# How to Improve CV and Limb Outcomes in the patients with PAD

## Tailored Protection for your cardiovascular patients : Insights from COMPASS Trial

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- **Current Treatment of PAD**
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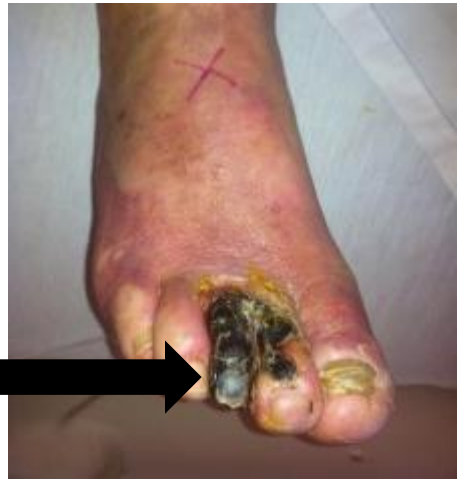
# Overview of PAD

A progressive and polyvascular disease caused by atherosclerosis

# Overview of PAD

- PAD is an atherosclerotic process that causes stenosis and occlusion of non-cerebral and non-coronary arteries[1–3]
- PAD typically refers to atherosclerosis affecting the arteries of the lower extremities – the resulting limb ischaemia can lead to amputation[1–3]
- PAD may also affect visceral arteries and carotid arteries[1]
- PAD is often asymptomatic[1–3]

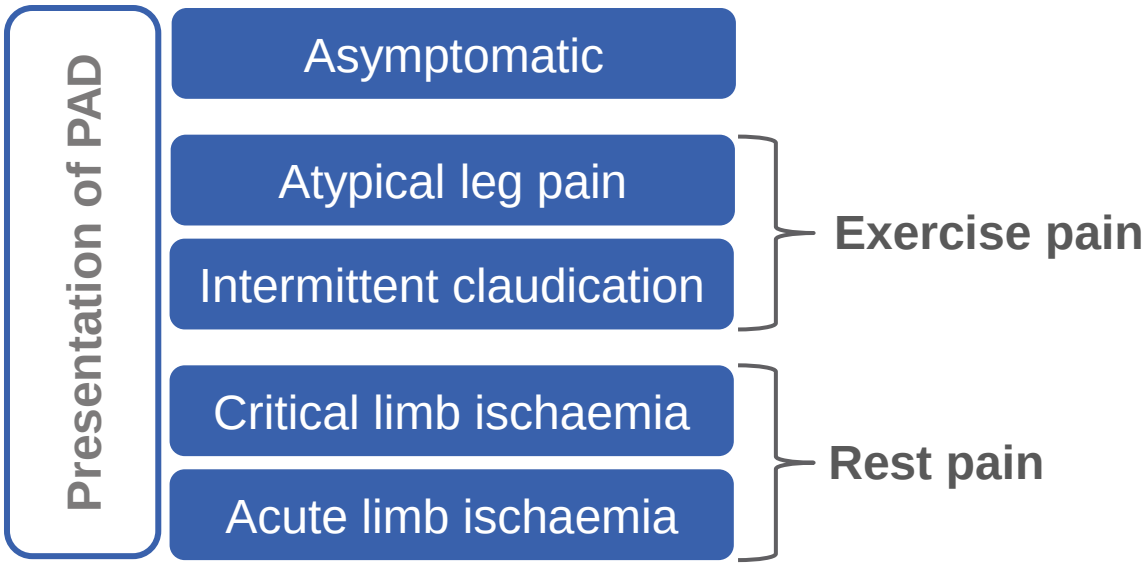
Toe gangrene



1. Tendera M *et al* – ESC PAD Guidelines, *Eur Heart J* 2011;32:2851–2906;
2. Gerhard-Herman MD *et al* – AHA/ACC lower extremity PAD Guidelines, *J Am Coll Cardiol* 2016;69:e71–e126 ;
3. Norgren L *et al* – Inter-Society Consensus for the Management of PAD (TASC II), *J Vasc Surg* 2007;45:S5–S67

# Lower Extremity Peripheral Artery Occlusion Leads to Limb Ischaemia

- Atherosclerotic plaques lead to occlusion of peripheral arteries with consecutive hypoperfusion and ischaemia of tissues distal to the obstruction[1]
- The most severe manifestations are:
  - Acute limb ischaemia – sudden (<2 weeks) decrease in limb perfusion[1,2]
  - Critical limb ischaemia – chronic (≥2 weeks) hypoperfusion that is inadequate to sustain viability in the distal tissue bed; typically associated with multisegment occlusive arterial disease[1–3]



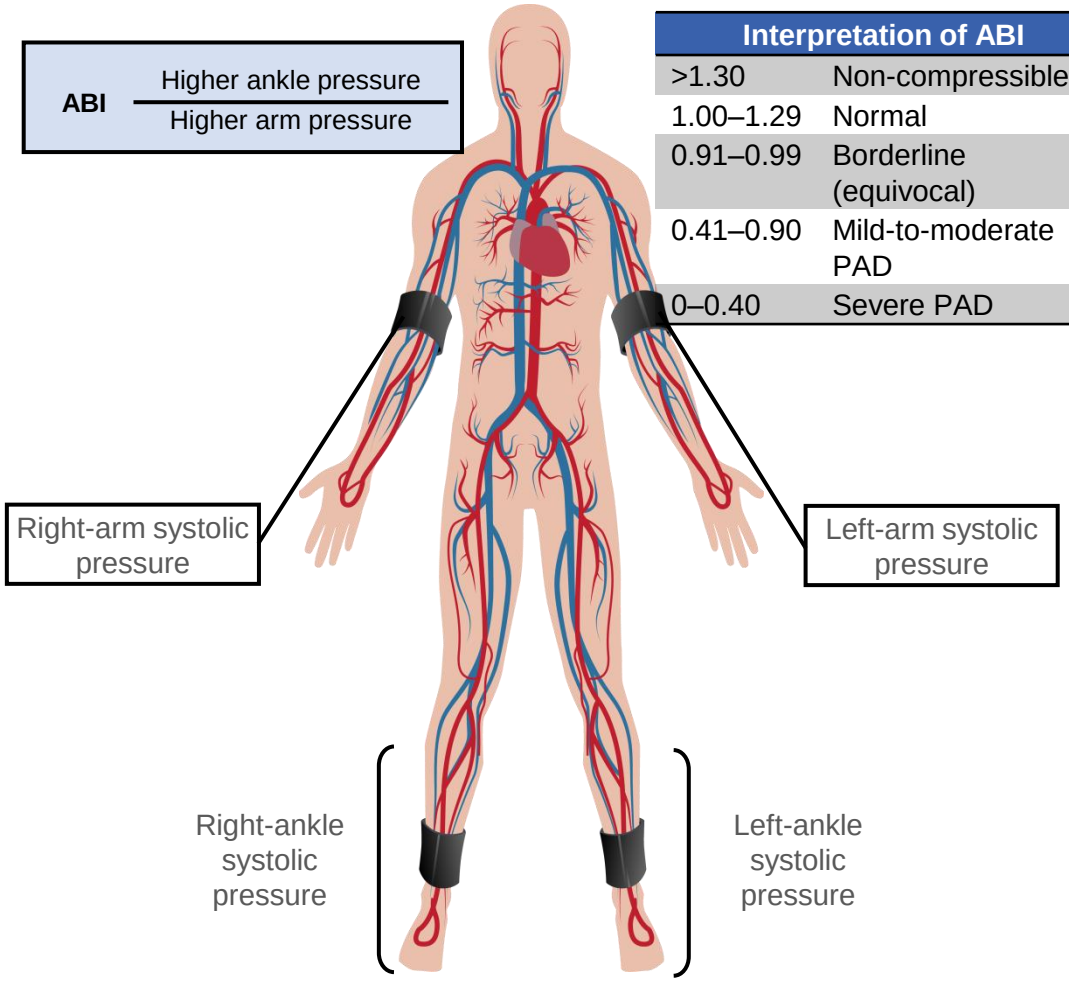

1. Norgren L *et al* – Inter-Society Consensus for the Management of PAD (TASC II), *J Vasc Surg* 2007;45:S5–S67;
2 Gerhard-Herman MD *et al* – AHA/ACC lower extremity PAD Guidelines, *J Am Coll Cardiol* 2016;69:e71–e126;
3. Hirsch AT *et al*, *Circulation* 2006;113:e463–e654

# Diagnosis of Lower Extremity PAD

## PAD can be diagnosed by measurement of resting ankle–brachial index (ABI)[1]

**ABI** = Higher ankle pressure / Higher arm pressure

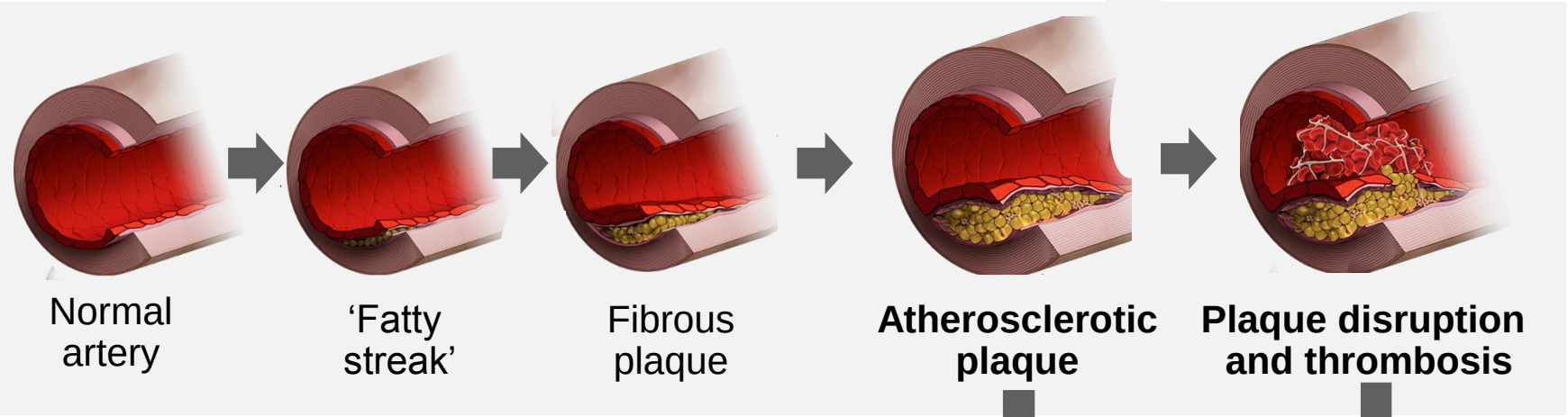
| Interpretation of ABI | |
|---|---|
| >1.30 | Non-compressible |
| 1.00–1.29 | Normal |
| 0.91–0.99 | Borderline (equivocal) |
| 0.41–0.90 | Mild-to-moderate PAD |
| 0–0.40 | Severe PAD |




- Resting ABI is the standard diagnostic test for lower extremity PAD[2]
- ABI can also be used for prognosis and monitoring interventions[2]
- Additional tests include pulse-volume recording, segmental pressures, duplex ultrasound and exercise test with ABI[2]

1. Hiatt WR, *N Engl J Med* 2001;344:1608–1621; 2. Hirsch AT *et al* – ACC/AHA PAD guidelines, *Circulation* 2006;113:e463–e654

# Atherosclerosis Is a Progressive Disease Leading to Atherothrombosis and Ischaemia




**Flow-limiting stenosis**
Symptoms with exercise, e.g. stable angina and intermittent claudication

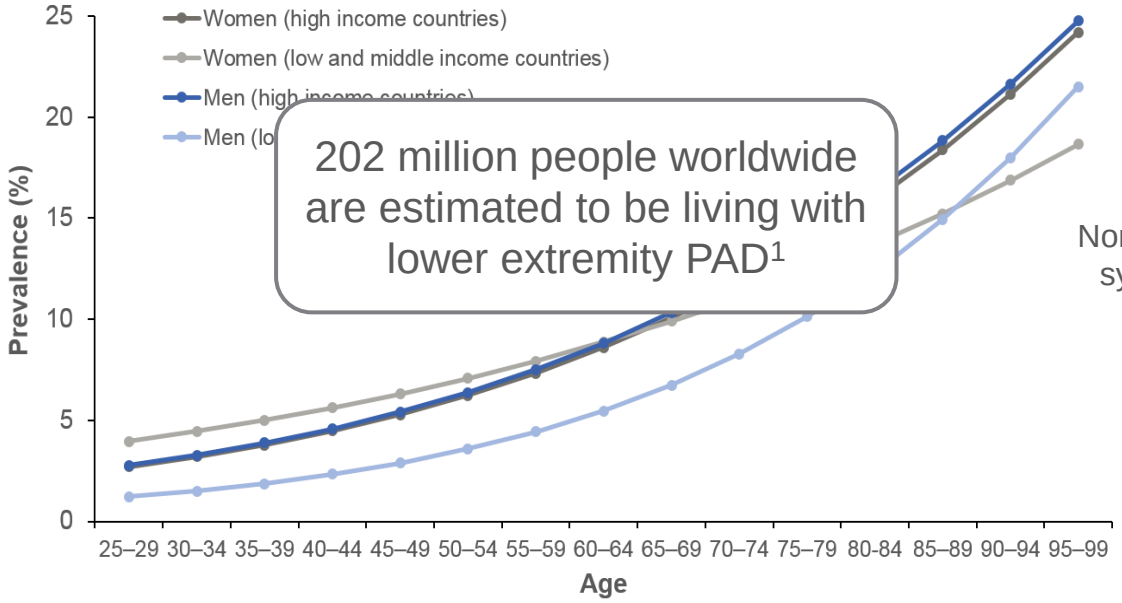
**Atherothrombosis**

- **MI**
- **Stroke**
- **CV death**
- **Limb ischaemia**

1. Insull W Jr, *Am J Med* 2009;122(1 Suppl):S3–S14; 2. Bradberry JC *et al*, *J Am Pharm Assoc* 2004;44:S37–S45

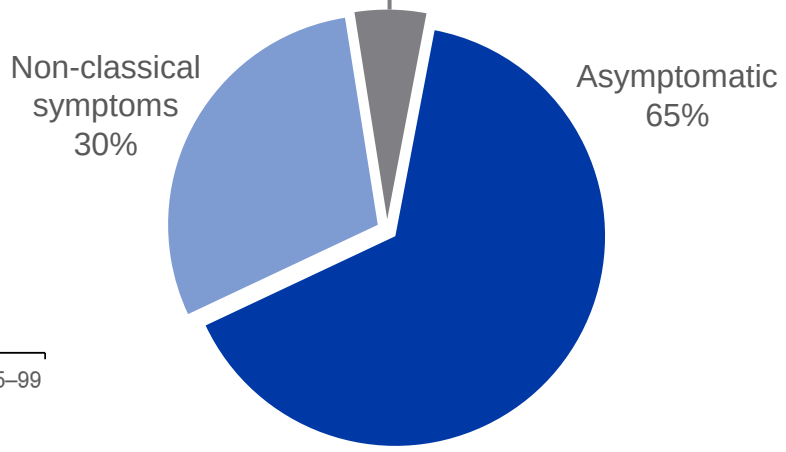
# PAD affects millions of patients worldwide

**Estimated age-specific prevalence of men and women living with lower extremity PAD in 2010[1]**




202 million people worldwide are estimated to be living with lower extremity PAD[1]

~5% of patients with PAD have classical symptoms of intermittent claudication[2]




1. Fowkes FGR *et al, Lancet* 2013;382:1329–1340; 2. McDermott MM *et al*, *J Am Heart Assoc* 2013;2:e000257

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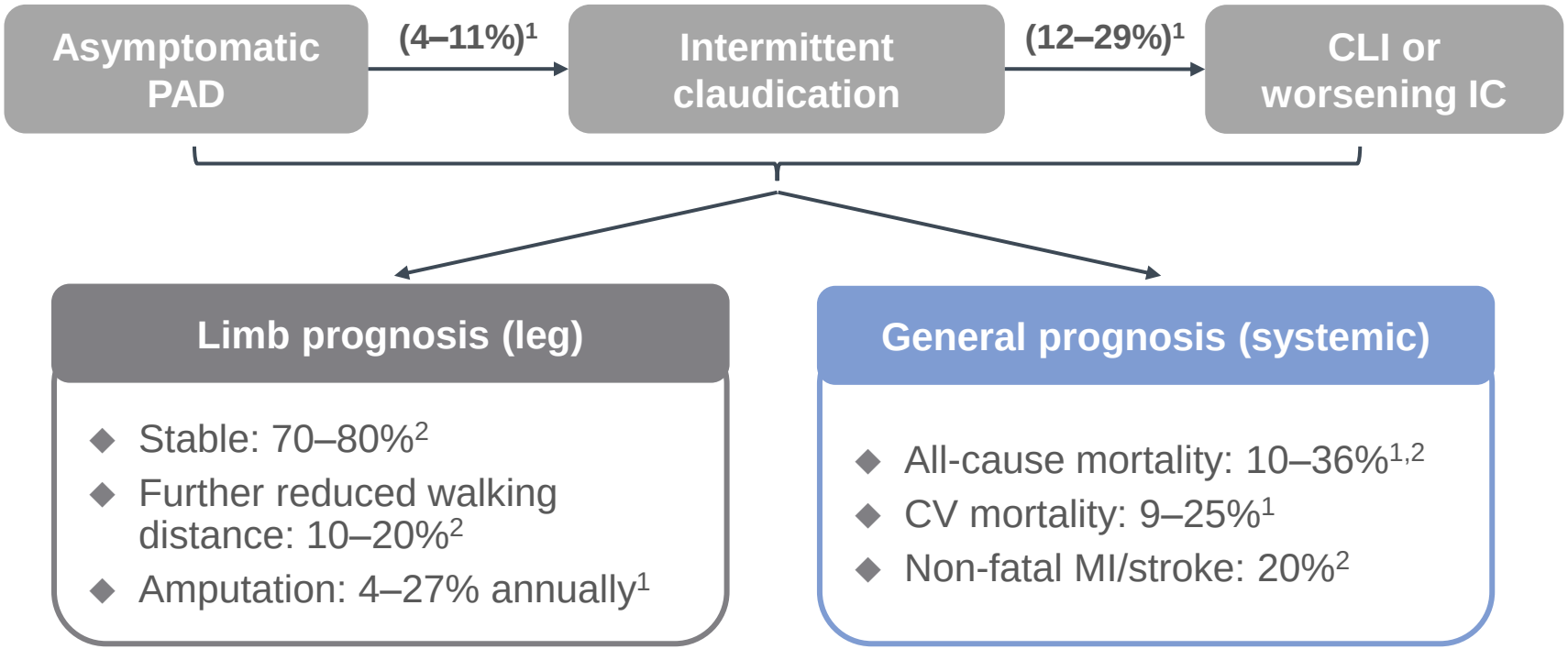
# Despite standard therapy, patients with intermittent claudication are at risk of adverse events and disease progression




1. Sigvant B *et al*, *Eur J Vasc Endovasc Surg* 2016;51:395–403; 2. Norgren L *et al*, *J Vasc Surg* 2007;45:S5–S67

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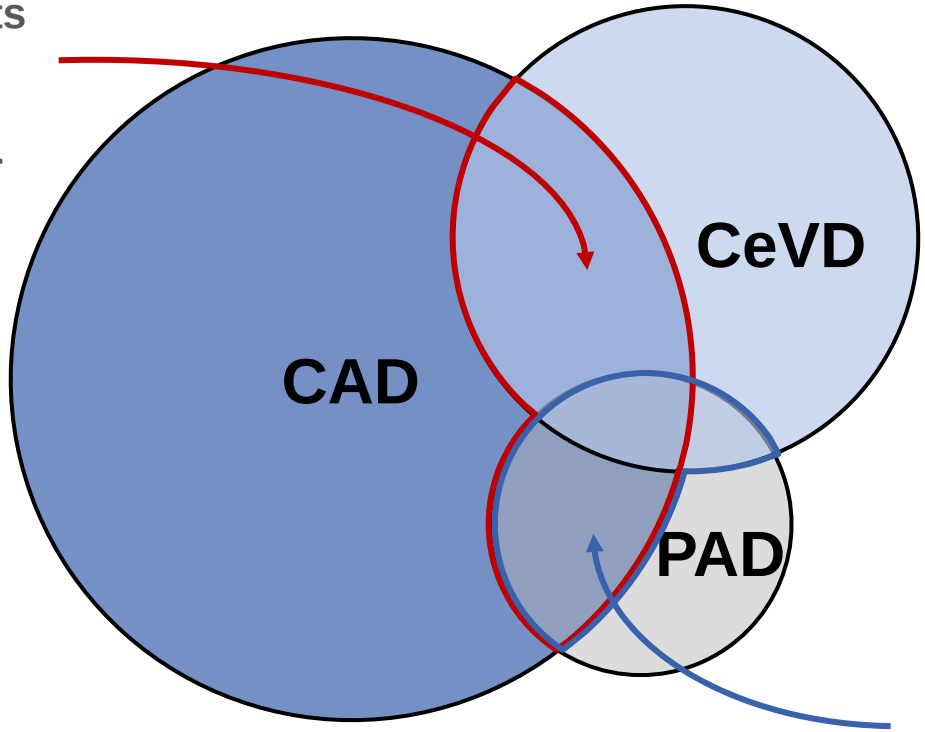
# PAD Is a Typical Polyvascular Disease

**REACH: More than 3 in 5 patients with PAD have atherothrombotic disease also in other arterial territories**

**24.7% of patients with CAD had concomitant disease in other vascular beds**



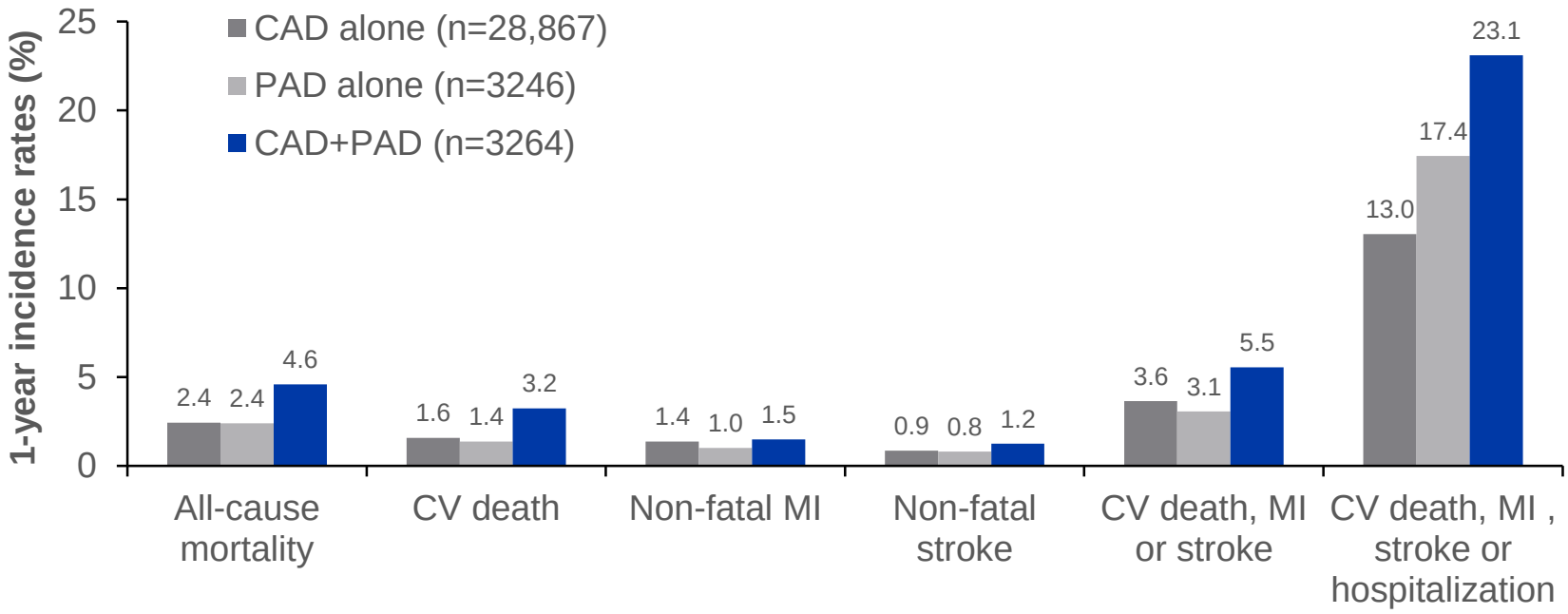

**61.5% of patients with PAD had concomitant disease in other vascular beds**

Percentages are calculated from the total population included in the REACH registry. N=67,888

Bhatt DL *et al*, *JAMA* 2006;295:180–189

# Real-world evidence shows that patients with PAD are at high risk of adverse cardiovascular events

**1-year outcomes in patients with CAD alone, PAD alone or CAD+PAD (REACH registry)**




Steg PG *et al*, *JAMA* 2007;297:1197–1206

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# Current Management of PAD

Current recommendations and unmet needs

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

## Vascular protection[1–4]

Control of cardiovascular risk factors to limit atherosclerosis progression and stabilize existing plaques

Prevention of blood clot formation over any ruptured/eroded atherosclerotic plaques

### Lifestyle changes

- Smoking cessation
- Regular exercise
- Healthy diet
- Weight management
- Psychosocial support

### Medical therapies

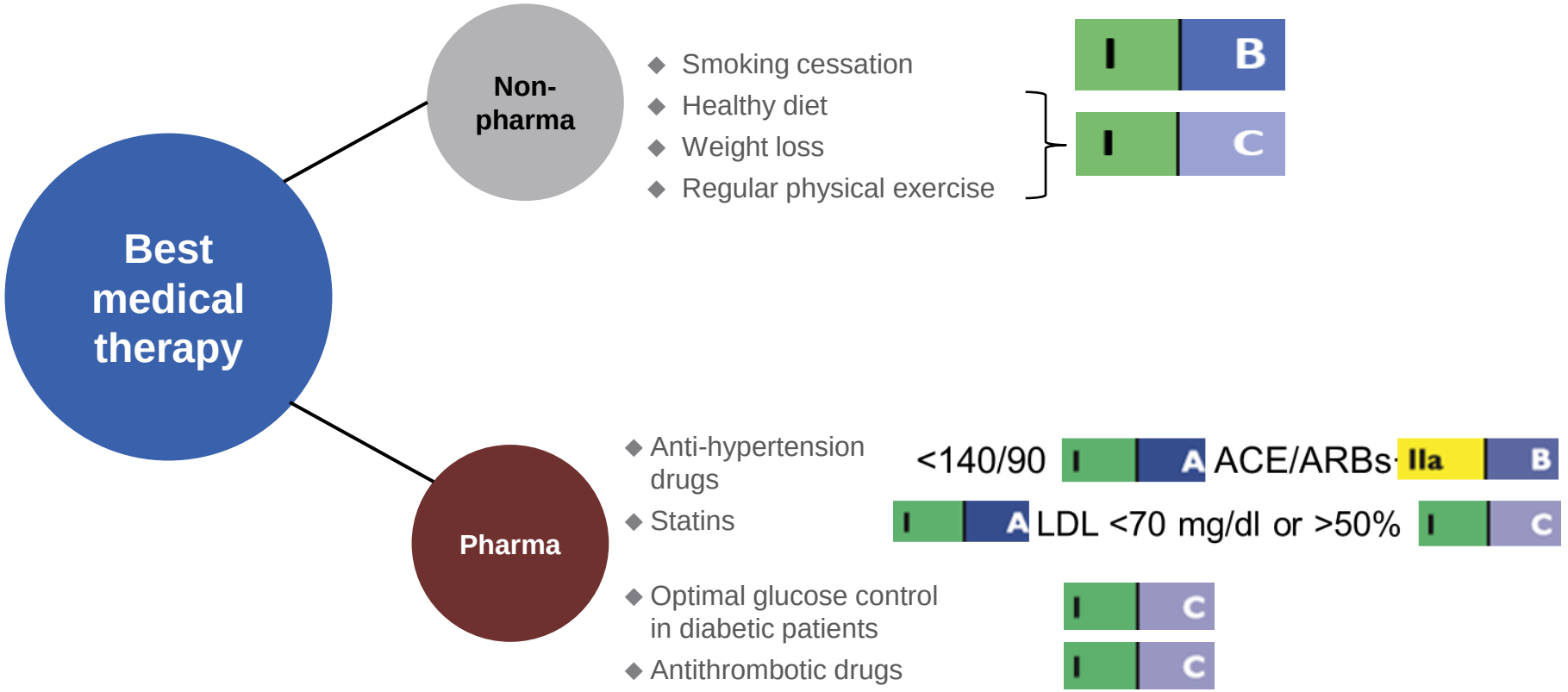
- Lipid control – statins
- Hypertension control – ACE inhibitors/ARBs
- Diabetes control – insulin/anti-glycaemic drugs

### Antithrombotic therapy

- Single antiplatelet therapy with aspirin or clopidogrel

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

# Current Guideline of Cardiovascular prevention in PAD




Aboyans V *et al*, *Eur Heart J* 2018;39:763–816

# The Current ESC Guidelines for PAD Management Recommend Treatment of Symptomatic PAD

## 2017 ESC guideline recommendations for antithrombotic therapies in patients with PAD

- SAPT is recommended for all patients with symptomatic PAD
- DAPT is recommended only for a limited period of time after certain revascularization procedures

| Patients with… | Recommendation | Class |
|---|---|---|
| Symptomatic PAD | Antiplatelet therapy is recommended | Ic |
| Lower extremity PAD | In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin | IIb |
| | Anticoagulation with VKAs may be considered after autogenous vein infrainguinal bypass | IIb |
| | DAPT (aspirin plus clopidogrel) for ≥1 month should be considered after infra-inguinal stent implantation | IIa |
| | DAPT (aspirin plus clopidogrel) may be considered in the case of below-knee bypass with a prosthetic graft | IIb |
| | Long-term SAPT is recommended in all patients who have undergone revascularization | Ic |
| | SAPT is recommended after infrainguinal bypass surgery | Ia |

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

# Evidence Supporting the Use of Aspirin or Clopidogrel to Prevent CV Events in Patients with PAD is Limited

## Aspirin[1]

- Meta-analysis: aspirin vs control
- Only non-significant reduction in MACE with aspirin
  - However, aspirin significantly reduced non-fatal stroke rate

| Outcome | HR (95% CI) | *p*-value |
|---|---|---|
| CV death | 0.94 (0.74–1.19) | 0.59 |
| Non-fatal MI | 1.04 (0.78–1.39) | 0.81 |
| Non-fatal stroke | 0.66 (0.47–0.94) | 0.02 |
| Composite | 0.88 (0.76–1.04) | 0.13 |

## Clopidogrel[2]

- CAPRIE trial: clopidogrel vs aspirin
- Only this subgroup analysis supports the use of clopidogrel over aspirin

| Subgroup | RRR (95% CI) | *p*-value |
|---|---|---|
| Prior MI | -3.7% (-22.1–12.0) | 0.66 |
| Prior stroke | 7.3 (-5.7–18.7) | 0.26 |
| PAD | 23.8% (8.9–36.2) | 0.0028 |
| All patients | 8.7% (0.3–16.5) | 0.043 |

- Another meta-analysis by the ATTC showed a reduction in MACE with antiplatelet treatment[3]
- REACH: no reduction in 4-year CV events with antiplatelet agents (60% aspirin)[4]

1. Berger JS *et al*, *JAMA* 2009;301:1909–1919; 2. CAPRIE Steering Committee, *Lancet* 1996;348:1329–1339; 3. Antithrombotic Trialists' Collaboration, *Br Med J* 2002;324:71-86; 4. Abtan J *et al*, *Clin Card* 2017: doi:10.1002/clc.22721

# Incidence of CV events among real-world patients with CAD or PAD receiving ASA

## Results

- A total of 1,285 patients met all selection criteria; 89% had CAD; 22%, PAD; and 12%, both.
- During follow-up (mean 2.3 years), 16% experienced CV events (MACE or MALE), which was more than twice that of the COMPASS "ASA only" arm (6%; mean F/U 1.9 years).
- Results were consistent for both CAD (14% vs. 6%) and/or PAD (28% vs. 9%)

| CV Event | CAD | | | PAD | | | Aggregate Cohort | | |
|---|---|---|---|---|---|---|---|---|---|
| | "Real-World" study | | COMPASS | "Real-World" study | | COMPASS | "Real-World" study | | COMPASS |
| | All Patients (N=85,754) | ASA Only (N=1,143) | ASA Only (N=8,261) | All Patients (N=25,695) | ASA Only (N=278) | ASA Only (N=2,504) | All Patients (N=99,730) | ASA Only (N=1,285) | ASA Only (N=9,126) |
| MACE | | | | | | | | | |
| MI | 3,818 (4.5) | 58 (5.1) | 195 (2.4) | 1,150 (4.5) | 13 (4.7) | 67 (2.7) | 4,270 (4.3) | 67 (5.2) | 205 (2.2) |
| Stroke | 3,538 (4.1) | 50 (4.4) | 130 (1.6) | 1,428 (5.6) | 14 (5.0) | 47 (1.9) | 4,262 (4.3) | 56 (4.4) | 142 (1.6) |
| CV-death | 2,398 (2.8) | 57 (5.0) | 184 (2.2) | 891 (3.5) | 18 (6.5) | 78 (3.1) | 2,722 (2.7) | 63 (4.9) | 203 (2.2) |
| Any of above | 8,318 (9.7) | 134 (11.7) | 460 (5.6) | 2,900 (11.3) | 39 (14.0) | 173 (6.9) | 9,578 (9.6) | 151 (11.8) | 496 (5.4) |
| Male | | | | | | | | | |
| CLI | 1,832 (2.1) | 21 (1.8) | NP | 2,880 (11.2) | 36 (12.9) | 24 (1.0) | 3,459 (3.5) | 44 (3.4) | NP |
| Amputation** | 353 (0.4) | 3 (0.3) | NP | 434 (1.7) | 7 (2.5) | 28 (1.1) | 574 (0.6) | 7 (0.5) | NP |
| Revascularization | 1,951 (2.3) | 26 (2.3) | NP | 1,664 (6.5) | 20 (7.2) | NP | 2,782 (2.8) | 40 (3.1) | NP |
| Any of above | 3,323 (3.9) | 41 (3.6) | NP | 3,788 (14.7) | 48 (17.3) | 60 (2.4) | 5,385 (5.4) | 72 (5.6) | NP |
| **Any CV event** | **10,609 (12.4)** | **163 (14.3)** | **470 (5.7)** | **5,887 (22.9)** | **77 (27.7)** | **222 (8.9)** | **13,585 (13.6)** | **205 (16.0)** | **516 (5.7)** |

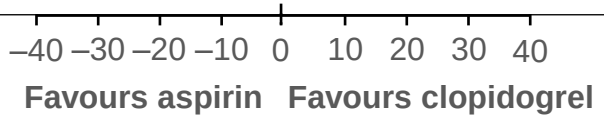
Berger J. *et al., ACC.19. Poster Contributions.* JACC March 12, 2019. Volume 73, Issue 9

NP: Not published

# Current recommendation for clopidogrel in PAD is based on twenty-year-old subanalysis data

## CAPRIE subanalysis: lower risk of CV events with clopidogrel versus aspirin in patients with symptomatic PAD

| | Clopidogrel (%/year) | Aspirin (%/year) | Risk reduction (95% CI) | p-value |
|---|---|---|---|---|
| Recent stroke (n=6431) | 7.15 | 7.71 | | 0.26 |
| Recent MI (n=6302) | 5.03 | 4.84 | | 0.66 |
| PAD (n=6452) | 3.71 | 4.86 | | 0.0028 |
| All patients (N=19,185) | 5.32 | 5.83 | | 0.043 |




**No reduction in limb events**

CAPRIE Steering Committee, *Lancet* 1996;348:1329–1339

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# Trials Investigating Intensified Antiplatelet Therapy in Patients with PAD Show Mixed Results

## CHARISMA (subgroup analysis)[1]

**Clopidogrel + aspirin** vs **aspirin** in patients with **prior MI, stroke or symptomatic PAD**

- MACE ↓17%
- No decrease in mortality
- No increase in severe bleeding

## TRA2°P-TIMI 50 (subgroup analysis)[2]

**Vorapaxar + aspirin** vs **aspirin** in patients with **stable symptomatic PAD**

- No reduction in risk of MACE
- Hospitalization for ALI ↓42%
- Major bleeding 1.5 ×

## EUCLID[3]

**Ticagrelor** vs **clopidogrel** in patients with **PAD**

- No reduction in risk of MACE
- No decrease in MALE*
- No decrease in mortality
- No increase in major bleeding

## PEGASUS (subgroup analysis)[4,5]

**Ticagrelor + aspirin** vs **aspirin** in patients with **prior MI + PAD**

- MACE ↓31%
- No decrease in MALE#
- Mortality ↓48%‡
- No increase in major bleeding

*Hospitalization for ALI or lower limb revascularization (individual endpoints); #Composite of ALI or peripheral revascularization; ‡No mortality benefit in the overall trial population[5]

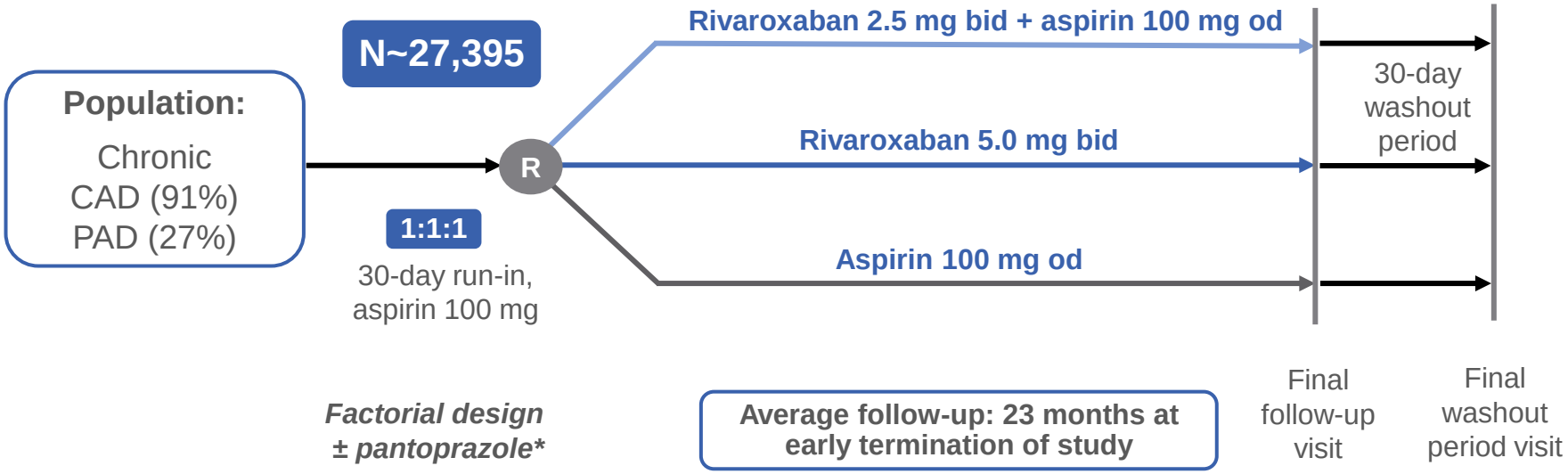
1. Bhatt DL *et al*, *J Am Coll Cardiol* 2007;49:1982–1988; 2. Bonaca MP *et al*, *Circulation* 2013;127:1522–1529; 3. Hiatt WR *et al*, *N Engl J Med* 2017;376:32–40; 4. Bonaca MP *et al*, *J Am Coll Cardiol* 2016;67:2719–2728; 5. Bonaca MP *et al, N Engl J Med* 2015;372:1791–1800

# COMPASS PAD Analysis

CAD PAD

# A Dual Pathway Approach Targeting Chronic Patients with CAD or PAD was Investigated in COMPASS

**Objective:** To determine the efficacy and safety of rivaroxaban, vascular dose of rivaroxaban plus aspirin or aspirin alone for reducing the risk of MI, stroke and cardiovascular death in CAD or PAD




**Antithrombotic investigations* were stopped 1 year ahead of expectations in Feb 2017 due to overwhelming efficacy in the rivaroxaban vascular dose 2.5 mg bid + aspirin arm**

*Patients who were not receiving a proton pump inhibitor (PPI) were randomized to pantoprazole or placebo (partial factorial design); the PPI pantoprazole component of the study is continuing; data will be communicated once complete

1. Eikelboom JW *et al*, *N Engl J Med* 2017;377:1319–1330; 2. Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035

COMPASS

# Inclusion and Exclusion Criteria Ensure That Patients with Chronic PAD are Enrolled

## Key inclusion criteria

- **Previous peripheral artery revascularization**
- **Previous limb or foot amputation for arterial vascular disease**
- **Intermittent claudication plus:**
  - **Low ABI (<0.90), or**
  - **Significant peripheral artery stenosis (≥50%)**
- **Previous carotid revascularization, or asymptomatic carotid artery stenosis ≥50%**
- **CAD + low ABI (<0.90)**

## Key exclusion criteria

- High risk of bleeding
- Stroke within 1 month
- History of haemorrhagic/lacunar stroke
- Severe heart failure (ejection fraction <30%)
- eGFR <15 ml/min
- A need for dual antiplatelet therapy
- A need for non-aspirin antiplatelet therapy
- An indication for anticoagulation therapy

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

COMPASS

# 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

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

# Major Adverse Limb Events and Major Amputation Were Included in PAD-Specific Net Clinical Benefit

- Primary safety outcome: modified ISTH
  - Major bleeding defined as:
    - Fatal bleeding, or
    - Bleeding into a critical organ, or
    - Surgical site bleeding requiring reoperation, or
    - Bleeding requiring hospitalization

- Net clinical benefit outcome defined as:
  - MACE
  - MALE including major amputation
  - Fatal bleeding
  - Bleeding into a critical organ

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

# COMPASS Included over 7000 Patients with Symptomatic PAD or Concomitant CAD and 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
- In addition, a patient could be defined as a PAD patient based on medical history and/or measurement of ABI at baseline visit
  - The latter category added patients with CAD and asymptomatic PAD patients into the overall PAD subgroup
- Median follow-up: 21 months

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

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# Baseline Characteristics Were Consistent across Treatment Arms and in Line with Those Usually Seen in 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) |

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

# Dual Pathway Inhibition with **Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin** Reduced **MACE by 28%** Versus Aspirin Alone

| Outcome | Rivaroxaban 2.5 mg bid + aspirin N=2492 N (%) | Rivaroxaban 5 mg bid N=2474 N (%) | Aspirin N=2504 N (%) | Rivaroxaban 2.5 mg bid + aspirin vs aspirin HR (95% CI) | Rivaroxaban 2.5 mg bid + aspirin vs aspirin *p*-value | Rivaroxaban 5 mg bid vs aspirin HR (95% CI) | Rivaroxaban 5 mg bid vs aspirin *p*-value |
|---|---|---|---|---|---|---|---|
| MACE | 126 (5) | 149 (6) | 174 (7) | 0.72 (0.57–0.90) | 0.0047 | 0.86 (0.69–1.08) | 0.19 |
| CV death | 64 (3) | 66 (3) | 78 (3) | 0.82 (0.59–1.14) | – | 0.86 (0.62–1.19) | – |
| Stroke | 25 (1) | 43 (2) | 47 (2) | 0.54 (0.33–0.87) | – | 0.93 (0.61–1.40) | – |
| MI | 51 (2) | 56 (2) | 67 (3) | 0.76 (0.53–1.09) | – | 0.84 (0.59–1.20) | – |

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

# Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Significantly Reduced **Major Amputation by 70%** Versus Aspirin Alone

| Outcome | Rivaroxaban 2.5 mg bid + aspirin N=2492 N (%) | Rivaroxaban 5 mg bid N=2474 N (%) | Aspirin N=2504 N (%) | Rivaroxaban 2.5 mg bid + aspirin vs aspirin HR (95% CI) | Rivaroxaban 2.5 mg bid + aspirin vs aspirin *p*-value | Rivaroxaban 5 mg bid vs aspirin HR (95% CI) | Rivaroxaban 5 mg bid vs aspirin *p*-value |
|---|---|---|---|---|---|---|---|
| MALE | 30 (1) | 35 (1) | 56 (2) | 0.54 (0.35–0.84) | 0.0054 | 0.63 (0.41–0.96) | 0.032 |
| Major amputation | 5 (<1) | 8 (<1) | 17 (<1) | 0.30 (0.11–0.80) | 0.011 | 0.46 (0.20–1.08) | 0.068 |
| MALE plus major amputation* | 32 (1) | 40 (2) | 60 (2) | 0.54 (0.35–0.82) | 0.0037 | 0.67 (0.45–1.00) | 0.046 |

*An additional 11 major amputations of a vascular cause were done that were unlinked to acute or chronic limb ischaemia, two in the low-dose rivaroxaban plus aspirin group, five in the rivaroxaban alone group, and four in the aspirin alone group

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

# Prognosis of MALE in PAD Patients: Results from the COMPASS Study

## Results

- Altogether 128 patients suffered MALE (2.0%). The one-year cumulative incidence of a subsequent hospitalization after MALE was 95.4%, that of total vascular amputations was 22.9%, for death it was 8.7%, and for MACE it was 3.8%
- The MALE index event significantly increased the risk of subsequent hospitalizations (HR: 7.21), subsequent amputations (HR: 197.5) and death (HR: 3.23)
- Following the first incidence of MALE, there was a 6-fold increase in the risk of death, and a 10-fold increase in the risk of the composite MACE or total vascular amputations among patients randomized to aspirin alone compared to those receiving the 'Xarelto' vascular dose 2.5 mg bid in combination with aspirin
- The 'Xarelto' vascular dose 2.5 mg bid in combination with aspirin significantly reduced the incidence of MALE by 43%, total vascular amputations by 58%, peripheral vascular interventions by 24%, and all peripheral vascular outcomes by 24% compared to aspirin alone

| | 'Xarelto' 2.5 mg bid + aspirin n=2,139 | Aspirin alone n=2,123 | 'Xarelto' 2.5 mg bid + aspirin vs. aspirin alone HR (95% CI) |
|---|---|---|---|
| MALE | 1.5% | 2.6% | 0.57 (0.37–0.88); p=0.01 |
| Total vascular amputation | 0.5% | 1.2% | 0.42 (0.21–0.85); p=0.01 |
| Periph. vasc. intervention | 5.5% | 7.1% | 0.76 (0.60–0.97); p=0.03 |
| All periph. vasc. outcomes | 6.2% | 8.0% | 0.76 (0.61–0.96); p=0.02 |

Anand *et al.*, Journal of the American College of Cardiology Mar 2018, 24747; DOI:10.1016/j.jacc.2018.03.008

# Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Significantly Reduced **MACE and MALE** Versus Aspirin Alone

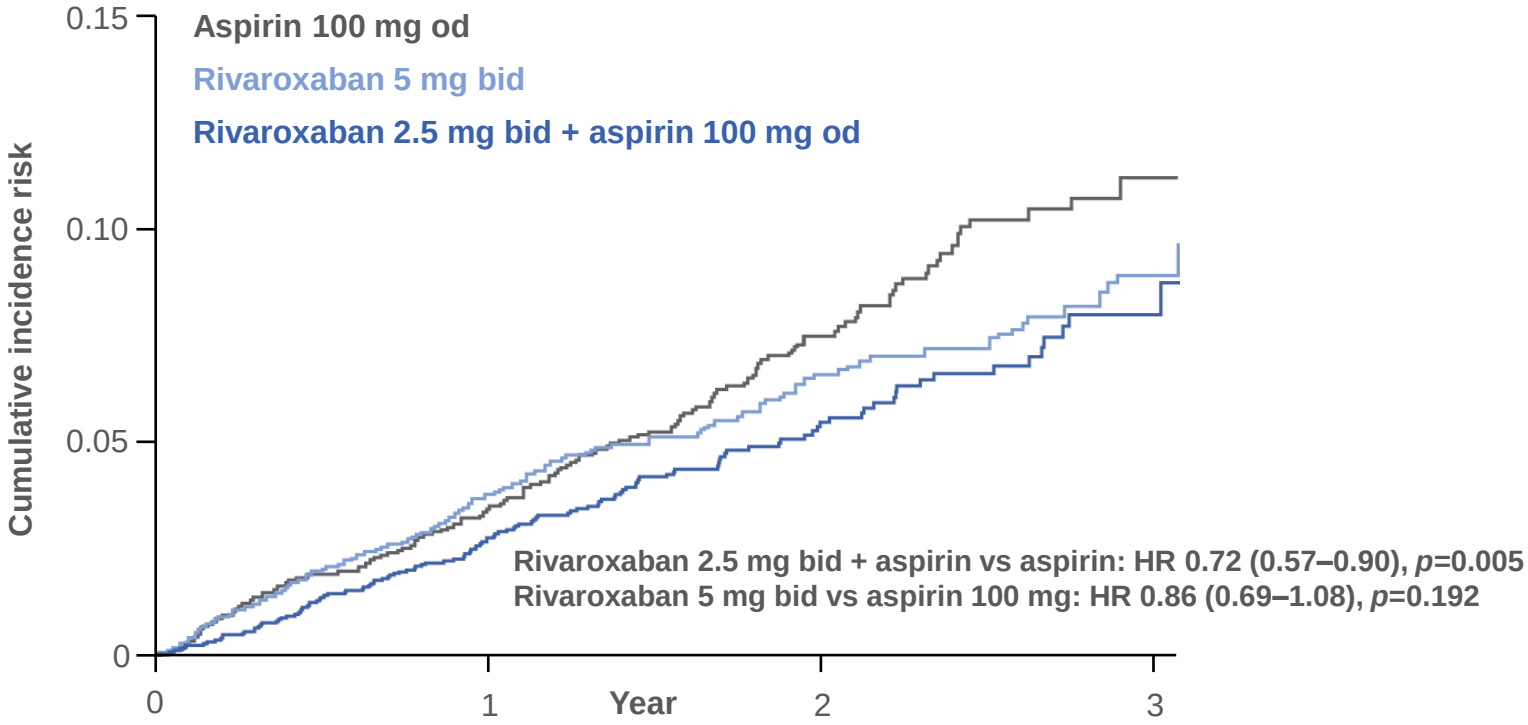
| Composite outcome | Rivaroxaban 2.5 mg bid + aspirin N=2492 N (%) | Rivaroxaban 5 mg bid N=2474 N (%) | Aspirin N=2504 N (%) | Rivaroxaban 2.5 mg bid + aspirin vs aspirin HR (95% CI) | *p*-value | Rivaroxaban 5 mg bid vs aspirin HR (95% CI) | *p*-value |
|---|---|---|---|---|---|---|---|
| MACE or MALE including major amputation | 157 (6) | 188 (8) | 225 (9) | 0.69 (0.56–0.85) | 0.0003 | 0.83 (0.69–1.02) | 0.077 |

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

COMPASS

# 28% RRR in MACE with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Versus Aspirin Alone

## Stroke/MI/cardiovascular death



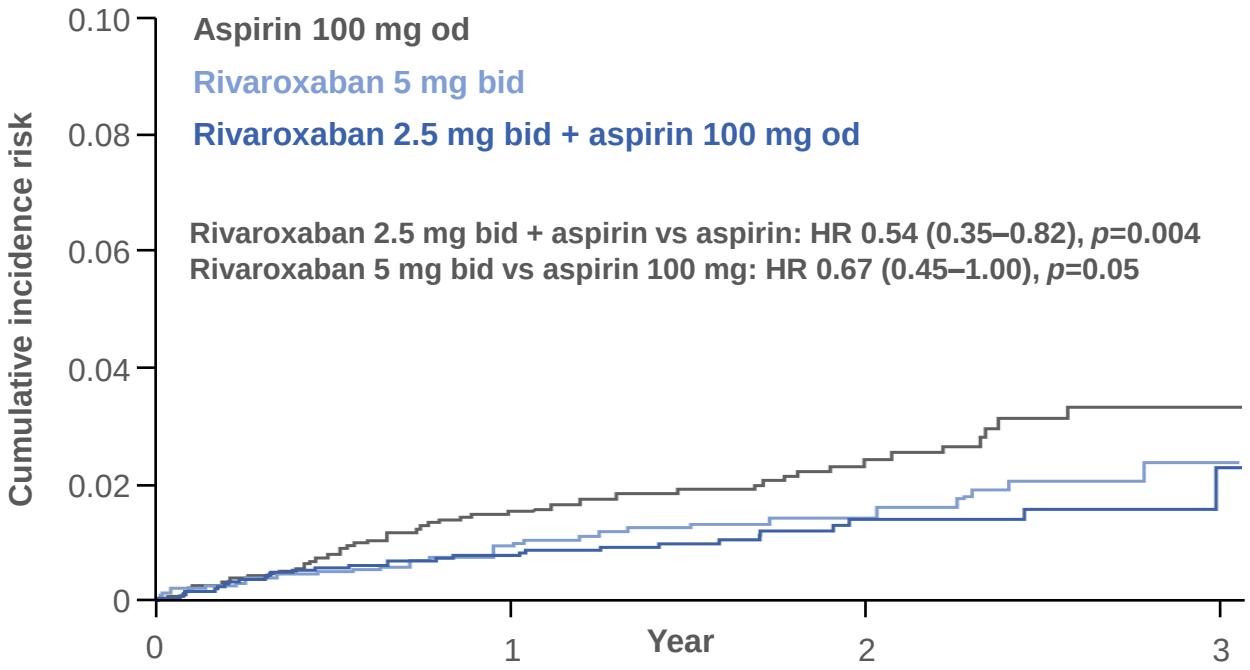

| Number at risk | | | | |
|---|---|---|---|---|
| Rivaroxaban + aspirin | 2492 | 2086 | 907 | 127 |
| Rivaroxaban | 2474 | 2044 | 870 | 147 |
| Aspirin | 2504 | 2065 | 930 | 119 |

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

# 46% RRR in MALE Including Major Amputation with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Versus Aspirin Alone

PAD

## MALE including major amputation




| Number at risk | | | | |
|---|---|---|---|---|
| Rivaroxaban + aspirin | 2492 | 2099 | 919 | 129 |
| Rivaroxaban | 2474 | 2071 | 902 | 151 |
| Aspirin | 2504 | 2072 | 951 | 120 |

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

COMPASS

# Bleeding Increased but Low with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Versus Aspirin Alone, with No Differences Seen in Fatal and Intracranial Bleeding

| 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) | - |

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

COMPASS

# 28% Reduction in Risk of the Composite Outcome with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Versus Aspirin Alone

| Rates at median follow-up of 21 months | Rivaroxaban 2.5 mg bid + aspirin N=2492 N (%) | Rivaroxaban 5 mg bid N=2474 N (%) | Aspirin N=2504 N (%) | Rivaroxaban 2.5 mg bid + aspirin vs aspirin HR (95% CI) | Rivaroxaban 2.5 mg bid + aspirin vs aspirin *p*-value | Rivaroxaban 5 mg bid vs aspirin HR (95% CI) | Rivaroxaban 5 mg bid vs aspirin *p*-value |
|---|---|---|---|---|---|---|---|
| Composite net clinical benefit outcome* | 169 (7) | 207 (8) | 234 (9) | 0.72 (0.59–0.87) | 0.0008 | 0.89 (0.74–1.07) | 0.23 |

- For every 1000 patients with PAD treated with rivaroxaban plus aspirin, 27 MACE or MALE (including major amputation) events would be prevented, and 1 fatal and 1 critical organ bleed would be caused over a 21-month period

*Defined as CV death, MI, stroke, MALE, major amputation, fatal bleeding or critical organ bleeding

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

COMPASS

CAD PAD

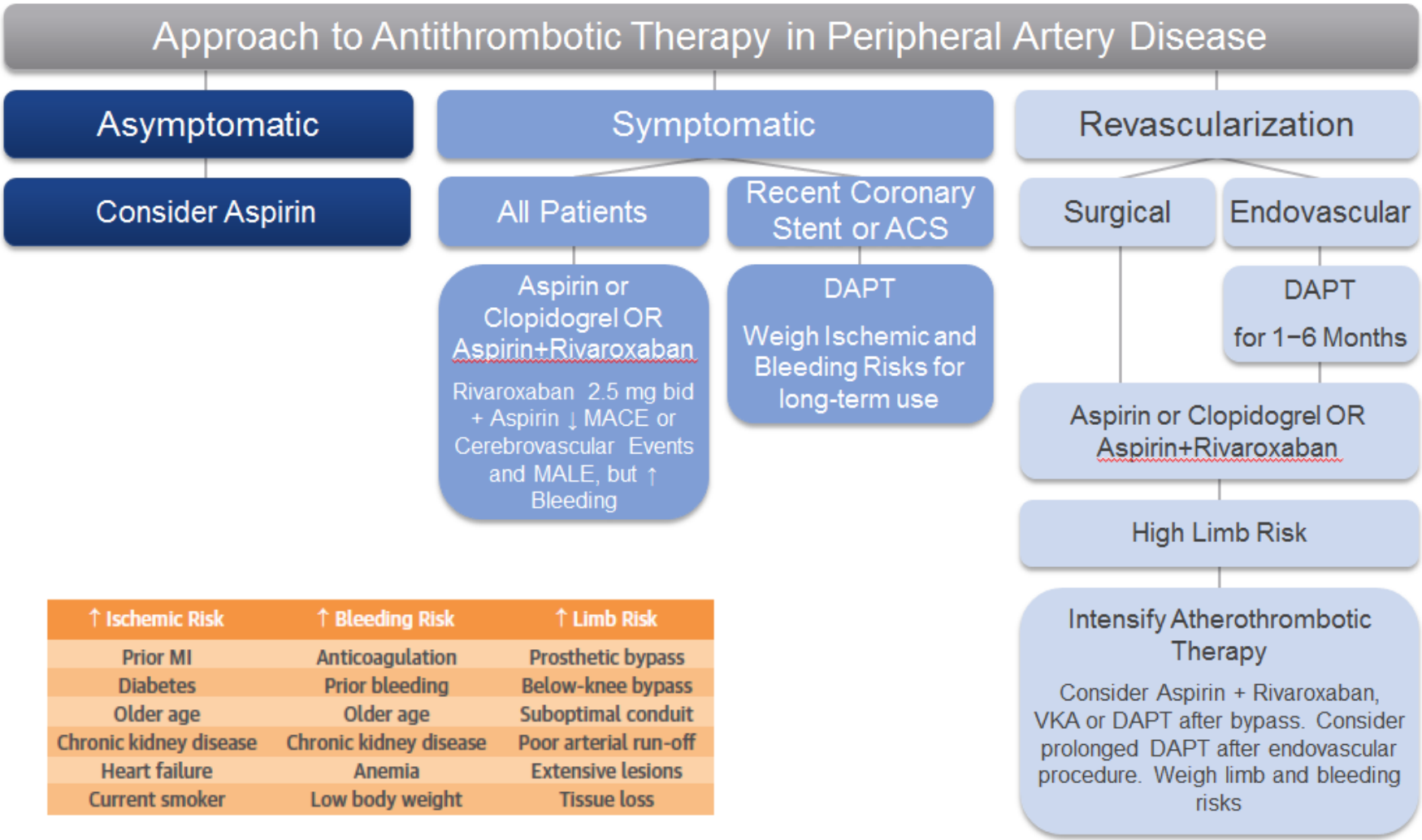
# Rivaroxaban 2.5 mg bid + Aspirin Improved Overall Survival in Patients with CAD or PAD

| Study / Treatment arm | Control %/year | Intervention %/year | HR | HR (95% CI) | *p*-value |
|---|---|---|---|---|---|
| **COMPASS[1]** | | | | | |
| Rivaroxaban 2.5 mg bid | 2.1† | 1.8† | 0.82 | | 0.01 |
| **CHARISMA[2]** | | | | | |
| Clopidogrel 75 mg od | 2.3‡ | 2.1‡ | 0.91 | | 0.32 |
| **PEGASUS[3]** | | | | | |
| Ticagrelor 90 mg bid | 1.7¶ | 1.7¶ | 1.00 | | 0.99 |
| Ticagrelor 60 mg bid | 1.7¶ | 1.6¶ | 0.89 | | 0.14 |
| **TRA2P-TIMI 50[4]** | | | | | |
| Vorapaxar 2.5 mg od | 1.8¶ | 1.7¶ | 0.95 | | 0.41 |


†Estimate calculated from reported overall % across 23 months of mean follow up; *p-value nominally significant because the study was stopped approximately 1 year ahead of schedule due to overwhelming efficacy; threshold for formal significance p=0.0025* ‡Estimate calculated from reported overall % across 28 months of median follow up; ¶Estimate calculated from reported 3-year Kaplan-Meier event rates

1. Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118; 2. Bhatt DL *et al. J Am Coll Cardiol* 2007;49:1982–1988;
3. Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800; 4. Morrow DA *et al. N Engl J Med* 2012;366:1404–1413

# Recent Advances in the Antithrombotic Management of PAD




| ↑ Ischemic Risk | ↑ Bleeding Risk | ↑ Limb Risk |
|---|---|---|
| Prior MI | Anticoagulation | Prosthetic bypass |
| Diabetes | Prior bleeding | Below-knee bypass |
| Older age | Older age | Suboptimal conduit |
| Chronic kidney disease | Chronic kidney disease | Poor arterial run-off |
| Heart failure | Anemia | Extensive lesions |
| Current smoker | Low body weight | Tissue loss |

Hussain *et al.*, JACC May 2018, 71 (21) 2450-2467; DOI: 10.1016/j.jacc.2018.03.483.

# Vascular Dose Rivaroxaban Showed Improved Outcomes for PAD Patients with a Need for Increased Vascular Protection

- Rivaroxaban vascular dose 2.5 mg bid plus aspirin reduced the composite endpoint of **stroke, MI or CV death by 28%.**
  - **MALE by 46%**
  - **Major amputations by 70%**
- Despite an expected increase in major bleeding events with rivaroxaban 2.5 mg bid plus aspirin, **no significant increase was observed in fatal or critical organ bleeding.**

- **This dual pathway inhibition of Rivaroxaban vascular dose and aspirin** represents a major advance in the management of PAD and is **the only available therapeutic option to significantly reduce both MACE and MALE.**

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

COMPASS

# Recent Advances in the Antithrombotic Management of PAD

- Although patients with PAD are at a high risk of adverse vascular and limb-related events, they are often under-treated with antithrombotic therapy, which is partly due to the lack of high-quality evidence and consensus recommendations.
- **Several unmet needs** including the management of patients with asymptomatic PAD, critical limb ischemia, or those undergoing peripheral vascular interventions have yet to be addressed.
- Recent advances, such as the COMPASS study with the **'Xarelto' vascular dose 2.5 mg bid** have opened up new perspectives in the antithrombotic management of PAD, and may offer even greater benefits for this high-risk patient population, than previous antithrombotic approaches.
- The ongoing **VOYAGER PAD study** with 'Xarelto' is expected to provide important information regarding the most effective antithrombotic regimen in patients who have undergone surgical or endovascular revascularization for PAD.

Hussain *et al.,* JACC May 2018, 71 (21) 2450-2467; DOI: 10.1016/j.jacc.2018.03.483.

Thank you for your attention.