

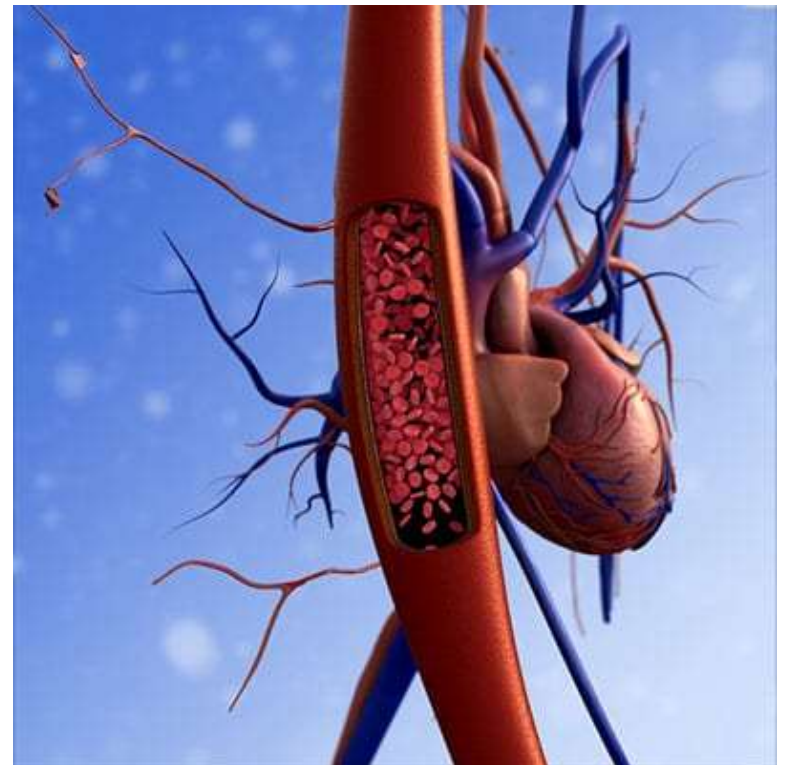
# Peripheral Arterial Disease and Chronic Kidney Disease: Dealing with Hidden Dangers

**Dr. Sonia Anand, MD, PhD, FRCPC**  
Professor, McMaster University

**Dr. Radha Joseph, MD, FRCPC**  
Clinical Scholar, McMaster University

# DISCLOSURES

- Dr. Sonia Anand
  - Dr. Anand has received honoraria and consulting fees from Bayer and Janssen
- Dr. Radha Joseph
  - N/A



# TERMINOLOGY

- Peripheral arterial disease (PAD): Presence of stenosis or occlusion in the aorta or arteries of the limbs
- **Major Adverse Cardiac Events (MACE):** Myocardial infarction (MI), ischemic stroke, cardiovascular (CV) death
- **Major Adverse Limb Events (MALE):** Acute limb ischemia (ALI, “heart attack of the leg”), amputation (“limb loss”), chronic limb threatening/critical limb ischemia (CLTI/CLI)

# PREVALENCE OF PAD

- Worldwide, prevalence of lower extremity PAD is between 3-12%
  - Estimated to affect >200 million people
  - Due to aging, estimated number of people with PAD increased by 24% between 2000-2010
- In Canada, 5% of ambulatory adults age  $\geq 50$  who underwent screening were diagnosed with PAD

Fowkes *et al. Lancet*. 2013, 382 (9901):1329-40.  
Selvin & Erlinger. *Circ*. 2004, 110(6):738-43.  
Bhagirath *et al. Can J Cardiol*. 2022, 38(5):634-644.

# SPECTRUM OF CLINICAL DISEASE IN PAD

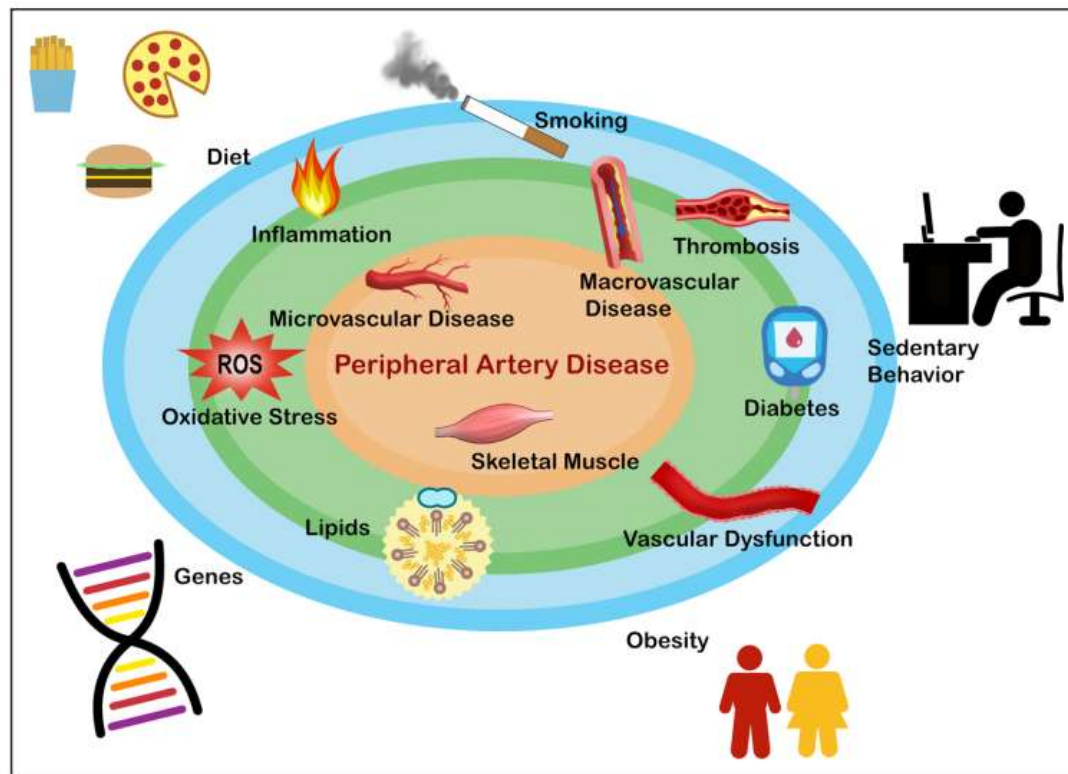
**Asymptomatic**

**Mild-severe  
claudication**

**Rest pain,  
night pain**

**Ischemic  
ulceration,  
wounds,  
gangrene**

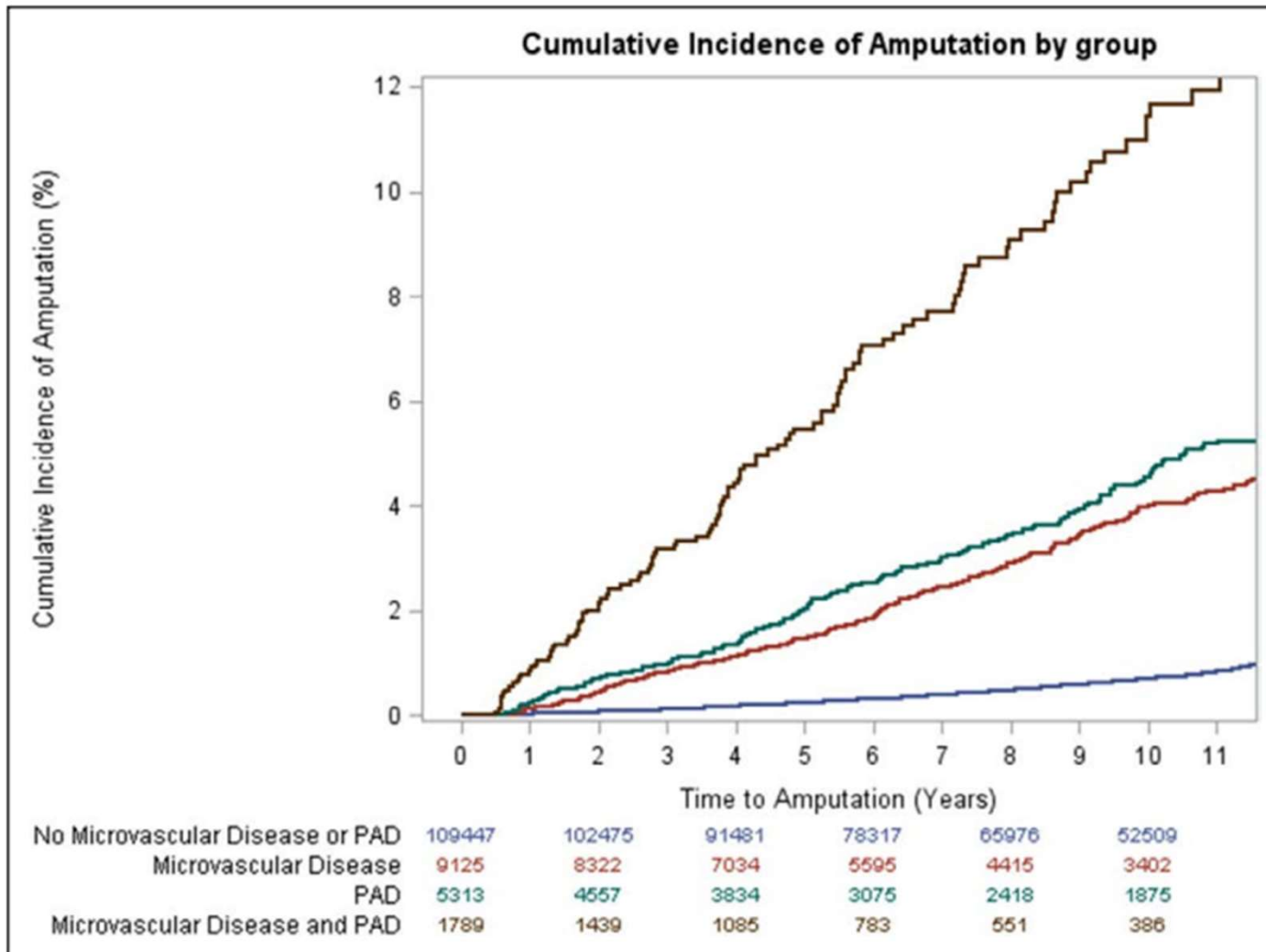
# PATHOBIOLOGY OF PAD



**Figure 1.** Pathobiologic drivers and pathways in the development of peripheral artery disease (PAD) and associated morbidity.

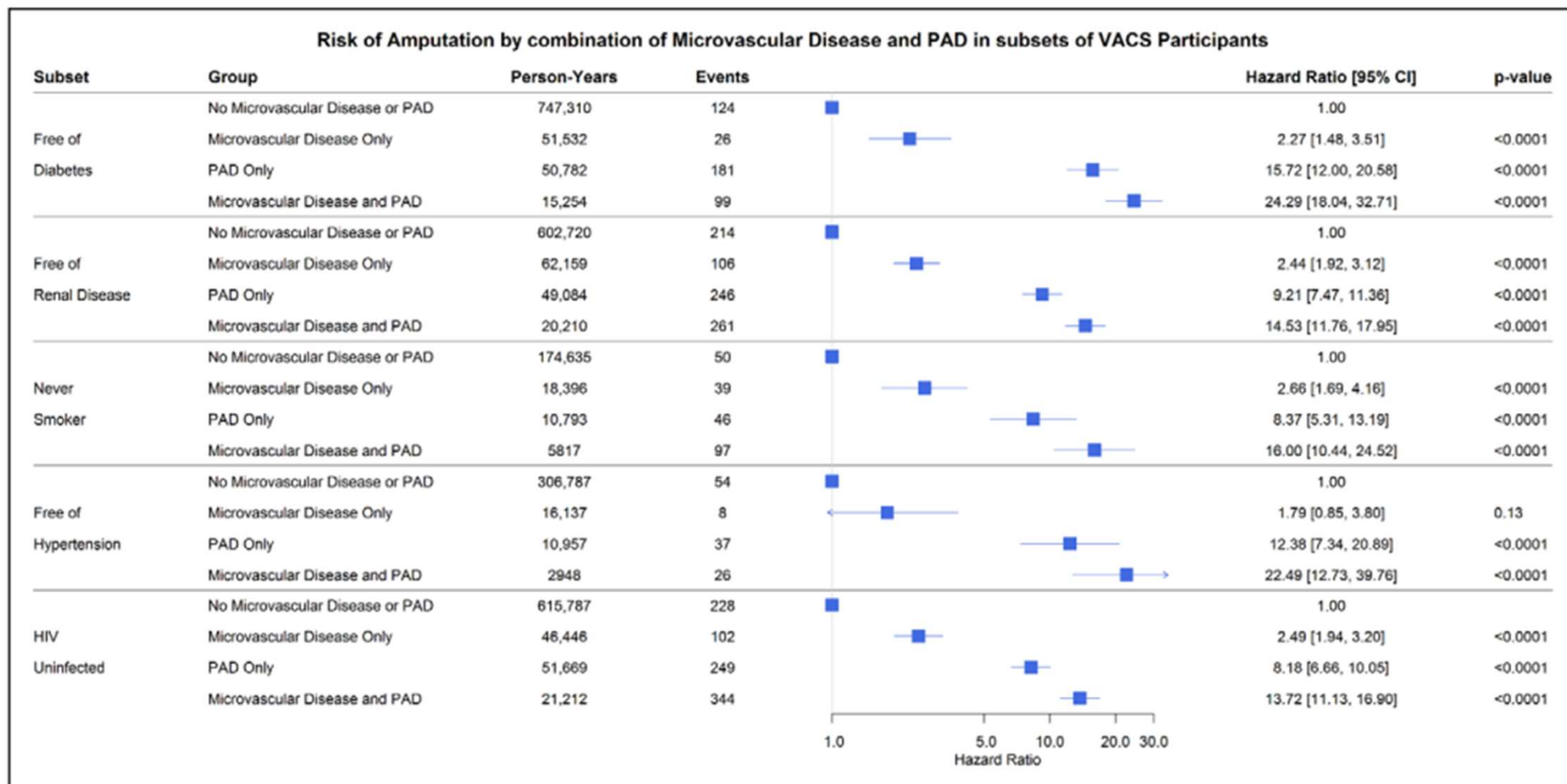
MALE indicates major adverse limb event.

Bonaca *et al.* *Circ Res.* 2021, 128(12):1868-1884.



**Figure 2. Cumulative incidence of amputation by baseline microvascular disease and PAD status.**

Kaplan-Meier survival curves illustrating the time to first amputation incident over 9.3 median years of follow-up for veterans with neither microvascular disease nor PAD, microvascular disease alone, PAD alone, and microvascular disease and PAD at baseline. PAD indicates peripheral artery disease.



**Figure 1. Risk of amputation by time-updated combination of microvascular disease and PAD in subsets of VACS participants.** Specific subsets include those who were free of diabetes mellitus, free of renal disease (estimated glomerular filtration rate > 60), never smokers, free of hypertension, and free of HIV infection. PAD indicates peripheral artery disease; and VACS, Veterans Aging Cohort Study.





# **PAD IN CKD & ESKD**



# PREVALENCE OF PAD IN CKD & ESKD

- In patients on dialysis, prevalence is between 23-46% (up to 10-fold higher)
- In non-dialysis patients with CKD  $\geq$ stage 3 (eGFR  $<$ 60 mL/min), prevalence is between 7.4-24% (up to 5.5-fold higher)

Table 1. Prevalence of PAD in Patients With Kidney Disease

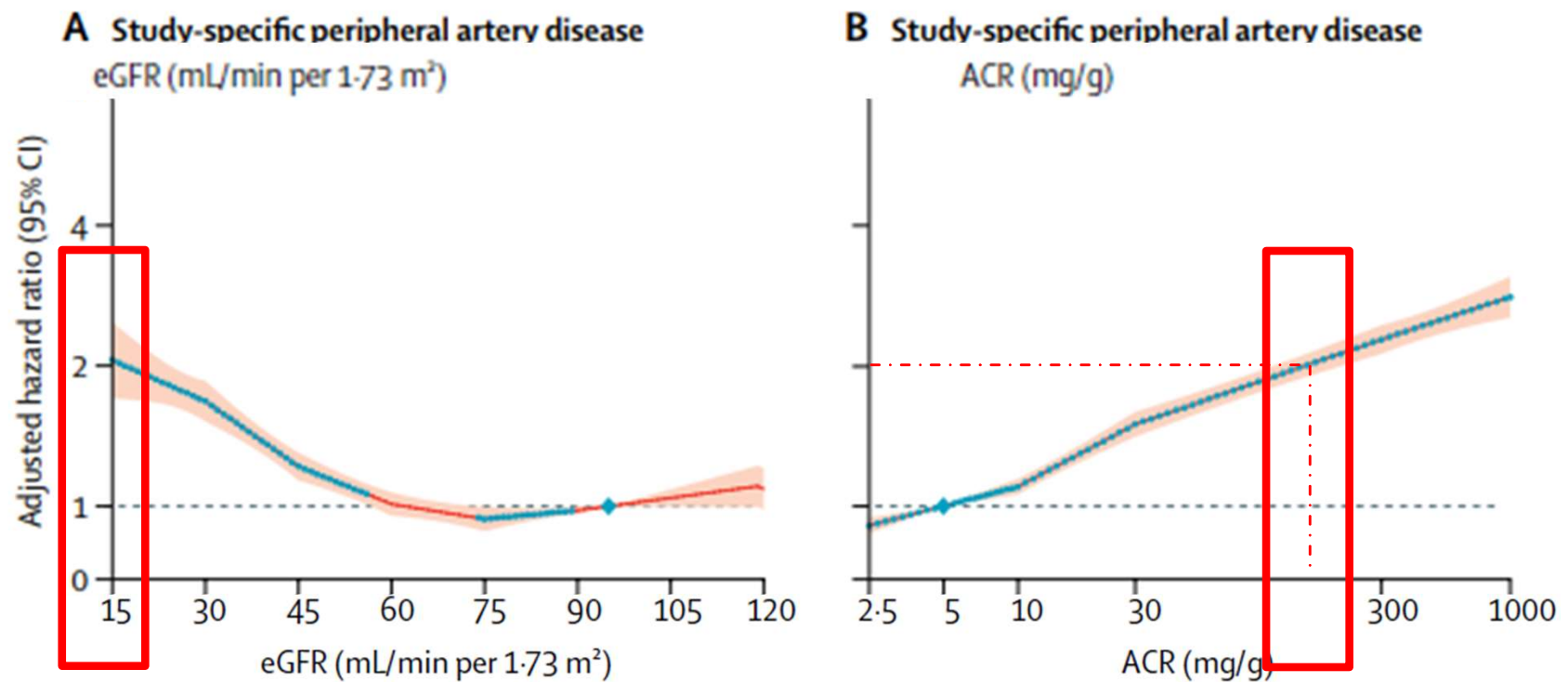
| Study   | Population   | Prevalence                             | Diagnostic Criteria                   |
|---|--|--|---------------------------------------|
| <b>Patients on Dialysis</b>                       |  |  |                                       |
| USRDS <sup>17</sup>                               | 35,438 incident dialysis patients                              | 45.9%                                  | Claims data                           |
| DOPPS <sup>18</sup>                               | 29,873 prevalent hemodialysis patients                         | 25.3%                                  | Clinical <sup>a</sup>                 |
| HEMO <sup>19</sup>                                | 936 prevalent hemodialysis patients                            | 23%                                    | Clinical <sup>a</sup>                 |
| Fishbane et al <sup>20</sup>                      | 132 prevalent hemodialysis patients                            | 35%                                    | ABI $<$ 0.9                           |
| Testa & Ottavio <sup>21</sup>                     | 226 prevalent hemodialysis patients                            | 33%                                    | ABI $<$ 0.9                           |
| <b>Patients With CKD Stage <math>\geq</math>3</b> |  |  |                                       |
| NHANES <sup>14</sup>                              | 211 participants with CCr $<$ 60 mL/min/1.73 m <sup>2</sup>    | 24%                                    | ABI $<$ 0.9                           |
| CRIC <sup>22</sup>                                | 3,199 participants with eGFR $<$ 60 mL/min/1.73 m <sup>2</sup> | 7.4%                                   | Self reported history of PAD          |
| CHS <sup>23</sup>                                 | 648 participants with kidney disease <sup>b</sup>              | 15.9%                                  | ABI $<$ 0.9                           |
| ARIC <sup>24</sup>                                | 376 participants with eGFR $<$ 60 mL/min/1.73m <sup>2</sup>    | 12%                                    | ABI $<$ 0.9                           |
| CHS <sup>25</sup>                                 | 648 participants with kidney disease <sup>b</sup>              | 8.6 incident cases/1,000 person-years  | Clinical <sup>a</sup> and ABI $<$ 0.9 |
|   |  | 10.7 incident cases/1,000 person-years | Incident intermittent claudication    |

Abbreviations: ABI, ankle-brachial index; ARIC, Atherosclerotic Risk in Communities; CHS, Cardiovascular Health Study; CKD, chronic kidney disease; CCr, creatinine clearance; CRIC, Chronic Renal Insufficiency Cohort; DOPPS, Dialysis Outcomes and Practice Patterns Study; eGFR, estimated glomerular filtration rate; HEMO, Hemodialysis Study; NHANES, National Health and Nutrition Examination Survey; PAD, peripheral artery disease; USRDS, US Renal Data System.

<sup>a</sup>Includes history of known PAD, amputation, revascularization, claudication, signs of critical limb ischemia, or reduced pulses on examination.

<sup>b</sup>Serum creatinine level  $\geq$  1.5 mg/dL in men and  $\geq$  1.3 mg/dL in women.

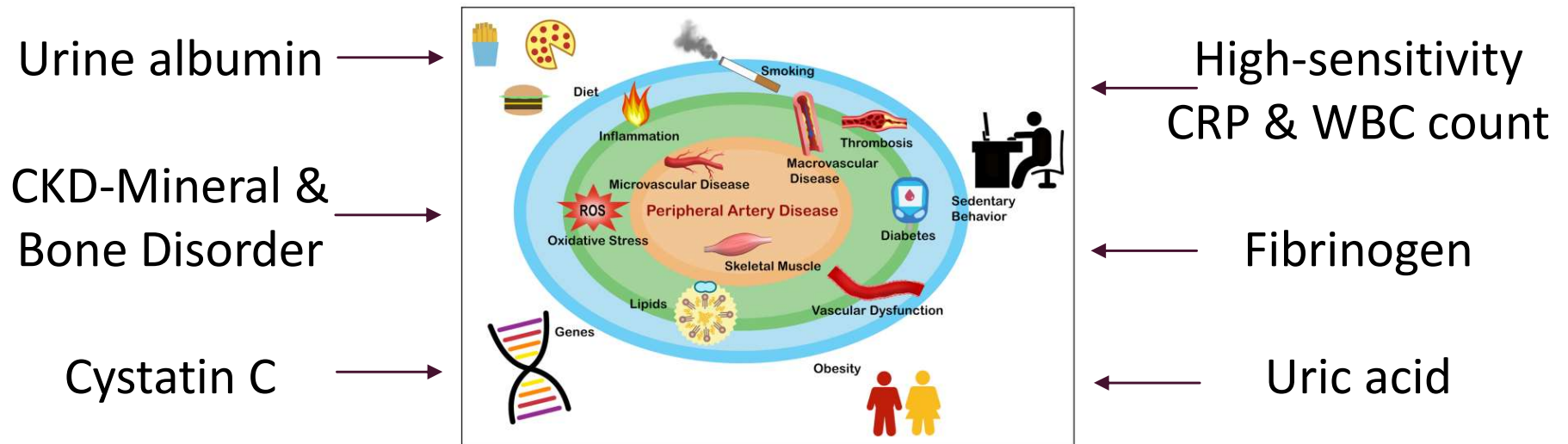
# INCIDENCE OF PAD BY EGFR AND ALBUMINURIA



**Figure 1: Relative risk of incident peripheral artery disease, by eGFR and ACR**

Matsushita et al. *Lancet Diabetes Endocrinol.* 2017, 5(9):718-728.

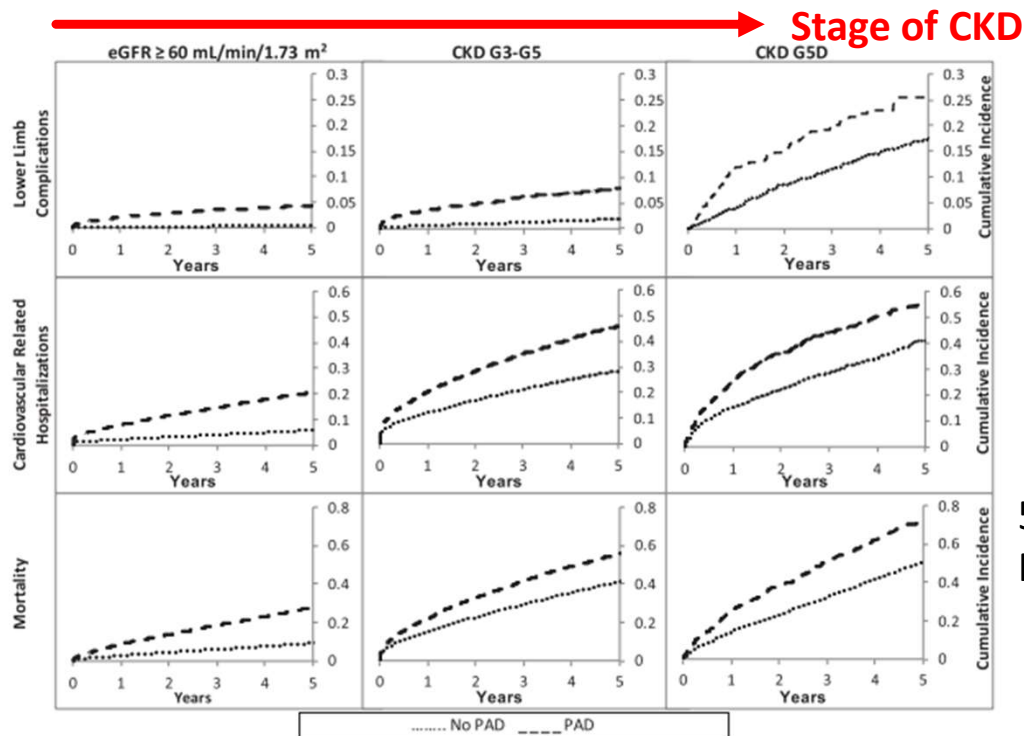
# PATHOBIOLOGY OF PAD IN CKD & ESKD



**Figure 1.** Pathobiologic drivers and pathways in the development of peripheral artery disease (PAD) and associated morbidity. MALE indicates major adverse limb event.

Chen *et al.* *Am J Cardiol.* 2012, 110(1):136-141.  
 Arinze *et al.* *Vasc Med.* 2019, 24(3):251-260.  
 Bonaca *et al.* *Circ Res.* 2021, 128(12):1868-1884.

# OUTCOMES IN CKD & ESKD



**CKD G5D (dialysis):**  
17% no PAD vs. 26% PAD

41% no PAD vs. 55% PAD

51% no PAD vs. 73% PAD

**Figure 2.** Cumulative incidence of lower-limb complications, cardiovascular-related hospitalizations, and mortality by kidney function with and without peripheral artery disease (PAD). Abbreviation: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

# OUTCOMES IN CKD & ESKD

- Among patients hospitalized with PAD +/- critical limb ischemia:
  - Patients with CKD also had a 2-fold higher amputation rate and nearly 3-fold higher in-hospital mortality rate
  - CKD remained a significant predictor of long-term outcome, with projected mortality rates after 4 years:
    - Patients without known CKD: 27%
    - Patients with known CKD:
      - Stage 2: 46%
      - Stage 3: 52%
      - Stage 4: 72%
      - Stage 5: 78%

# GUIDELINES ON DIAGNOSTIC EVALUATION

## ■ NKF KDOQI (2005)

- At the time of **dialysis initiation**, all patients should be evaluated for the presence of peripheral vascular disease
- Evaluation should include physical examination including assessment of arterial pulse and skin integrity
- Further specialized studies, such as Duplex studies or invasive testing, should be undertaken if abnormalities are detected upon physical examination and interventions are considered

## ■ KDIGO CKD (2012)

- We recommend that adults with CKD be regularly examined for signs of peripheral arterial disease and be considered for usual approaches to therapy

# EDINBURGH CLAUDICATION QUESTIONNAIRE

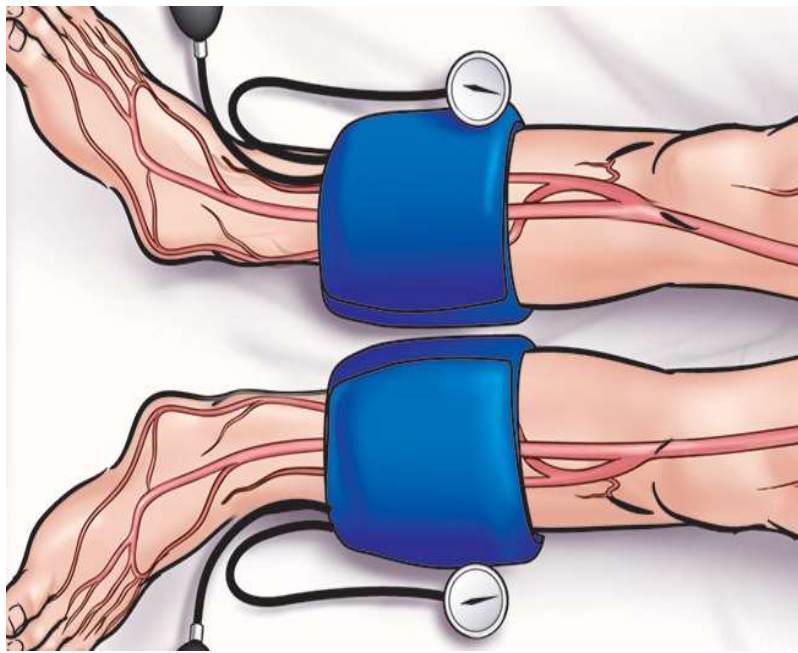
- Diagnostic questionnaire
  - 91.3% sensitivity and 99.3% specificity
- **Not validated in CKD**

**Table 2. Edinburgh Claudication Questionnaire**

- 
1. Do you get a pain or discomfort in your leg(s) when you walk?
  2. Does this pain ever begin when you are standing still or sitting?
  3. Do you get it if you walk uphill or hurry?
  4. Do you get it when you walk at an ordinary pace on the level?
  5. What happens to it if you stand still?  
Usually continues more than 10 minutes  
Usually disappears in 10 minutes or less
  6. Where do you get this pain or discomfort?
-



# ANKLE-BRACHIAL INDEX (ABI)



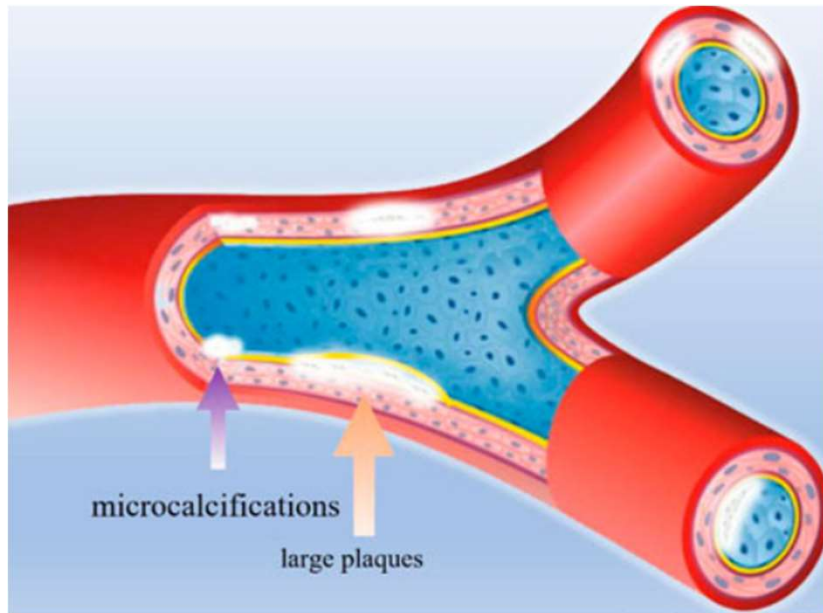
$$R - ABI = \frac{\text{Highest Pressure in Right Ankles}}{\text{Highest Pressure in Both Brachials}} \quad L - ABI = \frac{\text{Highest Pressure in Left Ankles}}{\text{Highest Pressure in Both Brachials}}$$

- First-line diagnostic tool
  - 61% sensitivity and 92% specificity in general population

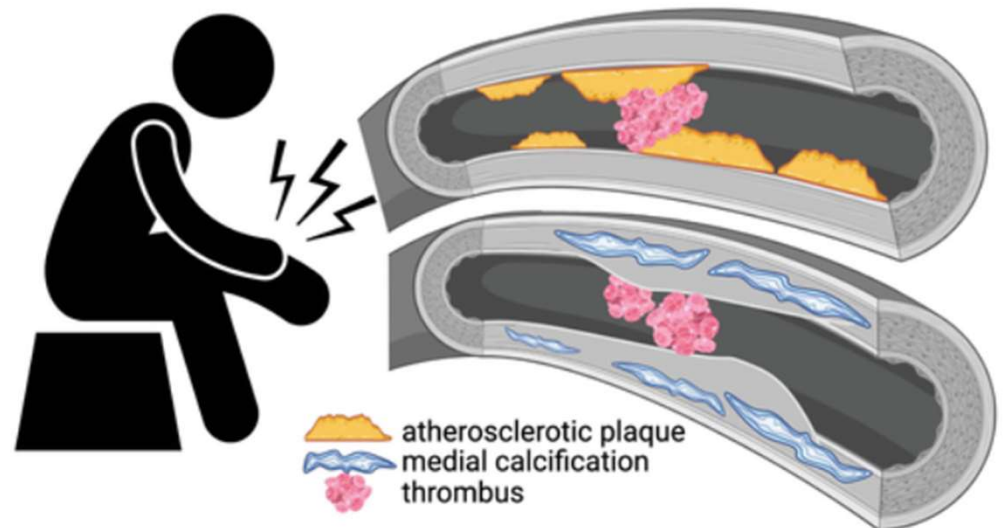
| ABI         |                               |
|-------------|-------------------------------|
| ≤0.9        | Occlusive arterial disease    |
| >0.9 to 1.0 | Borderline low                |
| >1.0 to 1.4 | Normal                        |
| >1.4        | Calcification of the arteries |

- Predictive of global vascular risk

# THE DILEMMA: MEDIAL ARTERIAL CALCIFICATION



<https://www.frontiersin.org/articles/10.3389/fphar.2022.907835/full>



<https://www.ahajournals.org/doi/10.1161/ATVBAHA.121.316252>

# TOE BRACHIAL INDEX (TBI)

- TBI is more useful in ruling out PAD in CKD, given toe arteries are less affected by MAC

| TBI         |                            |
|-------------|----------------------------|
| <0.6 or 0.7 | Occlusive arterial disease |
| >0.6 or 0.7 | Normal                     |

- Linear association between TBI and CV mortality



# THE DILEMMA: MEDIAL ARTERIAL CALCIFICATION

- Medial arterial calcification (MAC) results in decreased vessel compressibility and can lead to false normal ABI or elevated ABI
- Supranormal ABI in symptomatic patients requires evaluation for the presence and extent of PAD
  - 92 symptomatic patients with high ABI (>1.4) underwent angiography
    - 46.7% claudication, 52.2% critical limb ischemia
    - 18.5% on dialysis
    - 84% had infra-popliteal involvement, 48.8% found to have multi-level disease
    - PAD was absent in only 4.7%
    - **92% had TBI <0.7**

# GOALS OF THERAPY

- CV risk reduction
- Claudication
  - Relieve exertional symptoms
  - Improve walking capability
  - Improve quality of life
- CLTI
  - Relieve ischemic rest pain
  - Heal ischemic ulceration
  - Prevent limb loss

# MEDICAL MANAGEMENT

| DOMAIN  | RECOMMENDATION | EVIDENCE         |
|---|----------------|------------------|
| <b>Smoking cessation</b> – to prevent MACE and MALE   | Strong         | Moderate Quality |
| <b>Smoking cessation</b> – interventions including intensive counselling, NRT, bupropion, varenicline   | Strong         | High Quality     |
| <b>Exercise</b> – supervised exercise or structured home-based, preferably walking  | Strong         | High Quality     |
| <b>Exercise</b> – if unable to walk, try alternative forms of exercise or resistance training   | Weak           | Moderate Quality |
| <b>Diabetes</b> – tight glycemic control to prevent MALE  | Weak           | Low Quality      |
| <b>Diabetes</b> – SGLT-2 inhibitor in PAD for MACE  | Strong         | High Quality     |
| <b>Diabetes</b> – use GLP-1 agonist or DPP-4 inhibitor  | Weak           | Low Quality      |
| <b>Blood pressure</b> – use ACE inhibitor or ARB as first choice  | Strong         | Moderate Quality |
| <b>Lipid-lowering</b> – statin + ezetimibe + PCSK-9 inhibitor   | Strong         | High Quality     |
| <b>Lipid-lowering</b> – add highly-purified fish oil if on maximal statin with elevated triglycerides   | Strong         | Moderate Quality |
| <b>Dual pathway inhibition</b> – aspirin + low-dose rivaroxaban for symptomatic lower-extremity PAD with high-risk features ( <i>if low bleeding risk</i> ) | Strong         | High Quality     |
| <b>Dual pathway inhibition or single antiplatelet therapy</b> for low-risk symptomatic PAD ( <i>if low bleeding risk</i> )                                  | Strong         | High Quality     |

Abramson, AL-Omron, Anand *et al.* *Can J Cardiol.* 2022, 38(5):560-587.



## PERIPHERAL ARTERIAL DISEASE

(PAD) is common, debilitating, can be deadly, and fortunately preventable when you think about it.

### Think **SAVELIMB** with your at-risk patients

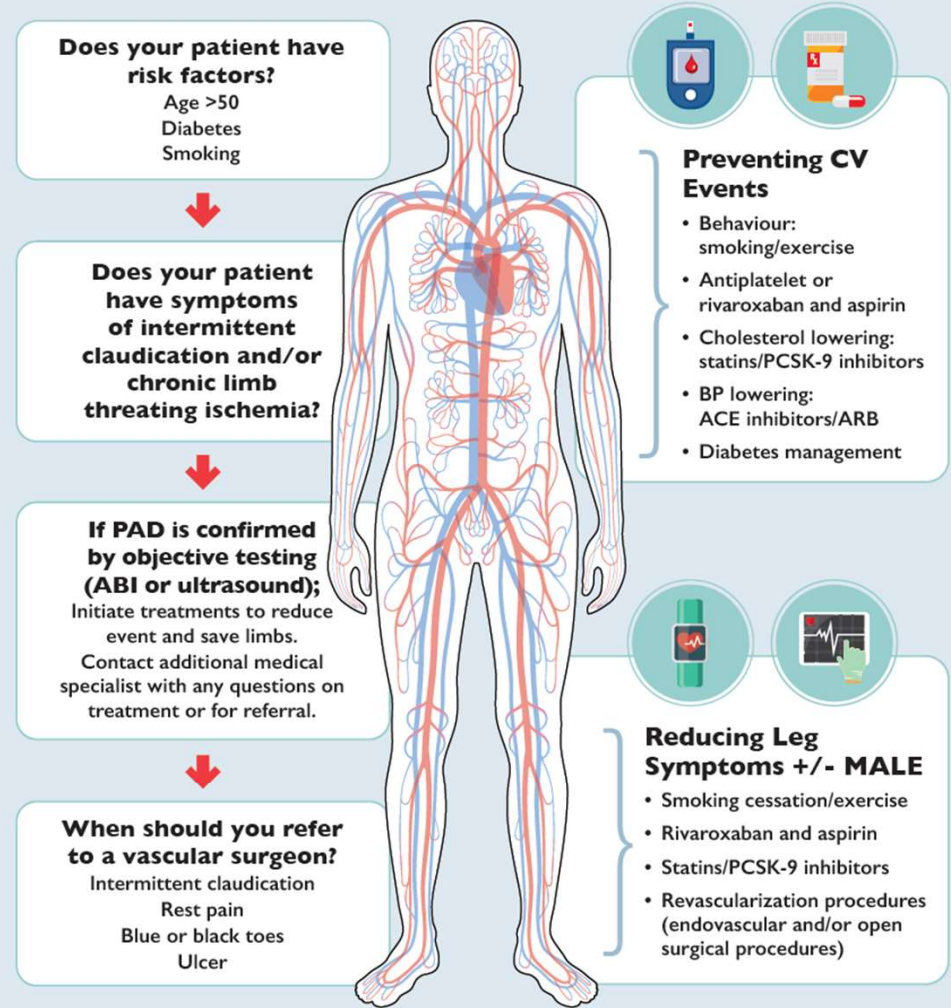
- S** **Screen** people at risk for: smoking, diabetes, cardiovascular risk factors, age
- A** **Assess and ask** about arterial diseases: ABI, AAA, and ask history of intermittent claudication
- V** **Vascular studies:** perform when indicated; such as ABI and arterial duplex scan
- E** **Etiology:** consider athero-thrombosis, embolism, and AF
- L** **Lifestyle behaviour changes:** reinforce exercise, smoking cessation, BP and cholesterol lowering, diabetes treatment, management
- I** **Intermittent claudication:** ask about quality of life (e.g. pain with walking), and document distance
- M** **Medication** to treat: prescribe antiplatelets, antithrombotics, statins, ACE inhibitor, and check meds for BP, cholesterol and diabetes
- B** **Bypass surgery/revascularization procedures:** think about when they are needed

**SAVELIMBs and Lives...**

[#SAVELIMBSANDLIVES](#)

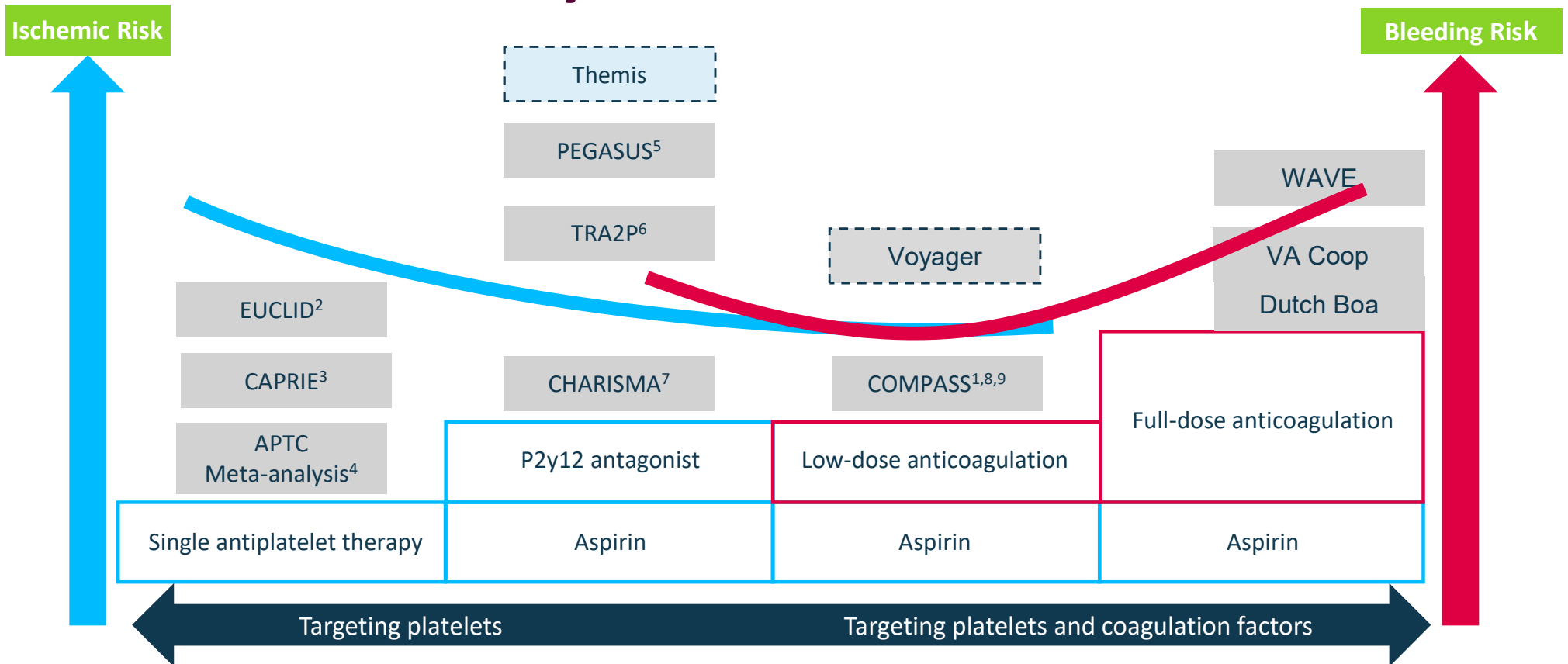
AAA, abdominal aortic aneurysm; ABI, Ankle-Brachial Index; AF, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure

## PAD — TO **SAVELIMBs** and Lives



ABI, Ankle-Brachial Index; ACE, Angiotensin converting enzyme; ARB, angiotensin receptor blockers; BP, blood pressure; CV, cardiovascular; MALE, major adverse limb events; PAD, peripheral arterial disease; PCSK-9, protein convertase subtilisin/Kexin-9

# Finding the Optimal Balance Between Efficacy and Safety in PAD: 3 Decades



APT, Antiplatelet Trialists' Collaboration; PAD, peripheral artery disease. 1. Anand SS, et al. *J Am Coll Cardiol* 2018; 71:2306-15; 2. Hiatt WR, et al. *N Engl J Med* 2017; 376:32-40; 3. CAPRIE Steering Committee. *Lancet* 1996; 348:1329-36; 4. Antithrombotic Trialists' Collaboration. *BMJ* 2002; 324:74-86; 5. Bonaca MP, et al. *N Engl J Med* 2015; 372:1791-800; 6. Bonaca MP, et al. *JACC: Cardiovasc Interv* 2014; 9:2157-64; 7. Bhatt DL, et al. *N Engl J Med* 2006; 354:1706-17; 8. Anand SS, et al. *Lancet* 2018; 391:219-29; 9. Eikelboom JW, et al. *N Engl J Med* 2017; 377:1319-330; 10. WAVE Investigators. *N Engl J Med* 2007; 357:217-27.



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ORIGINAL ARTICLE

## Oral Anticoagulant and Antiplatelet Therapy and Peripheral Arterial Disease

The Warfarin Antiplatelet Vascular Evaluation Trial Investigators\*

## Rivaroxaban in Peripheral Artery Disease after Revascularization

Marc P. Bonaca, M.D., M.P.H., Rupert M. Bauersachs, M.D., Sonia S. Anand, M.D., E. Sebastian Debus, M.D., Ph.D., Mark R. Nehler, M.D., Manesh R. Patel, M.D., Fabrizio Fanelli, M.D., Warren H. Capell, M.D., Lihong Diao, M.D., Nicole Jaeger, M.S., Connie N. Hess, M.D., M.H.S., Akos F. Pap, M.Sc., et al.

# Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial



*Sonia S Anand, Jackie Bosch, John W Eikelboom, Stuart J Connolly, Rafael Diaz, Peter Widimsky, Victor Aboyans, Marco Alings, Ajay K Kakkar, Katalin Keltai, Aldo P Maggioni, Basil S Lewis, Stefan Störk, Jun Zhu, Patricio Lopez-Jaramillo, Martin O'Donnell, Patrick J Commerford, Dragos Vinereanu, Nana Pogosova, Lars Ryden, Keith A A Fox, Deepak L Bhatt, Frank Misselwitz, John D Varigos, Thomas Vanassche, Alvaro A Avezum, Edmond Chen, Kelley Branch, Darryl P Leong, Shrikant I Bangdiwala, Robert G Hart, Salim Yusuf; on behalf of the COMPASS Investigators\**

THE LANCET

# COMPASS

## ■ Inclusion Criteria

### ■ Presence of CAD or PAD

- PAD defined as any of: Previous aorto-femoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty of iliac, infrainguinal arteries; previous limb or foot amputation for arterial vascular disease; history of claudication (with either ABI < 0.9 or ≥ 50% stenosis); previous carotid revascularization or asymptomatic carotid stenosis ≥ 50%

### ■ If included for CAD, also required either of:

- Age ≥65 years
- Age <65 years with:
  - Documented atherosclerosis or revascularization involving at least 1 additional vascular bed; current smoker; diabetes; **renal dysfunction (eGFR < 60 mL/min)**; heart failure; non-lacunar stroke ≥ 1 month prior to randomization

## ■ Exclusion criteria included eGFR <15 mL/min

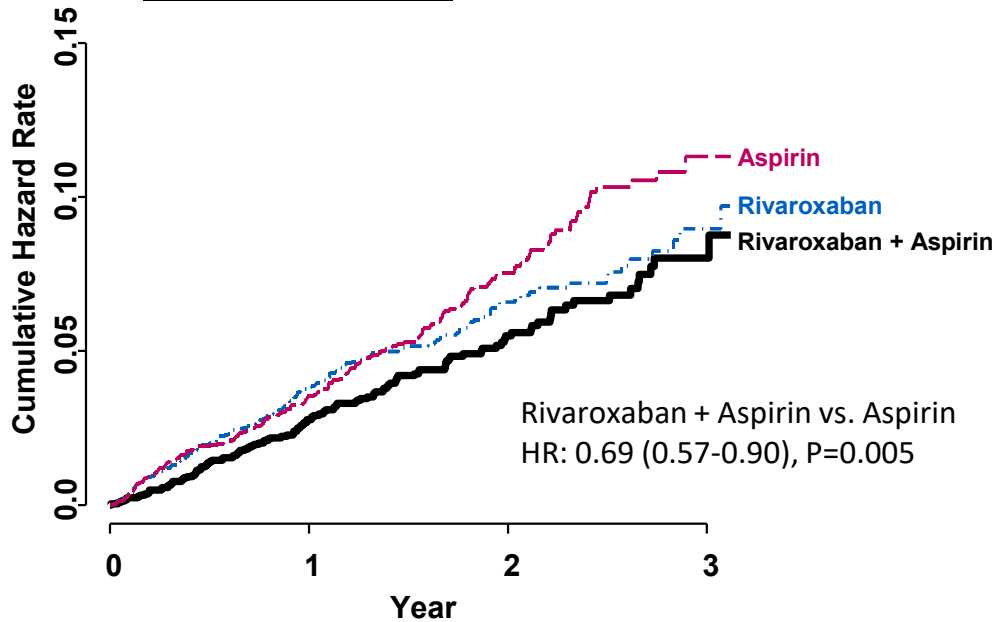
# Rivaroxaban Across the Spectrum of PAD



Population selected for PAD or CAD with enrichment

PAD outcome: CV death, MI, stroke, ALI, MVAMP

Concomitant CAD 65%

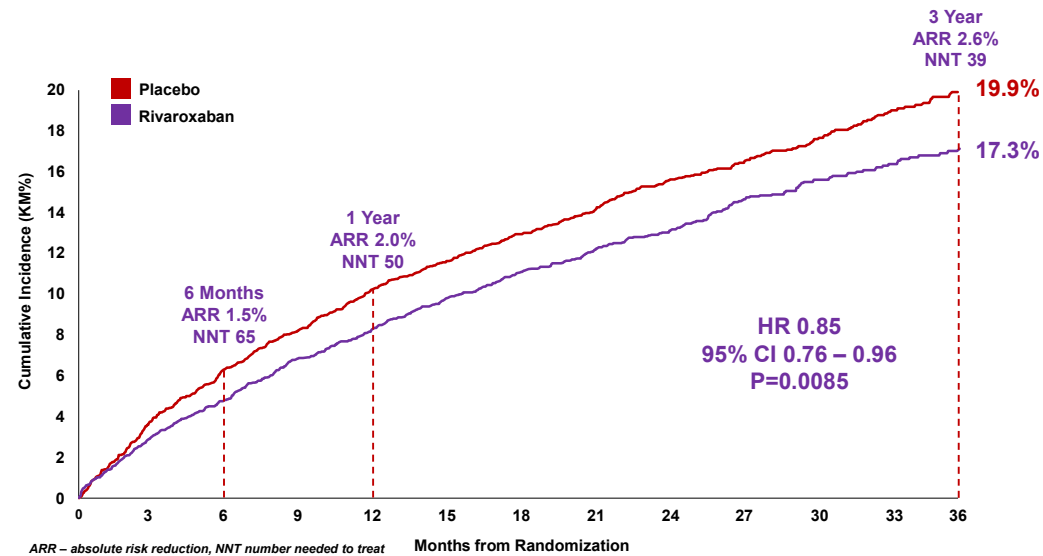


Anand et al. *Lancet*. 2018, 391:219-229.

Population selected for lower extremity PAD only (no CAD enrichment)

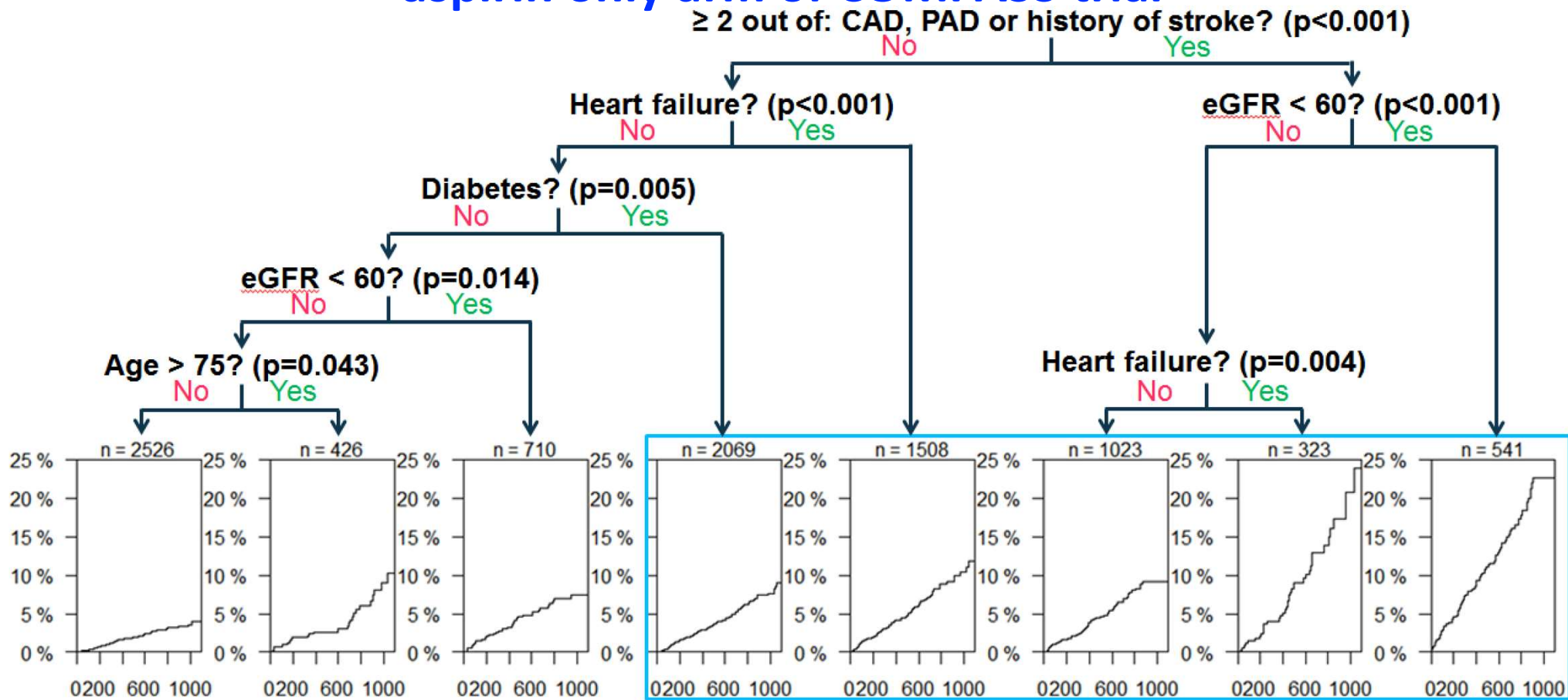
PEP: CV death, MI, ischemic stroke, ALI, MVAMP

Concomitant CAD 32%



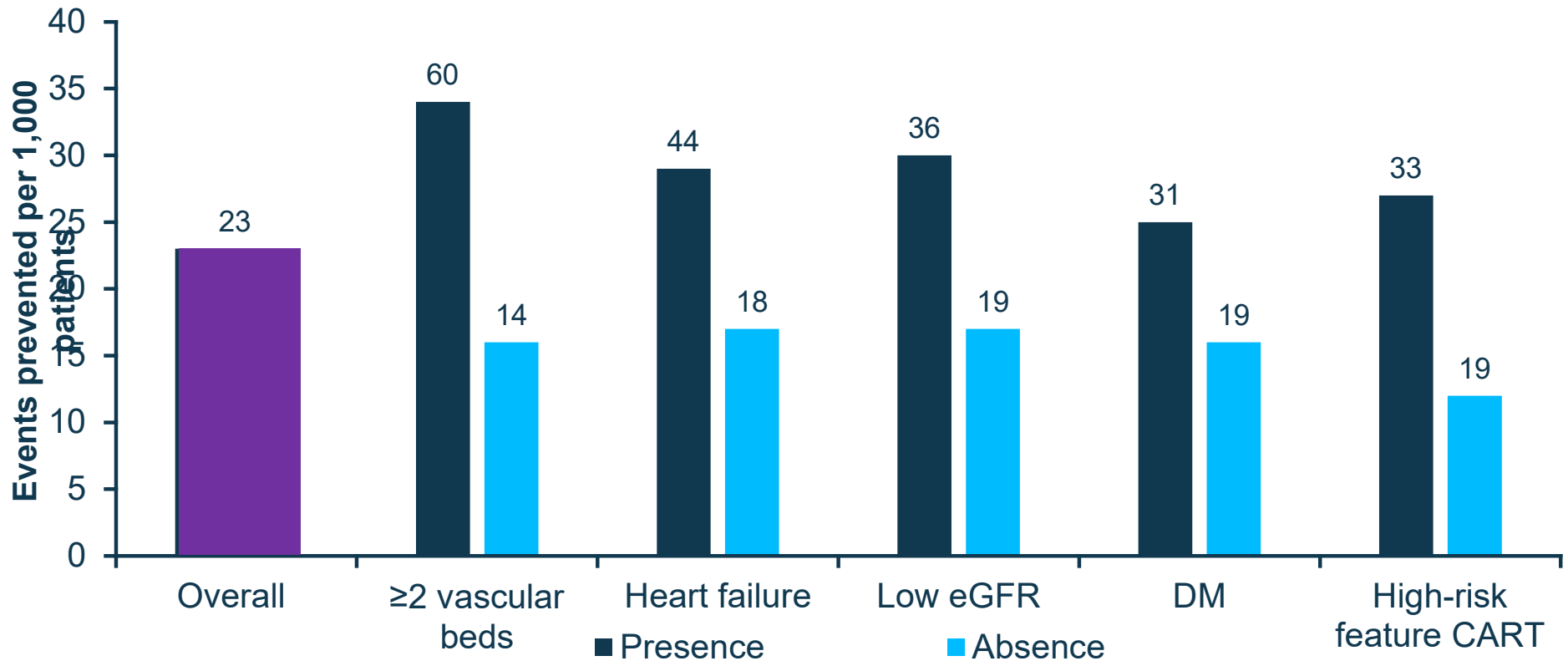
Bonaca et al. *New Engl J Med*. 2020, 382:1994-2004.

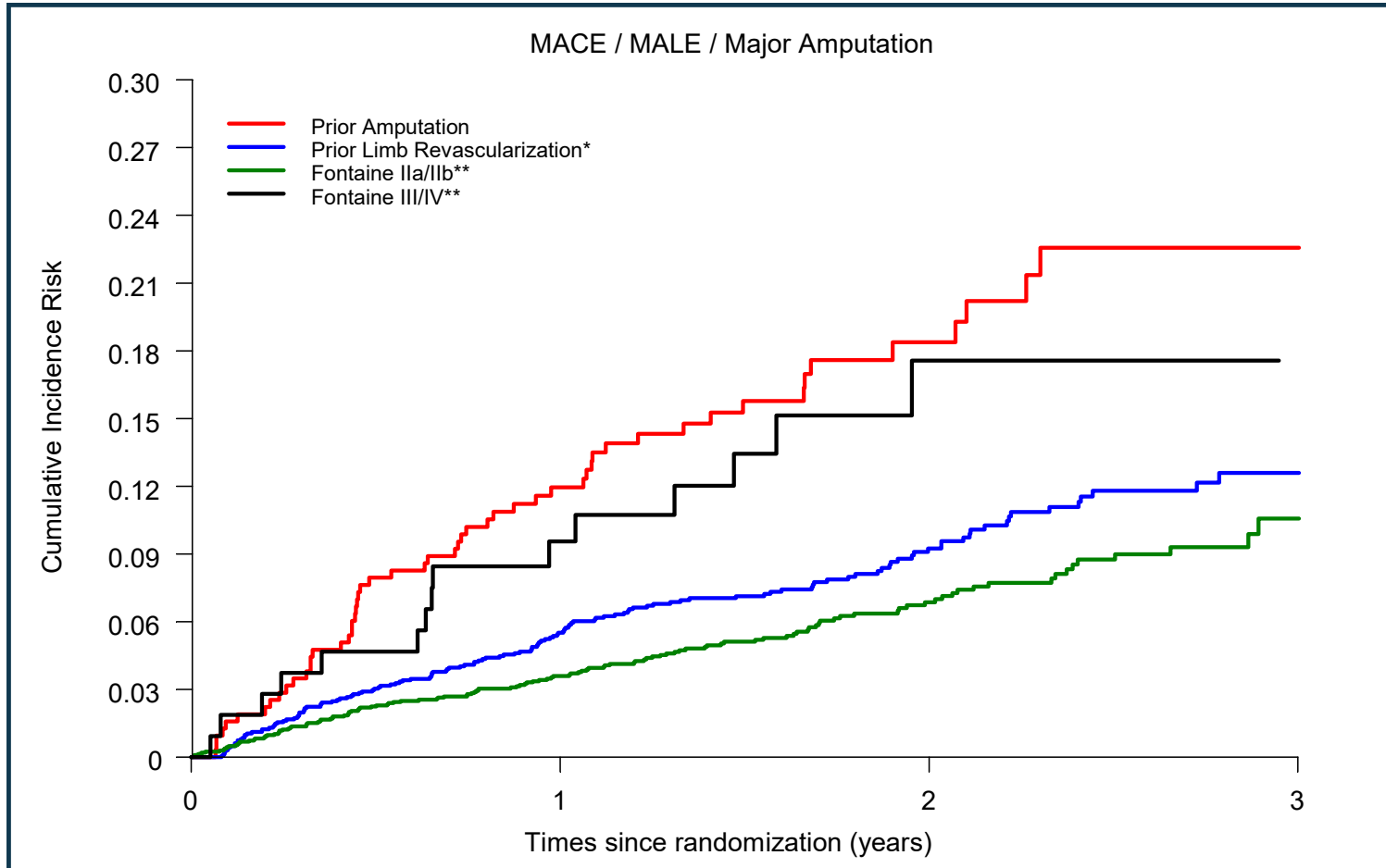
# CART: Selecting the highest risk independent groups in the aspirin only arm of COMPASS trial



# Who are the highest risk patients who benefit most?

Events Prevented Per 1,000 Patients Treated with Rivaroxaban + Aspirin Over 30 Months





\* without prior amputation

\*\* without prior amputation or prior limb revascularization

Legend: MACE: Major adverse cardiac event; MALE: major adverse limb event; PAD: Peripheral artery disease

**Figure 1: MACE, MALE Including Major Amputation Stratified by Subtype of PAD**

# COMPASS: SECONDARY ANALYSIS IN CKD

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VOL. 73, NO. 18, 2019

## ORIGINAL INVESTIGATIONS

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# Rivaroxaban Plus Aspirin in Patients With Vascular Disease and Renal Dysfunction



From the COMPASS Trial

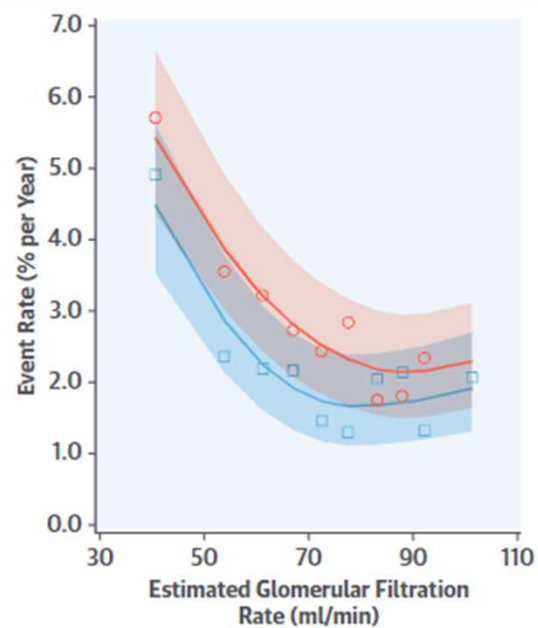
Keith A.A. Fox, MChB,<sup>a</sup> John W. Eikelboom, MBBS,<sup>b,c</sup> Olga Shestakovska, MSc,<sup>c</sup> Stuart J. Connolly, MD,<sup>c</sup>  
Kaj P. Metsarinne, MD,<sup>d</sup> Salim Yusuf, DPM.<sup>b,c</sup>

Fox et al. *J Am Coll Cardiol.* 2019, 73(18):2243-2250.

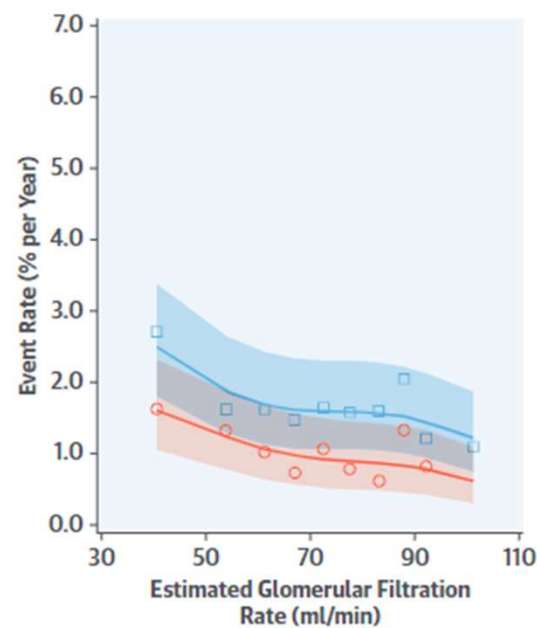
# COMPASS: SECONDARY ANALYSIS IN CKD

## CENTRAL ILLUSTRATION Rivaroxaban Plus Aspirin in Renal Dysfunction

### Cardiovascular Death, Stroke, or Myocardial Infarction



### Major Bleeding

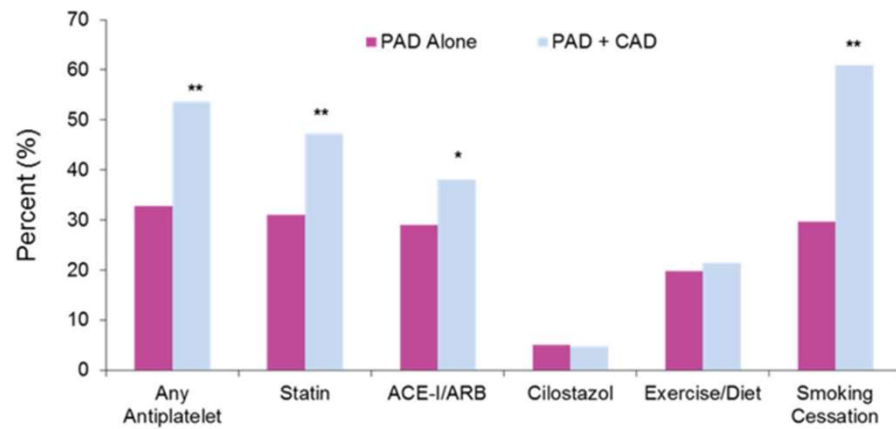


□□ Rivaroxaban Plus Aspirin ○○ Aspirin Alone

Fox et al. *J Am Coll Cardiol.* 2019, 73(18):2243-2250.

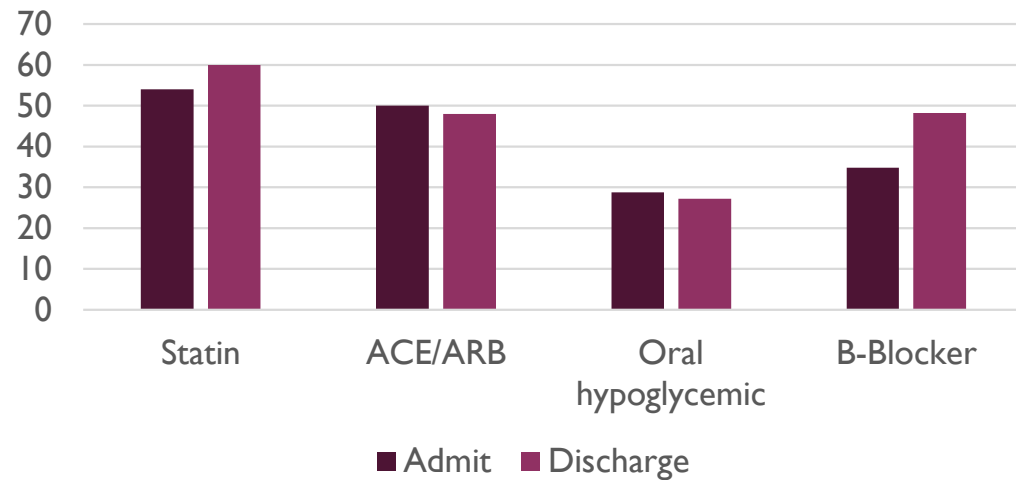


# PAD GAP



**Figure 2.** Prevalence of medication use and lifestyle counseling in patients with peripheral artery disease alone versus peripheral artery disease with concomitant coronary artery disease.

## Medication use - Admit vs Discharge to Vascular Surgery



Berger & Ladapo. *J Am Coll Cardiol.* 2017, 69(18):2293-2300.  
Kaplovitch et al. *Can J Cardiol.* 2021, 3(11):1325-1332.

# UNDERTREATMENT OF PAD IN CKD

- 28,652 patients underwent peripheral vascular intervention for critical limb ischemia, 47.5% with CKD (eGFR <60 mL/min)
  - Goal-directed medical therapy included the composite use of antiplatelet therapy and statin, and ACE inhibitor or ARB if hypertension was present
  - Patients **with CKD** versus those **without CKD** had lower prescription rates both before (**31.7%** vs. **38.9%**) and after (**36.5%** vs. **48.8%**) peripheral vascular intervention ( $p < 0.0001$ )

## TAKE-HOME POINTS

- PAD is a disease with devastating consequences, that remains underdiagnosed and undertreated
- Patients with CKD are at significantly increased risk of developing PAD, and co-existence of PAD and CKD is associated with distinctly higher rates of amputation, in-hospital and long-term mortality
- Patients with PAD and CKD have unique considerations in terms of risk factors, diagnostic evaluation and treatment
- PAD patients would ideally be served by close collaboration between surgical specialists, medical specialists and primary care



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