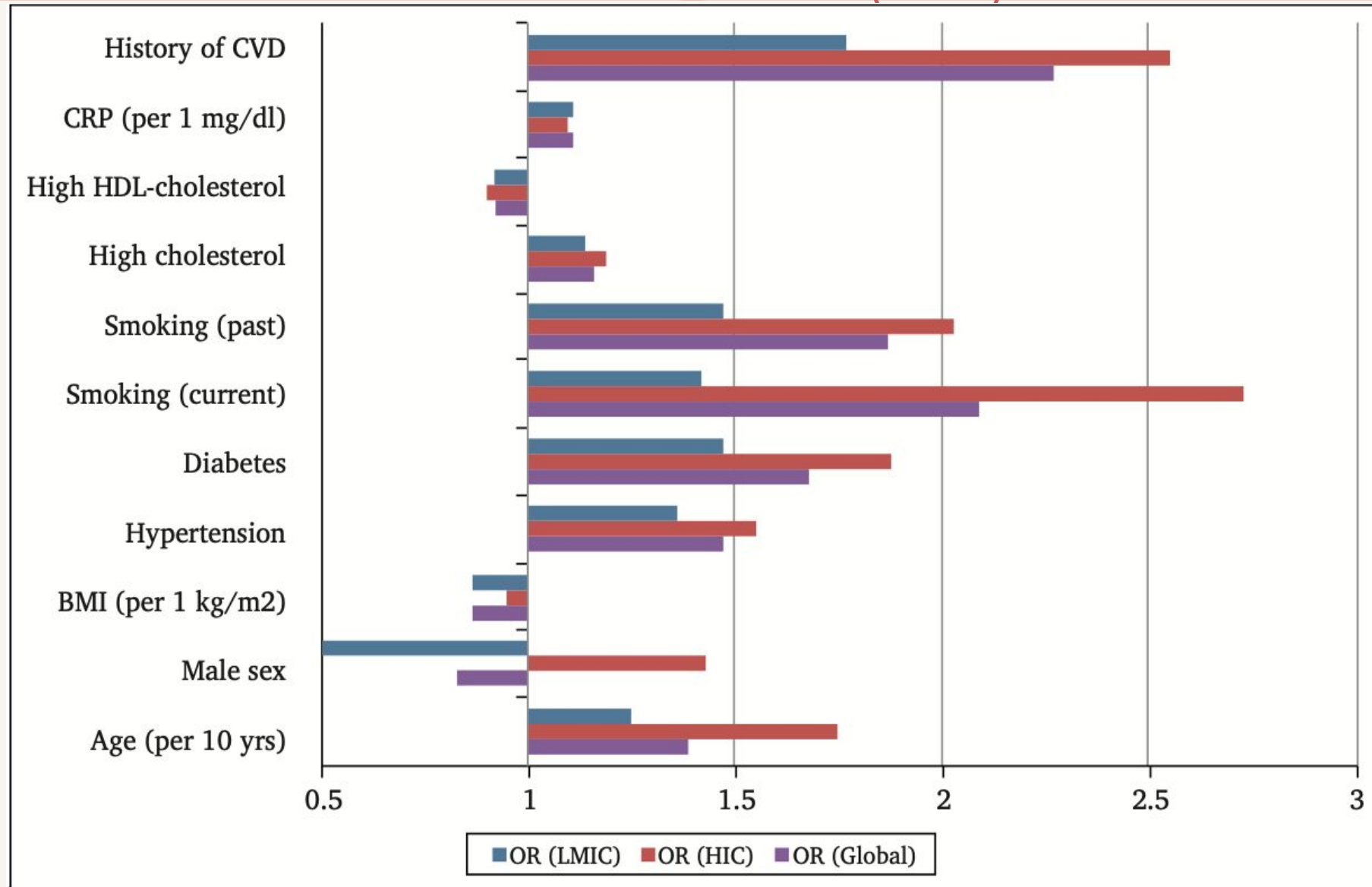


significant cost

PAD e DIABETE: epidemiologia

- Nei pazienti con diabete di tipo 2, la PAD è 2-3 volte più diffusa rispetto alla popolazione generale
- La prevalenza aumenta anche con la durata del diabete, come dimostrato dallo UK Prospective Diabetes Study (UKPDS): 1,2% al momento della diagnosi di diabete e 12,5% dopo 18 anni di progressione del diabete
- Prevalenza può talvolta variare da uno studio all'altro, a causa della variabilità della definizione di PAD e delle differenze nelle caratteristiche della popolazione, tra cui l'età e l'etnia
- La PAD degli arti inferiori è una delle principali cause di amputazione non traumatica
- I pazienti con diabete hanno un rischio di amputazione da 4 a 5 volte superiore a quello dei pazienti senza diabete. Dati recenti indicano che il rischio di **AMPUTAZIONE** dovuta a ischemia critica può essere addirittura fino a 13 volte superiore nei pazienti con diabete rispetto a quelli senza diabete

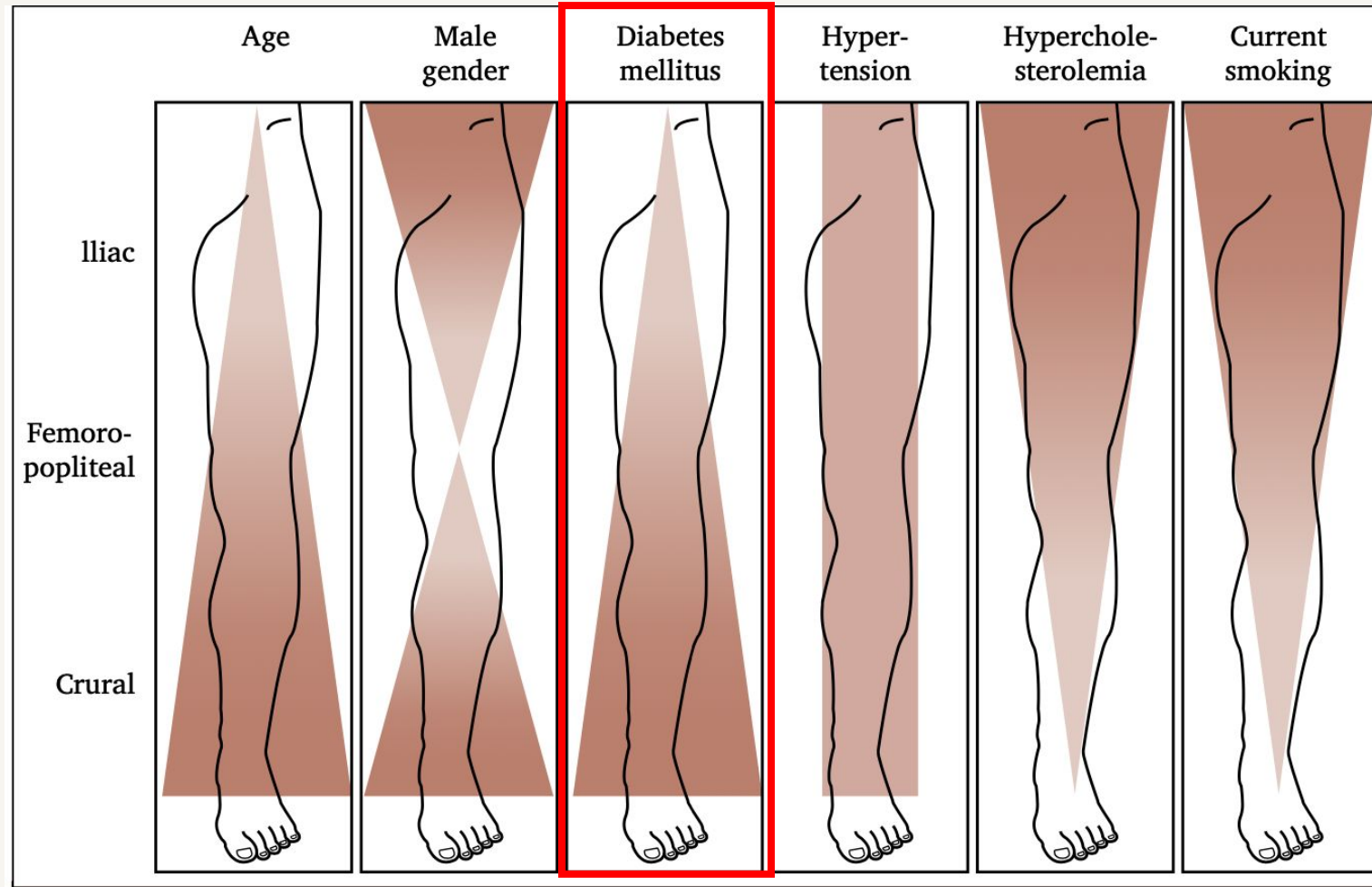
Odds ratios (ORs) for peripheral artery disease (PAD) in high-income countries (HICs) and low- and middle-income countries (LMICs)



PAD e DIABETE: FDR per PAD nel paziente Diabetico

- **MICROANGIOPATIA: la macroalbuminuria e la retinopatia diabetica**, sono fattori di rischio indipendenti per la **PAD**
- **Ridotta filtrazione glomerulare e l'albuminuria** patologica sono associati in modo indipendente a un eccesso di rischio di **PAD**
- Relazione «dose-risposta» indipendente tra gli **stadi della retinopatia** diabetica e la **PAD**
- La presenza di **diabete** è stata associata a un tasso più elevato di **amputazione** e l'uso di statine a un rischio inferiore
- **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
- **Amputazione correlata a < GFR e albuminuria**
- Inoltre, è stata riportata una relazione dose-risposta indipendente tra gli stadi della **retinopatia diabetica e la AMPUTAZIONE**

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



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*	
		3 Severe claudication*	
CLI	III Ischaemic rest pain	4 Rest pain	
	IV Ulceration or gangrene	5 Minor tissue loss	
		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 patients⁴

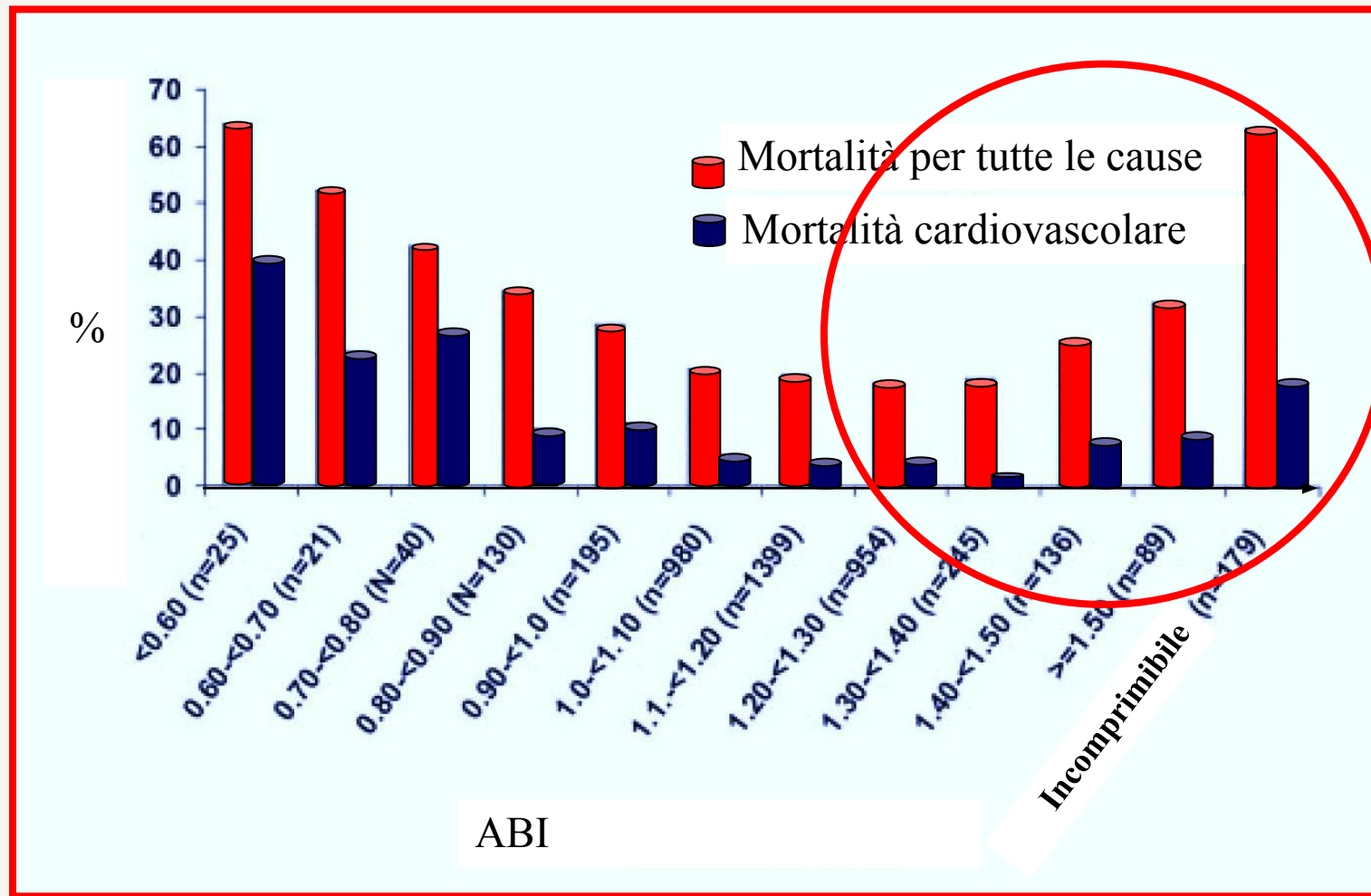
*Or atypical leg pain

PAD e DIABETE: Screening

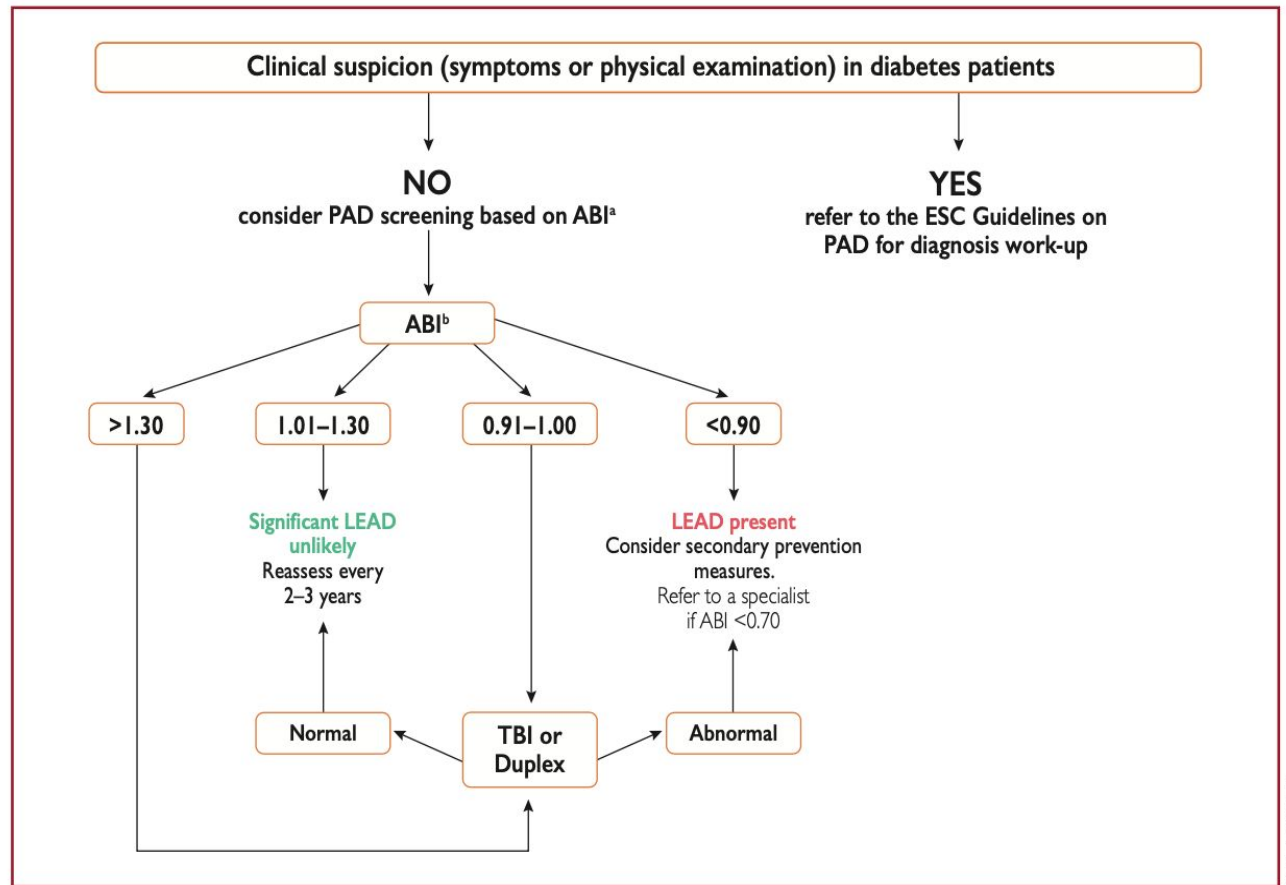
I pazienti con diabete hanno spesso una un esordio direttamente con ISCHEMIA CRITICA senza una precedente storia di claudicatio intermittens

Una diagnosi precoce di PAD e la corretta identificazione dei pazienti con ischemia critica sono fondamentali nei pazienti con diabete per migliorare gli esiti

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



2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

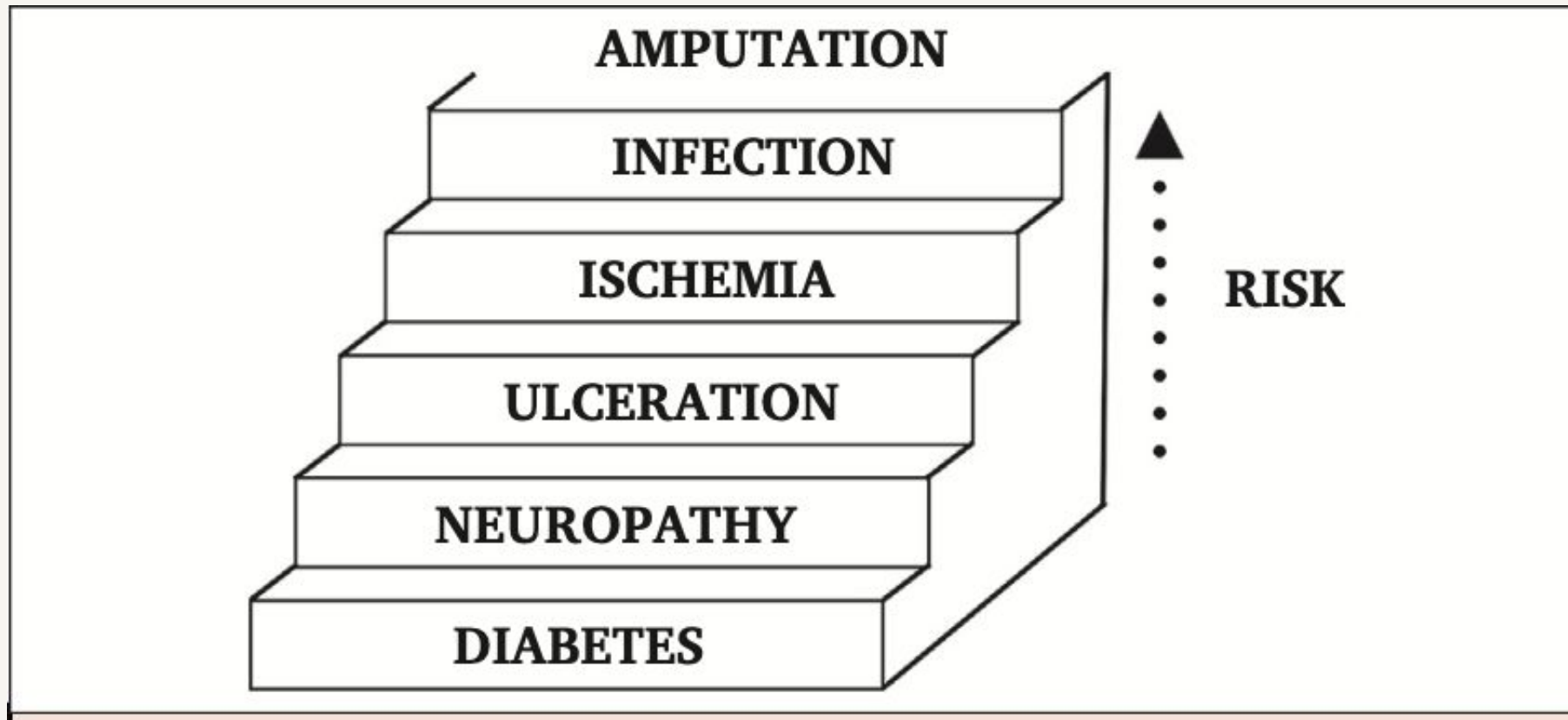


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PAD e DIABETE: caratteristiche e progressione

- Nei pazienti con diabete, la PAD è una delle principali cause di **piede diabetico**: Il 49% dei pazienti con piede diabetico nello studio dell'European Study Group on Diabetes and the Lower Extremity (EURODIALE) presentava PAD
- I pazienti con diabete e PAD hanno una prognosi peggiore rispetto ai pazienti non diabetici con PAD, con una necessità più frequente **di rivascolarizzazione e un rischio più elevato di amputazione (MALE)**
- I pazienti con diabete di **lunga durata** presentano un rischio più **elevato di amputazione** rispetto a quelli con una durata più breve
- I pazienti con diabete e PAD, rispetto a quelli senza PAD, hanno anche **un rischio più elevato di malattia e mortalità cardiovascolare (MACE) e di morte per tutte le cause, incluso il cancro**
- I tassi di **mortalità dopo amputazione nei pazienti con diabete** sono stati stimati a 1 e 4 anni, rispettivamente, al **33% e al 65% per la amputazione maggiore e al 18% e al 45% per la amputazione minore**

The elevating risk of the “stairway to an amputation” or the natural history of diabetes-related amputations



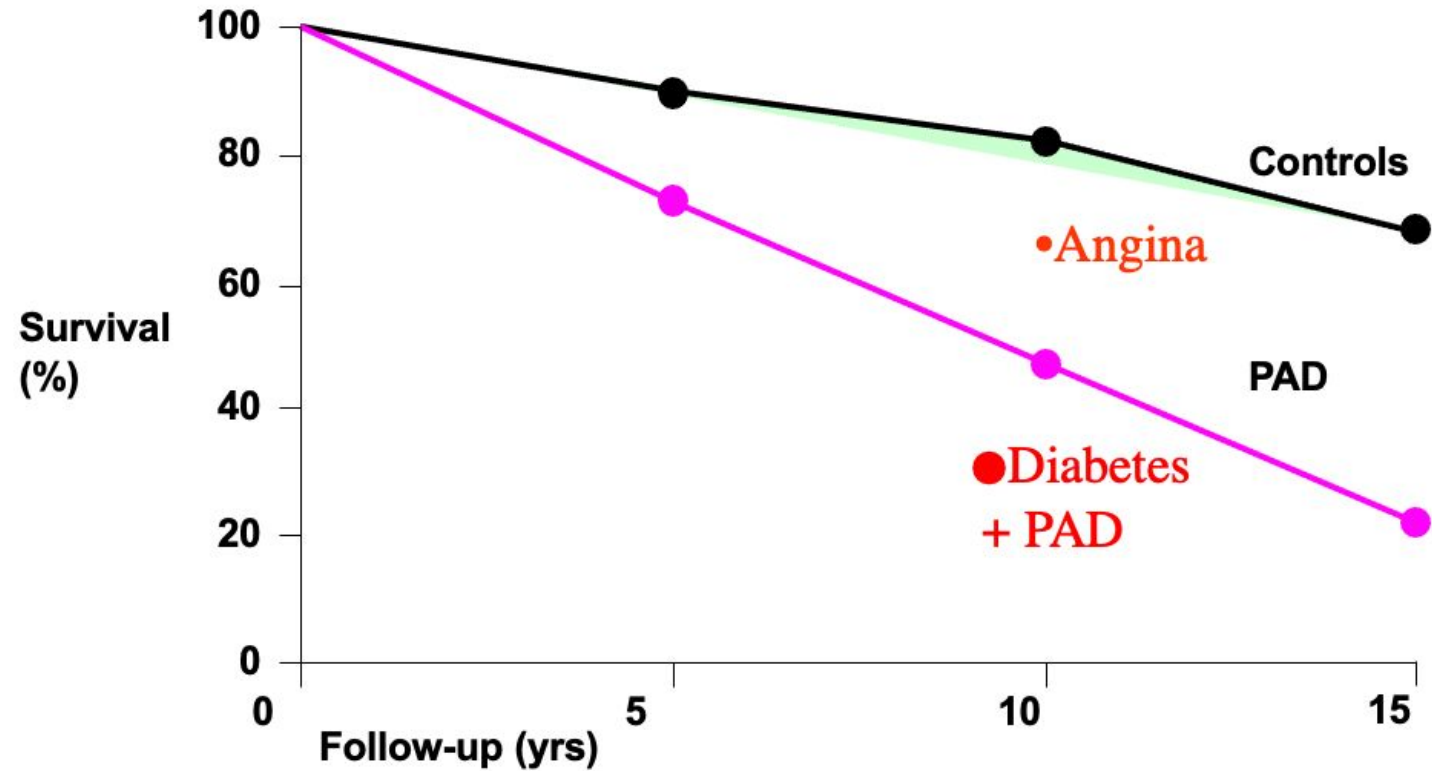
WI-FI

Score	Wound	Ischaemia			foot Infection
		ABI	Ankle pressure (mmHg)	Toe pressure or TcPO2	
0	No ulcer (ischaemic rest pain)	≥0.80	>100	≥60	No symptoms/signs of infection
1	Small, shallow ulcer (distal leg or foot), no gangrene	0.60–0.79	70–100	40–59	Local infection involving only skin and subcutaneous tissue
2	Deep ulcer (exposed bone, joint, or tendon) ± gangrenous changes limited to toes	0.40–0.59	50–70	30–39	Local infection involving deeper than skin/subcutaneous tissue
3	Extensive deep ulcer, full thickness heel ulcer ± extensive gangrene	<0.40	<50	<30	Systemic inflammatory response syndrome

One-year amputation risk																	
Estimated risk of amputation at 1 year for each combination																	
	Ischaemia – 0				Ischaemia – 1					Ischaemia – 2				Ischaemia – 3			
W-0	VL	VL	L	M	VL	L	M	H		L	L	M	H	L	M	M	H
W-1	VL	VL	L	H	VL	L	M	H		L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H		M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H		H	H	H	H	H	H	H	H
	fl-0	fl-1	fl-2	fl-3	fl-0	fl-1	fl-2	fl-3		fl-0	fl-1	fl-2	fl-3	fl-0	fl-1	fl-2	fl-3

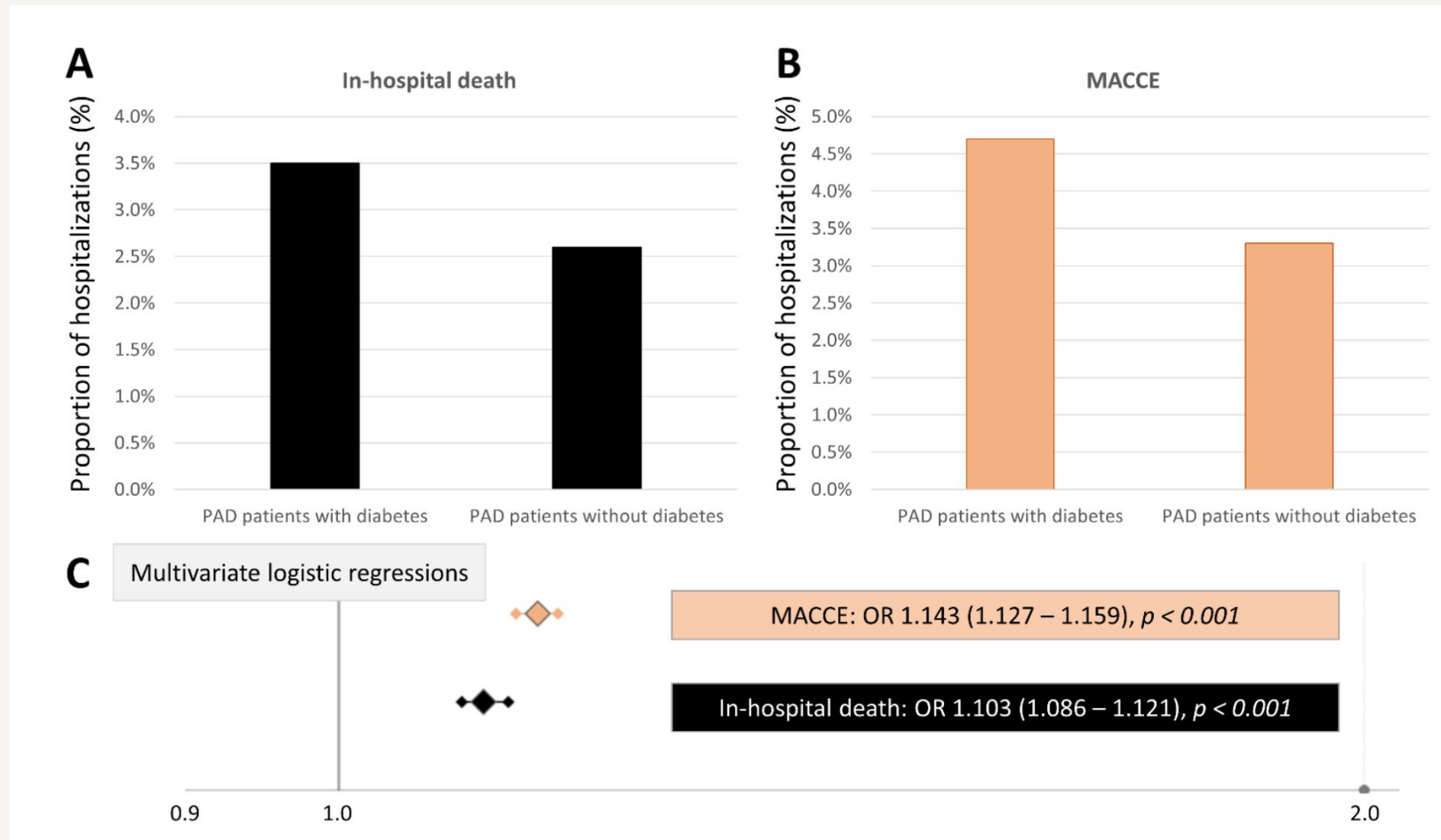
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Link between presence of PAD and survival



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](#)

DM affecting In- HOSPITAL MORTALITY and MACE during Hospitalizations of PAD Patients



Recommendations in patients with peripheral arterial diseases: best medical therapy

Recommendations	Class ^a	Level ^b
Smoking cessation is recommended in all patients with PADs. ^{27,28}	I	B
Healthy diet and physical activity are recommended for all patients with PADs.	I	C
Statins are recommended in all patients with PADs. ^{31,32}	I	A
In patients with PADs, it is recommended to reduce LDL-C to < 1.8 mmol/L (70 mg/dL) or decrease it by $\geq 50\%$ if baseline values are 1.8–3.5 mmol/L (70–135 mg/dL). ²⁵	I	C
In diabetic patients with PADs, strict glycaemic control is recommended.	I	C
Antiplatelet therapy is recommended in patients with symptomatic PADs. ⁵¹	I	C ^d
In patients with PADs and hypertension, it is recommended to control blood pressure at < 140/90 mmHg. ^{41,42,52}	I	A
ACEIs or ARBs should be considered as first-line therapy ^c in patients with PADs and hypertension. ^{47,53}	IIa	B

Vascular protection

Standard pharmacological secondary prevention

Healthy lifestyle¹

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

Antithromboti c¹

Aspirin
DAPT

Rivaroxaban vascular dose plus
aspirin

Lipid lowering²

Statins
Ezetimibe

PCSK-9 inhibitors

Blood pressure control¹

ACEI/ARB
BB/MRA

Other antihypertensives
Sacubitril + valsartan⁴

Glucose control in diabetic patients³

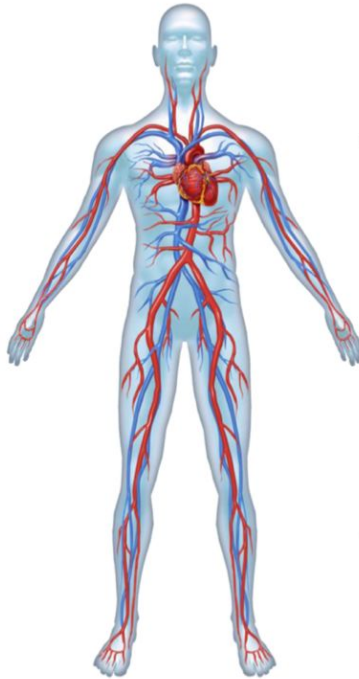
Insulin
Metformin

SGLT-2 inhibitors
GLP-1 R agonists
DPP-4 inhibitors

Additional pharmacological secondary prevention

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 Risk-reduction Therapies



Therapies for all Patients

- Lifestyle Modification & Exercise
- Tobacco Cessation Therapies (behavioral and pharmacologic)
- Targeting blood pressure goals with preference for ACEi
- LDL-C lowering with statin ± ezetimibe and/or PCSK9i
- Antiplatelet monotherapy (symptomatic), preference for P2Y₁₂ inhibition

Therapies for MACE Reduction in Selected Patients

Diabetes

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

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

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

Therapies for MALE Reduction in all Patients

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

Therapies for MALE Reduction in Selected Patients

Prior peripheral revascularization & low bleeding risk

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

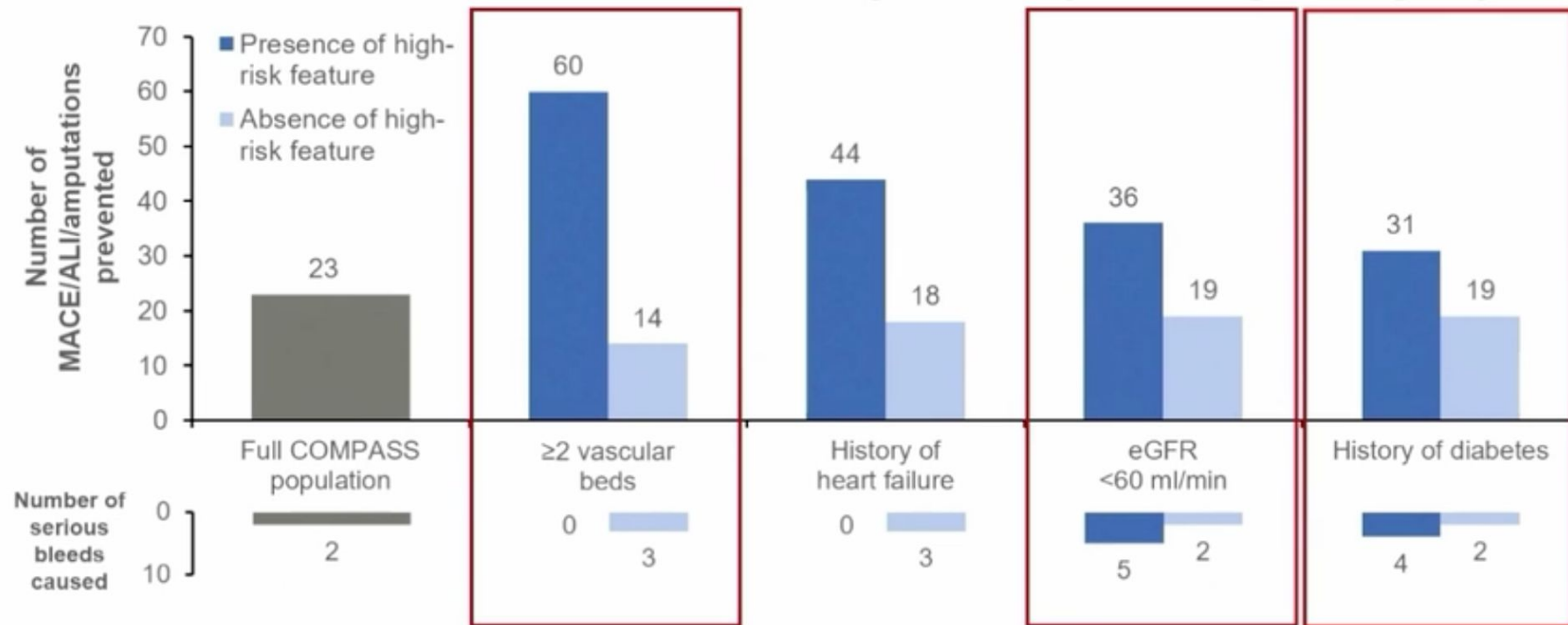
Therapies for Claudication

Symptomatic Patients

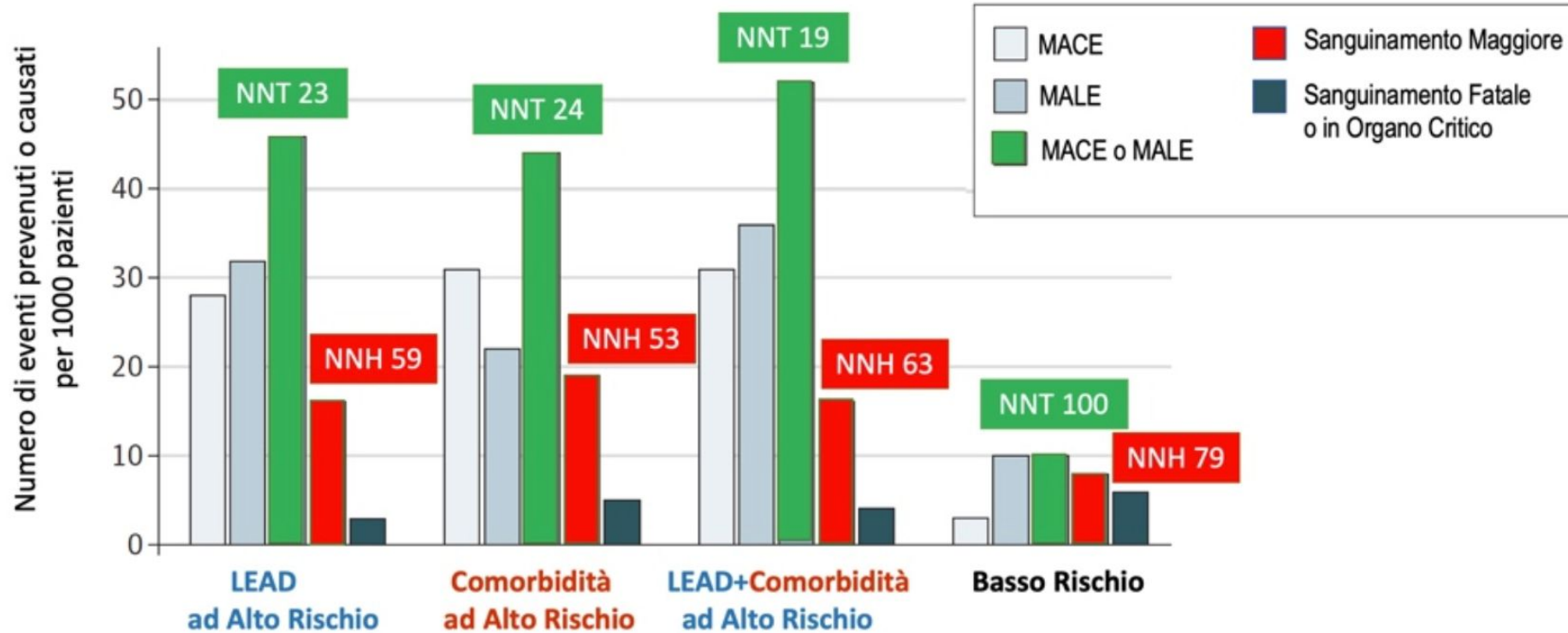
- Cilostazol 100 mg BID

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



Stratificazione del rischio



Comorbidità ad Alto Rischio: polivasculopatia, scompenso cardiaco, diabete, insufficienza renale

LEAD ad Alto Rischio: storia di amputazione, storia di rivascularizzazione, Fontaine stadio III o IV

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

In the **FOURIER** trial, **27,564 patients** with prior MI, non-hemorrhagic stroke, or symptomatic PAD were randomized to **evolocumab** (PCSK9 inhibitor) vs **placebo** with a median follow-up of 2.2 years.

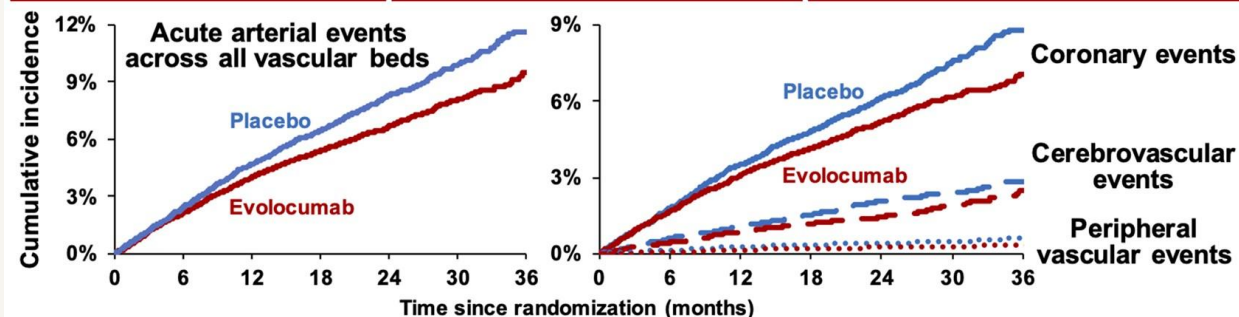
Effect of evolocumab on acute arterial events across all vascular territories

(Acute coronary, cerebrovascular, or peripheral vascular events)

First event: ↓ **19%** HR 0.81 (95% CI 0.74-0.88) P<0.001

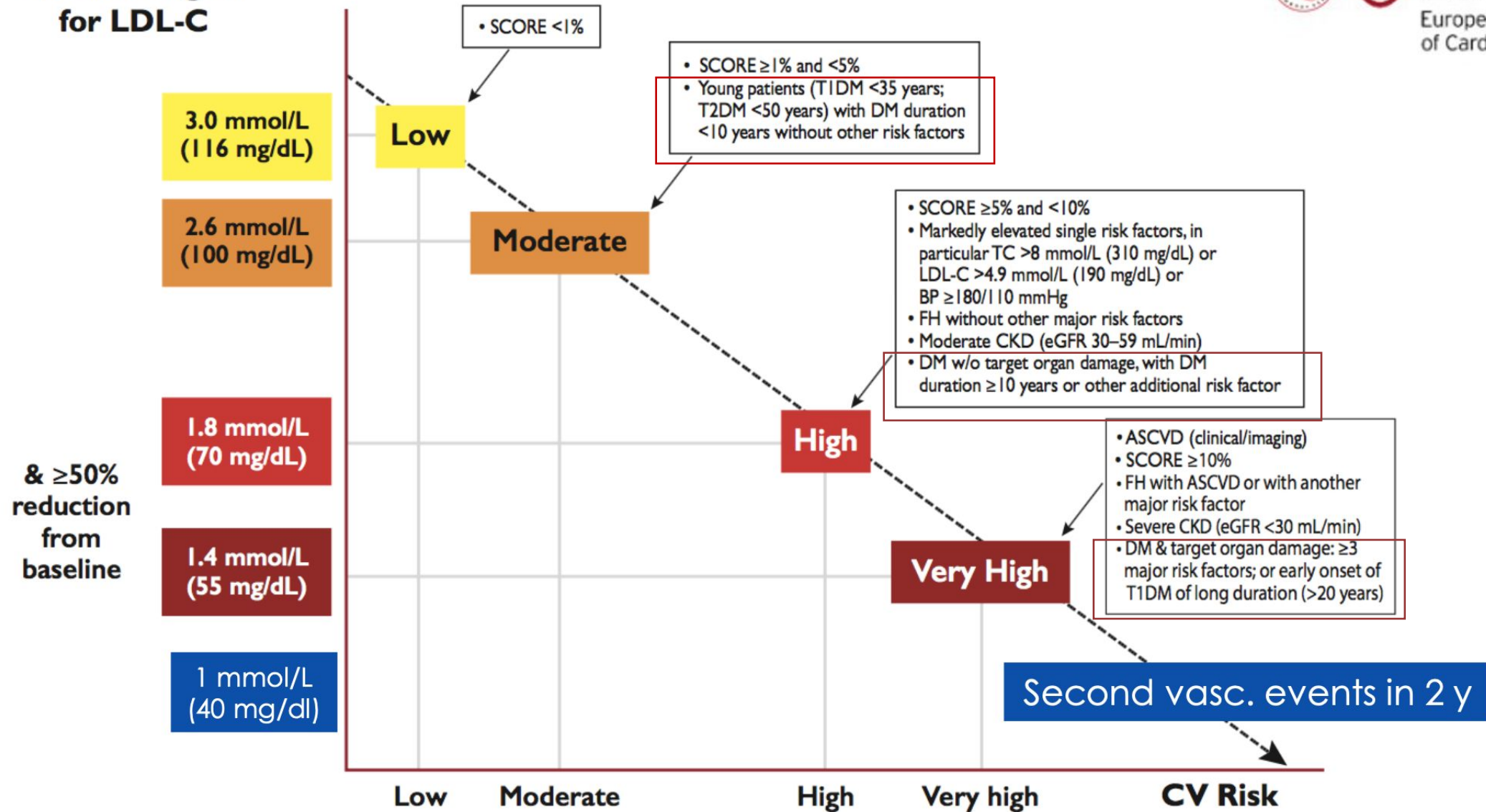
Total events: ↓ **24%** RR 0.76 (95% CI 0.69-0.85) P<0.001

Acute coronary events	Acute cerebrovascular events	Acute peripheral vascular events
(CHD death, MI, or urgent coronary revascularization)	(Ischemic stroke, TIA, or urgent cerebral revascularization)	(ALI, major amputation, or urgent peripheral revascularization)
↓ 17% (First event)	↓ 23% (First event)	↓ 42% (First event)
HR 0.83 (95% CI 0.75-0.91)	HR 0.77 (95% CI 0.65-0.92)	HR 0.58 (95% CI 0.38-0.88)





Treatment goal for LDL-C



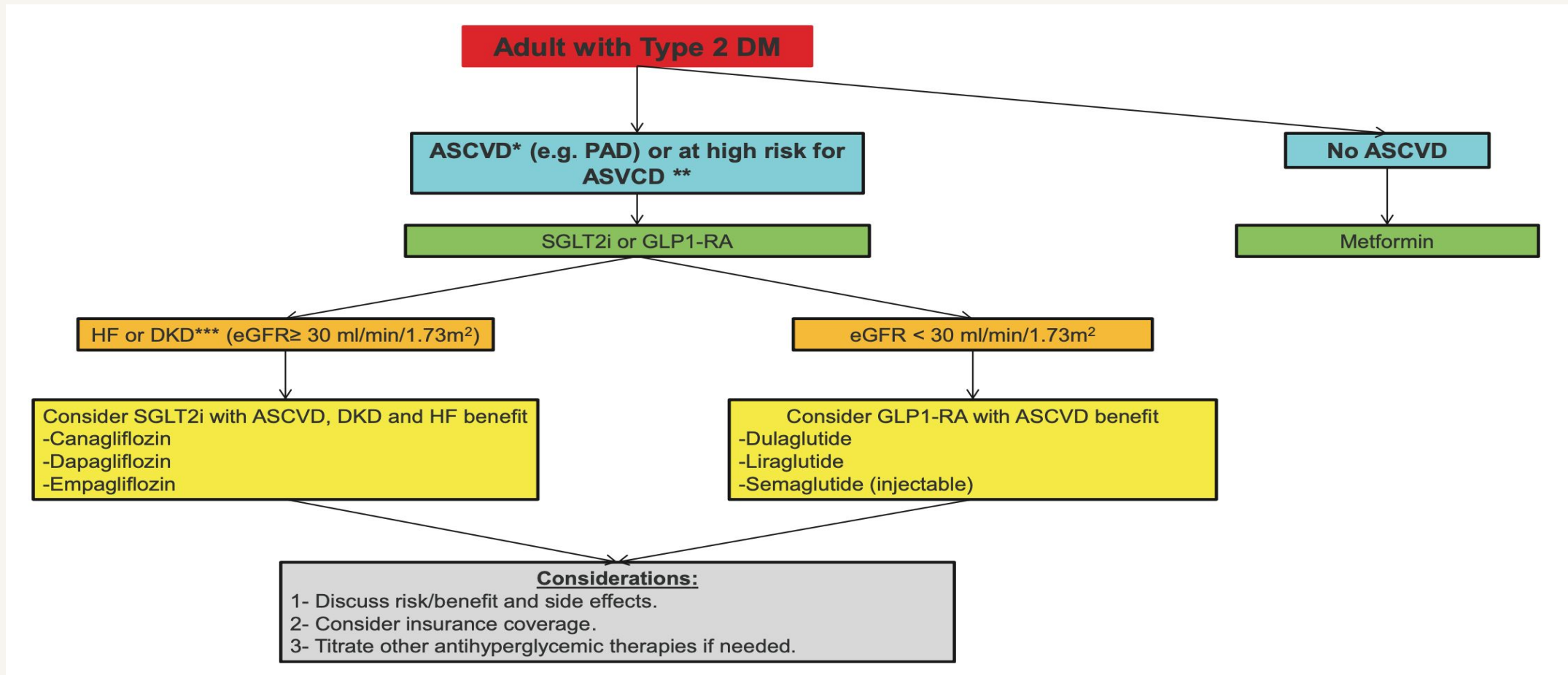
PAD e DIABETE: linee Guida ESVM

Recommendation	Class of recommendation	Level of evidence
It is recommended that patients with diabetes should be screened for PAD	I	B
It is recommended that all PAD patients should be screened for diabetes and effectively treated in the case of a proven diagnosis of diabetes. In type 2 diabetics in addition to metformin empaglifozin and/or liraglutid should be considered.	I	B
Appropriate diabetic control is recommended in patients with PAD.	I	B

Diabete e Malattie Cardiovascolari

Le nuove linee guida recepiscono le evidenze prodotte dagli studi clinici sui benefici cardio-vascolari di alcune classi di farmaci come gli **SGLT2 inibitori e i GLP-1 agonisti**, che vengono dunque poste in una posizione importante all'interno degli algoritmi terapeutici. Questi farmaci vanno considerati in seconda linea, dopo la metformina, nei pazienti senza malattie cardiovascolari note, mentre vanno prescritti già in **prima linea nei pazienti con patologie cardiovascolari**

Evidence-based algorithm summarizing current recommendations to reduce CV risk in patients with T2D and CV risk such as PAD



Summary of societal guideline recommendations for antiglycemic therapies.

Societal guidelines	Recommendations
2021 – American Diabetic Association ⁷⁵	<ul style="list-style-type: none">– <i>Glycemic control</i>: recommend metformin as first-line pharmacological agent.– <i>T2D and high risk for or eASCVD, KD, or HF</i>: recommend SGLT2i or GLPI-RA with demonstrated CV benefit independent of A1C<ul style="list-style-type: none">• GLPI-RA is preferred to insulin when possible.• HFrEF: consider SGLT2i with proven benefit.• CKD and albuminuria: consider a SGLT2i with evidence of reducing CKD progression.• Consider GLPI-RA with proven CV benefit as an alternative if SGLT2i is not tolerated.
2019 – American College of Cardiology (ACC) and American Heart Association (AHA) ⁷⁶	<ul style="list-style-type: none">– <i>Glycemic control</i>: recommend metformin as first-line pharmacological agent.– <i>T2D and additional ASCVD risk factors</i>: reasonable to initiate a SGLT2i or a GLPI-RA as add on to metformin.
2020 – ACC ¹¹	<ul style="list-style-type: none">– <i>T2D and ASCVD</i>: recommend starting SGLT2i or GLPI-RA with CV benefit.– <i>DKD and/or HF</i>: consider a SGLT2i<ul style="list-style-type: none">• eGFR < 30 mL/min/1.73 m²: consider a GLPI-RA as an alternative.– <i>At discharge after ASCVD admission</i>: consider a SGLT2i or GLPI-RA<ul style="list-style-type: none">• Consider SGLT2i in case of HFrEF.
2022 – ACC/AHA/Heart Failure Society of America ^{79,80}	<ul style="list-style-type: none">– <i>HFrEF</i>: recommend SGLT2i regardless of T2D<ul style="list-style-type: none">• SGLT2i can also be beneficial in HFmrEF and HFpEF.
2019 – European Society of Cardiology ^{77,78}	<ul style="list-style-type: none">– <i>T2D and CVD or high CV risk</i>: recommend empagliflozin, canagliflozin, dapagliflozin, liraglutide, semaglutide, or dulaglutide to reduce CV events<ul style="list-style-type: none">• Recommend empagliflozin or liraglutide to reduce risk of CV death.

LEAD management

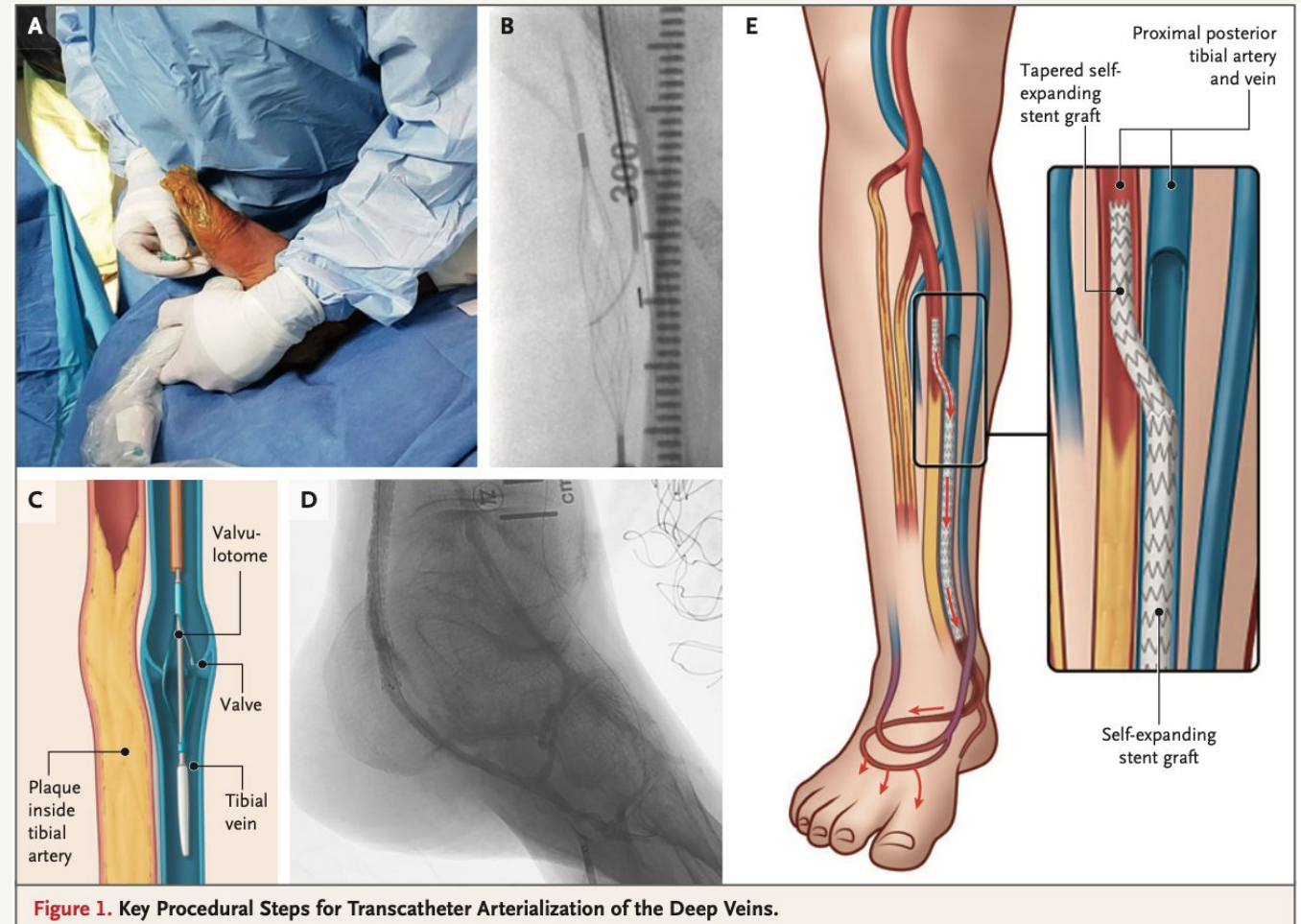
In patients with DM and symptomatic LEAD, antiplatelet therapy is recommended. ⁵⁴¹	I	A
As patients with DM and LEAD are at very high CV risk, ^d an LDL-C target of <1.4 mmol/L (<55 mg/dL), or an LDL-C reduction of at least 50% is recommended. ^{200,201,210}	I	B
In patients with DM with CLTI, the assessment of the risk of amputation is recommended; the Wifl 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

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Transcatheter Arterialization of Deep Veins in Chronic Limb-Threatening Ischemia

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	All Patients (N = 105)
Median age (range) — yr	70 (38–89)
Male sex — no. (%)	72 (68.6)
Race — no. (%)†	
White	64 (61.0)
Black or African descent	16 (15.2)
Asian	2 (1.9)
Unknown or declined to state	23 (21.9)
Ethnic group — no. (%)†	
Not Hispanic or Latino	76 (72.4)
Hispanic or Latino	29 (27.6)
Median body-mass index (range)‡	26.2 (18.0–48.8)
History of smoking — no. (%)	44 (41.9)
Current	6 (5.7)
Former	38 (36.2)
Previous stroke — no. (%)	9 (8.6)
Previous myocardial infarction — no. (%)	24 (22.9)
Hypertension — no. (%)	96 (91.4)
Dyslipidemia — no. (%)	73 (69.5)
Diabetes mellitus — no. (%)	81 (77.1)
Type I	11 (10.5)
Type II	70 (66.7)
Chronic kidney disease — no. (%)	41 (39.0)
Dialysis — no. (%)	19 (18.1)
Rutherford classification — no. (%)§	
Stage 5	68 (64.8)
Stage 6	37 (35.2)
Previous intervention in target limb — no. (%)	78 (74.3)



Lower-Limb peripheral arterial disease and amputations in people with diabetes: risk Factors, prognostic value and management.

LOWER-LIMB PERIPHERAL ARTERIAL DISEASE (PAD)



3th manifestation of atherosclerosis associated with cardiovascular (CV) risk factors



major endemic disease alarming increased prevalence



advances in medical, surgical, endovascular techniques,



but still lead to poor prognosis, including amputation



disabilities, reduced functional performances impaired mental health and quality of life



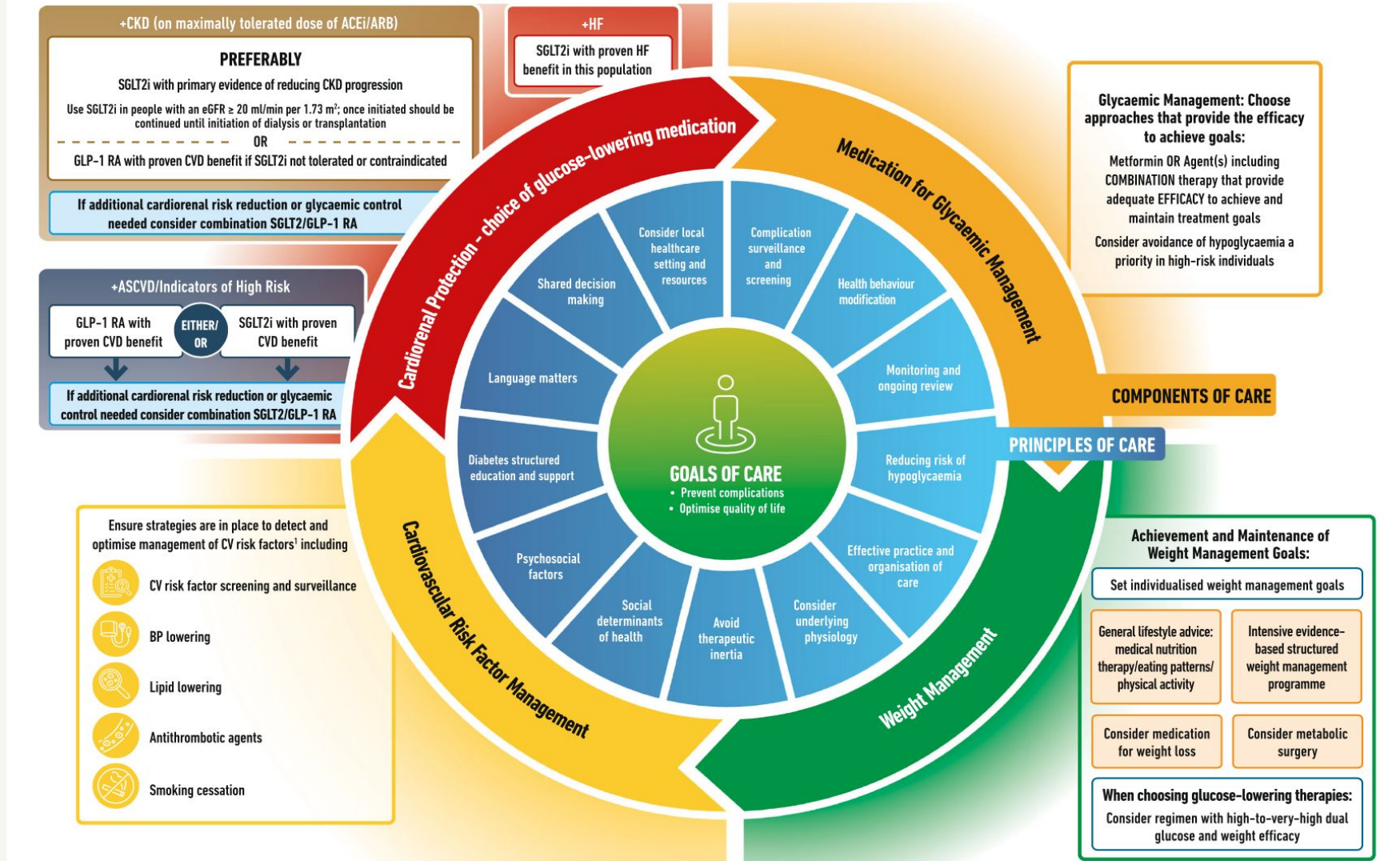
PAD associated : with CV and non CV disease and mortality



significant cost

PAD e DIABETE: approccio MULTIDISCIPLINARE

HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT





European Society
of Vascular Medicine

IX

CONGRESS OF THE
EUROPEAN SOCIETY
OF VASCULAR MEDICINE

SAVE the DATE

Milan, 12-14 October 2023

REGISTRO START SIAPAV PAD
aderisci!



Società Italiana di Angiologia e Patologia Vascolare
Italian Society for Angiology and Vascular Medicine

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Torino, 23-25 novembre 2023

