



SISA LOMBARDIA 24 ottobre 2019

Il Paziente con Malattia Vascolare Periferica (PVD)



Alberto Zambon
Università di Padova

AGENDA

- Setting the Background: ESC/ESVS 2017 and ESC/EAS 2019 Guidelines
- Come valutiamo la presenza di PAD
- Il colesterolo LDL è un predittore di arteriopatia periferica?
- La terapia ipocoolesterolemizzante riduce eventi e mortalità CV nei pazienti con arteriopatia periferica?
- La terapia ipocoolesterolemizzante riduce l'incidenza delle complicanze ischemiche a carico degli arti inferiori nei pazienti con arteriopatia periferica?

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



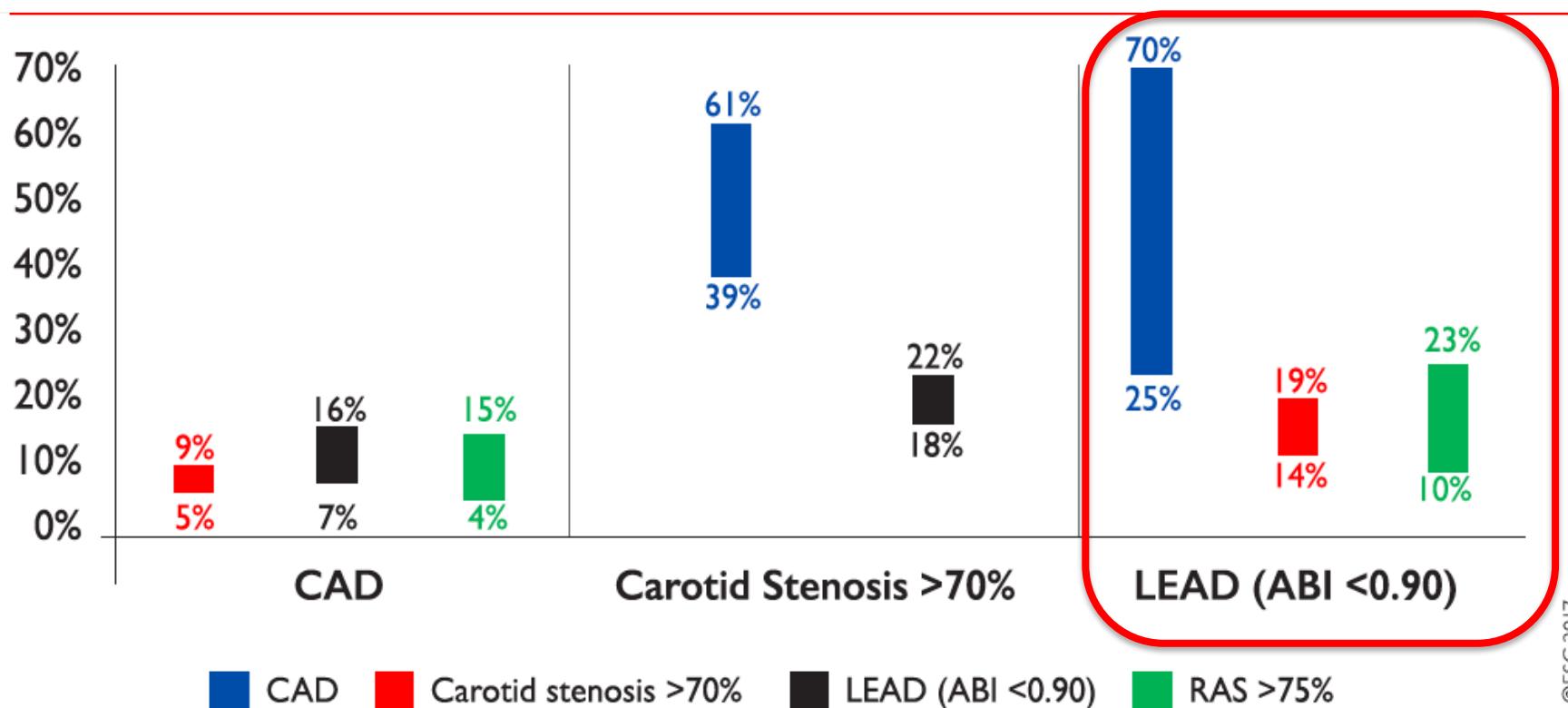
- Approximately 202 million people are affected with LEAD* worldwide, of whom almost 40 million are living in Europe
- LEAD usually appears after the age of 50 years, with an exponential increase after the age of 65 years. This rate reaches 20% by the age of 80 years

*LEAD: Lower extremity artery disease - Patologia aterosclerotica del tratto aortoiliaco, femoro-popliteo e sottopopliteo

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

Authors/Task Force Members: Victor Aboyans* (ESC Chairperson) (France), Jean-Baptiste Ricco*¹ (Co-Chairperson) (France), Marie-Louise E. L. Bartelink (The Netherlands), Martin Björck¹ (Sweden), Marianne Brodmann (Austria), Tina Cohnert¹ (Austria), Jean-Philippe Collet (France), Martin Czerny (Germany),

REPORTED RATE RANGES OF OTHER LOCALIZATIONS OF ATHEROSCLEROSIS IN PATIENTS WITH A SPECIFIC ARTERIAL DISEASE

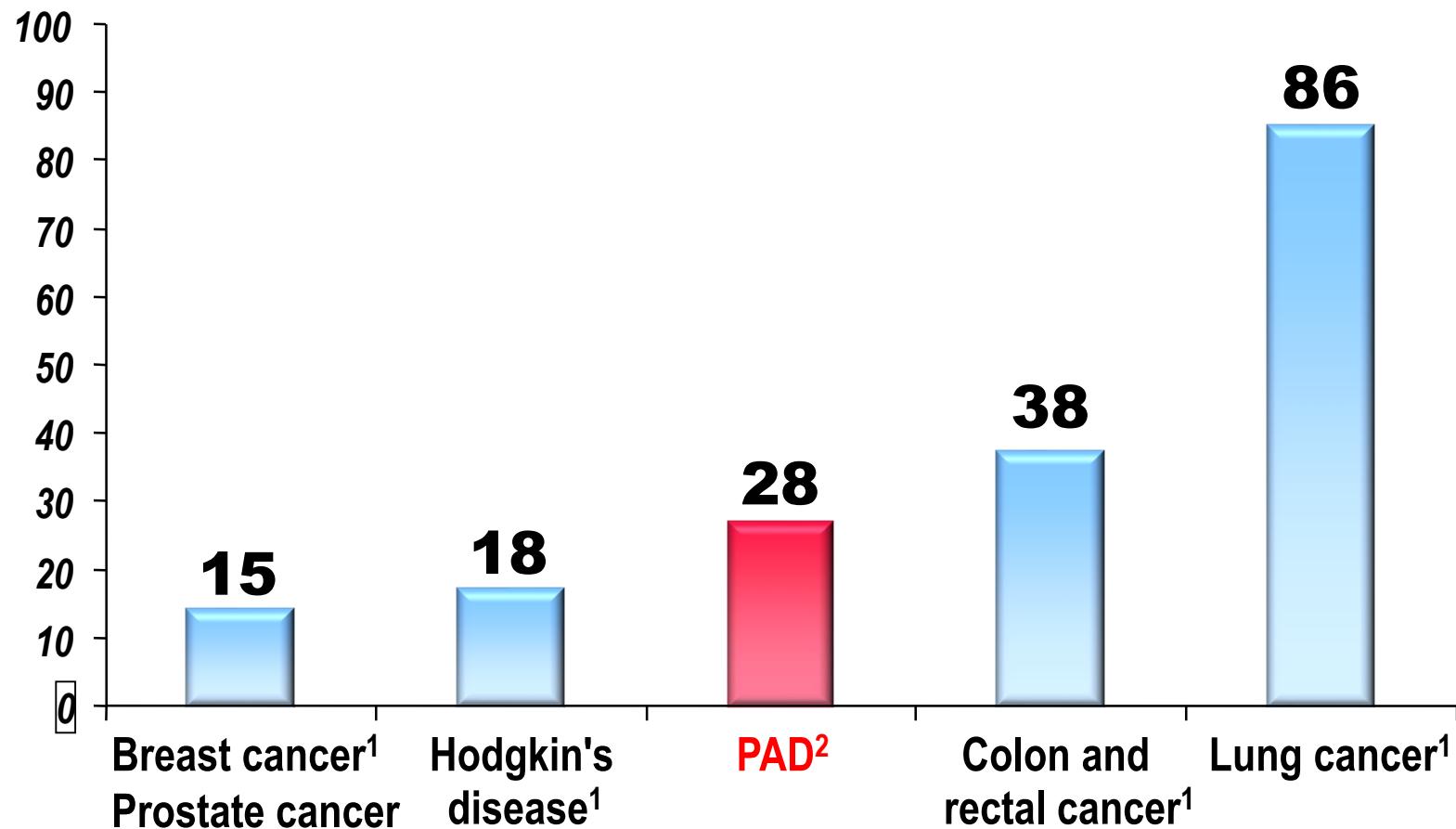


LEAD: Lower extremity artery disease

RAS: Renal artery disease

ESC/ESVS 2017 - European Heart Journal (2018) 39, 763–821

Relative 5-year PAD mortality rates versus other common pathologies



¹American Cancer Society. Cancer Facts and Figures – 2007.

²Kamposzinski RF, Bernhard VM. In: Vascular Surgery (Rutherford RB, ed). Philadelphia, PA: WB Saunders; 1999;chap 53.

2019 ESC/EAS GUIDELINES: CV RISK CATEGORIES

VERY HIGH RISK	HIGH RISK	MODERATE RISK	LOW RISK
<p>People with any of the following:</p> <ul style="list-style-type: none"> • Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularisation (PCI, CABG, and other arterial revascularisation procedures), stroke and TIA, and PERIPHERAL ARTERIAL DISEASE. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound • Diabetes Mellitus with target organ damage,* or at least three major risk factors, or early onset of T1DM of long duration (>20 years) • Severe CKD (eGFR <30 mL/min/1.73 m²) • A calculated SCORE ≥10% for 10-year risk of fatal CVD • FH with ASCVD or with another major risk factor 	<p>People with:</p> <ul style="list-style-type: none"> • Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg • Patients with FH without other major risk factors • Patients with DM without target organ damage, with DM duration ≥10 years or another additional risk factor • Moderate CKD (eGFR 30—59 L/min/1.73 m²) • A calculated SCORE ≥ 5% and <10% for 10-year risk of fatal CVD 	<ul style="list-style-type: none"> • Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors • Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD 	<ul style="list-style-type: none"> • Calculated SCORE <1% for 10-year risk of fatal CVD

ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM = type 2 DM; TC = total cholesterol; TIA = transient ischaemic attack.

Adapted from: Mach F, et al. Eur Heart J 2019. doi:10.1093/eurheartj/ehz455. Epub ahead of print.

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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 ≥ 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

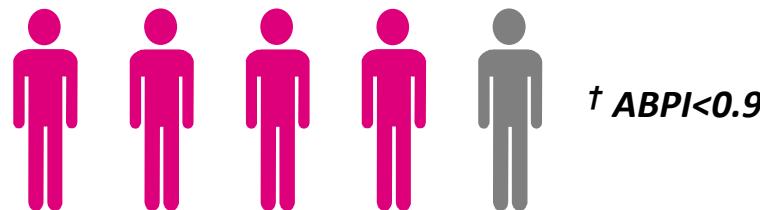
→ **LDL-C < 55 mg/dl**
(ESC EAS 2019 Guidelines)

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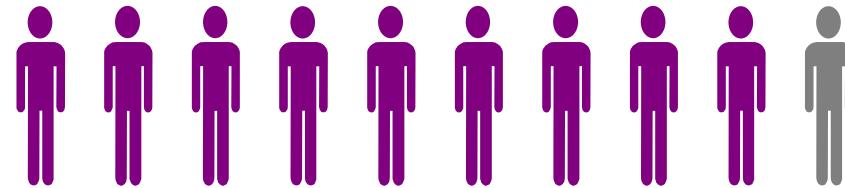
- Setting the Background: ESC/ESVS 2017 and ESC/EAS 2019 Guidelines
- **Come valutiamo la presenza di PAD:**
 - Esame Obiettivo
 - **Ankle Brachial Index (ABI)** - First line test
 - Doppler Ultrasound (DUS) – First line imaging
 - CTA Computed tomography angiography e MRA risonanza

Reliance on classical IC symptoms leads to an underestimation of PAD prevalence

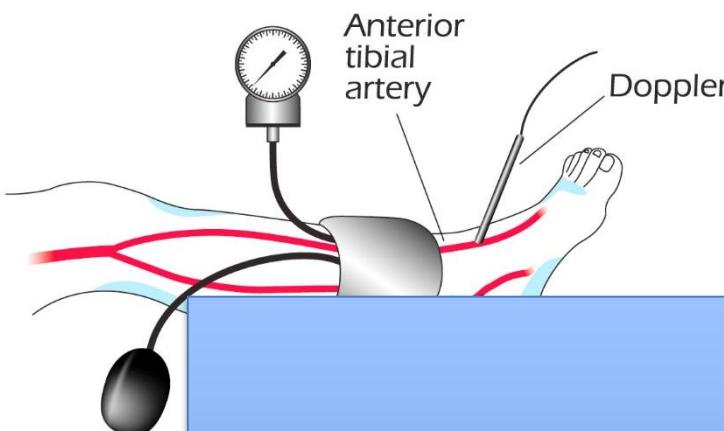
1 in 5 people over 65 visiting the GP has PAD[†]



Only 1 in 10 of these PAD patients will have classical symptoms of intermittent claudication (IC)



ESC/ESVS 2017 - Ankle Brachial Index (ABI)

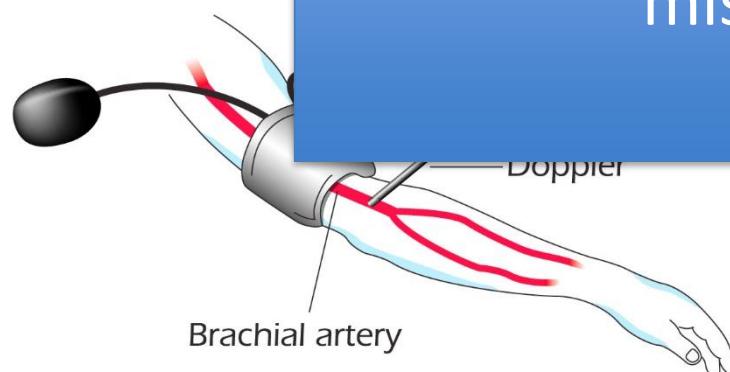


I. Who should have an ABI measurement in clinical practice?

- Patients with clinical suspicion for LEAD:
 - Lower extremities pulse abolition and/or arterial bruit
 - Typical intermittent claudication or symptoms suggestive for LEAD

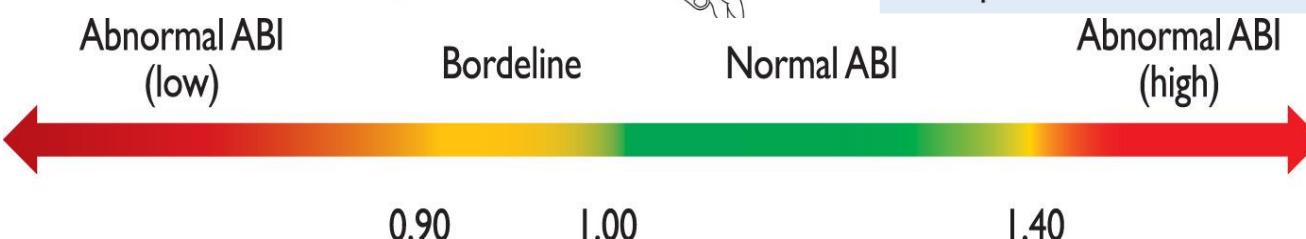
wing clinical

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



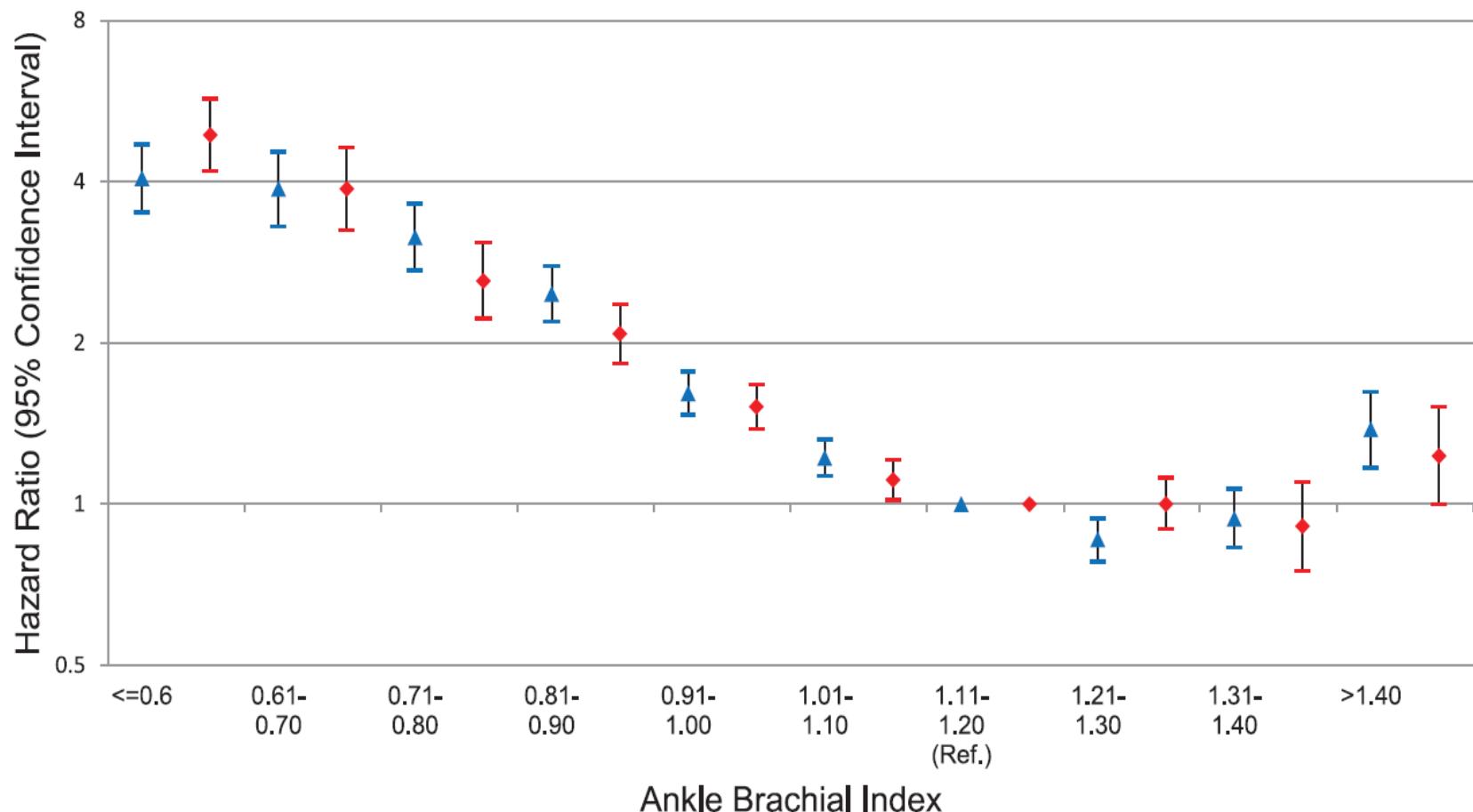
3. How to interpret the ABI?

- For diagnosis of LEAD interpret each leg separately (one ABI per leg).
- For the CV risk stratification: take the lowest ABI between the two legs.
- Interpretation:



Hazard ratios for total MORTALITY in men and women by ankle-brachial index (ABI) at baseline for all studies combined in the ABI collaboration

2886 adults aged 70 to 79 followed for a mean of 6.7 years



Ankle-brachial index measurement

Recommendations	Class	Level
Measurement of the ABI is indicated as a first-line non-invasive test for screening and diagnosis of LEAD.	I	C

Imaging in patients with LEAD

Recommendations	Class	Level
DUS is indicated as first-line imaging method to confirm LEAD lesions.	I	C
DUS and/or CTA and/or MRA are indicated for anatomical characterization of LEAD lesions and guidance for optimal revascularization strategy.	I	C
Data from an anatomical imaging test should always be analyzed in conjunction with symptoms and haemodynamic tests prior to treatment decision.	I	C
DUS screening for AAA should be considered.	IIa	C

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L'impatto del colesterolo LDL in diversi distretti arteriosi

EPIC-Norfolk prospective population study

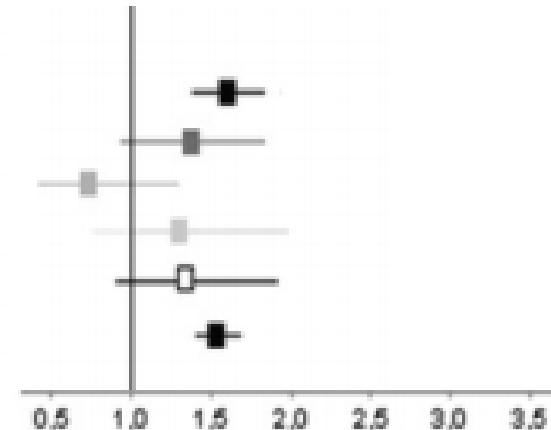
21.798 participants

LDL-C and CAD
HR: 1.50 (1.35, 1.68)



LDL-c
CAD
Ischemic stroke
Hemorrhagic stroke
Abdominal aneurysm
PAD
Overall CVD

LDL-C and PAD
NS



Hazard ratios for PAD by LDL-C quartiles

(Model 1 unadjusted, Model 2 age- and sex-adjusted, Model 3 is multiple-adjusted)

	LDL-c quartiles				P-value*
	1 <3.24	2 3.25–3.88	3 3.89–4.59	4 >4.60	
Range, mmol/L	<125 mg/dl				
PAD (n = 227)					>180 mg/dl
Model 1	1.00	0.91 (0.59–1.38)	1.48 (1.02–2.16)	1.60 (1.11–2.32)	0.002
Model 2	1.00	0.80 (0.53–1.22)	1.21 (0.83–1.77)	1.24 (0.85–1.81)	0.072
Model 3	1.00	0.80 (0.53–1.22)	1.20 (0.82–1.77)	1.24 (0.84–1.82)	0.08

Predittori a 20 anni di coronaropatia e arteriopatia periferica

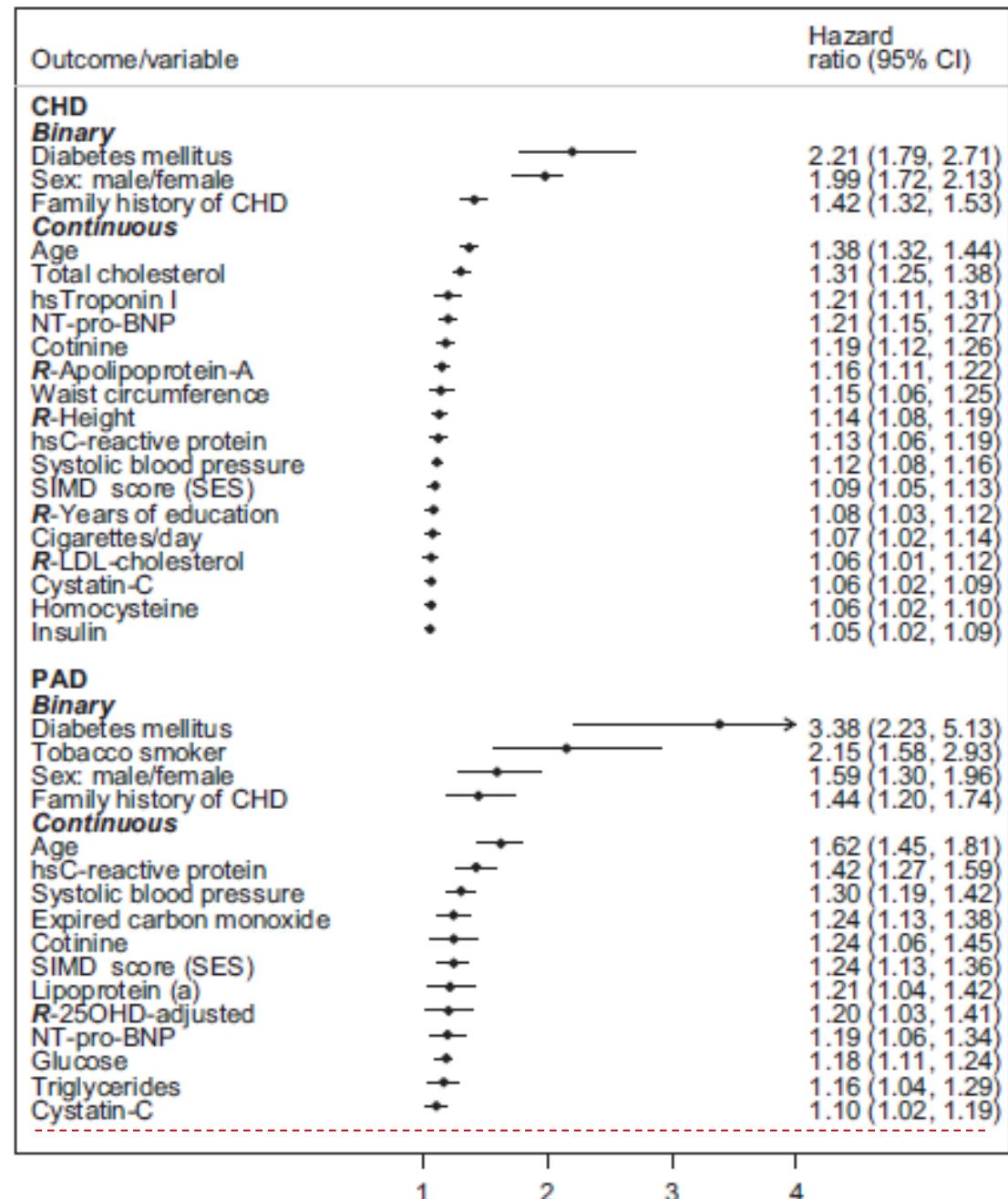
Scottish Heart Health Extended Cohort
15.737 participants

LDL-C and CHD
HR: 1.06 (1.01, 1.12)

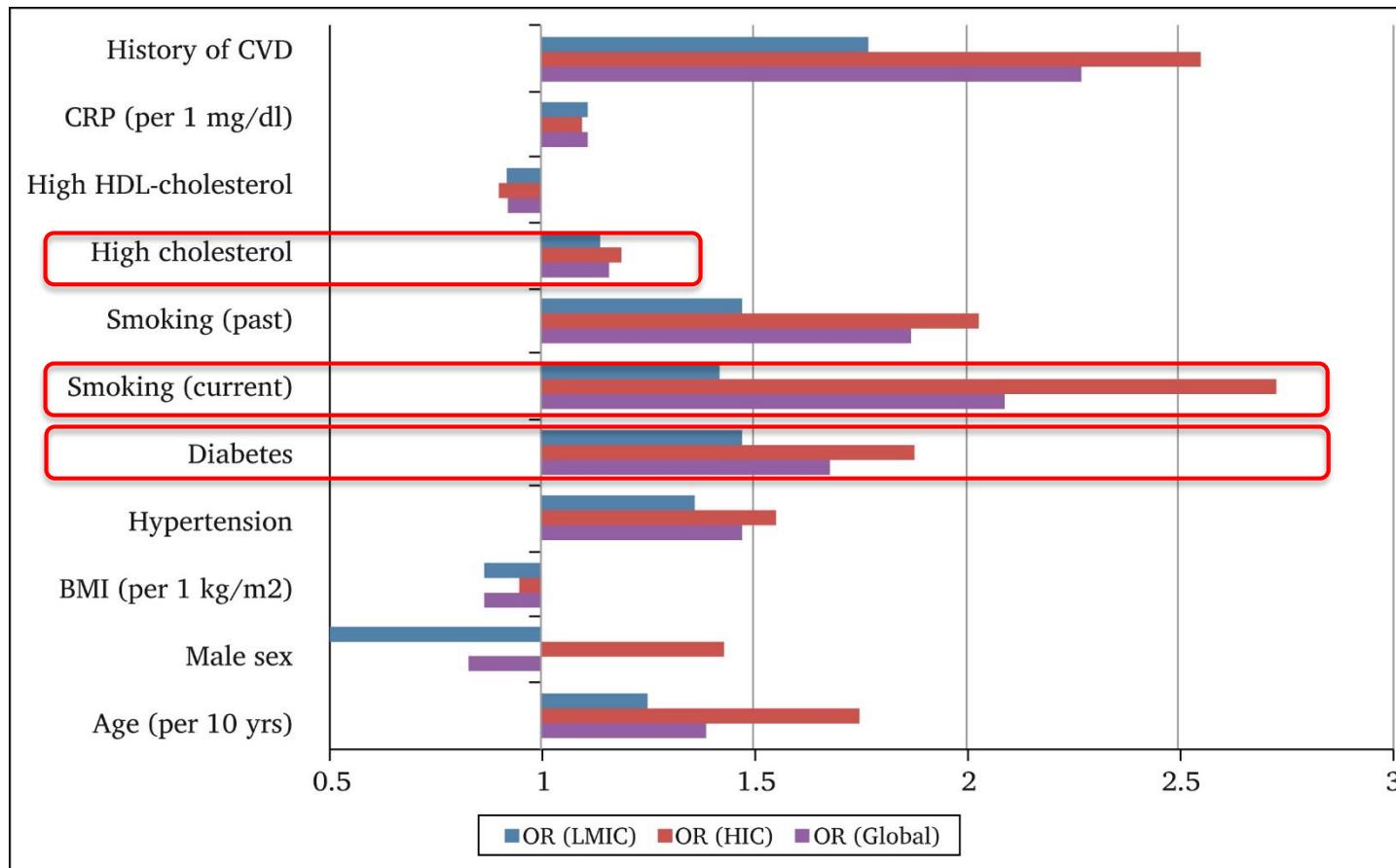


Diabete/fumo/infiammazione

LDL-C and PAD
NS



EPIDEMIOLOGY OF PERIPHERAL ARTERY DISEASE



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

BMI = Body mass index; CRP = C-reactive protein;

CVD = cardiovascular disease; HDL = high-density lipoprotein.

Lipoprotein (a) and risk of coronary, cerebrovascular and peripheral artery disease; the EPIC-Norfolk prospective population study

- N=21,798 male and female inhabitants of Norfolk, United Kingdom, aged between 39 and 79 years old
- During 212,981 person-years at risk, a total of 2365 CAD, 284 ischemic stroke and 596 PAD events occurred in 18,720 participants

Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P value
Mean Lp(a) level ,mg/dl	4.1(1.1)	8.5(1.5)	17.3(4.3)	54.7(24.9)	<0.001
Lp(a) range, mg/dl	0.1-6.2	5.9-11.7	11.2-27.9	26.6-175.0	

Cardiovascular outcomes by sex-specific Lp(a) quartiles and per 1 standard deviation increase in Ln[Lp(a)]

Outcome	Model	n	events	Q1	Q2	Q3	Q4	1 SD Ln[Lp(a)]	P-trend *	P-nonlinearity †
PAD	1	18716	596	1	1.01(0.79-1.31)	1.04(0.81-1.34)	1.94(1.55-2.43)	1.32(1.22-1.43)	<0.00001	0.0002
	2	17867	544	1	1.07(0.82-1.41)	1.06(0.81-1.38)	2.09(1.64-2.65)	1.36(1.25-1.48)	<0.00001	0.0002
	3	15930	484	1	1.02(0.76-1.37)	1.09(0.82-1.45)	2.06(1.59-2.67)	1.37(1.25-1.50)	<0.00001	0.0002
CAD	1	18715	2365	1	1.07(0.95-1.21)	1.12(0.99-1.26)	1.49(1.33-1.67)	1.17(1.13-1.22)	<0.00001	0.009
	2	17866	2202	1	1.09(0.96-1.24)	1.11(0.98-1.26)	1.49(1.32-1.68)	1.17(1.13-1.23)	<0.00001	0.007
	3	15930	1984	1	1.01(0.88-1.16)	1.11(0.97-1.27)	1.33(1.17-1.52)	1.13(1.04-1.22)	<0.00001	0.174

Model 1 adjusted for age and sex.

Model 2 adjusted for age, sex, body mass index, total cholesterol adjusted for Lp(a) levels, HDL cholesterol, and triglycerides.

Model 3 was adjusted for all covariates in Model 2 in addition to smoking, alcohol consumption, baseline antihypertensive therapy, baseline lipid-lowering therapy, diabetes mellitus, physical activity level, serum creatinine levels, fibrinogen levels, apolipoprotein A-I, apolipoprotein B, CRP levels, history of myocardial infarction at baseline, history of stroke at baseline, family history of myocardial infarction, family history of stroke, postmenopausal status and use of hormone replacement therapy.

Conclusion: Lp(a) levels were associated with future PAD and CAD events. The association between Lp(a) and cardiovascular disease was not modified by LDL-C levels.

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Adapted from: Mach F, et al. Eur Heart J 2019. doi:10.1093/eurheartj/ehz455.

2019 ESC/EAS GUIDELINES: Recommendations for lipid-lowering drugs in patients with peripheral arterial disease (including carotid artery disease)

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

Recommended treatment goals for LDL-C Lowering therapy

Risk category	LDL goals (starting with untreated LDL-C)	
	2016	2019
Very-high risk	<1.8 mmol/L (70 mg/dL) or >50% ↓ if LDL-C 1.8–3.5 mmol/L (70–135 mg/dL)	<1.4 mmol/L (<55 mg/dL) and >50% ↓

ASCVD = atherosclerotic cardiovascular disease; PAD = peripheral arterial disease;

PCSK9 = proprotein convertase subtilisin/kexin type 9.

RISCHI NEI PAZIENTI CON ARTERIOPATIA PERIFERICA

MACE

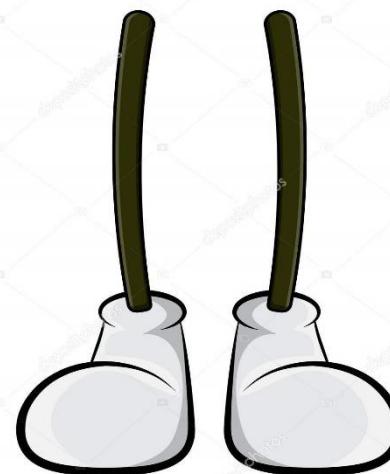
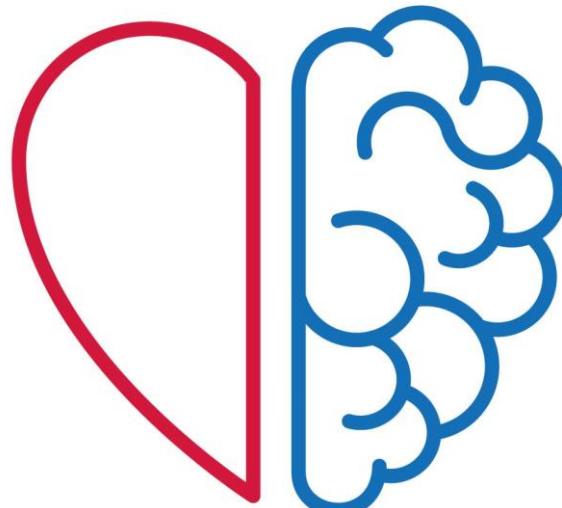
rischio di eventi avversi
cardiovascolari maggiori inclusi

- infarto miocardico
- ictus
- morte cardiovascolare

MALE

maggiori eventi avversi degli arti

- l'ischemia acuta degli arti
- rivascolarizzazione periferica urgente
- l'amputazione maggiore



Statine: effetti sugli *outcomes* CV nell'arteriopatia periferica

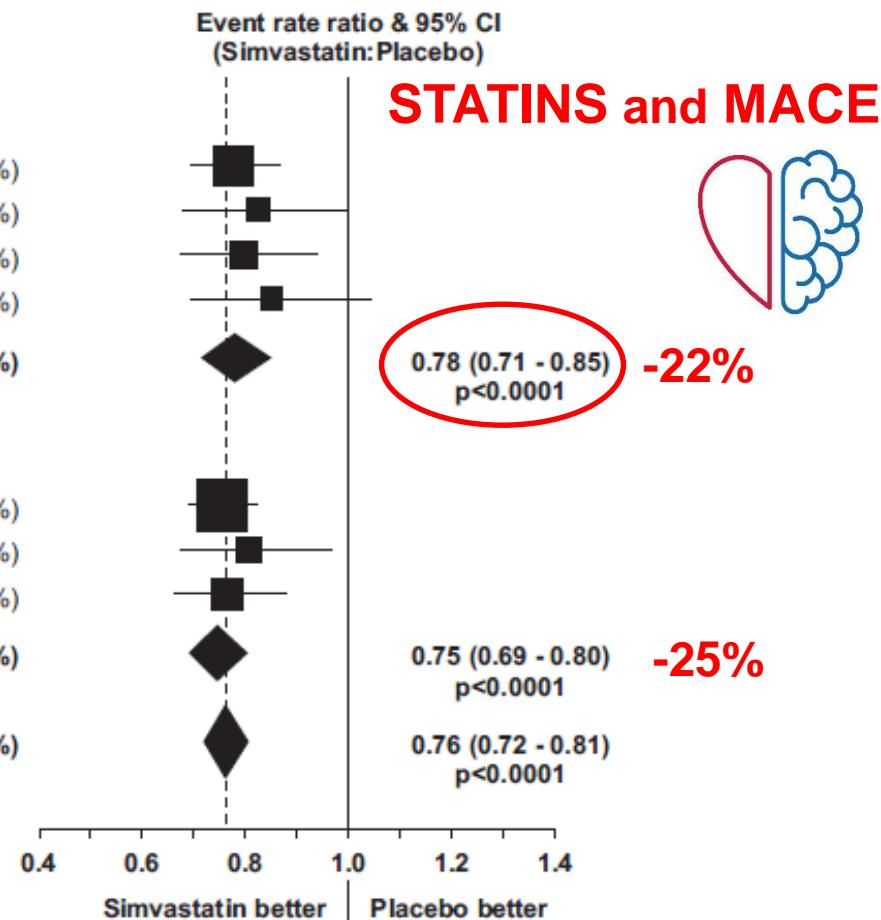
Heart Protection Study Collaborative Group

6.748 participants with PAD (2% with amputation) and 13.788 other high-risk participants

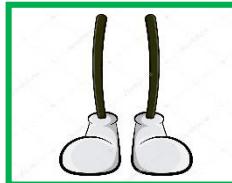
Simvastatin 40 mg VS placebo

Endpoints: myocardial infarction, coronary death, stroke, or revascularization

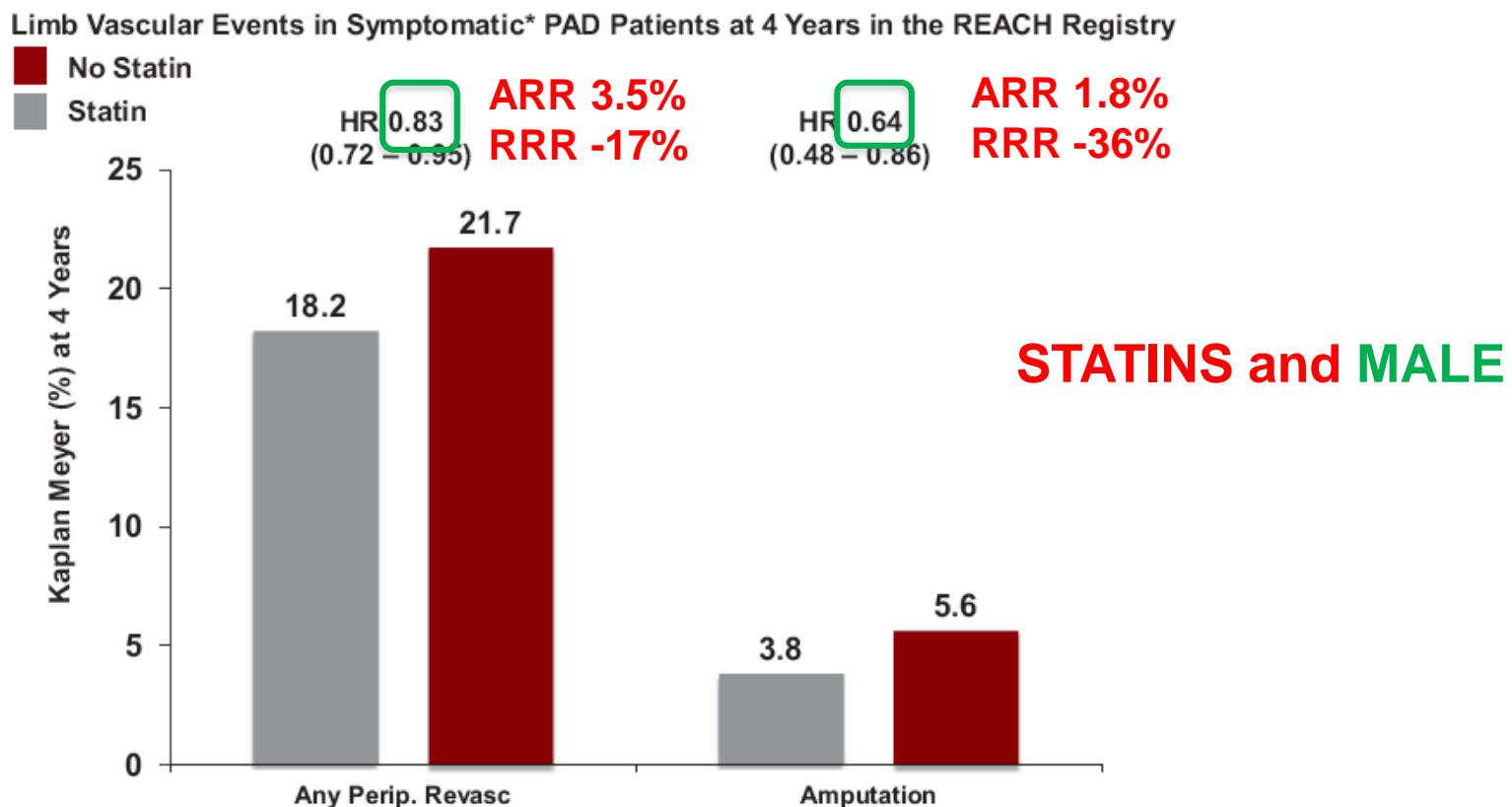
Prior disease categories	Vascular events/people (& %)	
	Simvastatin	Placebo
PAD		
+ CHD	568/ 2059 (27.6%)	681/ 1988 (34.3%)
+ Cerebrovascular	182/ 554 (32.9%)	227/ 584 (38.9%)
+ Diabetes mellitus	256/ 787 (32.5%)	309/ 792 (39.0%)
+ None of above	163/ 699 (23.3%)	208/ 766 (27.2%)
Any PAD	895/ 3384 (26.4%)	1101/ 3364 (32.7%)
No PAD		
+ CHD	891/ 4635 (19.2%)	1160/ 4704 (24.7%)
+ Cerebrovascular	224/ 1091 (20.5%)	261/ 1051 (24.8%)
+ Diabetes mellitus	345/ 2191 (15.7%)	439/ 2193 (20.0%)
No PAD	1138/ 6885 (16.5%)	1484/ 6903 (21.5%)
ALL PATIENTS	2033/10269 (19.8%)	2585/10267 (25.2%)



Effect of statin treatment on limb vascular events, including peripheral revascularization and amputation, in patients with symptomatic PAD* in REACH REGISTRY



5861 patients with symptomatic PAD, 62.2% in statin therapy at baseline



* PAD defined as current intermittent claudication and an ABI <0.90 and a history of intermittent claudication in addition to a history of peripheral vascular intervention

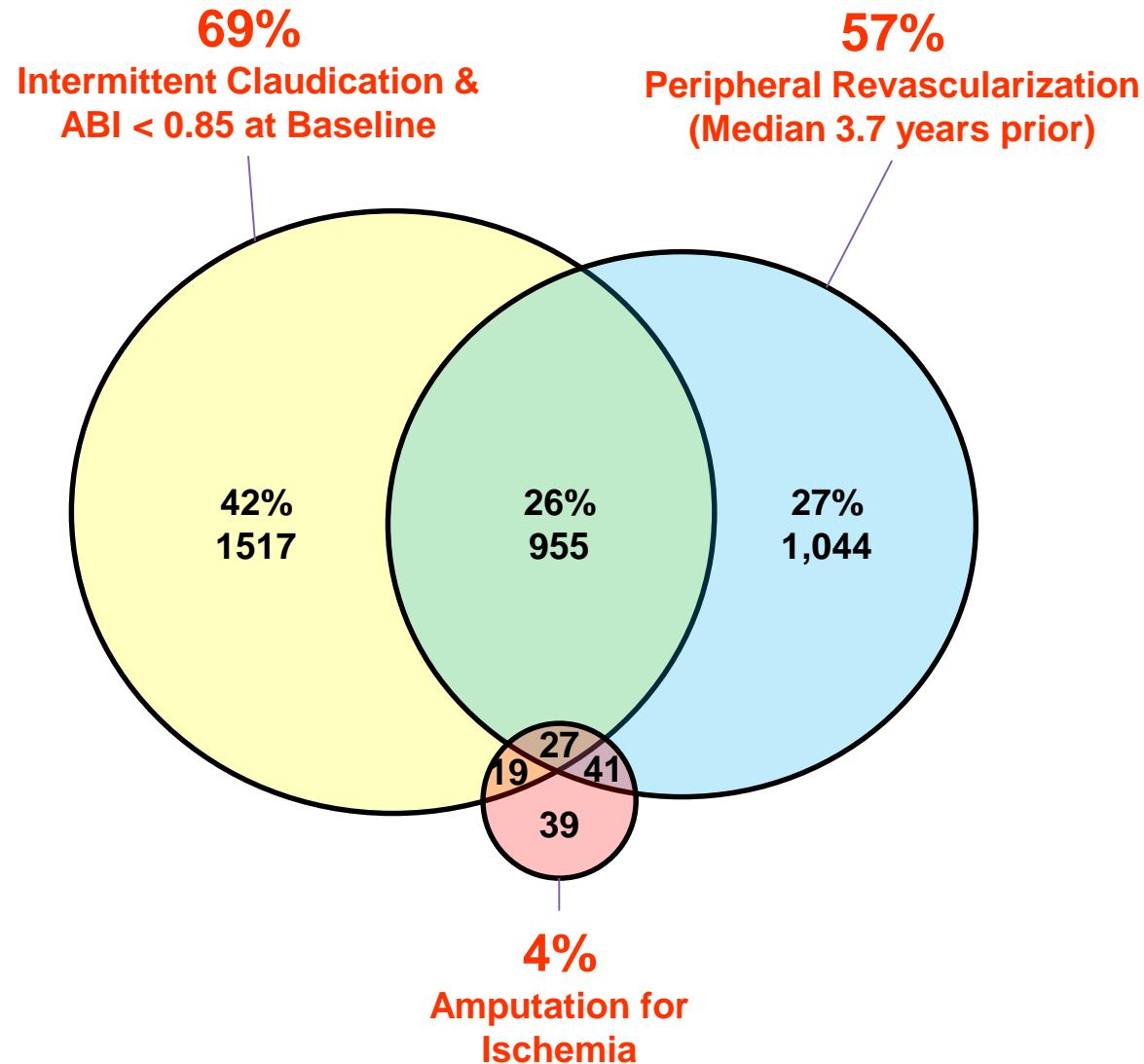
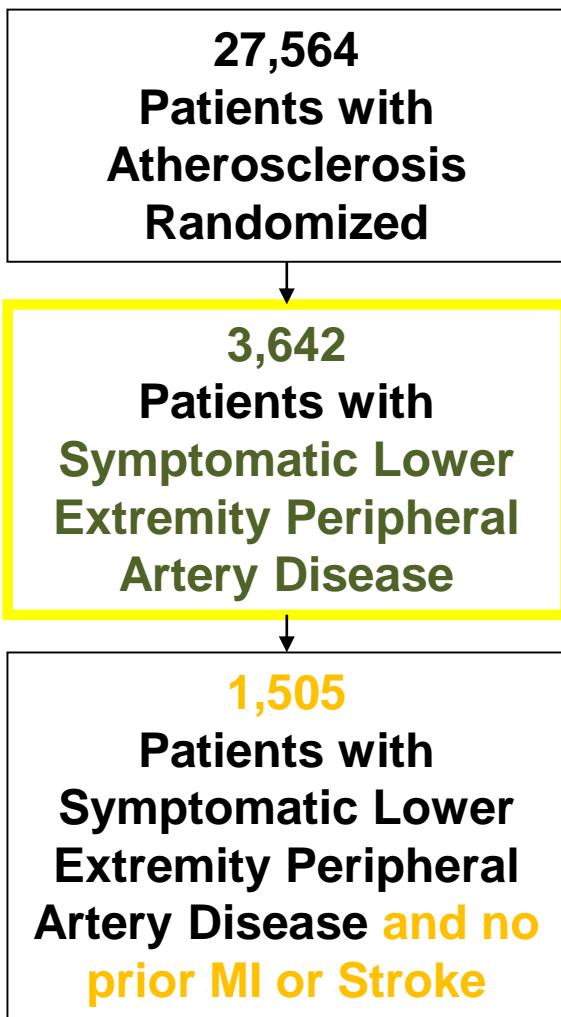
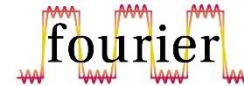
LDL Cholesterol Lowering with Evolocumab and Outcomes in Patients with Peripheral Artery Disease: Insights from the FOURIER Trial

Marc P. Bonaca, Patrice Nault, Robert P. Giugliano, Anthony C. Keech, Armando Lira Pineda, Estella Kanevsky, Julia Kuder, Sabina A. Murphy, J. Wouter Jukema, Basil S. Lewis, Lale Tokgozoglu, Ransi Somaratne, Peter S. Sever, Terje R. Pedersen, Marc S. Sabatine

for the FOURIER Steering Committee & Investigators

*American Heart Association – Annual Scientific Session
Late-Breaking Science in Prevention
November 13, 2017*

Patients with Peripheral Artery Disease

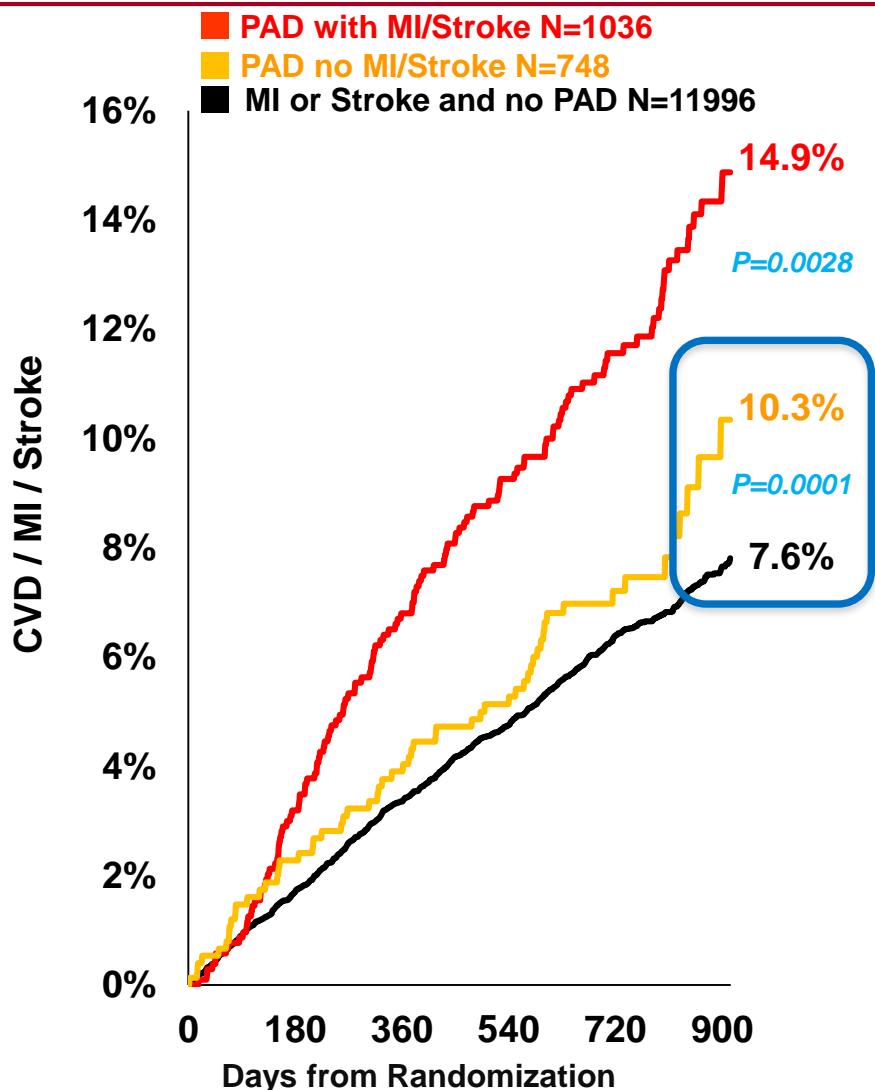




Peripheral Artery Disease and Risk in Placebo Patients

fourier

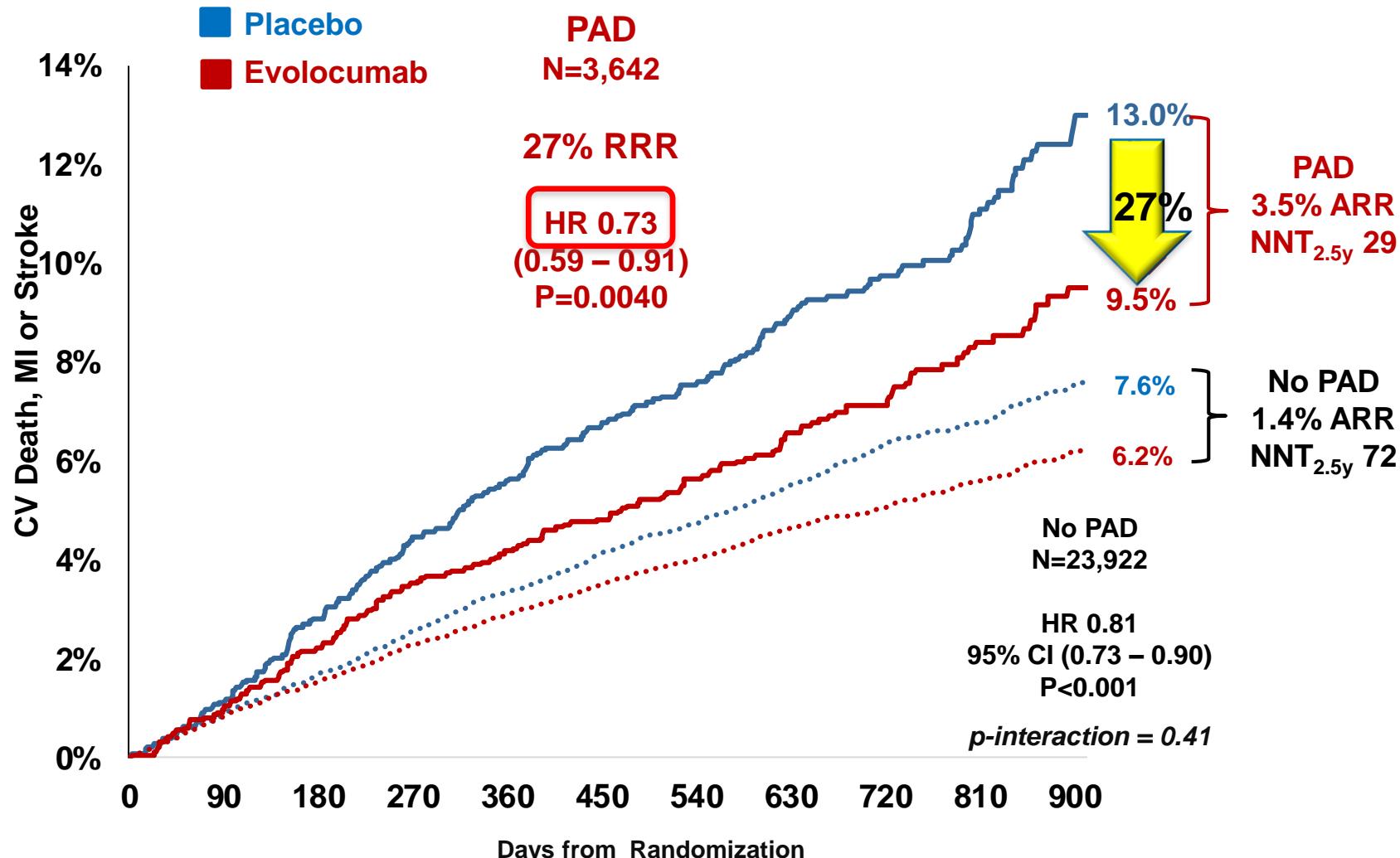
Circulation 2018;137:338



An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

adjusted age, sex, race, BMI, diabetes, hypertension, smoking, eGFR, CHF, prior MI, CABG/PCI, and history of stroke or TIA.

MACE in Patients WITH AND WITHOUT Peripheral Artery Disease

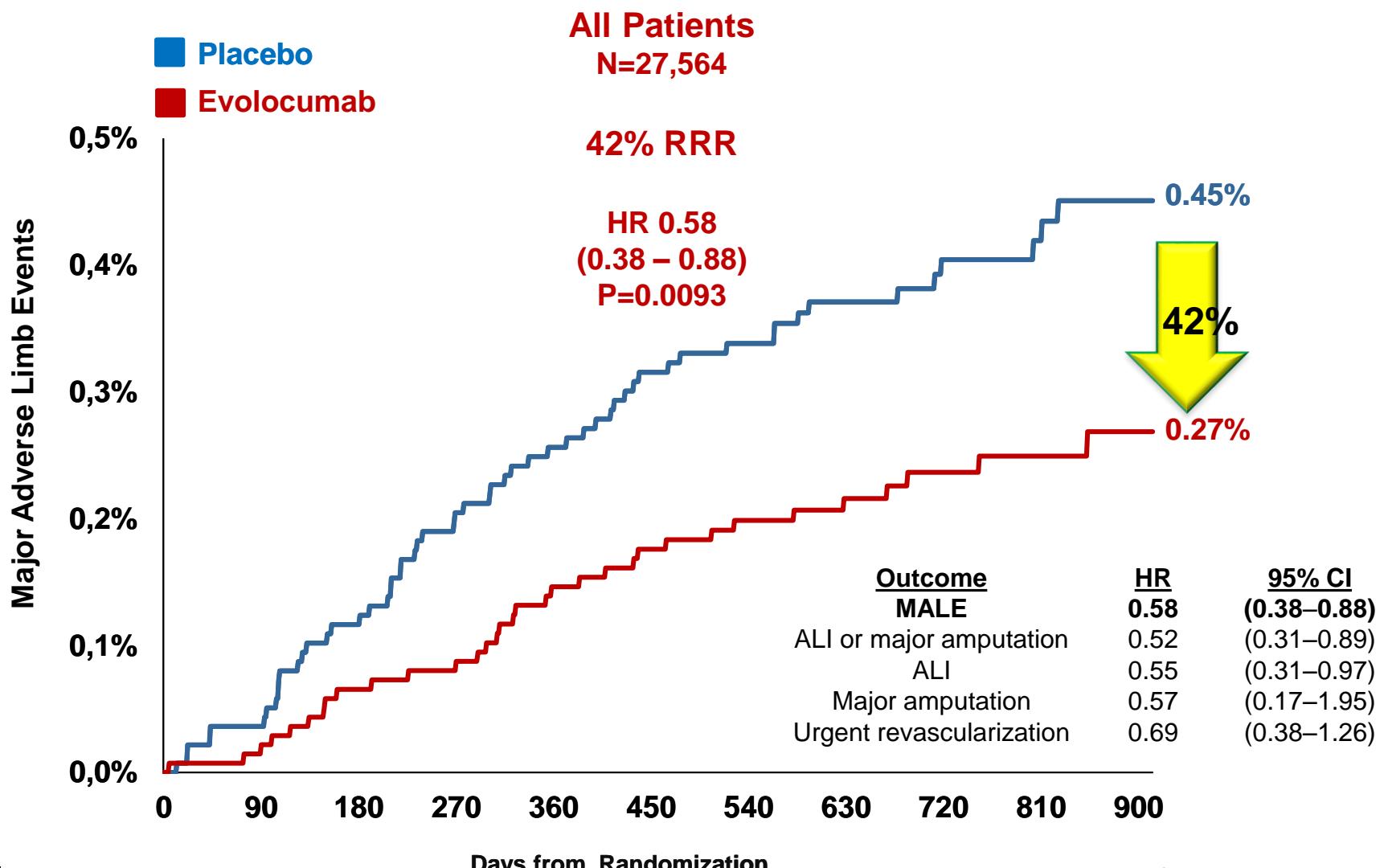


AGENDA

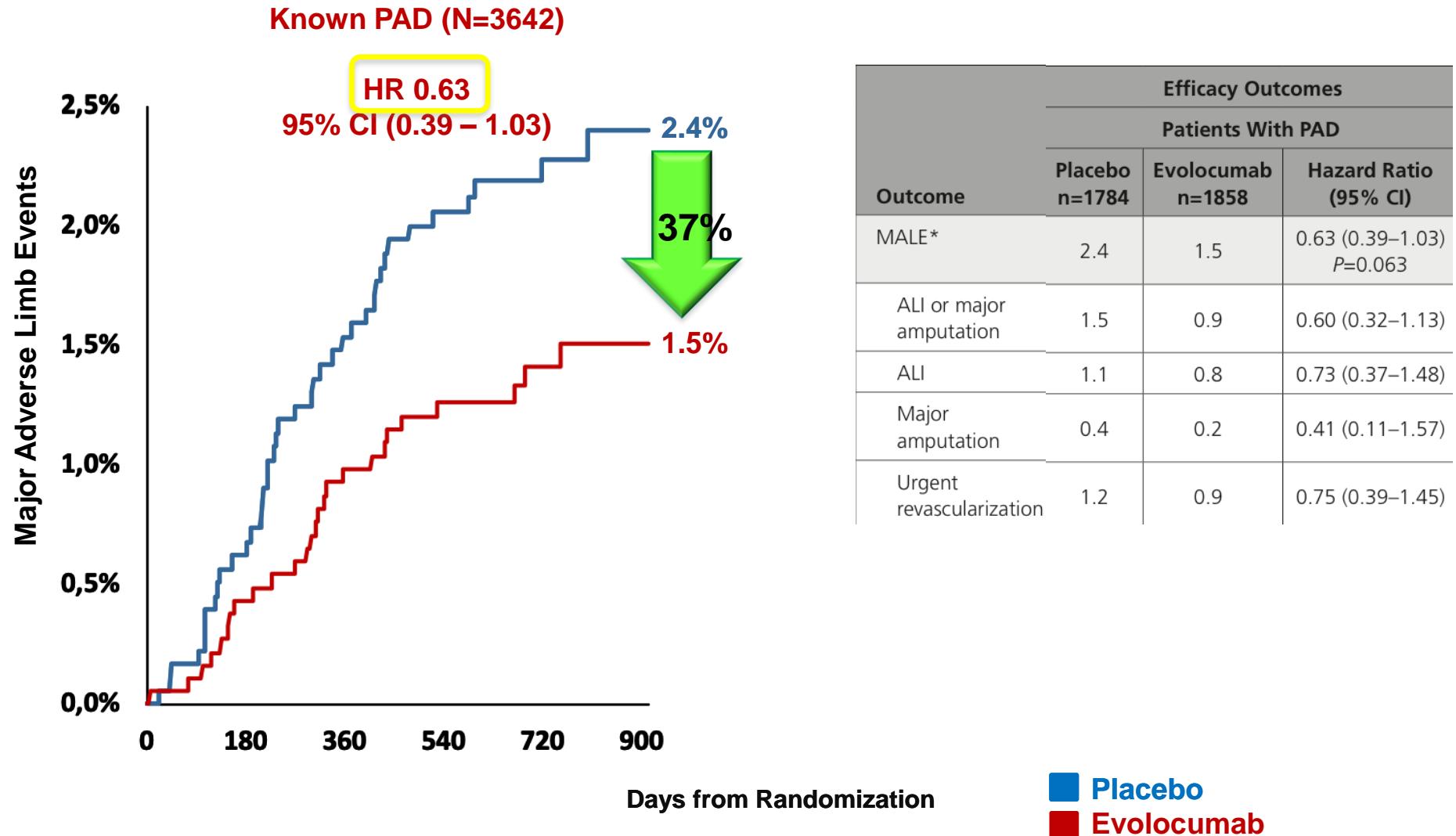
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Major Adverse Limb Events

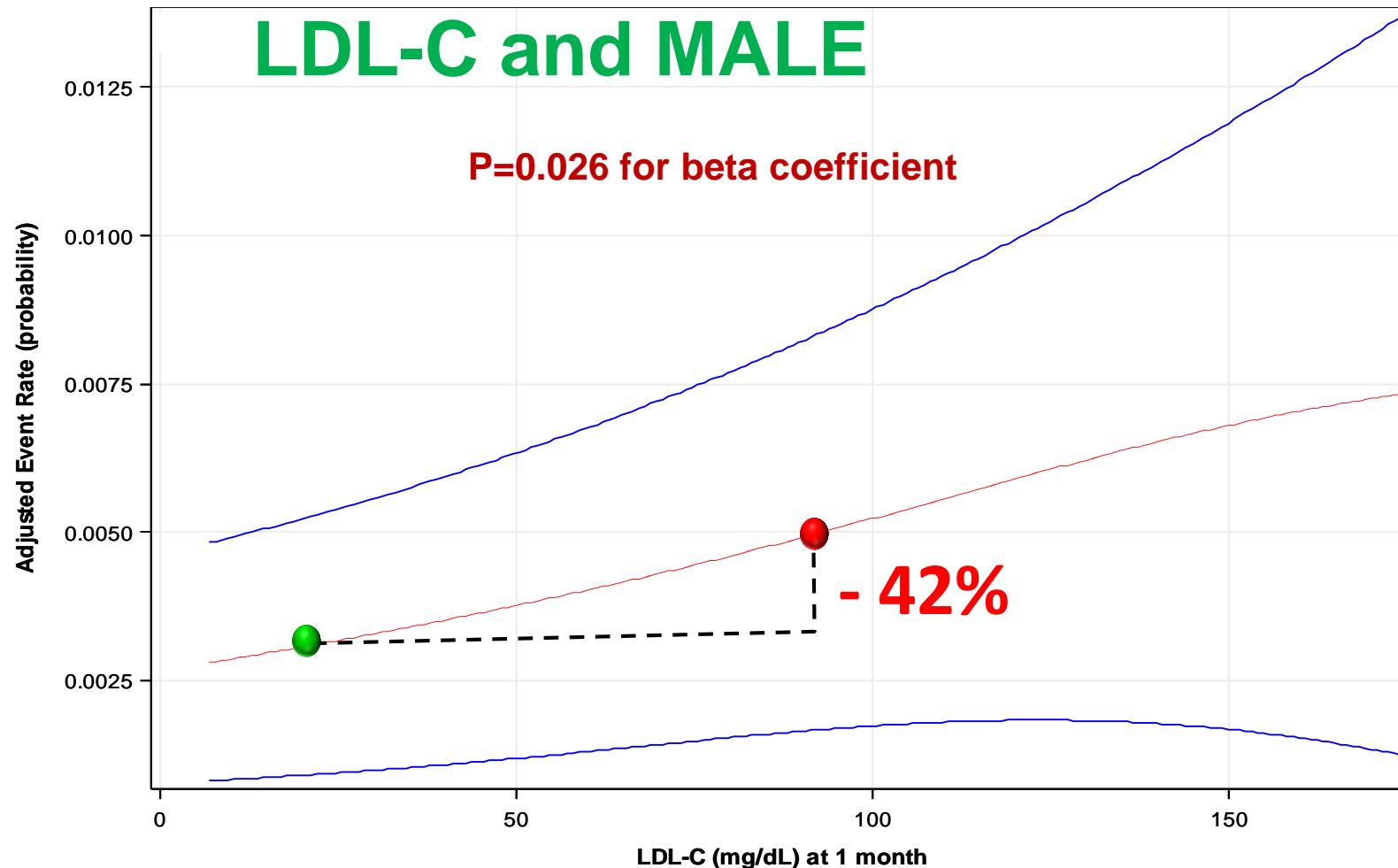
MALE All Patients



MALE in Patients with Known PAD

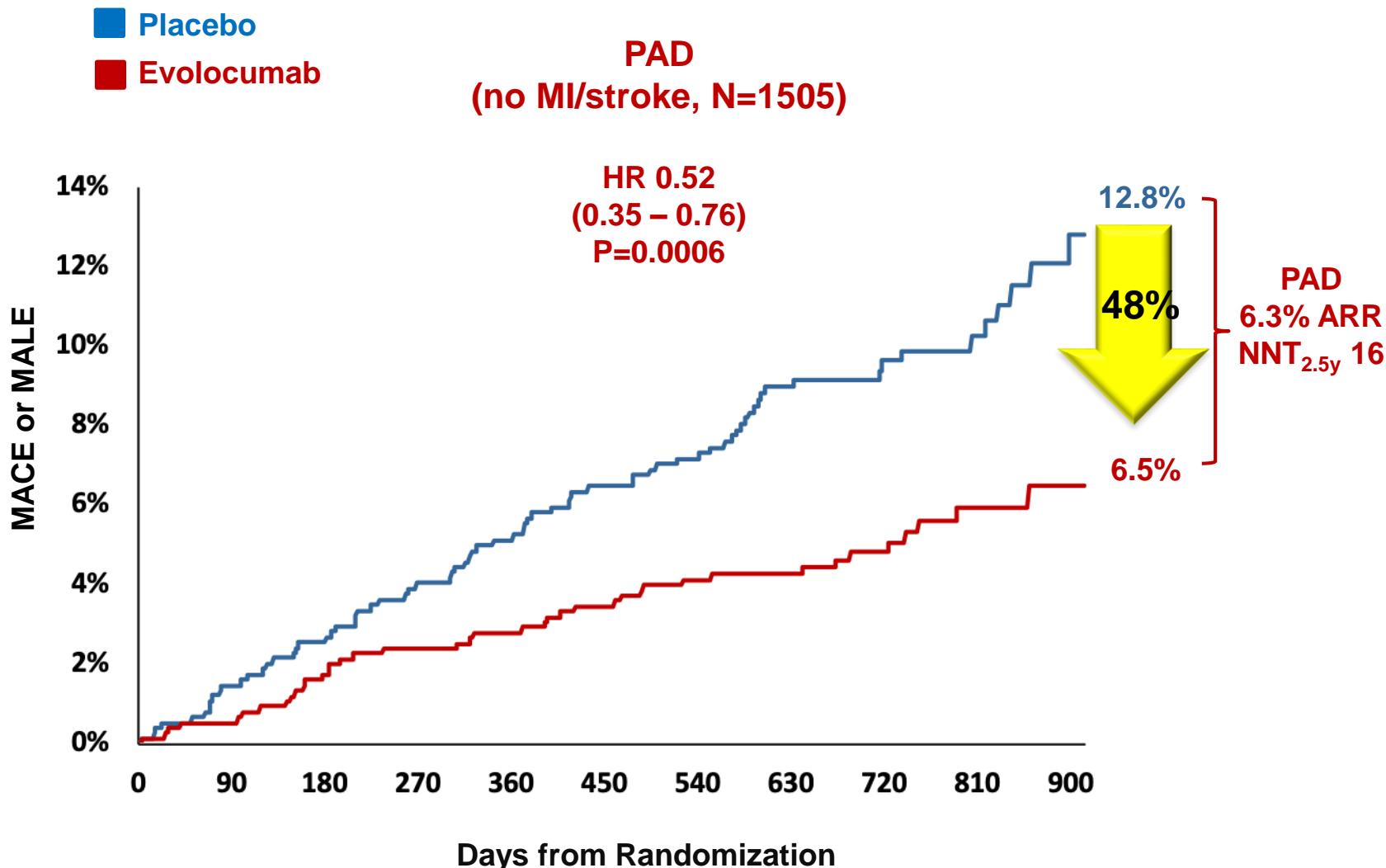


Achieved LDL-C and Major Adverse Limb Events



adjusted for significant ($p < 0.05$) predictors of LDL-C cholesterol at 1 month after randomization including age, BMI, LDL-C at baseline, male sex, race, randomized in North America, current smoker, high intensity statin.

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



Conclusioni

- I pazienti con **PAD sono a rischio di MACE molto elevato**: goal di LDL-C <55 mg/dl (ESC/EAS 2019)
- La valutazione della PAD si avvale di **strumenti non invasivi (ABI/DUS)**, ampiamente disponibili ed accurati ma sottoutilizzati
- Il **colesterolo** rappresenta un fattore di **rischio significativo di PAD** anche se probabilmente meno impattante di altri: es. fumo, diabete
- **Lp(a)**: fattore di rischio verosimilmente significativo per PAD
- La **riduzione del LDL-C** con statina e PCSK9i in pazienti con PAD:
 - Riduce** i maggiori eventi CV (**MACE**)
 - Riduce** i maggiori eventi avversi degli arti (**MALE**) con benefici che si estendono a livelli molto bassi di LDL-C
- I benefici si estendono ai pazienti con **PAD senza storia di eventi CV**

RECOMMENDATIONS FOR TREATMENTS THAT REDUCE THE RISK OF MAJOR ADVERSE CV AND LIMB VASCULAR EVENTS AND IMPROVE SYMPTOMS IN PATIENTS WITH PAD

Asymptomatic PAD

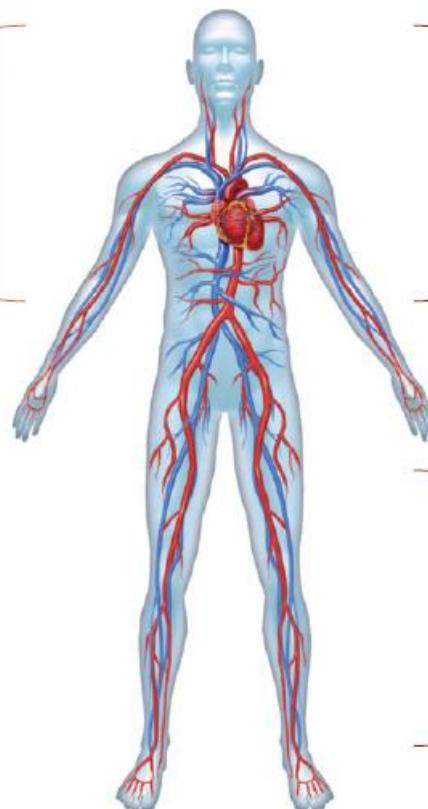
No Symptoms + ABI < 0.90
No history of
Peripheral
Revascularization

Symptomatic PAD

Current History of
Symptoms Symptoms
+ +
ABI < 0.85 Peripheral Revasc.

Therapies for MACE Reduction

- Lifestyle Modification
- Tobacco Cessation Therapies
- Statin therapy
- Blood Pressure control (ACEi or ARB preferred)
- Antiplatelet monotherapy may be beneficial in selected patients



Therapies for MACE Reduction

- Lifestyle Modification
- Tobacco Cessation Therapies
- Statin therapy
- Blood Pressure control (ACEi or ARB preferred)
- ASA or Thienopyridine
- PAR-1 Antagonist

Therapies for Limb Vascular Event Risk Reduction

- Statin therapy may be beneficial
- PAR-1 Antagonist for selected patients

Therapies for Symptom Improvement

- Exercise
- Cilostazol
- Statin therapy may be beneficial
- Revascularization