Lower Extremity Artery Disease: a neglected major CV disease

Diagnose and clinical management in primary care

IdIBGi · Institut Català de la Salut · REGICOR 35 anys Registre Gironí del Cor www.regicor.org · ARTPER PERART · IDIAP Jordi Gol

Clinical Practice Guidelines

ESC European Society of Cardiology
European Heart Journal (2018) **39**, 763–816
doi:10.1093/eurheartj/ehx095

ESC GUIDELINES

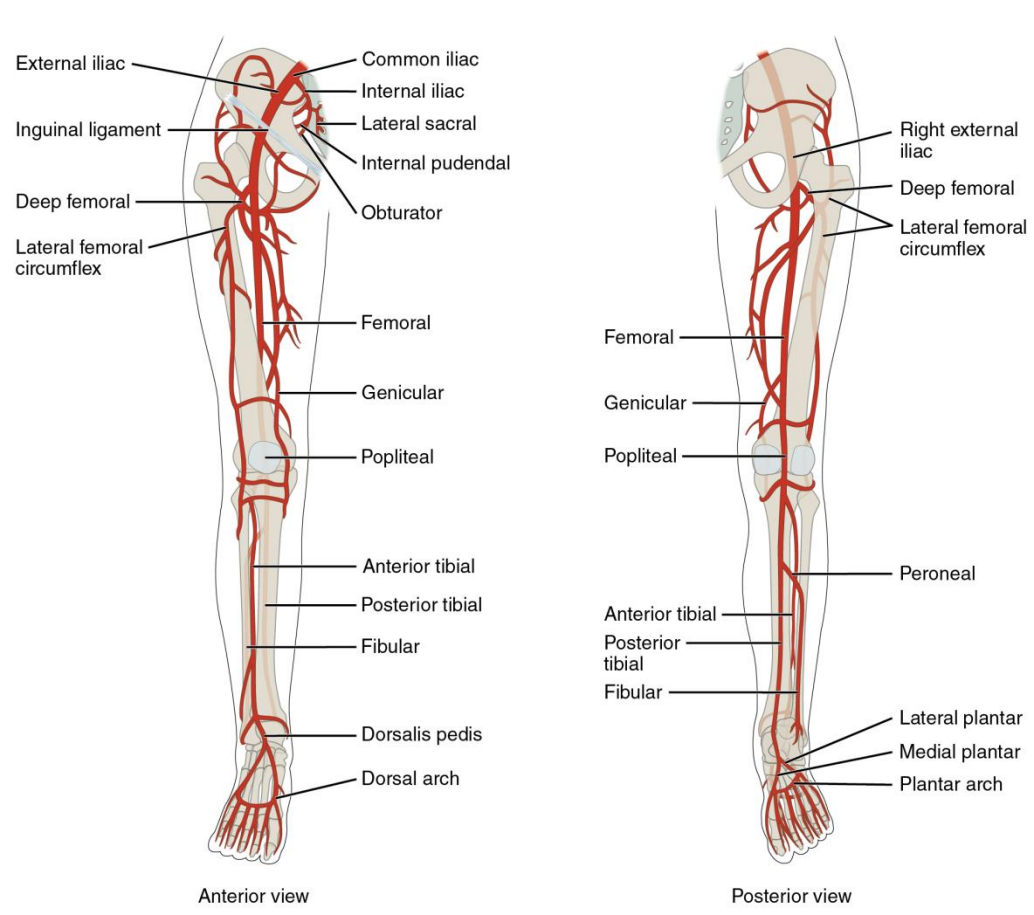
2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)

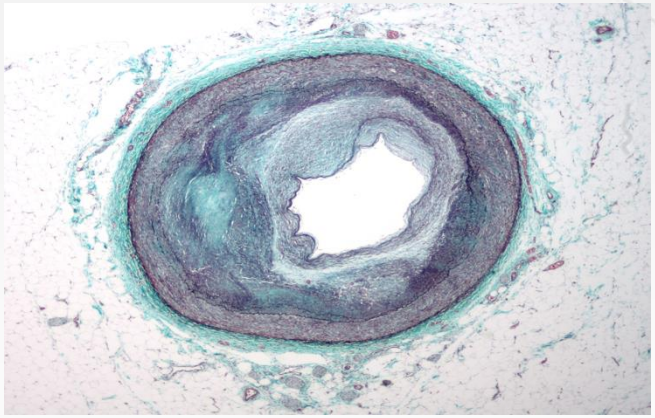
AHA/ACC GUIDELINE

2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Lower Extremity Artery Disease





Femoral and popliteal arteries: 80-90%
Tibial and fibular arteries: 40-50%
Aorta and iliac artery: 30%

Prevalence of Symptomatic and Asymptomatic Peripheral Arterial Disease and the Value of the Ankle-brachial Index to Stratify Cardiovascular Risk

R. Ramos [a,b,c,*], M. Quesada [b,c,d], P. Solanas [b,c], I. Subirana [a], J. Sala [c,e], J. Vila [a], R. Masiá [c,e], C. Cerezo [b,c], R. Elosua [a], M. Grau [a,d], F. Cordón [b,c], D. Juvinyà [f], M. Fitó [a], M. Isabel Covas [a], A. Clarà [g], M. Ángel Muñoz [d,h], J. Marrugat [a], on behalf of the REGICOR Investigators[1]

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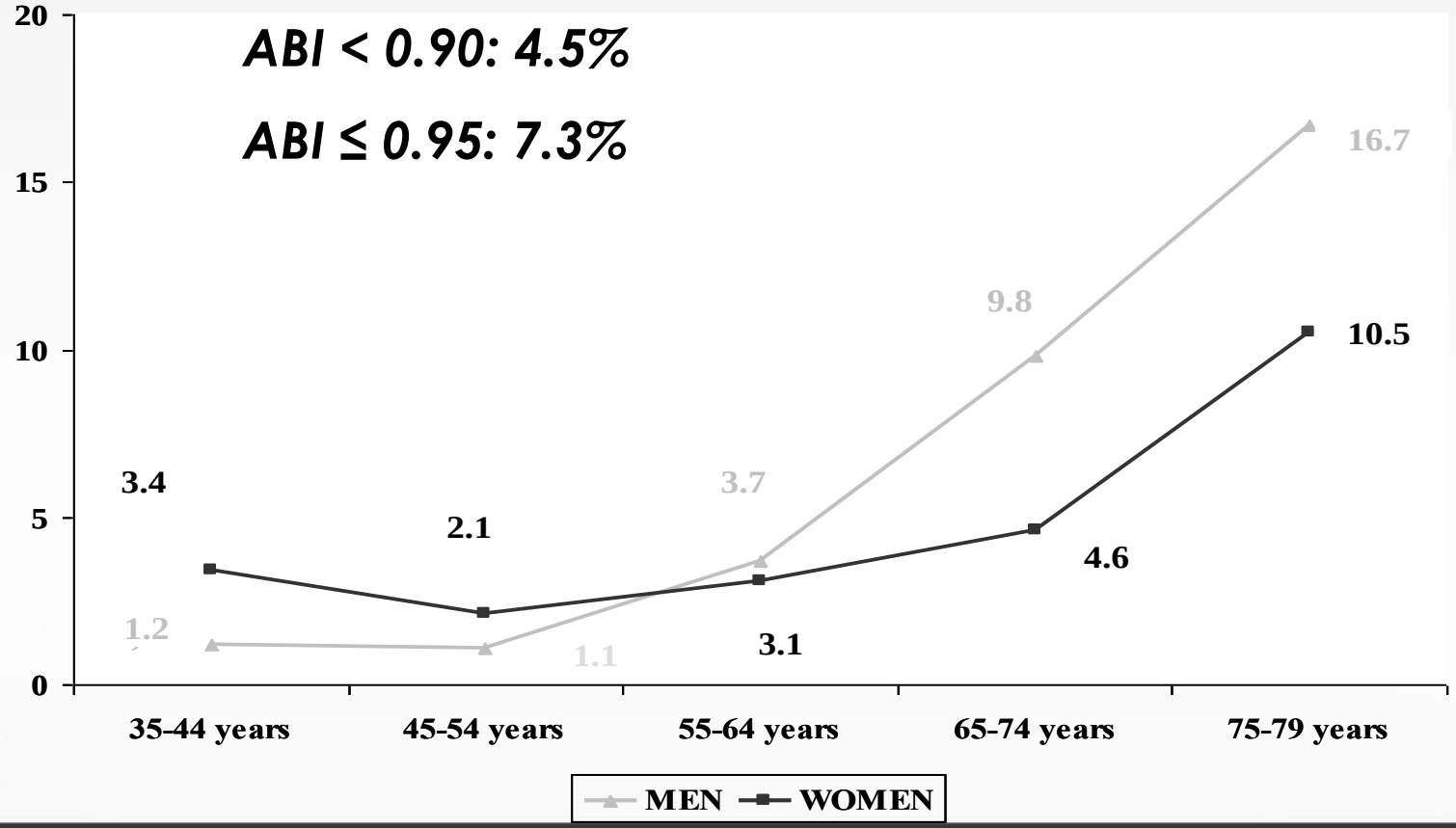
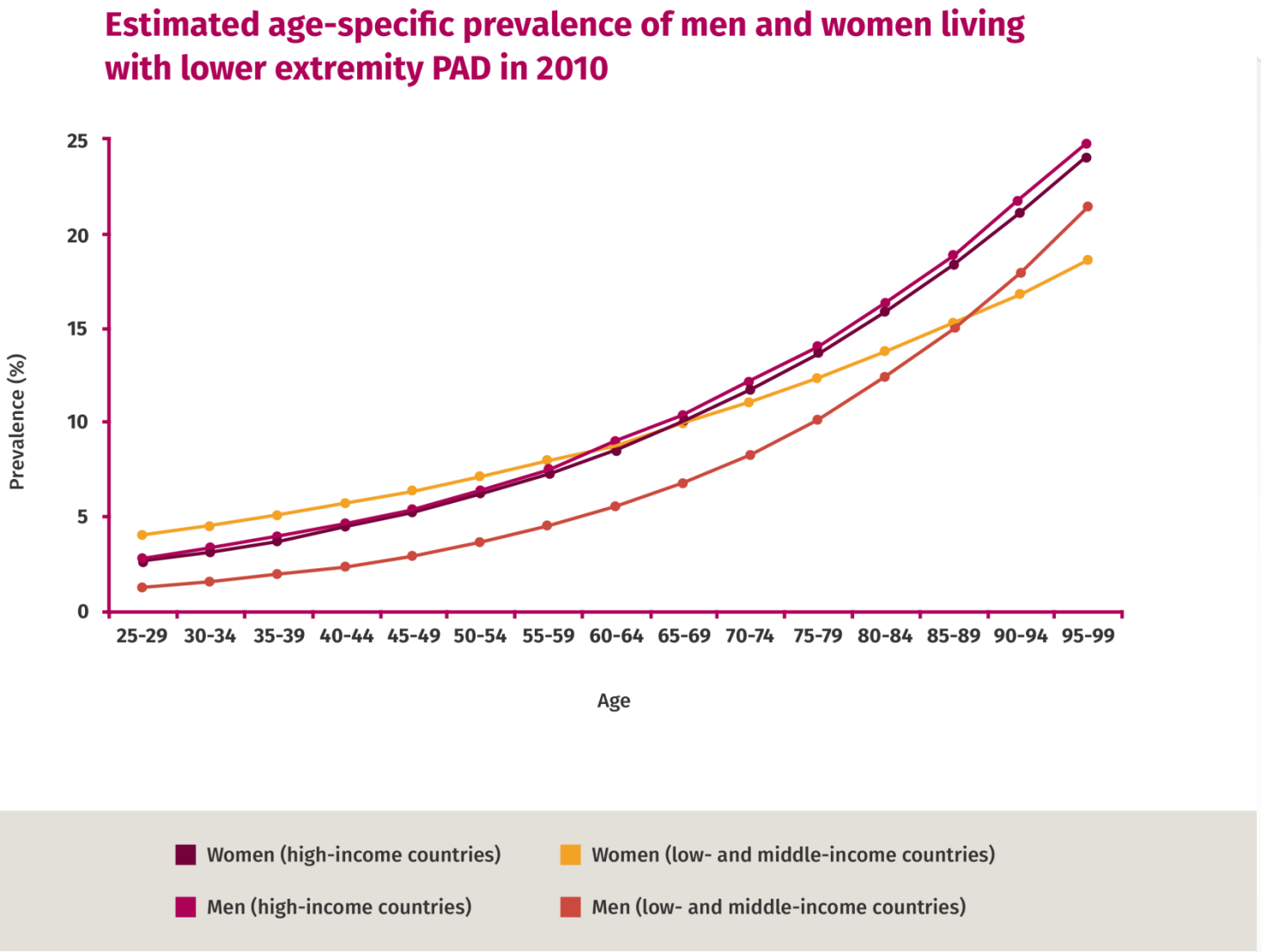
Prevalence of ankle-brachial index < 0.9 by sex and age in a population sample



Ramos R et al. Eur J Vasc Endovasc Surg. 2009 Sep;38(3):305-11

Lower Extremity Artery Disease



Fowkes FG. Lancet 2013;382:1329–1340

Lower Extremity Artery Disease

- **About 200 million people affected in the world**

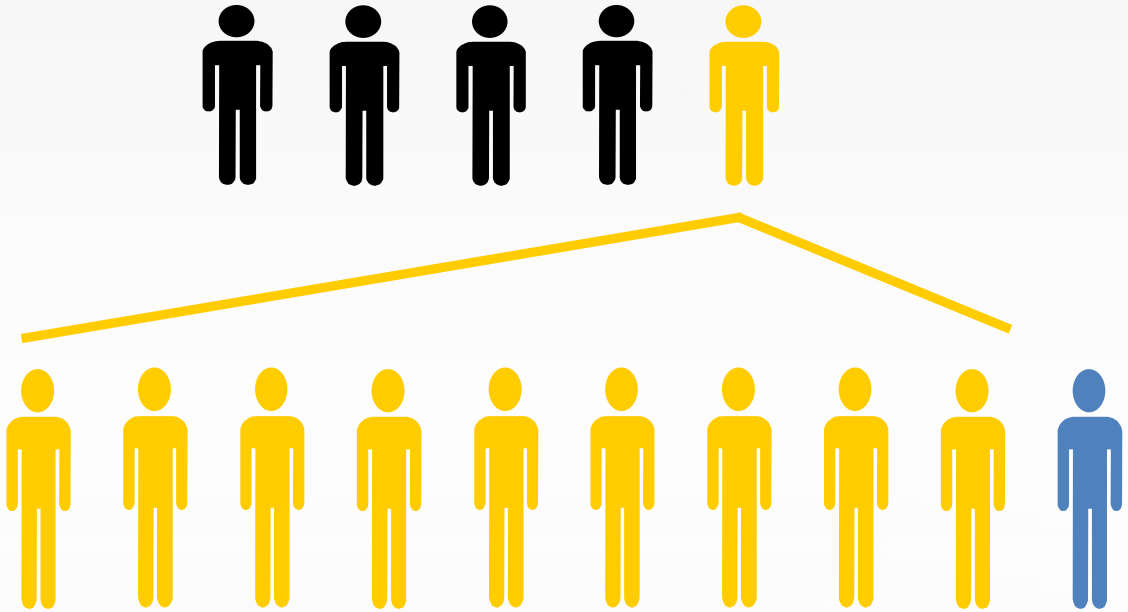
- **Close to 40 million people in Europe**

Fowkes FG. Lancet 2013;382:1329–1340

Lower Extremity Artery Disease

1-2 in every 10 individuals over 65 years*

Only one in ten present symptoms



* ABI < 0,9

Diehm et al. Atherosclerosis 2004; 172; 95- 105.

Prevalence of Symptomatic and Asymptomatic Peripheral Arterial Disease and the Value of the Ankle-brachial Index to Stratify Cardiovascular Risk

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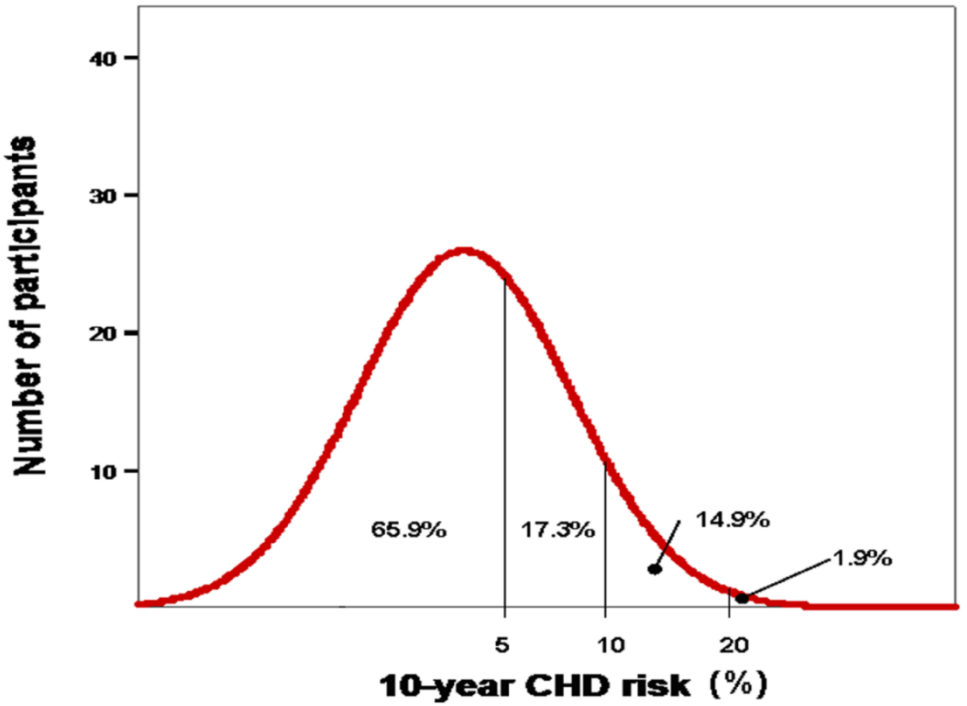
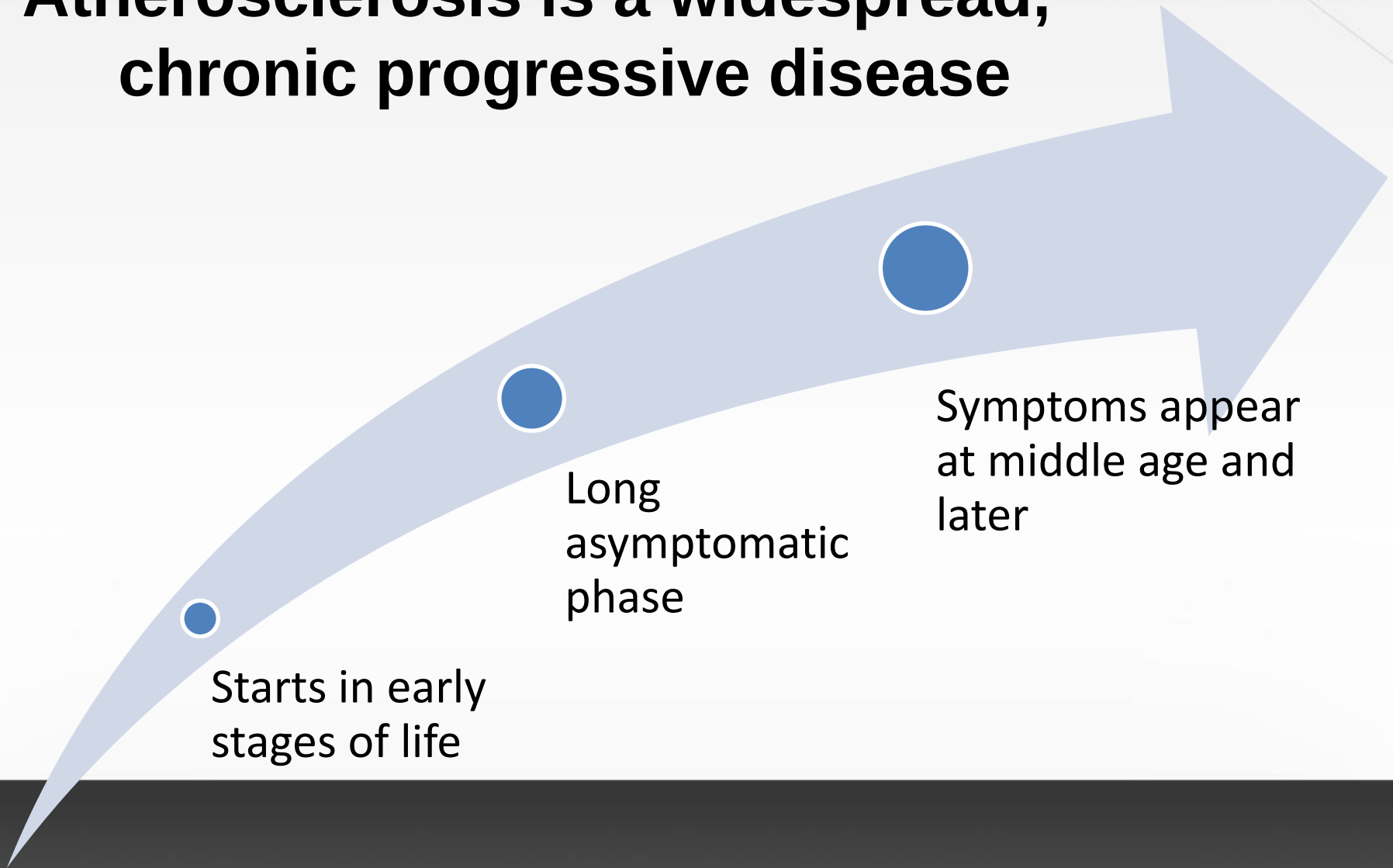
Distribution of 10-year CHD risk estimation in participants free of CVD with ABI<0.9.



Ramos R et al. Eur J Vasc Endovasc Surg. 2009 Sep;38(3):305-11

Clinical Presentations

Atherosclerosis is a widespread, chronic progressive disease



Clinical Presentations and natural history

- Chronic Limb Ischemia:

Stage I: Asymptomatic:

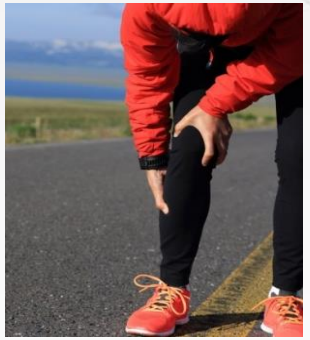
Mild Trophic Alterations.

Stage II: Intermittent Claudication.

IIa > 150m

IIb < 150m

FONTAINE Classification



Stage III: Ischemic Rest Pain

Stage IV: Ulceration or Gangrene

Clinical Presentations

- **Acute Limb Ischemia:**

✓ Pain.
✓ Paleness / cyanosis.
✓ Functional impairment.
✓ Cold Lower limb.
✓ Absence of pulse.

Clinical Presentations

- **Masked LEAD:**
- **Asymptomatic LEAD**, which can be related to their **incapacity to walk enough to reveal symptoms** (e.g. heart failure) and/or **reduced pain sensitivity** (e.g. diabetic neuropathy).
- It may be a severe disease without symptoms,

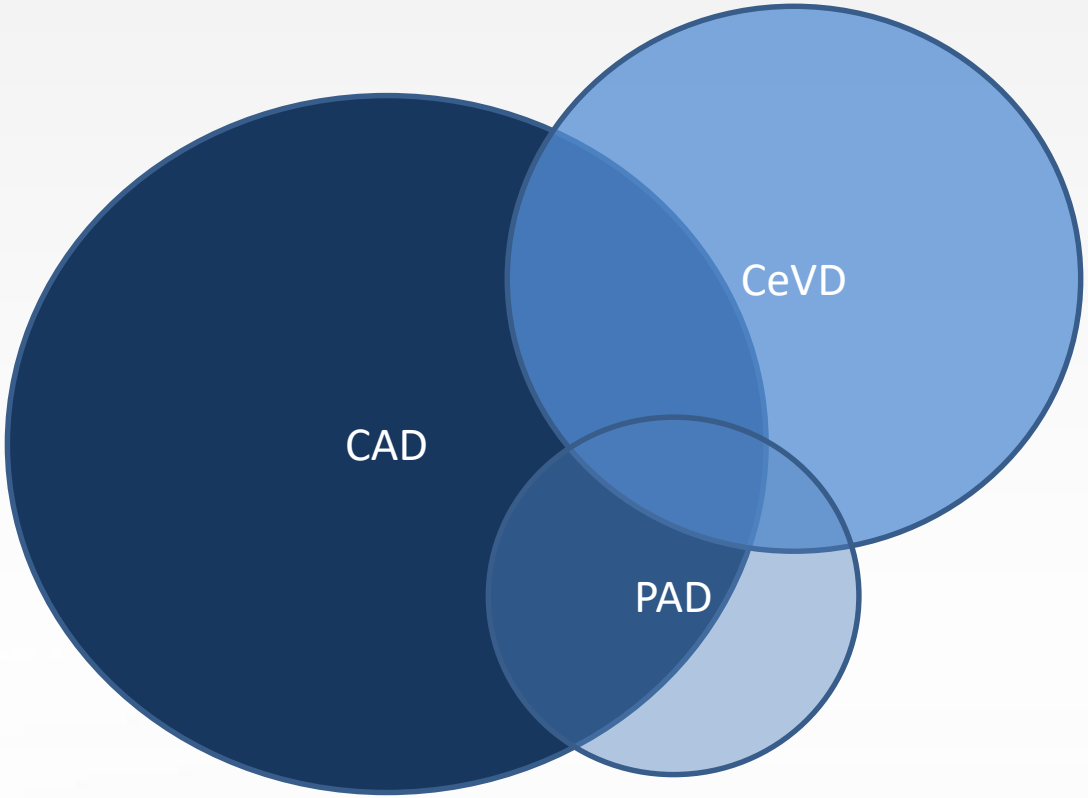
Editorial

The Ankle-Brachial Index as a Biomarker of Cardiovascular Risk

It's Not Just About the Legs

Todd S. Perlstein, MD, MMSc; Mark A. Creager, MD

Atherosclerosis: A systemic Disease



More than 60% of patients with LEAD has also disease in other vascular beds

Deepak et al. JAMA. 2006;295:180-189

Ankle Brachial Index Combined With Framingham Risk Score to Predict Cardiovascular Events and Mortality
A Meta-analysis

JAMA®
Online article and related content current as of July 9, 2008.

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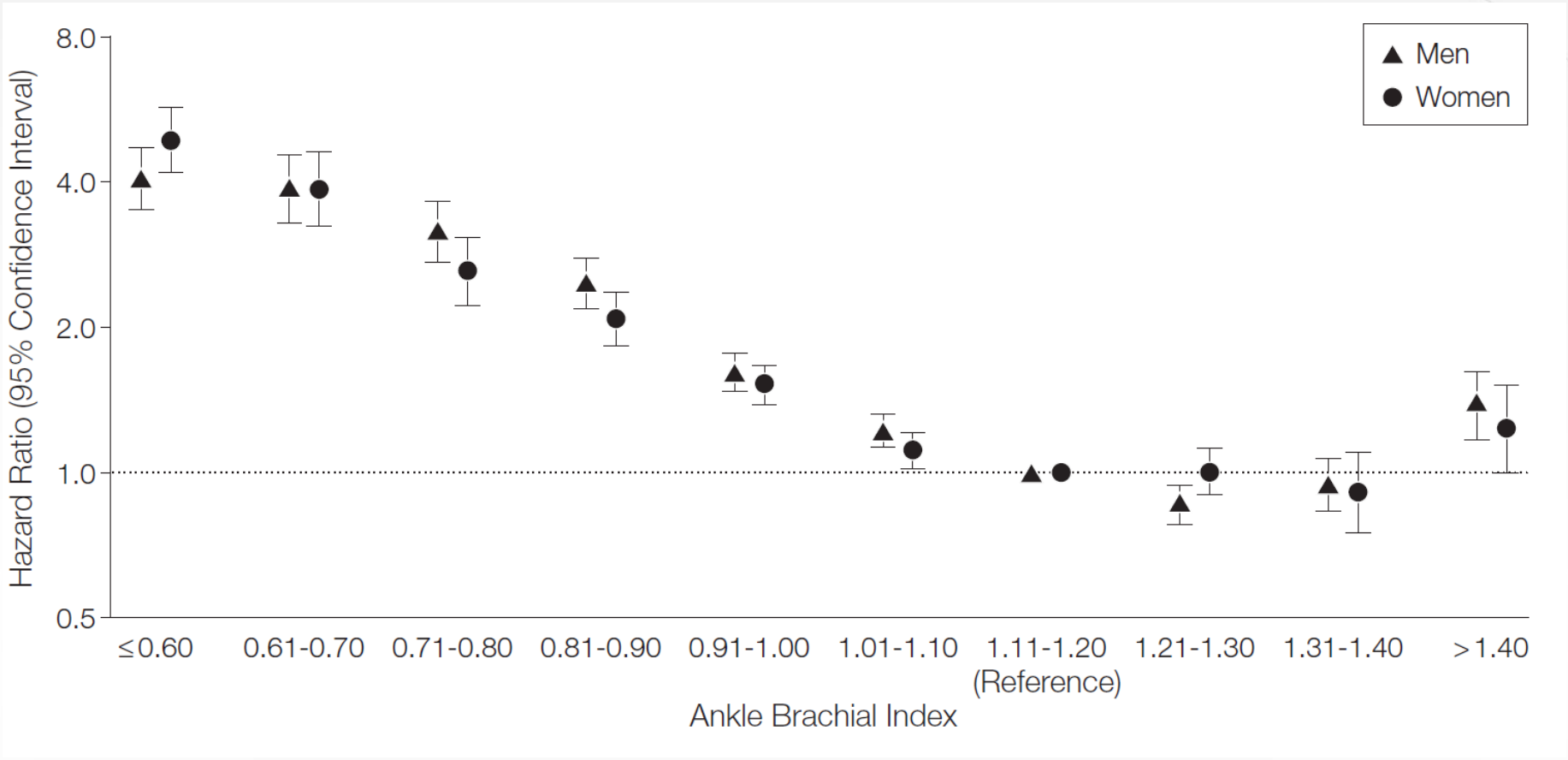
Hazard Ratios for Total Mortality in Men and Women by ABI



ABI Collaboration. JAMA. 2008;300:197-208

Ankle Brachial Index Combined With Framingham Risk Score to Predict Cardiovascular Events and Mortality
A Meta-analysis

JAMA®
Online article and related content current as of July 9, 2008.

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10-Year Mortality in Men by Framingham Risk Category and ABI

Framingham Risk Category[b]	ABI			
	≤0.90	0.91-1.10	1.11-1.40	>1.40
	Total Mortality, % (95% CI)			
1 (Lowest; n = 5746)	27.1 (16.0-38.2)	11.4 (5.9-16.8)	8.3 (5.4-11.2)	14.1 (4.2-24.0)
2 (n = 4319)	37.3 (17.8-56.9)	15.8 (10.6-21.0)	11.3 (8.2-14.5)	19.9 (7.5-32.4)
3 (n = 3544)	37.6 (26.1-49.1)	19.7 (13.6-25.9)	14.2 (9.9-18.5)	23.5 (9.5-37.6)
4 (n = 5814)	38.1 (28.5-47.8)	23.6 (16.9-30.4)	19.2 (14.8-23.5)	38.4 (12.3-64.6)
5 (Highest; n = 5532)	57.1 (45.4-68.9)	36.4 (29.1-43.7)	31.0 (25.2-36.7)	43.6 (28.1-59.1)
Overall (n = 24 955)	46.3 (36.1-56.6)	23.0 (15.8-30.2)	16.7 (12.4-21.0)	29.2 (18.9-39.5)

ABI Collaboration. JAMA. 2008;300:197-208

Contents lists available at ScienceDirect

Atherosclerosis

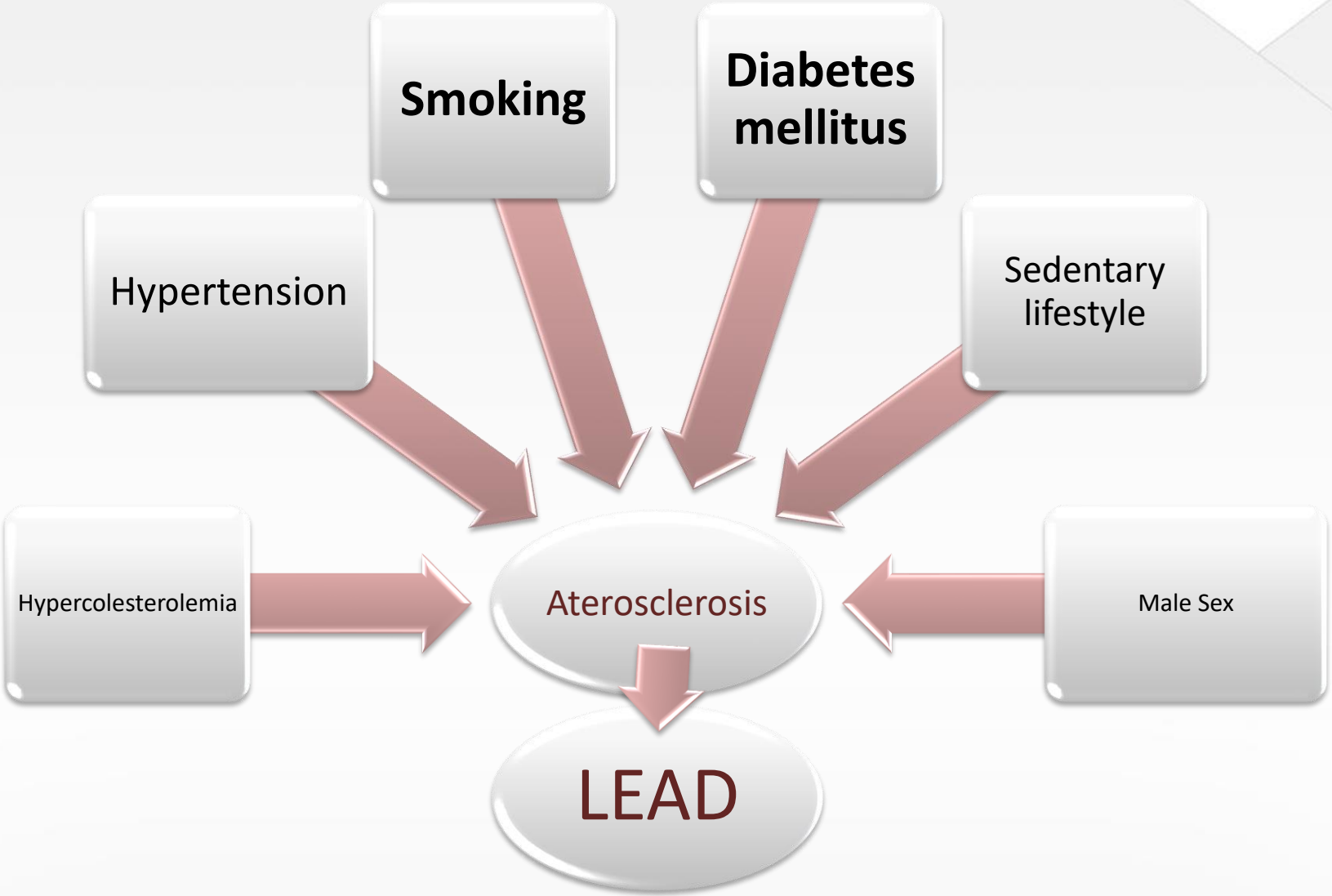
journal homepage: www.elsevier.com/locate/atherosclerosis

Adding low ankle brachial index to classical risk factors improves the prediction of major cardiovascular events. The REGICOR study

A. Velescu [a, b, c], A. Clara [a, b], J. Peñafiel [b], R. Ramos [d, e, f], R. Marti [c, d], M. Grau [b], I.R. Dégano [b], J. Marrugat [b], R. Elosua [b, *], the REGICOR Study Group[1]

Velescu A et al. Atherosclerosis 2015

RISK FACTORS

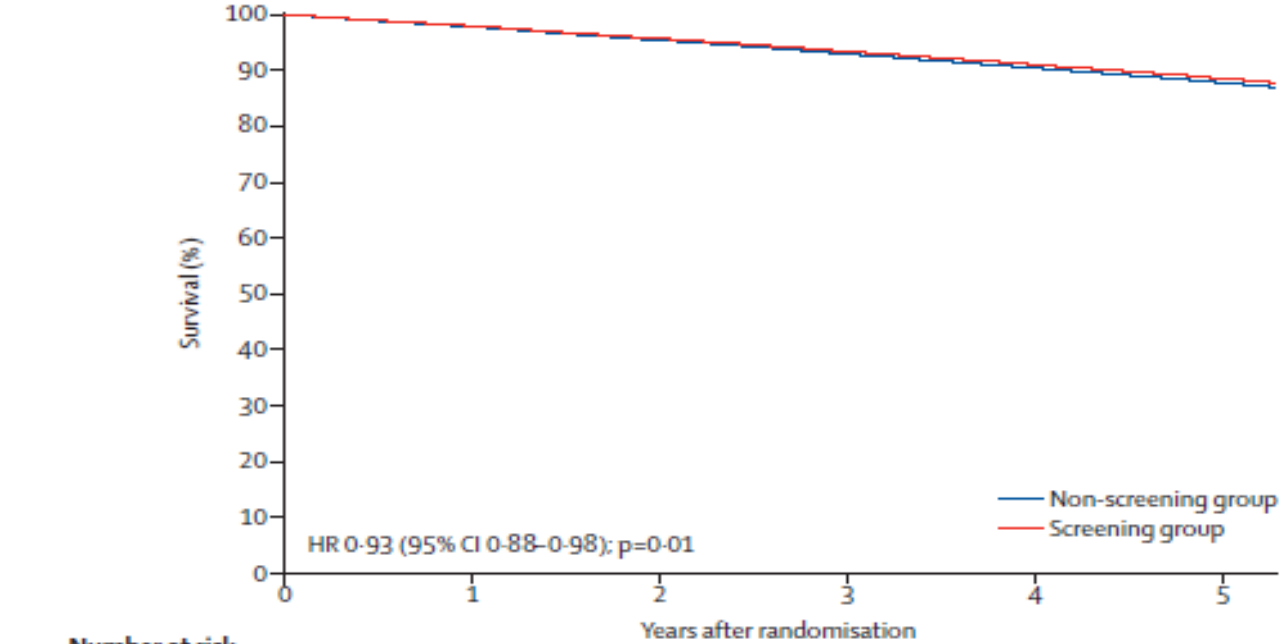


HiattWR.JVascSurg.2002; 36:1.283-1.291.
BelchJJet al.ArchInternMed2003; 163:884-892.

Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial

Jes S Lindholt, Rikke Søgaard

They randomly allocated (1:1) all men aged 65–74 years to screening for AAA, PAD, and hypertension, or to no screening



Number at risk (number censored)						
Non-screening group	25078	24514	23893	23257	15183	5229
	(0)	(0)	(0)	(7500)	(9668)	(5195)
Screening group	25074	24560	23985	23407	15628	5727
	(0)	(0)	(0)	(7221)	(9593)	(5694)

Lindhold J et a. ***Lancet* 2017; 390: 2256–65**

Eur J Vasc Endovasc Surg (2010) 39, 70–86

ELSEVIER

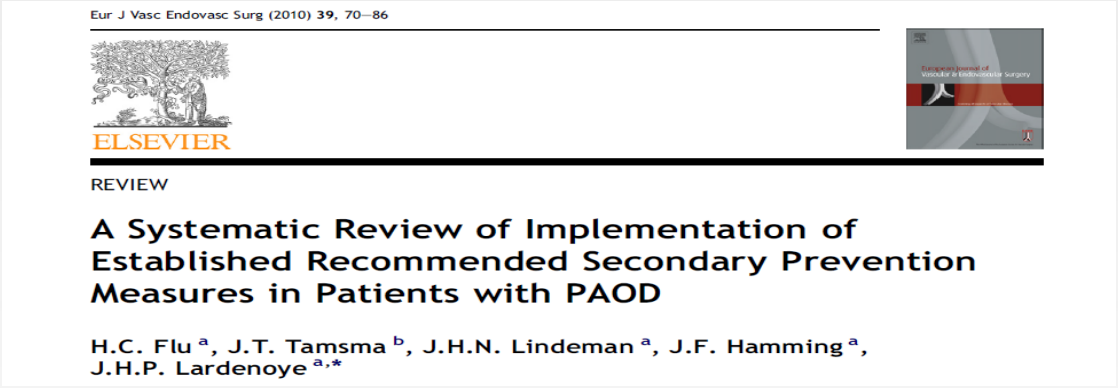
REVIEW

A Systematic Review of Implementation of Established Recommended Secondary Prevention Measures in Patients with PAOD

H.C. Flu [a], J.T. Tamsma [b], J.H.N. Lindeman [a], J.F. Hamming [a], J.H.P. Lardenoye [a,*]

IDIAP Jordi Gol

Flu H. et al. Eur J Vasc Endovasc Surg (2010) 39, 70e86



Eur J Vasc Endovasc Surg (2010) 39, 70–86

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IDIAP Jordi Gol

- Only 39% of registered smokers entered a smoking cessation programme
- Only 23% of the patients entered a walking exercise programme

Baseline of a Cohort Study of 12.186 patients with PAD from EHR

	All	LEAD only	LEAD + Other CVD	p-value
Antiplatelet Agents	62.4%	51.6%	79.4%	<0.001
Lipid Lowering agents	48.7%	37.9%	65.9%	<0.001

	All	Women	Men	p-value
Antiplatelet Agents	62.4%	55.3%	64.9%	<0.001
Lipid lowering Agents	48.7%	44.6%	50.2%	<0.001

Data from SIDIAP. Unpublished Data

What we know...

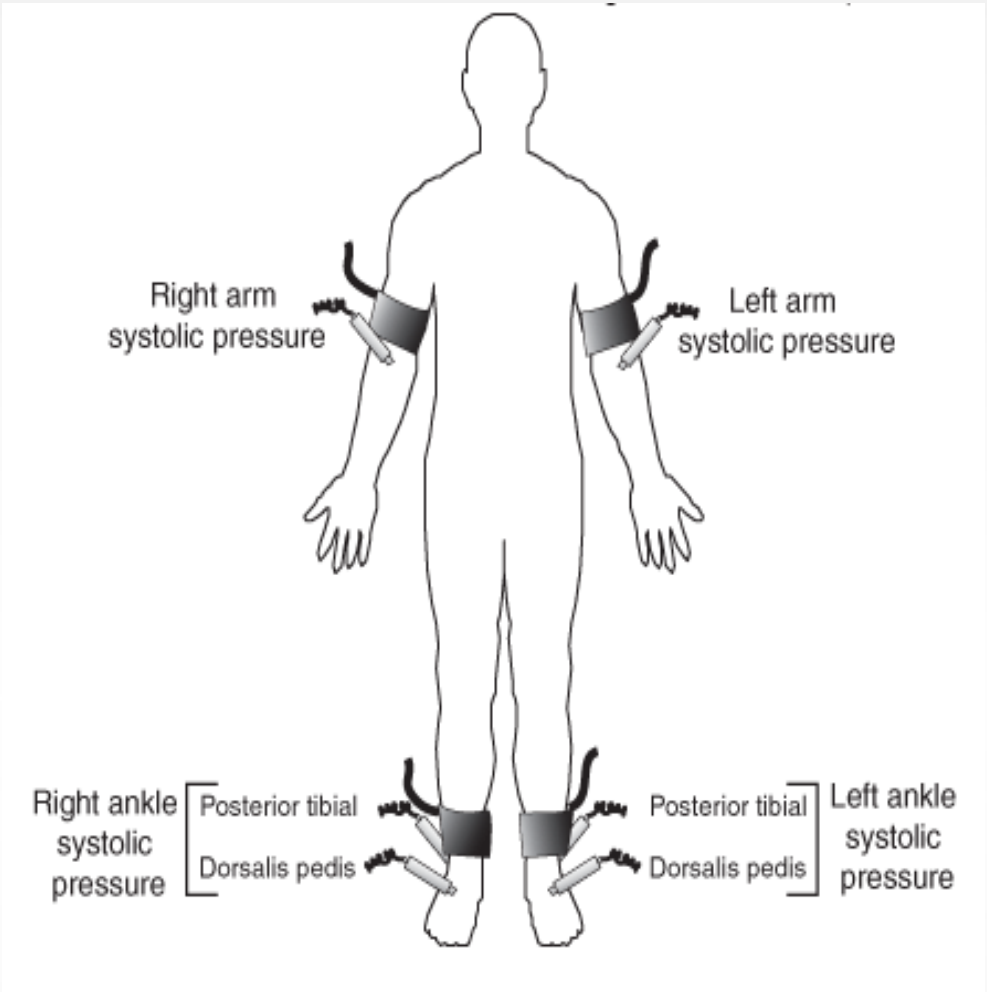
- LEAD is highly prevalent disease, specially in its asymptomatic presentation
- Individuals with LEAD are at increased risk of lower limb events, CVD and death.
- There exist therapies that reduce the risk of CVD and death in this population

However...

- LEAD is underdiagnosed
- The majority of patients suffering form LEAD do not receive the medical therapies recommended in guidelines.

Diagnosis of
Lower Extremity Artery Disease

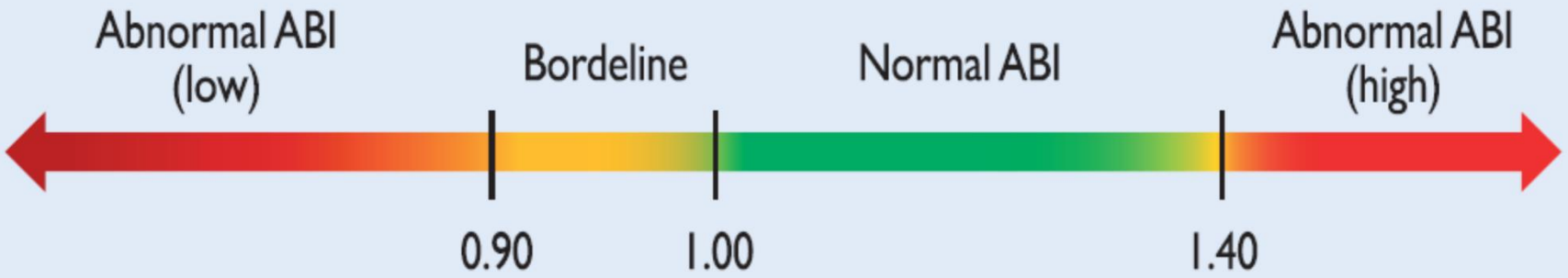
The Ankle Brachial Index Measurement



- Supine position
- 5-10 minute rest
- The ABI in each leg is calculated by dividing the highest ankle SBP by the highest arm SBP

Interpretation of 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:



Special situations

- TBI should be measured to diagnose patients with suspected PAD when the ABI is greater than 1.40.
- Patients with exertional leg symptoms and normal or borderline resting ABI (>0.90 and ≤1.40) should undergo exercise treadmill ABI testing to evaluate for PAD.

Diagnostic of LEAD

Who should have an ABI measurement in clinical practice?

Population with clinical suspicion for LEAD

History / Anamnesis

- Intermittent Claudication
- Other non–joint-related exertional lower extremity symptoms (not typical of claudication)
- Impaired walking function
- Ischemic rest pain

Population with clinical suspicion for LEAD

Physical Examination

- Abnormal lower extremity pulse examination
- Vascular bruit
- Non-healing lower extremity wound
- Lower extremity gangrene
- Other suggestive lower extremity physical findings (e.g., elevation pallor/dependent rubor)

Population at increased risk of LEAD

- Individuals with known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric artery stenosis)
- Other conditions AAA, CKD or Heart failure

Population at increased risk of LEAD

- Age ≥65 y
- Age <65 y, classified at high CV risk according ESC Guidelines
- Men and women aged >50 y with family history for LEAD

[2016 AHA Guidelines: 50–64 y, with risk factors for atherosclerosis (e.g., diabetes mellitus, history of smoking, hyperlipidemia, hypertension) <50 with diabetes mellitus and 1 additional risk factor for atherosclerosis]

Contents lists available at ScienceDirect

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Derivation and validation of REASON: A risk score identifying candidates to screen for peripheral arterial disease using ankle brachial index☆

Rafel Ramos[a,e,*,1], Jose Miguel Baena-Díez[b,h,1], Miquel Quesada[a,c,e,1], Pascual Solanas[a,e,1], Isaac Subirana[b,1], Joan Sala[d,e,1], Maite Alzamora[f,1], Rosa Forès[f,1], Rafel Masiá[d,1], Roberto Elosua[b,1], María Grau[b,1], Ferran Cordón[a,e,1], Guillem Pera[g,1], Fernando Rigo[i,1], Ruth Martí[a,1], Anna Ponjoan[a,1], Carlos Cerezo[a,1], Ramon Brugada[e,1], Jaume Marrugat[b,1]

Odds ratio (OR), 95% confidence interval and p-value of the model derived from the derivations dataset. HERMES Study

	OR (CI 95%)	Beta	p-value
Sex (women)	1.14 (0.79-1.65)	0.134	0.479
Age	1.08 (1.06-1.10)	0.075	<0.001
Never smoker (%)	Ref.	Ref.	Ref.
Former smoker >1year	2.26 (1.51-3.36)	0.814	<0.001
Current or former smoker ≤1year	3.54 (2.27-5.51)	1.264	<0.001
Pulse pressure	1.02 (1.01-1.03)	0.020	<0.001
Diabetes	1.21 (0.89-1.65)	0.193	0.220
Constant		-9.493	

REASON calculator

Català | Castellano | English

Age:

Sex: Man Woman

Smoker:
Never
Smoking or quit no more than one year ago
No smoking since at least one year ago

Diabetic: Yes No

Systolic blood pressure (mmHg):

Diastolic blood pressure (mmHg):

Clean Calculate

Instructions More information

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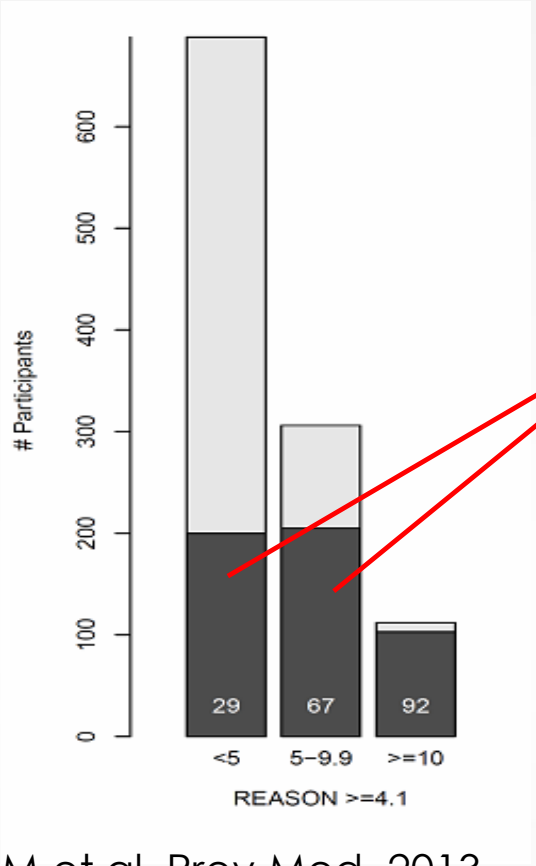
Classification matrix of the REASON pre-screening test compared to ISC criteria to detect individuals with ABI<0.9. HERMEX Study

	REASON at 4.1		The ISC Practice Guidelines	
	Estimation	**95% CI**	**Estimation**	**95% CI**
Sensitivity, %	87.3	76.5 – 94.4	90.5	80.4 – 96.4
Specificity, %	48.3	45.5 – 51.2	30.9	28.3 – 33.6
Positive predicted value, %	8.0	6.1 – 10.3	6.3	4.8 – 8.1
Negative predicted value, %	98.7	97.4 – 99.4	98.4	96.6 – 99.4
Likelihood ratio of a positive	1.7	1.5 – 1.9	1.3	1.2 – 1.4
Likelihood ratio of a negative	0.3	0.1 – 0.5	0.3	0.1 – 0.7
Percentage to screen	53.4	50.6 – 56.2	70.2	67.6 – 72.7
Youden's Index	0.4	0.2 –0.5	0.2	0.1 –0.3

Grau M et al. Prev Med. 2013

Number and percentage of individuals to screen by CHD risk categories. HERMEX Study



≈ 40-45% of low-medium risk people would require to perform an ABI measurement

≈ 5-6 % of population reclassified

Grau M et al. Prev Med. 2013

Therapeutic Approach of **Lower Extremity Artery Disease**


FRUIT
VEGETABLES
FITNESS
AIR
LIFESTYLE
WATER
(2L A DAY)
GREEN TEA
WATER
CEREALS
designed by freepik.com

Best medical therapy includes non-pharmacological measures

- **Smoking cessation**
- **Regular physical exercise**
- Healthy diet
- Weight loss


QUIT
SMOKING
SCIENCE
MUSCLE
LIVING
POSITIVE
BODY
NATURE
ENERGY
ACTIVITY
CHEERFUL
FIT
TRAINING
DIETING
RELAXATION
HAPPINESS
MOTION
ATHLETE
INFORMATION
ENVIRONMENT
MEDICAL
RUNNING
SPORT
ENJOYMENT
RELAXED
CHEERFUL
DIET
MIND
EXERCISE
EVERYDAY
FITNESS
GYM
MAINTENANCE
MENTAL
HAPPY
HAPPINESS
BODY
NATURE
HEALTHCARE
LIFESTYLE
HEALTHY
ACTIVITY
LIVING
SPIRIT
MUSCLE
SELF-CARE
ENERGY
PHYSICAL
MEDICAL
SCIENCE
LIFESTYLE
HEALTHY
SPIRIT
POSITIVE
NUTRITION
HAPPINESS
DIET
ENJOYMENT
HYGIENE
MEDICINE
CARE
HEALTHCARE
MENTAL
WELLNESS
WELL BEING
SPIRIT
BODY
RUNNING
FIT
DIET
RELAXED
EVERYDAY
MOTION
DIETING
ENJOYMENT
MEDICAL
LIFESTYLE
RUNNING
DIET
CHEERFUL
POSITIVE

Smoking Cessation

- There is great evidence supporting the benefits of smoking cessation in **reducing CV events and mortality**.

- Smoking cessation provides the most noticeable **improvement in WD** when combined with regular exercise.

Smoking Cessation

- Patients with PAD who smoke cigarettes or use other forms of tobacco should be **advised at every visit** to quit.

- We should develop a **plan** for quitting that includes **pharmacotherapy** (i.e., varenicline, buproprion, and/or nicotine replacement therapy) and/or **referral to a smoking cessation program** if necessary.

Smoking Cessation

- Moreover, they should **avoid exposure to environmental tobacco** smoke at work, at home, and in public places.

Physical Activity

- Exercise Therapy has proven to improve maximal walking distance and QoL.

- Supervised ExT is more effective than unsupervised.

Supervised Exercise Program

- It is a good treatment option for claudication before possible revascularization.

- At least 3 months, with a minimum of 3 h/week, with walking to the maximal or submaximal distance.

Structured Home-based Exercise Therapy

- A structured community- or home-based exercise program with behavioral change techniques, can be beneficial to improve walking ability and functional status.

Structured Home-based Exercise Therapy

- In patients with moderate to intense claudication, **alternative strategies of exercise therapy**, including upper-body ergometry, cycling, and pain-free or low-intensity walking

Medical Treatments

Antiplatelet Therapy

- 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.

Antiplatelet Therapy

- In asymptomatic patients with PAD (ABI ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death [2016 AHA GD].

- SAPT in a general population (with ABI <0.95) and another in diabetic patients (with ABI <1.0), found no benefit from aspirin in subclinical LEAD [2017 ESC GD].

Oral Anticoagulants

- Rivaroxaban...
- COMPASS RCT: The combination of **rivaroxaban plus aspirin** compared with aspirin alone **reduced CVD** and also reduced **major adverse limb events** in PAD patients.

- But **increased major bleeding** compared with the aspirin alone group

Anand SS. Lancet. 2017 Nov 10. pii: S0140-6736(17)32409-1.

Lipid Lowering Agents

- Treatment with a statin medication is indicated for patients with symptomatic LEAD.

*The U.S. Preventive Services Task Force has defined as a **priority** to **determine** the net clinical **benefit** of aggressive **treatment** of persons reclassified on the basis of additional information obtained from the ABI*

U.S. Preventive Services Task Force. *Ann Intern Med.* 2009;151:474–482.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 67, NO. 6, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.11.052

Statins for Prevention of Cardiovascular Events in a Low-Risk Population With Low Ankle Brachial Index

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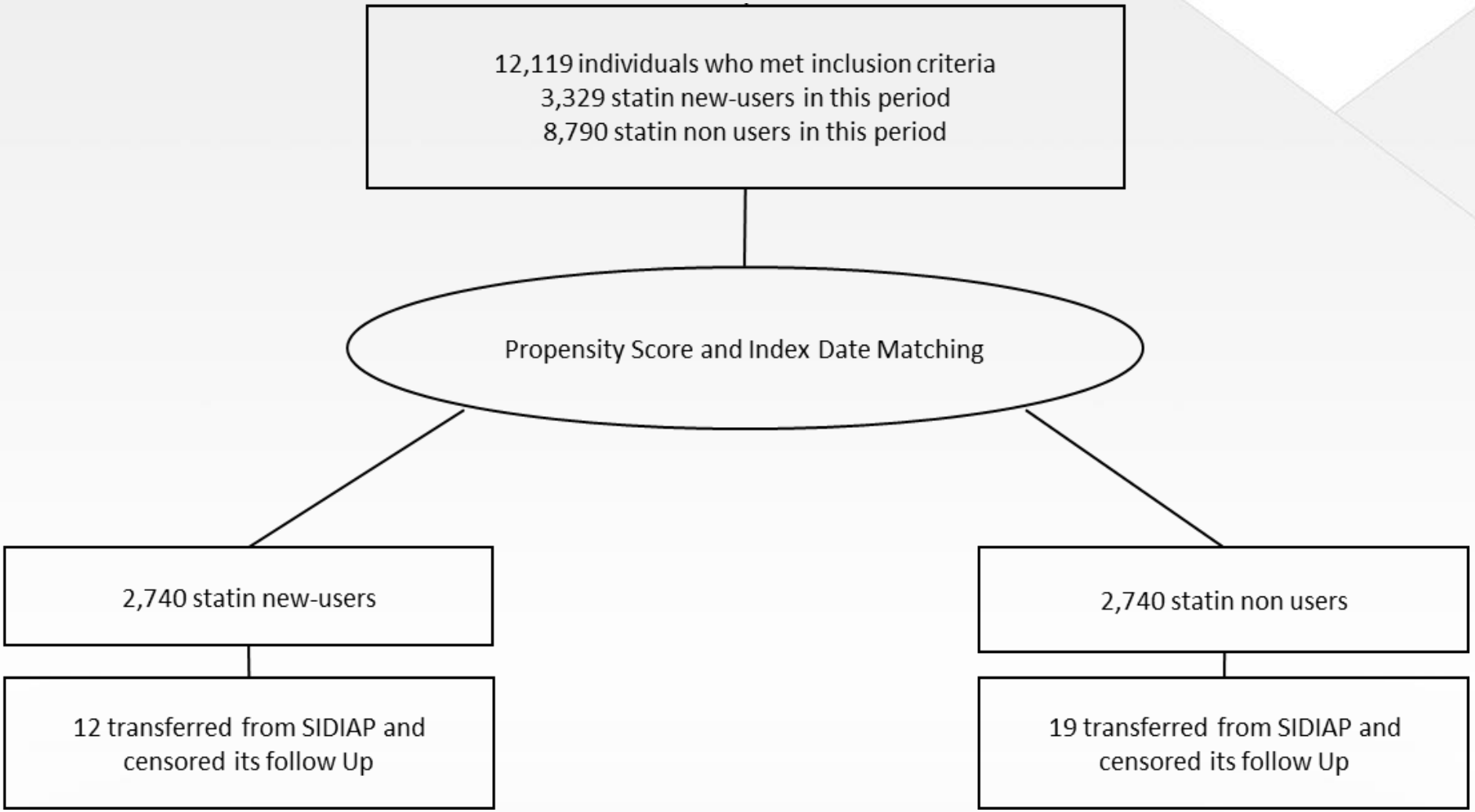

Ramos et al. J Am Coll Cardiol. 2016;67:630–40

Table 2. Hazard Ratios of incident cardiovascular events and mortality and the 1-yearNumber Needed To Treat to prevent 1event by the use of statins: Intention-to-Treat Analysis.

	Statins new-users		Statins non-users			
	Events	Incidence Rate* (95%CI)	Events	Incidence Rate* (95%CI)	HR (95%CI)	NNT
Outcomes of interest						
Hard coronary heart disease	88	8.4 (6.8-10.4)	124	12.2 (10.2-14.5)	0.70 (0.52-0.94)	276
Angina	68	6.5 (5.1- 8.2)	85	8.3 (6.7-10.2)	0.89 (0.69-1.16)	----
Coronary heart disease	123	11.9 (9.9-14.2)	162	16.1 (13.8-18.7)	0.74 (0.58-0.95)	233
Stroke	123	11.8 (9.9-14.1)	134	13.2 (11.1-15.6)	0.77 (0.54-1.12)	----
Major cardiovascular event	201	19.7 (17.2-22.5)	245	24.7 (21.8-27.8)	0.80 (0.66-0.97)	200
All-cause mortality	263	24.8 (22.0-27.8)	316	30.3 (27.2-33.6)	0.81 (0.68-0.97)	239
Adverse effects						
Cancer	154	22.2 (18.9-25.8)	140	20.6 (17.4-24.2)	1.08 (0.82-1.39)	----
Hemorrhagic stroke	37	4.7 (3.3-6.5)	36	4.7 (3.3- 6.5)	1.01 (0.61-1.68)	----
Diabetes	82	34.8 (27.9-42.6)	68	30.3 (23.7-38.0)	1.16 (0.80-1.69)	----
Hepatotoxicity	3	----	1	----	----	----
Myopathy	3	----	2	----	----	----

*1000 person year
NNT: Number needed to treat. HR: Hazard Ratio. CI: Confidence Interval

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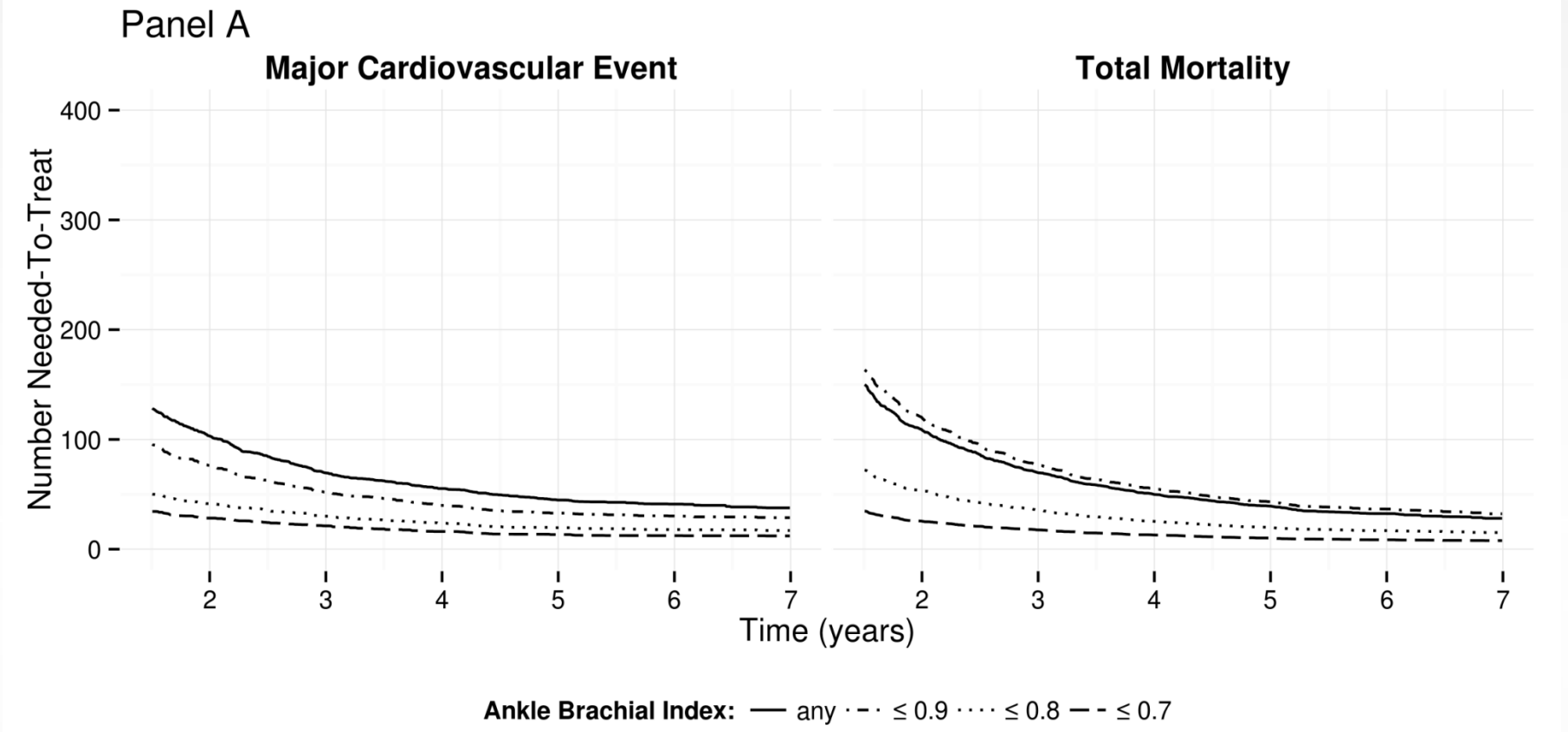

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Lipid Lowering Agents

- Treatment with a statin medication is indicated for patients with **asymptomatic** LEAD.

Lipid Lowering Agents

- PCSK9 Inhibitors…
- FOURIER trial: Showed **additional benefits** of evolocumab to **reduce CV events and MALE** in patients with LEAD over statins alone.
- Further results are awaited.

Bonaca M et al. Circulation. 2018;137:338–350

Pharmacotherapy to decrease walking impairment

- Cilostazol, Naftidrofuryl…
- Mild to moderate beneficial effects on MWD
- Evidence is limited

More about limb health…

Minimizing Tissue Loss in Patients With PAD

- Patients with PAD and diabetes mellitus should be counseled about **self–foot examination and healthy foot behaviors**.

- Prompt diagnosis and treatment of **foot infection** are recommended to avoid amputation.

Revascularization for Claudication

- **Revascularization** is a reasonable treatment option for the patient with **lifestyle-limiting claudication** with an inadequate response to lifestyles changes and medical therapy.

Multidisciplinary team for LEAD management

General practitioner, **primary care nurses**, vascular medical and surgical specialists, podiatrists, endocrinologists, rehabilitation clinicians…