SID
Società Italiana di Diabetologia

AMD
ASSOCIAZIONE MEDICI DIABETOLOGI
1974

XXIX Congresso Congiunto
SID AMD Friuli Venezia Giulia

La diabetologia nel post COVID tra resilienza e ripartenza

UDINE
19 marzo 2022

La terapia medica dell'arteriopatia periferica

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SSD Endocrinologia e Mal.del Metabolismo
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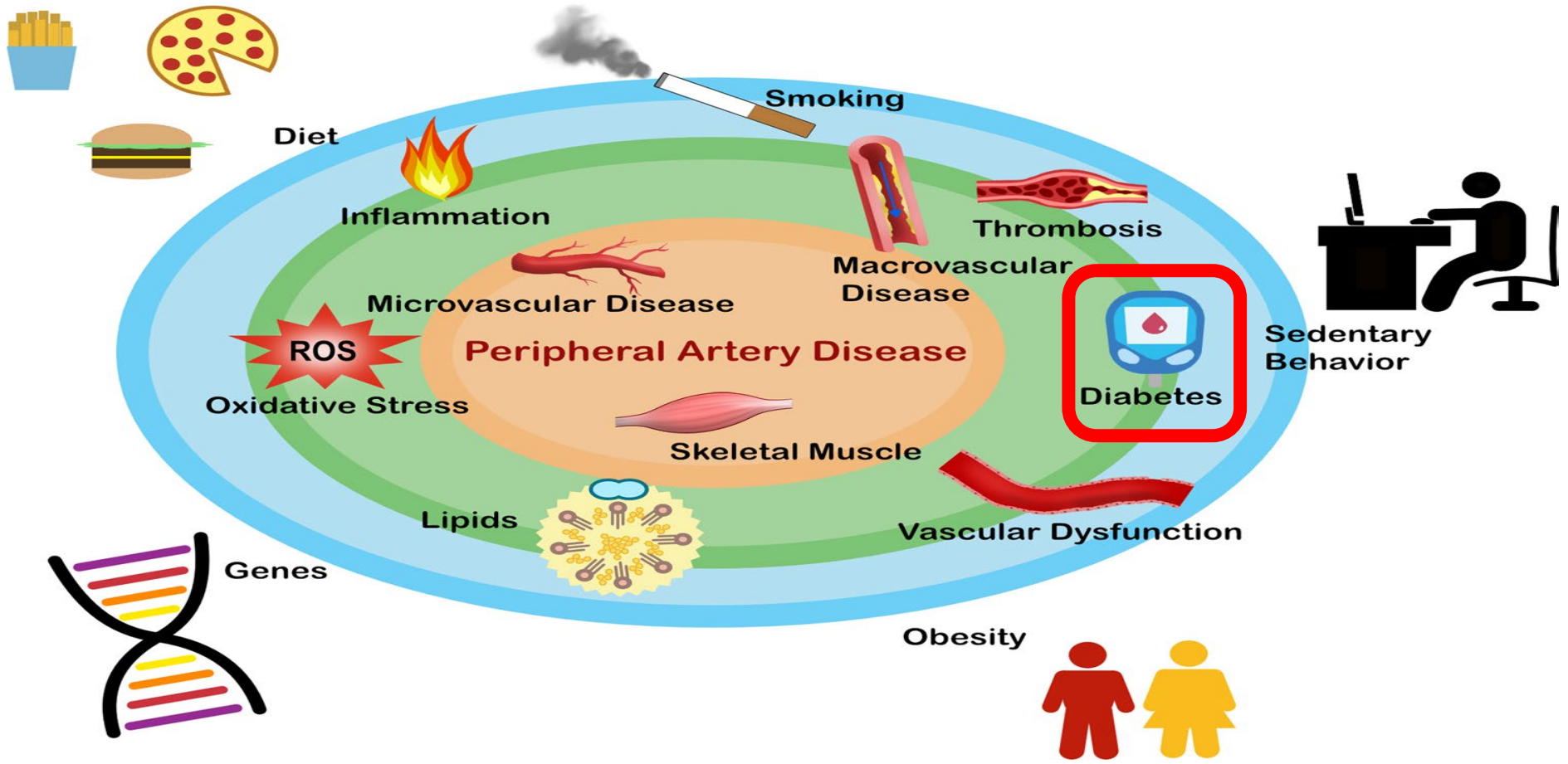
ASFO

NON sono pervenute informazioni dal Dr. Cesare Miranda in merito all'aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

•*Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).*

Pathobiologic drivers and pathways in the development of peripheral artery disease (PAD) and associated morbidity



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

Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people

Anoop Dinesh Shah, Claudia Langenberg, Eleni Rapsomaniki, Spiros Denaxas, Mar Pujades-Rodriguez, Chris P Gale, John Deanfield, Liam Smeeth, Adam Timmis, Harry Hemingway

Lancet Diabetes Endocrinol
2015; 3: 105–13

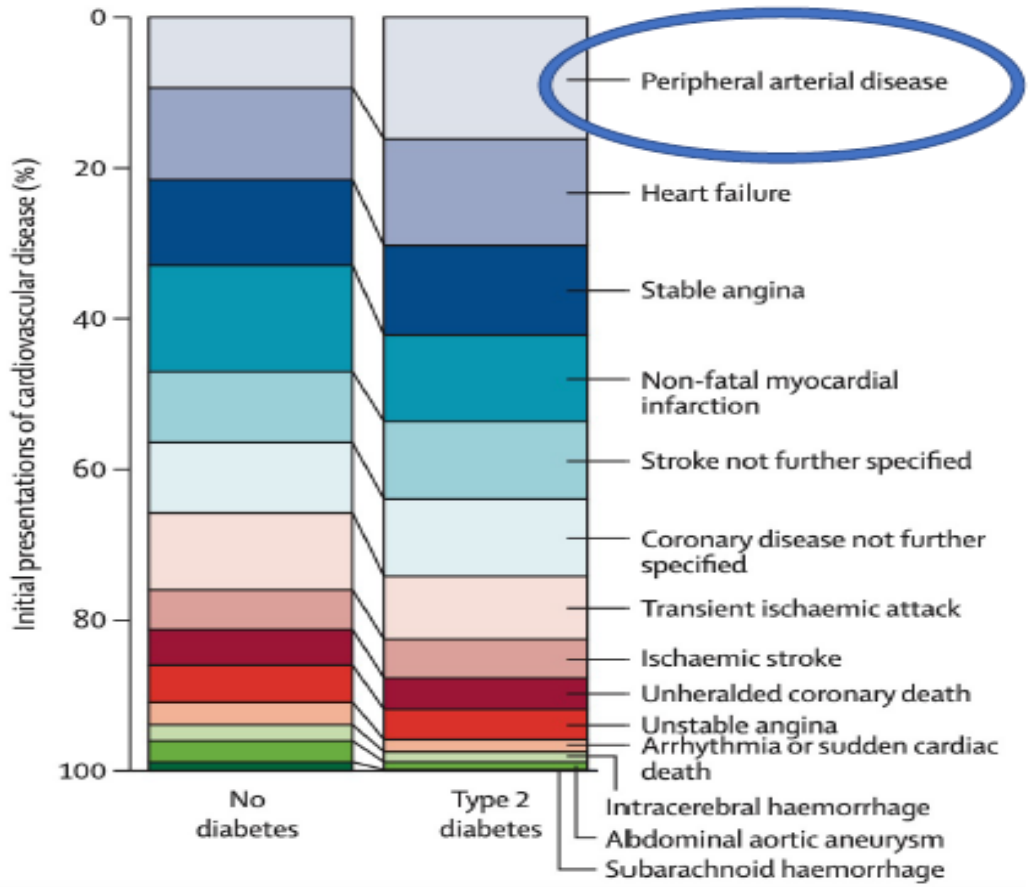
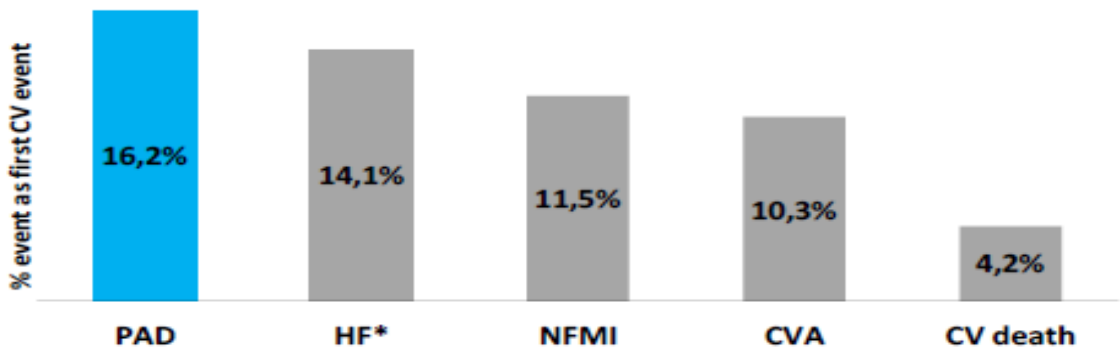


***Figure 1*: Distribution of initial presentations of cardiovascular diseases**
Distribution of initial presentations of cardiovascular disease in participants with and without type 2 diabetes and no history of cardiovascular disease.

CALIBER
(**CA**rdiovascular disease research using **LI**nked **B**espoke studies and **E**lectronic health **R**ecords): electronic health data in England;

Cohort study of 1,921,260 individuals;
34,198 (1·8%) had T2D with 113,638 CV events

(median follow-up 5.5 yrs)



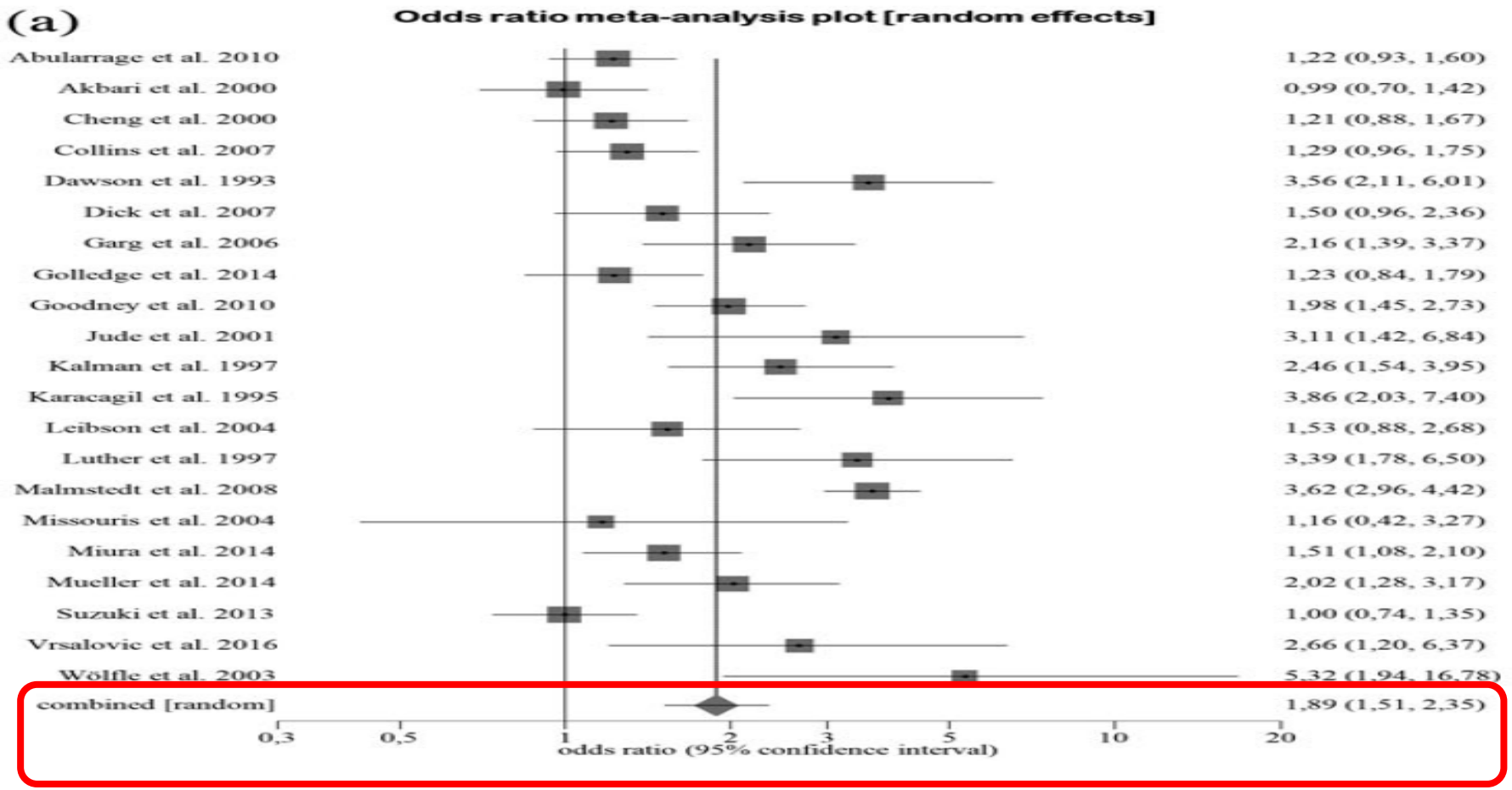
Received: 20 September 2016 | Revised: 7 November 2016 | Accepted: 11 November 2016
DOI 10.1002/clc.22657

PREVENTION WILEY CLINICAL CARDIOLOGY

CLINICAL INVESTIGATIONS

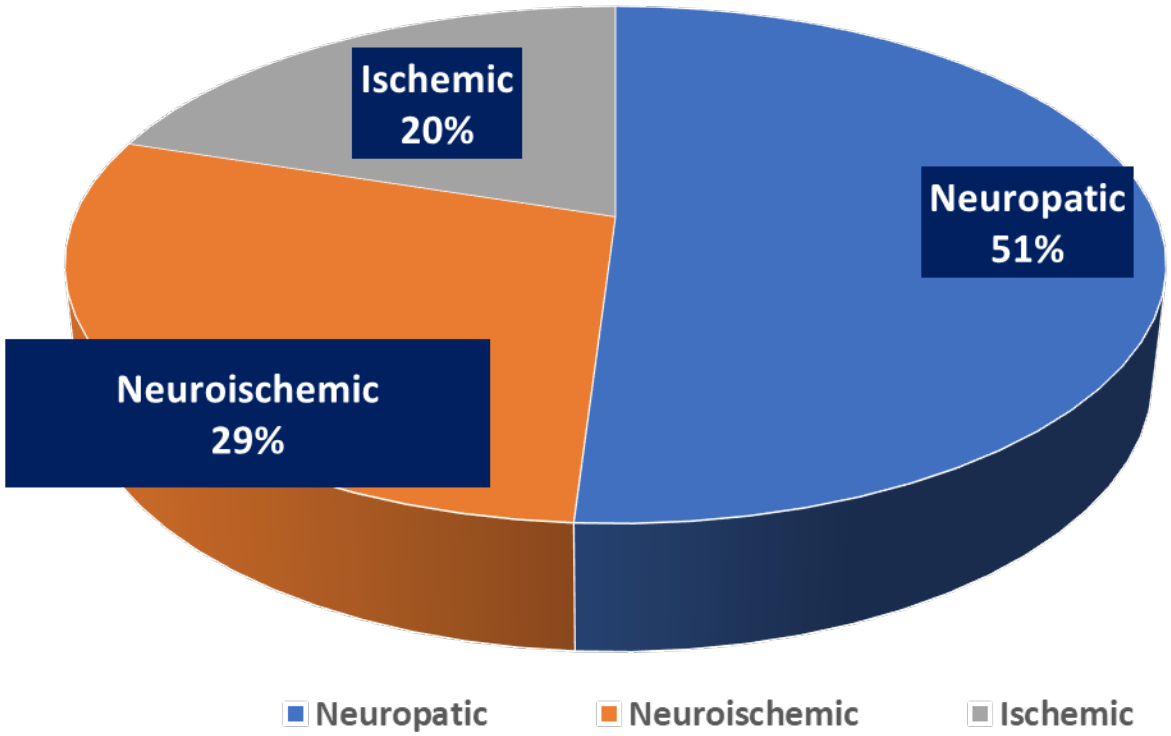
Impact of diabetes on mortality in peripheral artery disease: a meta-analysis

Mislav Vrsalovic MD, PhD[1,2] | Ksenija Vucur MD[3] | Ana Vrsalovic Presecki PhD[4] | Damir Fabijanic MD, PhD[5] | Milan Milosevic MD, PhD[1,6]



Epidemiology of ischemic ulcers in diabetes

EURODIALE STUDY



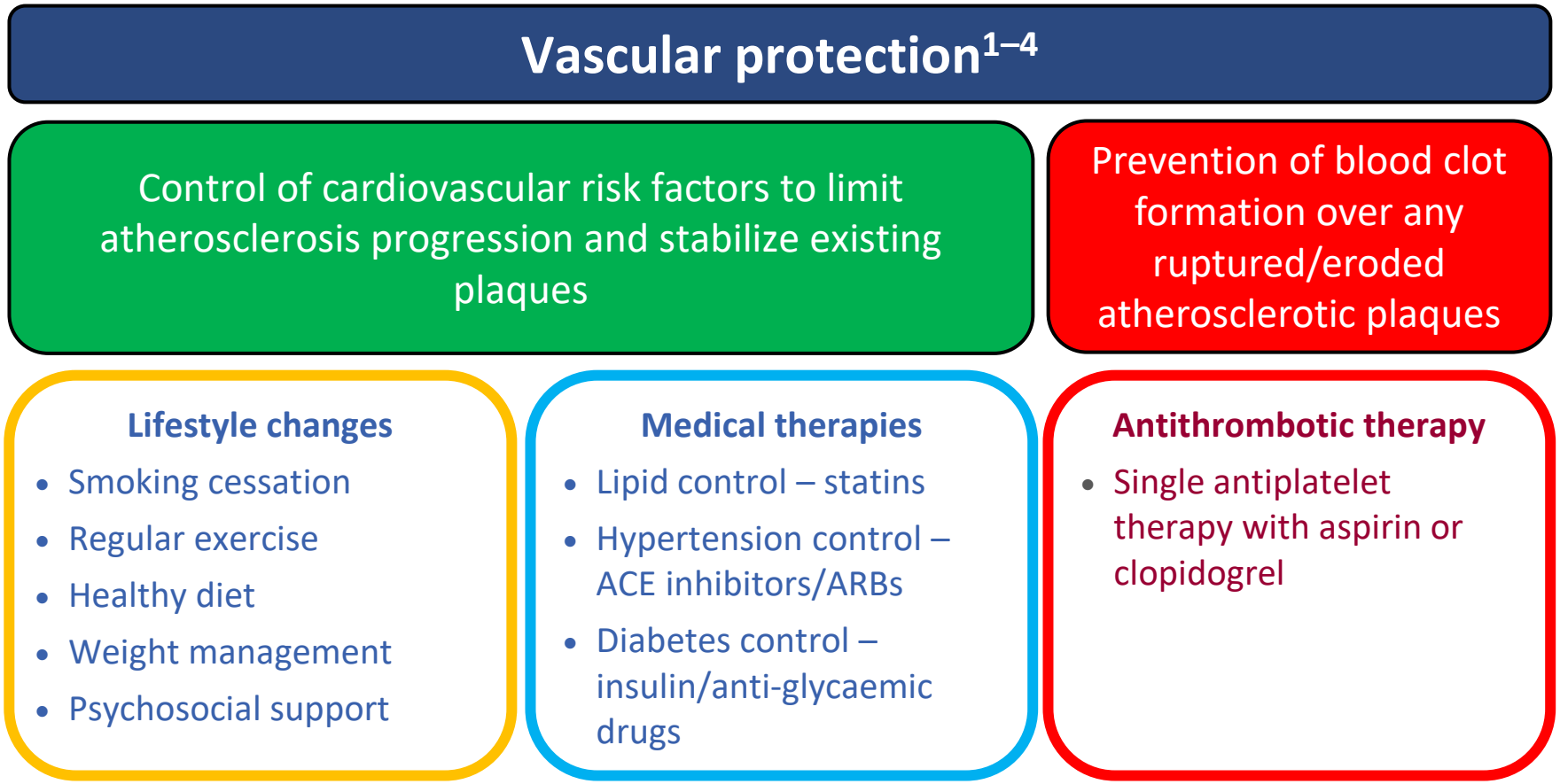
Prompers L et al. Diabetologia 2007

Obiettivi della terapia medica della PAD nel diabete

- **La terapia medica o non invasiva della PAD** nel diabete mellito ha i seguenti **obiettivi**:
- evitare la progressione della malattia e la comparsa di lesioni ai piedi ,
- migliorare la sintomatologia e la capacità d'esercizio fisico,
- prevenire gli eventi cardiovascolari fatali e non fatali .
- **La terapia medica della PAD** non è un'alternativa alla rivascolarizzazione, poiché al momento non vi sono evidenze scientifiche.

Documento Consenso Trattatamento Arteriopatia Periferica nel Diabetico. Amd/SICVE/SID/SIRM. Dicembre 2012.

Current Vascular Protection Strategies Aim to Reduce Risk of Atherothrombotic CV and Limb Events in Patients with PAD



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. Gerhard-Herman MD *et al*, *J Am Coll Card* 2016: doi:10.1016/j.jacc.2016.11.007;
4. Cortés-Beringola A *et al*, *Eur J Prevent Cardiol* 2017;24:22–28

Lifestyle changes:Smoking cessation

2016 AHA/ACC Lower Extremity PAD Guidelines

Recommendations for Smoking Cessation		
COR	**LOE**	**Recommendations**
I	A	Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit.[153–155]
I	A	Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (ie, varenicline, bupropion, and/or nicotine replacement therapy) and/or referral to a smoking cessation program.[153,156–158]
I	B-NR	Patients with PAD should avoid exposure to environmental tobacco smoke at work, at home, and in public places.[159,160]

2017 ESC-ESVS PAD Guidelines

Recommendations	Class	Level
Smoking cessation is recommended in all patients with PADs.	I	B

Lifestyle changes: structured exercise therapy

2016 AHA/ACC Lower Extremity PAD Guidelines

COR	LOE	Recommendations
I	A	In patients with claudication, a supervised exercise program is recommended to improve functional status and QoL and to reduce leg symptoms.[24–26,28–34,36,169,170]
I	B-R	A supervised exercise program should be discussed as a treatment option for claudication before possible revascularization.[24–26]
IIa	A	In patients with PAD, a structured community- or home-based exercise program with behavioral change techniques can be beneficial to improve walking ability and functional status.[37,80,86,171]
IIa	A	In patients with claudication, alternative strategies of exercise therapy, including upper-body ergometry, cycling, and pain-free or low-intensity walking that avoids moderate-to-maximum claudication while walking, can be beneficial to improve walking ability and functional status.[27,173,175,176]

2017 ESC-ESVS PAD Guidelines

Recommendations	Class[a]	Level[b]
In patients with intermittent claudication:		
• supervised exercise training is recommended[273,287–289]	I	A
• unsupervised exercise training is recommended when supervised exercise training is not feasible or available.	I	C

LDL control

2016 AHA/ACC Lower Extremity PAD Guidelines

COR	LOE	Recommendations
I	A	**Treatment with a statin medication is indicated for all patients with PAD.**

2017 ESC-ESVS PAD Guidelines

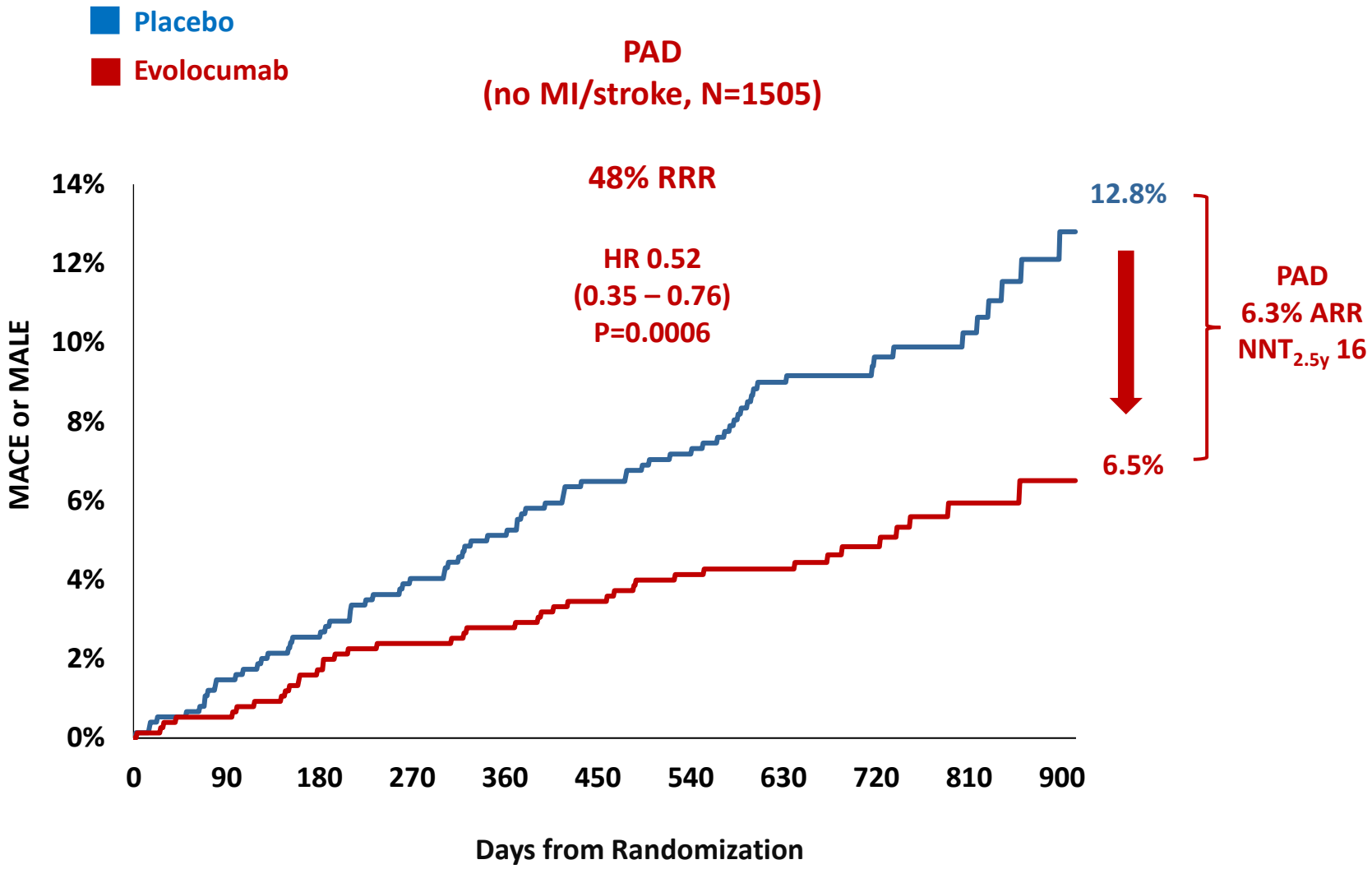
Recommendations	Class	Level
Statins are recommended in all patients with PADs.	I	A
In patients with PADs, it is recommended to reduce LDL-C to <1.8 mmol/L (70 mg/dL) or decrease it by ≥50% if baseline values are 1.8-3.5 mmol/L (70-135 mg/dL).	I	C

ESC European Society of Cardiology

2019 ESC EASD Guideline on diabetes, prediabetes and cardiovascular disease

Recommendations	Class	Level
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

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



PAD- Hypertension control

2016 AHA/ACC Lower Extremity PAD Guidelines

COR	LOE	Recommendations
IIa	A	The use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD

2017 ESC-ESVS PAD Guidelines

Patients with peripheral arterial diseases: best medical therapy *(continued)*

ESC European Society of Cardiology

Recommendations	Class	Level
In patients with PADs and hypertension, it is recommended to control blood pressure at <140/90 mmHg.	I	A
ACEIs or ARBs should be considered as first line therapy in patients with PADs and hypertension.	IIa	B

Antiplatelet therapy

2016 AHA/ACC Lower Extremity PAD Guidelines

COR	LOE	Recommendations
Antiplatelet Agents		
I	A	Antiplatelet therapy with aspirin alone (range 75–325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD.[121–124]

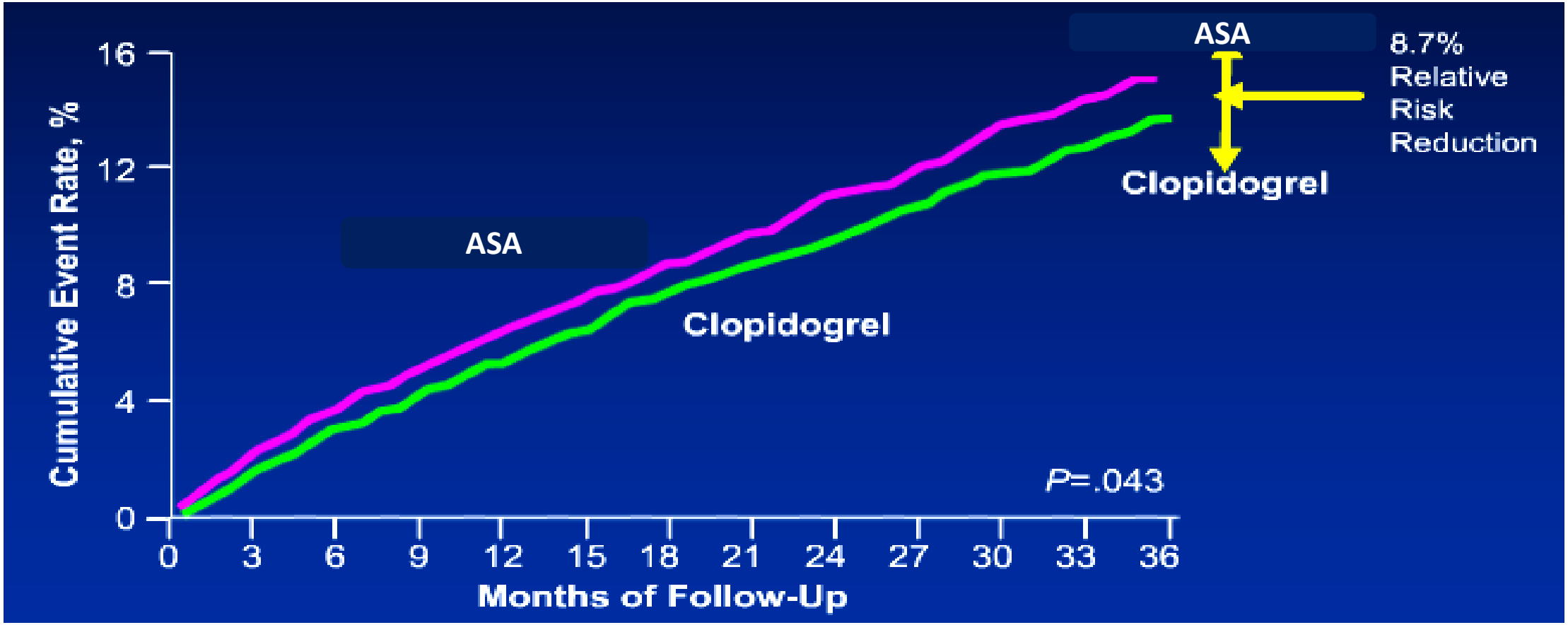
2017 ESC-ESVS PAD Guidelines

Recommendations	Class	Level
Long-term SAPT is recommended in symptomatic patients.[51,54,68]	I	A
In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin.[51,69]	IIb	B

2019 ESC EASD Guidelines on Diabetes, prediabetes and cardiovascular disease

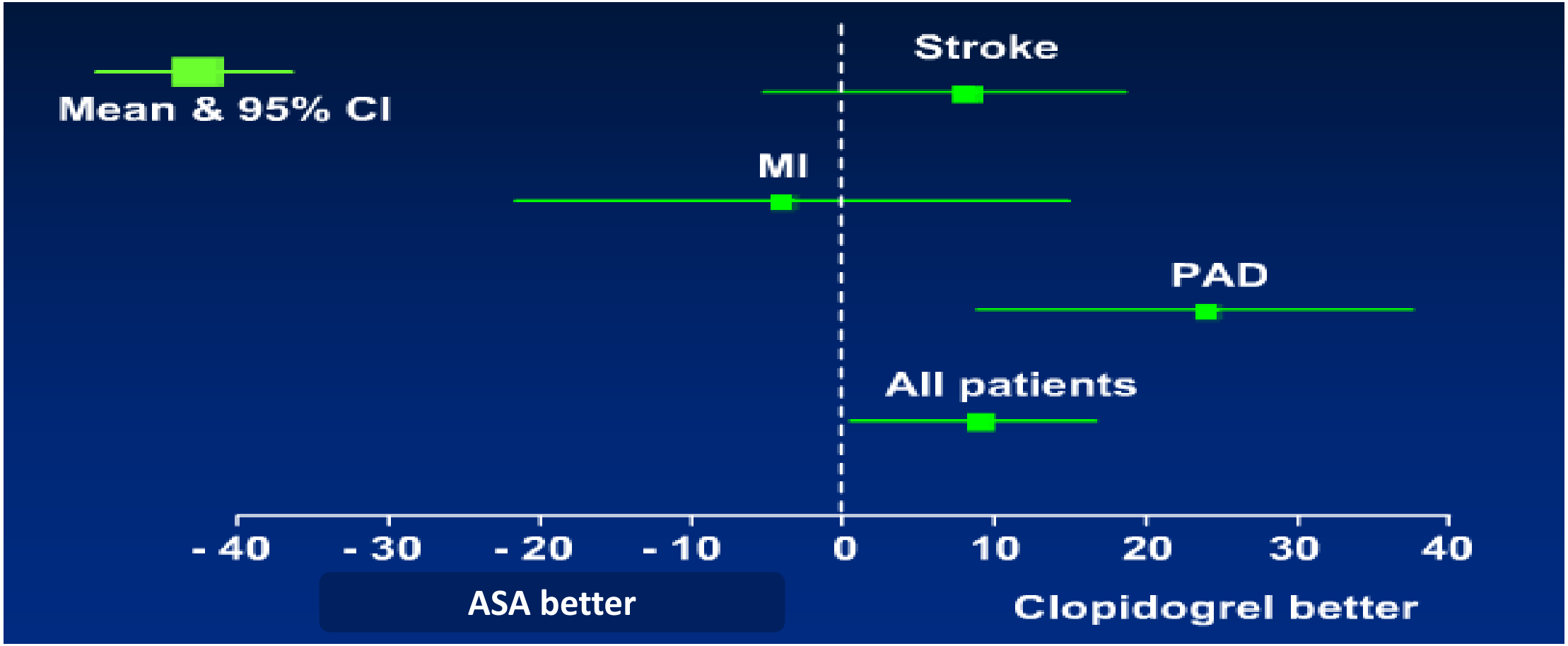
In patients with DM and symptomatic LEAD, antiplatelet therapy is recommended.	I	A

CAPRIE Study Efficacy of Clopidogrel in Primary Analysis of MI, Ischemic Stroke, or Vascular Death



CAPRIE Steering Committee Lancet 1996; 348: 1329-1339

CAPRIE Study Outcome by Subgroup



CAPRIE Steering Committee Lancet 1996; 348: 1329-1339

Antiplatelet therapy

2016 AHA/ACC Lower Extremity PAD Guidelines

COR	LOE	Recommendations
Antiplatelet Agents		
IIa	C–EO	In asymptomatic patients with PAD (ABI ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death.
IIb	B–R	In asymptomatic patients with borderline ABI (0.91—0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain.[67,68]

2017 ESC-ESVS PAD Guidelines

Recommendations	Class	Level
Lower extremity artery disease *(continued)*		
Because of a lack of proved benefit, antiplatelet therapy is not routinely indicated in patients with isolated asymptomatic LEAD.	III	A

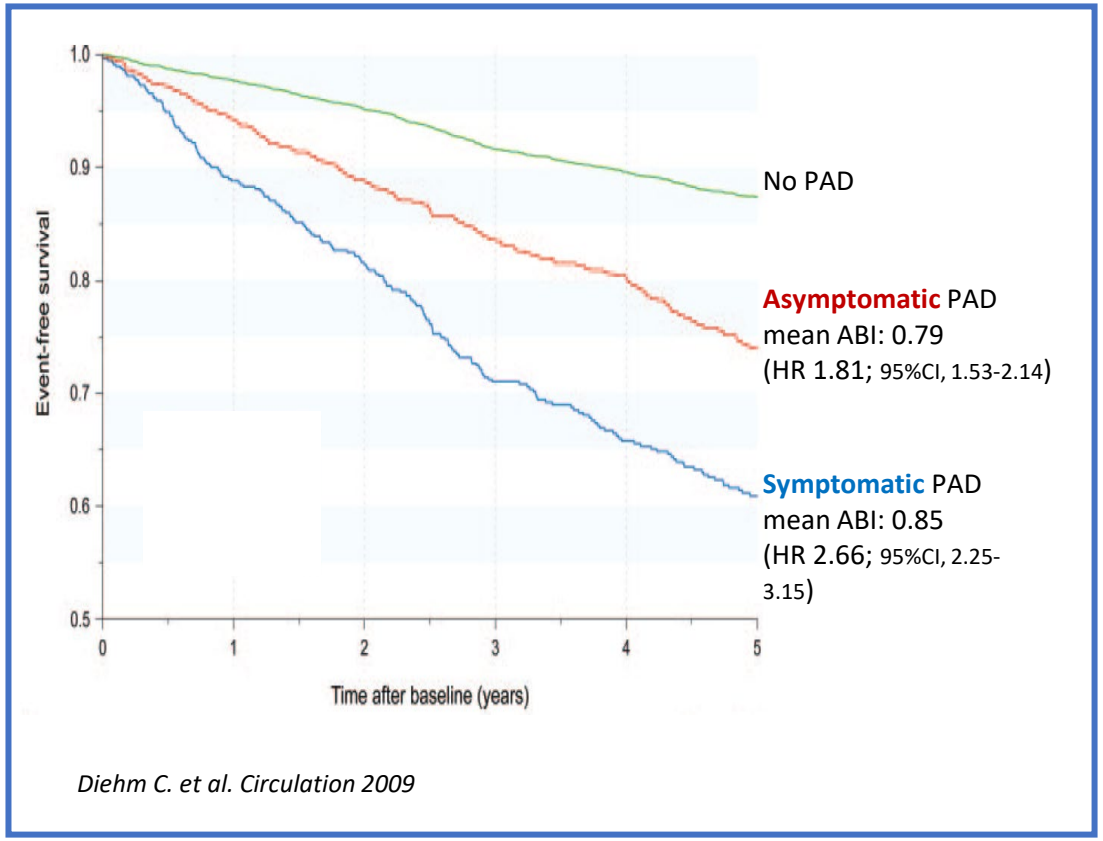
What is new in the 2017 PAD Guidelines? *(continued)*

2017 New/Revised concepts

ESC European Society of Cardiology

- "**Masked PAD**" → pazienti "asintomatici" perché incapaci di camminare per 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 cardiovascolari.
- I pazienti con "masked PAD" hanno in aggiunta un rischio aumentato di eventi sfavorevoli (MALE) agli arti inferiori → PAD più severa

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



Diehm C. et al. Circulation 2009

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

Antiplatelet therapy: DAPT

2016 AHA/ACC Lower Extremity PAD Guidelines

IIb	B-R	The effectiveness of dual antiplatelet therapy (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established.[125,126]
IIb	C-LD	Dual antiplatelet therapy (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization.[127–130]
IIb	B-R	The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain.[131–134]

2017 ESC-ESVS PAD Guidelines

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

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)

2019 New reccomendentions

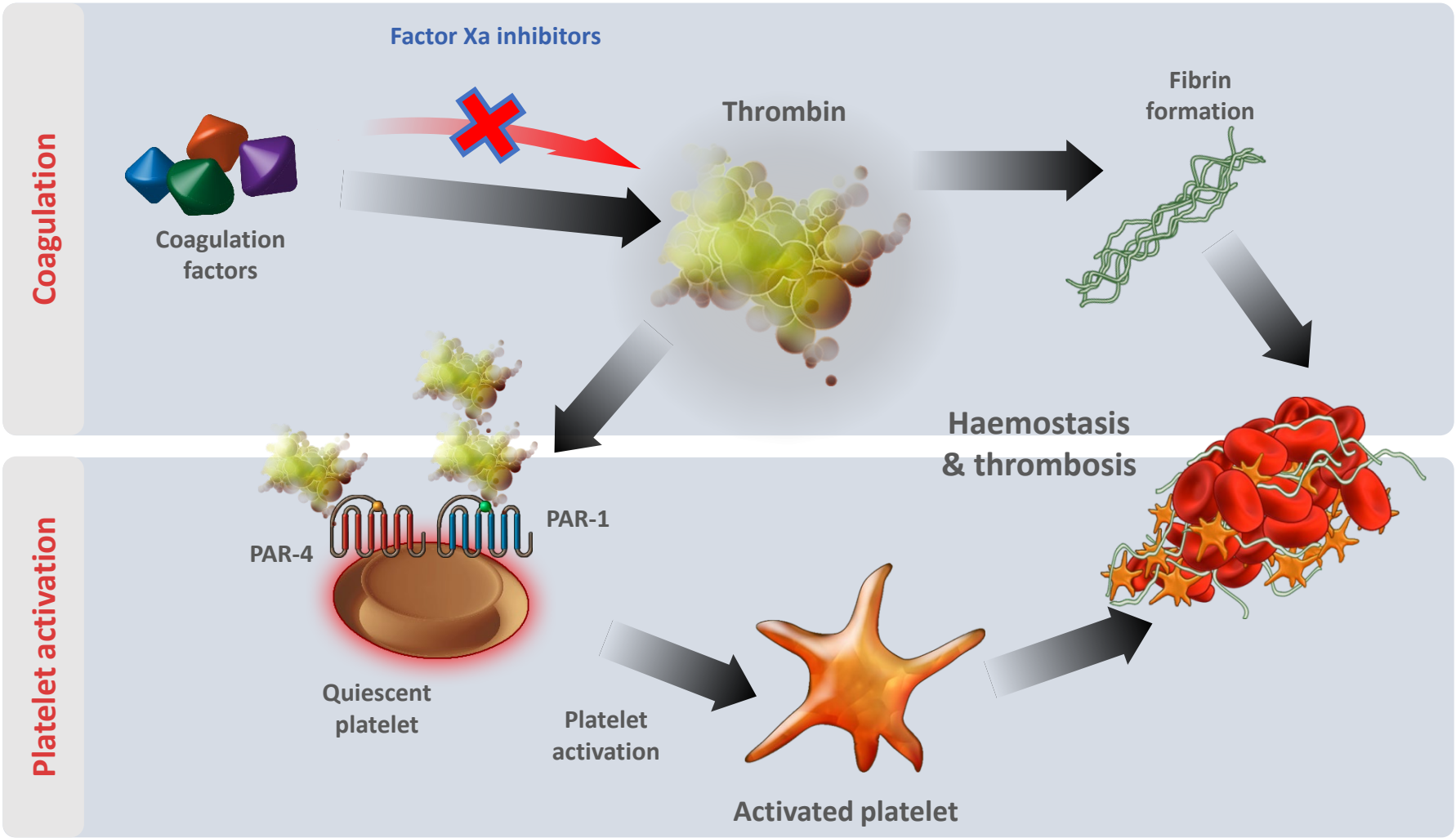
Recommendations for the diagnosis and management of PAD in patients with DM (6)

ESC European Society of Cardiology

Recommendations	Class	Level
LEAD management		
In case of CLTI, revascularization is indicated whenever feasible, for limb salvage.	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 a high bleeding risk, a combination of low-dose rivaroxaban (2.5 mg twice daily) and aspirin (100 mg once daily) should be considered.	IIa	B

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

Rivaroxaban Targets Essential Components of Atherothrombosis to Provide Vascular Protection

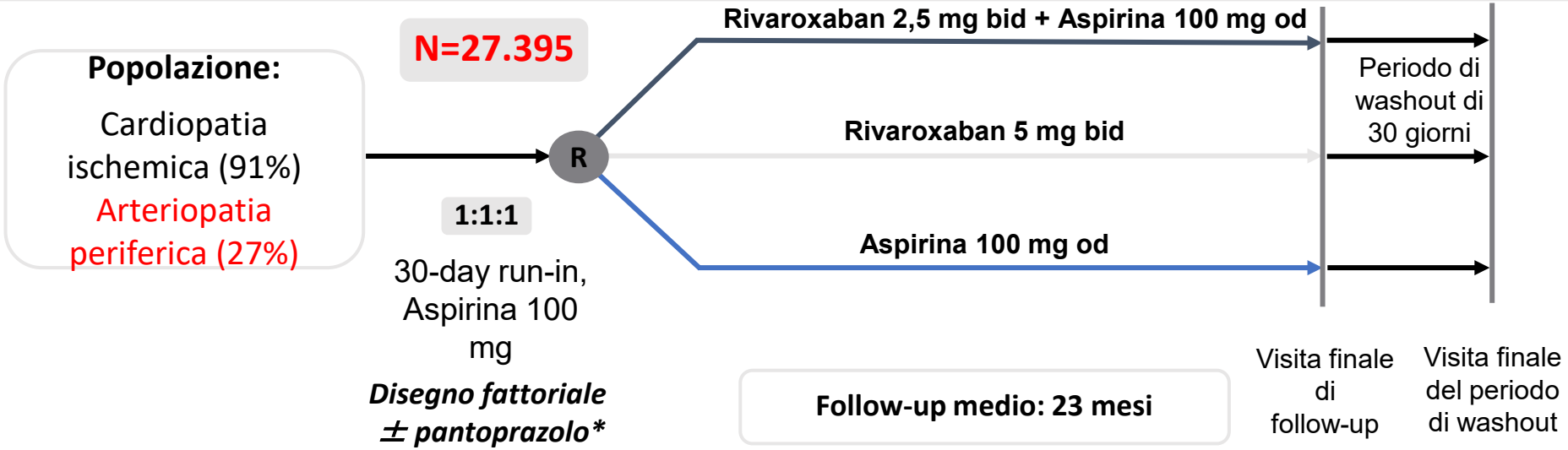


Rivaroxaban impacts not only fibrin formation, but also platelet activation

Angiolillo DJ *et al*, *Eur Heart J* 2010;31:17–28

COMPASS (Cardiovascular OutcoMes for People using Anticoagulation StrategieS)

Obiettivo: **valutare se il trattamento con rivaroxaban da solo o in associazione con ASA sia migliore dell'ASA da solo nella prevenzione di IMA, ictus cerebrale e mortalità cardiovascolare in pazienti con cardiopatia ischemica o arteriopatia periferica**



Lo studio* è stato sospeso prima del previsto in Febbraio 2017 per l'eccesso di efficacia nel braccio rivaroxaban 2,5 mg bid + ASA

* I pazienti che non erano in terapia con un PPI erano randomizzati a pantoprazolo o placebo (disegno fattoriale parziale); la componente PPI pantoprazolo dello studio sta continuando; i dati saranno comunicati una volta completi

Eikelboom JW *et al. N Engl J Med* 2017;377:1319-30

Bosch J *et al. Can J Cardiol* 2017;33:1027-35

PAD-Specific inclusion criteria

- Aorto-femoral bypass surgery
- Limb bypass surgery
- PTA revascularization of the iliac, or the infrainguinal arteries
- Limb or foot amputation for arterial vascular disease
- Intermittent claudication and ABI <0.90 OR peripheral artery stenosis ≥50%
- Carotid revascularization
- Asymptomatic carotid artery stenosis of at least 50%

- Patients with CAD with ABI <0.90 were included in the overall PAD cohort

COMPASS

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

PAD-Specific Limb Outcomes Were Added to Main Study Outcomes for COMPASS

- **Primary cardiovascular outcome was MACE**, defined as:
  - Composite of cardiovascular death, stroke or MI

- **Key composite outcomes for PAD**:
  - Primary limb outcome was major adverse limb events (MALE), defined as development of ALI or CLI and major amputations not included in ALI or CLI
  - The composite of MACE and MALE
  - The composite of MACE, MALE and major amputations not included in ALI or CLI

COMPASS

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

COMPASS: >7000 Patients with symptomatic PAD or CAD+PAD

	Number of patients
All patients with PAD	7470
Symptomatic lower-extremity PAD	4129
Carotid disease	1919
CAD + asymptomatic PAD (ABI <0.90)	1422

- PAD was defined according to patient presentation at enrolment
- Median follow-up: 21 months

COMPASS

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

Baseline Characteristics of Patients with PAD

Characteristic	Rivaroxaban 2.5 mg bid + aspirin N=2492	Rivaroxaban 5 mg bid N=2474	Aspirin N=2504
Age, years, mean ± SD	67.9±8.5	67.8±8.5	67.8±8.5
Current smoker, n (%)	682 (27.4)	685 (27.7)	685 (27.4)
Former smoker, n (%)	1147 (46.0)	1154 (46.6)	1143 (45.6)
Diabetes, n (%)	1100 (44.1)	1083 (43.8)	1104 (44.1)
Hypertension, n (%)	1966 (78.9)	1939 (78.4)	2017 (80.6)
Prior CAD, n (%)	1656 (66.5)	1609 (65.0)	1641 (65.5)
Prior stroke, n (%)	171 (6.9)	177 (7.2)	154 (6.2)
Lipid lowering, n (%)	2088 (83.8)	2074 (83.8)	2074 (82.8)
ACE inhibitor/ARB, n (%)	1715 (68.8)	1757 (71.0)	1765 (70.5)

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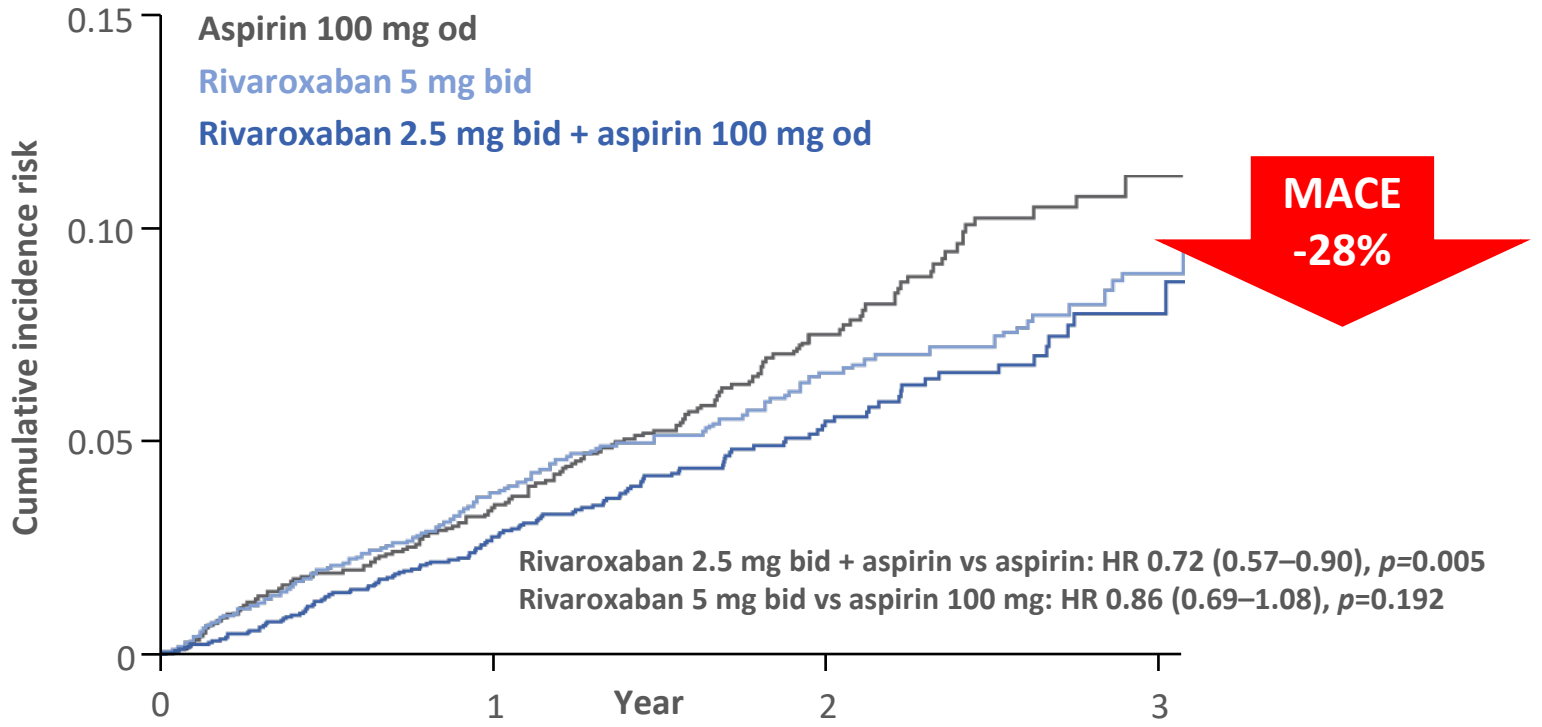
Anand SS *et al*, *Lancet* 2017: doi:10.1016/S0140-6736(17)32757-5

Cumulative incidence of the primary efficacy outcome



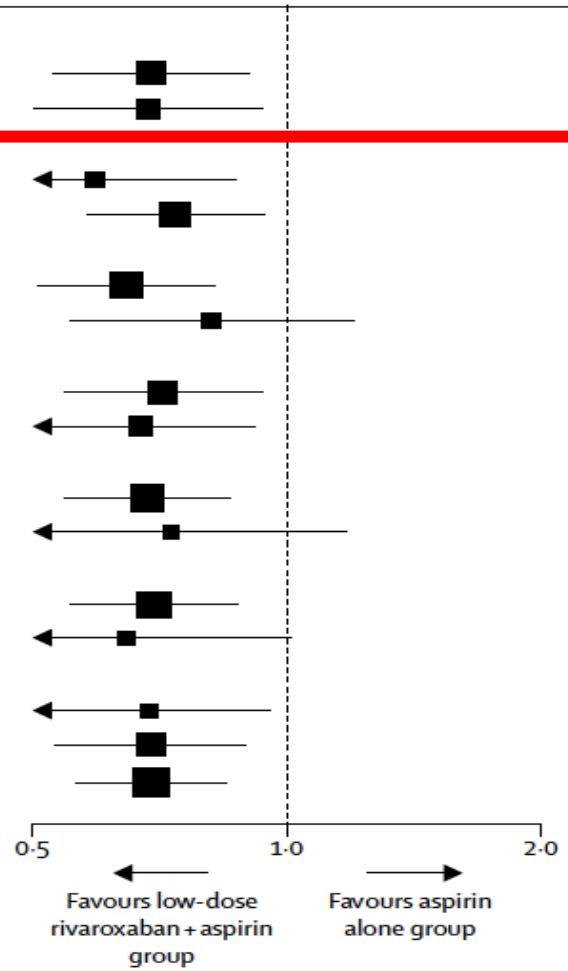
Number at risk				
Rivaroxaban + aspirin	2492	2086	907	127
Rivaroxaban	2474	2044	870	147
Aspirin	2504	2065	930	119

COMPASS

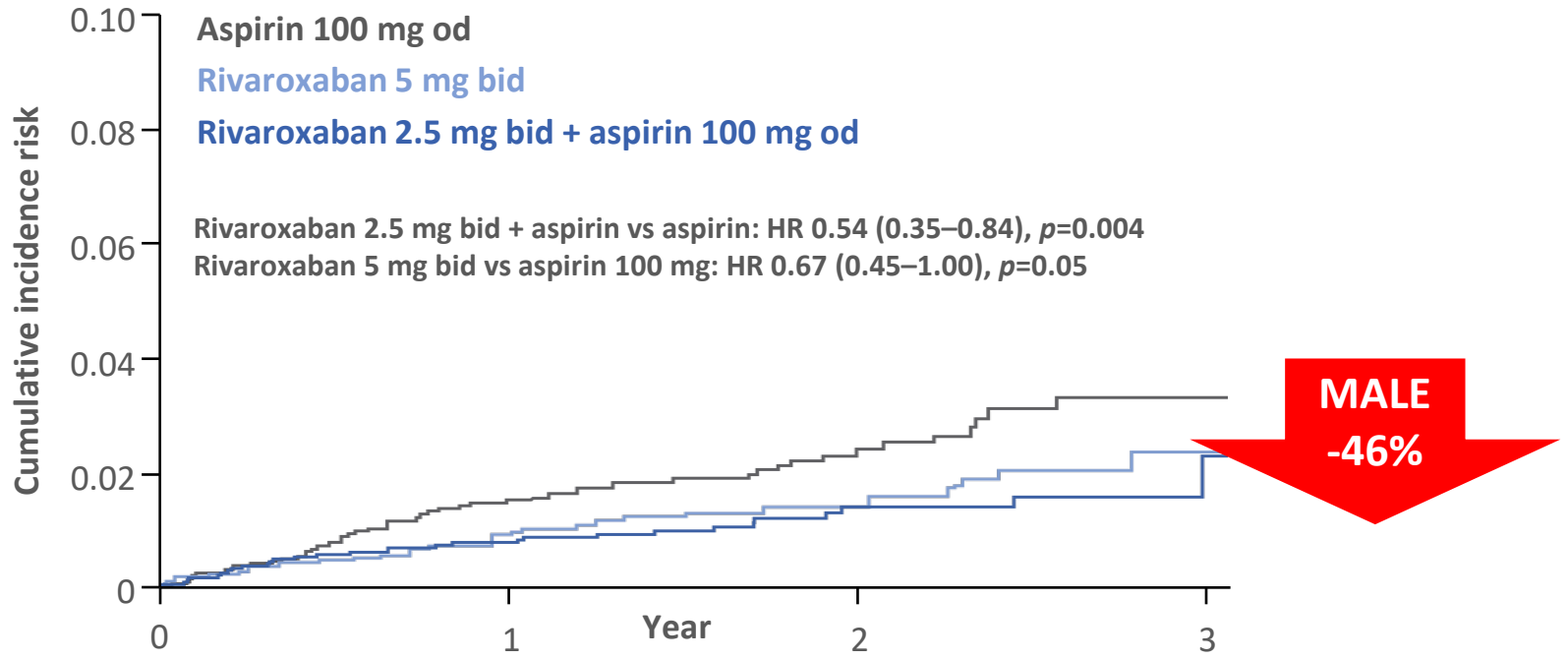
Anand SS *et al*, *Lancet* 2017: doi:10.1016/S0140-6736(17)32757-5

COMPASS AND DIABETES

	Low-dose rivaroxaban + aspirin group	Aspirin alone group	HR (95% CI)	$p_{interaction}$
	No of events/total N (%)	No of events/total N (%)		
Diabetes				
Yes	91/1100 (8%)	128/1104 (12%)	0·69 (0·53–0·91)	0·97
No	66/1392 (5%)	97/1400 (7%)	0·69 (0·50–0·94)	
Smoking status				
Current	41/682 (6%)	71/685 (10%)	0·59 (0·40–0·87)	0·32
Former or never	116/1810 (6%)	154/1819 (9%)	0·74 (0·58–0·94)	
CAD				
Yes	111/1656 (7%)	168/1641 (10%)	0·65 (0·51–0·82)	0·33
No	46/836 (6%)	57/863 (7%)	0·82 (0·55–1·20)	
ABI				
<0·9	89/1266 (7%)	129/1313 (10%)	0·71 (0·54–0·94)	0·76
≥0·9	68/1226 (6%)	96/1191 (8%)	0·67 (0·49–0·92)	
Symptomatic PAD				
Yes	128/2026 (6%)	186/2039 (9%)	0·68 (0·55–0·86)	0·80
No	29/466 (6%)	39/465 (8%)	0·73 (0·45–1·18)	
PAD lower extremities				
Yes	127/1875 (7%)	175/1824 (10%)	0·70 (0·55–0·88)	0·79
No	30/617 (5%)	50/680 (7%)	0·64 (0·41–1·01)	
eGFR				
<60	60/688 (9%)	86/706 (12%)	0·69 (0·49–0·96)	0·99
≥60	97/1803 (5%)	139/1798 (8%)	0·69 (0·53–0·89)	
Overall PAD	**157/2492 (6%)**	**225/2504 (9%)**	**0·69 (0·56–0·85)**	



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

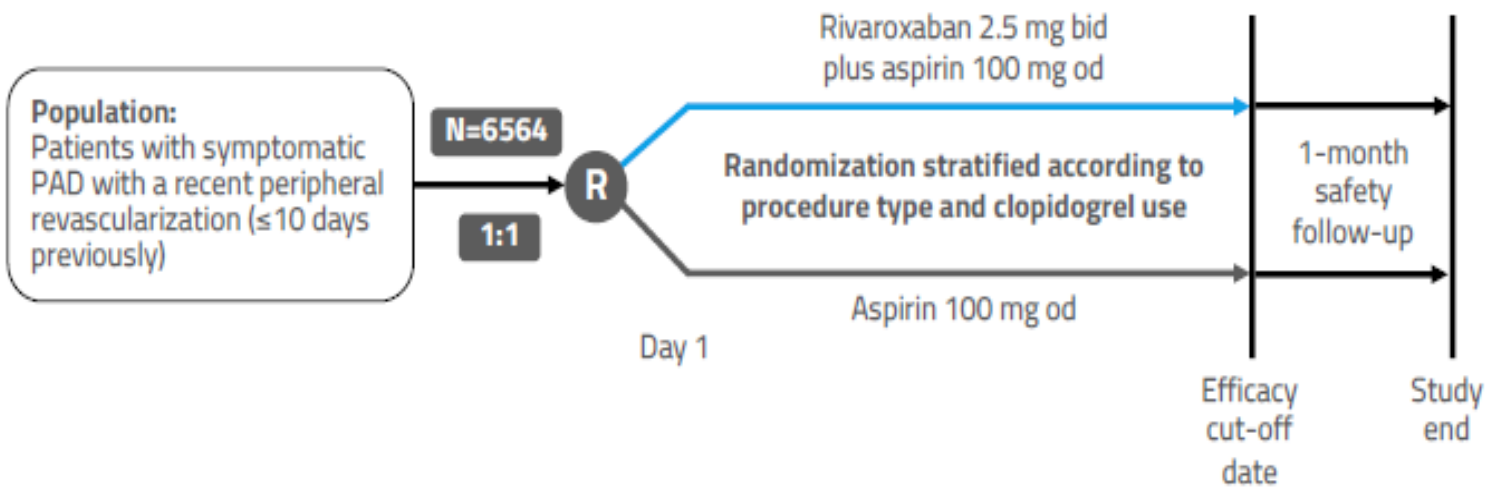
Safety outcomes

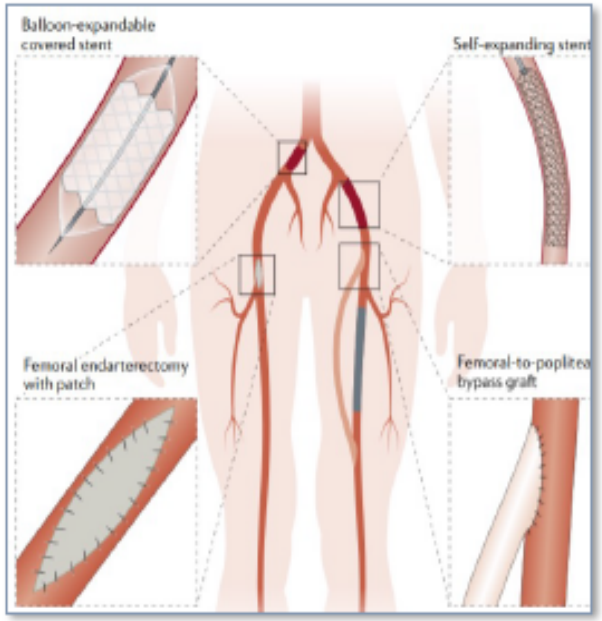
Outcome	Rivaroxaban 2.5 mg bid + aspirin N=2492	Rivaroxaban 5 mg bid N=2474	Aspirin N=2504	Rivaroxaban 2.5 mg bid + aspirin vs aspirin		Rivaroxaban 5 mg bid vs aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Major bleeding	77 (3)	79 (3)	48 (2)	**1.61 (1.12–2.31)**	**0.0089**	1.68 (1.17–2.40)	0.0043
Fatal	4 (<1)	5 (<1)	3 (<1)	–	–	–	–
Intracranial	5 (<1)	6 (<1)	9 (<1)	0.56 (0.19–1.66)	–	0.68 (0.24–1.91)	–
Fatal or symptomatic bleeding into a critical organ	21 (1)	26 (1)	19 (1)	1.10 (0.59–2.05)	-	1.39 (0.89–3.09)	-

COMPASS

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

VOYAGER :the Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (peripheral artery disease)

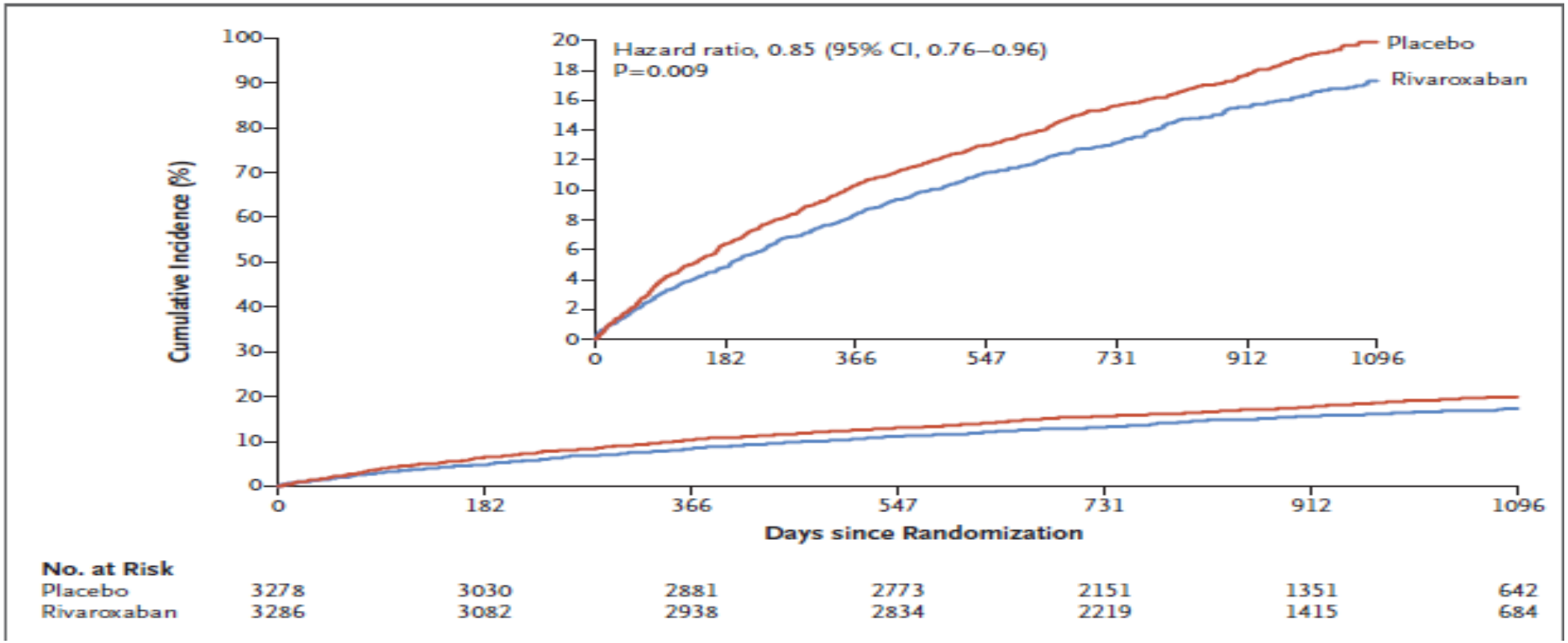




Primary efficacy endpoint: ALI, major amputation of vascular aetiology, MI, ischaemic stroke or CV death

Bonaca MP *et al. N Engl J Med* 2020;382:1994—2004.

VOYAGER :the Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (peripheral artery disease)



Bonaca MP *et al. N Engl J Med* 2020;382:1994—2004.

Circulation

Circulation. 2021;143:e875–e891. DOI: 10.1161/CIR.0000000000000967

AHA POLICY STATEMENT

Reducing Nontraumatic Lower-Extremity Amputations by 20% by 2030: Time to Get to Our Feet

A Policy Statement From the American Heart Association

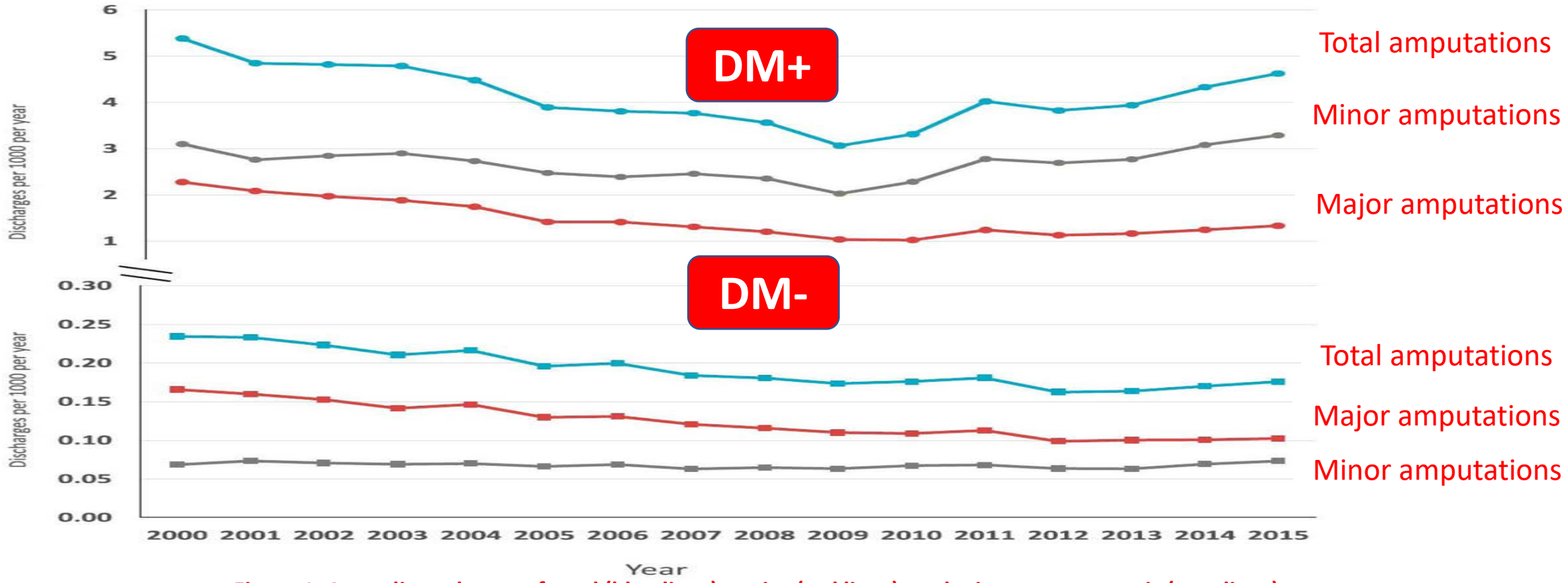


Figure 1. Age-adjusted rates of total (blue lines), major (red lines), and minor nontraumatic (gray lines) lower-extremity amputations in adults with diabetes (top) and without diabetes (bottom).

State of the art review

Update on prevention of diabetic foot ulcer

Arch Med Sci Atheroscler Dis 2021; 6: e123–e131
DOI: https://doi.org/10.5114/amsad.2021.107817

Cesare Miranda[1], Roberto Da Ros[2], Raffaele Marfella[3]

Multisciplinary approach

Glycaemic control	Management of PAD	Identifying the at-risk foot	Regularly inspecting and examining the at-risk foot
HbA1c target : • for most adults is <7.0%(<53 mol/mol). • for young patients is <6.5% (48 mol/mol) if this can be achieved without significant hypoglycaemia or other adverse effects of treatment. • for elderly patients is <8% (64 mmol/mol) or ≤9% (75 mmol/mol) may be adequate .	**Lifestyle changes:** • Smoking cessation. • Regular exercise. • Healthy diet. • Weight management. **Medical therapy:** • Lipid control: LDL<55 mg/dl. • Hypertension control. • SGLT2 inhibitor or GLP-1 RA with demonstrated CVD benefit. **Antithrombotic therapy:** • antiplatelet therapy in symptomatic PAD.	• Medical history. • Objective examination of the feet. • Screening of peripheral neuropathy and PAD.	• IWGDF Risk Stratification Follow-up.
Educating the patient, family and healthcare providers	**Ensuring routine wearing of appropriate footwear**	**Treating risk factors for ulceration**	**Integrated foot care**
• Design and implementation of appropriate assessment tools.	• Footwear fits. • Custom-made orthopaedic footwear. • Custom-made insoles.	• Pre-ulcerative lesion treatment. • Preventative surgery.	• Combination of key elements that underpin prevention of foot problems.

Grazie per l'attenzione