Αντιαιμοπεταλική αγωγή στις παθήσεις των περιφερεικών αγγείων: νεότερα δεδομένα

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ESC 2017 Guidelines
Antithrombotic drugs in peripheral arterial diseases

Key messages

- Antiplatelet therapy is indicated in all patients with carotid artery stenosis irrespective of clinical symptoms and revascularization. Dual antiplatelet therapy (DAPT) should be given for at least 1 month after CAS.
- Single antiplatelet therapy (SAPT) is indicated only if patients are symptomatic or have undergone revascularization. Clopidogrel is the preferred antiplatelet drug in LEAD patients.
- Chronic anticoagulation therapy is given only if there is a concomitant indication and may be combined with SAPT when there is a recent revascularization procedure.
ESC 2017 Guidelines
Antithrombotic treatment in Carotid Artery Stenosis
ESC 2017 Guidelines

Antithrombotic treatment in Lower Extremity Artery Disease

Management of antiplatelet therapy in patients with lower extremity artery disease not requiring anticoagulation

Asymptomatic

Symptomatic

Revascularization

Percutaneous

Surgery

No SAPT\textsuperscript{b}

SAPTC

DAPT\textsuperscript{A + C} Class II\textsubscript{a}C

SAPTC \textsuperscript{A or C} Class II\textsubscript{a}C

SAPTC \textsuperscript{A or C} Class II\textsubscript{b}C

Time delay

0

1 mo.

1 year

Long term\textsuperscript{t}

\textsuperscript{a}ESC 2017 Guidelines

\textsuperscript{b}No SAPT

\textsuperscript{c}SAPT

\textsuperscript{A + C} DAPT

\textsuperscript{A or C} Aspirin

\textsuperscript{t}Long term

\textsuperscript{C} Clopidogrel 75 mg/day

\textsuperscript{A} Aspirin 75–100 mg/day

\textsuperscript{d}Oral Anticoagulation

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ESC 2017 Guidelines
Antithrombotic treatment in Lower Extremity Artery Disease and *need for Oral Anticoagulation*

**LEAD in patients requiring long-term oral anticoagulation**

- **(A)symptomatic**
  - Surgery
  - Percutaneous intervention
    - Bleeding risk low
    - Bleeding risk high

**Time delay**
- 0 month
- 1 year
- Long term

**OAC Monotherapy**
- Class I

**DAT**
- A or C
  - Class IIa

**OAC Monotherapy**
- Class IIb

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C Clopidogrel 75 mg/day  
A Aspirin 75–100 mg/day  
O Oral Anticoagulation (VKA or NOACs)
Targets and Mechanisms for Antithrombotic Agents in PAD

Additional Factors:
- Shear Stress
- Inflammation

Collagen/vWF

Vorapaxar

PAR-1

Clopidogrel
Prasugrel
Ticagrelor
Cangrelor

P2Y₁₂

TF + FVIIa

VKA

Prothrombin

TP

Txₐ₂

Aspirin

Granule Secretion

ADP

Thrombin

Factor Xa

Rivaroxaban
Apixaban
Edoxaban
Betrixaban

Fibrinogen

Fibrin

Platelet-Fibrin Clot

Platelet Aggregation

Ischemic Events

Clinical Consequences of Atherothrombosis

Brain:
- Stroke
- Transient Ischemic Attack

Heart:
- Cardiovascular Death
- Myocardial Infarction
- Heart Failure

Limb:
- Acute Limb Ischemia
- Major Amputation
- Limb Revascularization
- Symptom Progression
- ABI/TBI Change
- Peak Walk Distance

Safety: Bleeding

Recent Trials: Vorapaxar in PAD

Vorapaxar in Patients With Peripheral Artery Disease
Results From TRA2*P-TIMI 50

Marc P. Bonaca, MD, MPH; Benjamin M. Scirica, MD; Mark A Creager, MD; Jeffrey Olin, MD; Henri Bounaumeaux, MD; Mikael Dellborg, MD; Jessica M. Lamp, BA; Sabina A. Murphy, MPH; Eugene Braunwald, MD; David A. Morrow, MD, MPH

3787 patients with PAD (hx: claudication or ABI<0.85)
1:1 randomisation to Vorapaxar 2.5 mg BD or placebo
(Hypothesis: Can Varapaxar prevent MI or stroke?)

Vorapaxar: protease activated reeptor-1 inhibitor

Recent Trials: Vorapaxar in PAD Efficacy

Figure 1. Kaplan-Meier rates for the composite of cardiovascular death (CVD), myocardial infarction (MI), or stroke by treatment allocation in the peripheral artery disease cohort. HR indicates hazard ratio.

# Recent Trials: Vorapaxar in PAD

**Efficacy and Safety**

Table 3. Efficacy and Bleeding End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Vorapaxar (n=1892, n (%))</th>
<th>Placebo (n=1895, n (%))</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD/MI/stroke</td>
<td>206 (11.3)</td>
<td>218 (11.9)</td>
<td>0.94 (0.78–1.14)</td>
<td>0.53</td>
</tr>
<tr>
<td>CVD/MI/stroke/urgent coronary revascularization</td>
<td>233 (12.7)</td>
<td>245 (13.4)</td>
<td>0.95 (0.79–1.14)</td>
<td>0.57</td>
</tr>
<tr>
<td>CVD/MI/stroke/urgent vascular hospitalization</td>
<td>294 (15.9)</td>
<td>338 (18.6)</td>
<td>0.85 (0.73–0.998)</td>
<td>0.047</td>
</tr>
<tr>
<td>CVD/MI/stroke/revascularization/urgent vascular hospitalization</td>
<td>615 (32.7)</td>
<td>694 (38.0)</td>
<td>0.87 (0.78–0.97)</td>
<td>0.009</td>
</tr>
<tr>
<td>Peripheral limb vascular efficacy</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hospitalization for acute limb ischemia</td>
<td>40 (2.3)</td>
<td>68 (3.9)</td>
<td>0.58 (0.39–0.86)</td>
<td>0.006</td>
</tr>
<tr>
<td>Any peripheral revascularization</td>
<td>341 (18.4)</td>
<td>401 (22.2)</td>
<td>0.84 (0.73–0.97)</td>
<td>0.017</td>
</tr>
<tr>
<td>Urgent peripheral revascularization</td>
<td>56 (3.1)</td>
<td>85 (4.7)</td>
<td>0.65 (0.46–0.91)</td>
<td>0.012</td>
</tr>
<tr>
<td>Elective peripheral revascularization</td>
<td>305 (16.5)</td>
<td>352 (19.5)</td>
<td>0.86 (0.74–0.9995)</td>
<td>0.049</td>
</tr>
<tr>
<td>Any vascular* efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent vascular hospitalization</td>
<td>105 (5.8)</td>
<td>143 (8.0)</td>
<td>0.72 (0.56–0.93)</td>
<td>0.011</td>
</tr>
<tr>
<td>Any revascularization</td>
<td>486 (26.2)</td>
<td>546 (30.3)</td>
<td>0.88 (0.78–0.99)</td>
<td>0.036</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GUSTO moderate/severe bleed</td>
<td>115 (7.4)</td>
<td>73 (4.5)</td>
<td>1.62 (1.21–2.18)</td>
<td>0.001</td>
</tr>
<tr>
<td>GUSTO severe bleed</td>
<td>36 (2.4)</td>
<td>26 (1.6)</td>
<td>1.41 (0.85–2.34)</td>
<td>0.18</td>
</tr>
<tr>
<td>Fatal bleed</td>
<td>7 (0.5)</td>
<td>7 (0.4)</td>
<td>1.02 (0.36–2.90)</td>
<td>0.98</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>14 (0.9)</td>
<td>7 (0.4)</td>
<td>2.03 (0.82–5.02)</td>
<td>0.13</td>
</tr>
<tr>
<td>Intracranial hemorrhage†</td>
<td>8 (0.7)</td>
<td>5 (0.4)</td>
<td>1.66 (0.54–5.08)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CVD, cardiovascular death; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; and MI, myocardial infarction.

*Includes vascular events involving the coronary, cerebral, or peripheral vasculature.
†Excluding patients with cerebrovascular disease.
Use of Vorapaxar in Pts with PAD

• Conclusions:
  – Vorapaxar does not reduce the risk of CV death, MI or stroke
  – Vorapaxar reduce the over 3 yrs risk of acute limb ischemia (2.3% vs 3.9%) and revascularization procedures (18.4% vs 22.2%)
  – Vorapaxar increases the risk of bleeding
Recent Trials: Ticagrelor use in PAD

**EUCLID Study Design**

Patients with symptomatic PAD

- Key exclusion criteria:
  - Poor metabolizer for CYP2C19
  - Patients requiring dual anti-platelet therapy

- Ticagrelor 90 mg bid
  - Double-blind
  - Double-dummy
  - 1:1
  - N=13,885

- Clopidogrel 75 mg od

Duration: Event Driven Trial
- Approximately 14-month recruitment and 26-month follow-up

Primary Endpoint: cardiovascular death, myocardial infarction, or ischemic stroke

Primary Safety Endpoint: TIMI major bleeding

Inclusion criteria:
- Symptomatic PAD AND one of the following:
  - A. ABI ≤0.80 at Visit 1 ≤0.85 at Visit 2 OR
  - B. Prior lower extremity revascularization > 30 days

Recent Trials: Ticagrelor use in PAD

**Efficacy**

 Patients with previous revascularization >30days

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Figure 1. Kaplan-Meier plot of primary efficacy outcome (composite of cardiovascular [CV] death, myocardial infarction [MI], or ischemic stroke).

Recent Trials: Ticagrelor use in PAD Safety

Use of Ticagrelor in PAD patients

• Conclusions:
  – Pts with Hx of lower extremity revascularization have a higher risk of future MI and limb events compared to pts with low ABI regardless the severity of RF
  – Ticagrelor although equally safe, does not reduce the risk of future CV mortality, MI or stroke compared to clopidogrel
Recent Trials: Rivaroxaban in PAD

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 Abhayans, Marco Alings, Ajay K Kakkar, Katalin Keltai, Aldo P Maggioni, Basil S Lewis, Stefan Störk, Jun Zhu, Patricia Lopez-Jaramillo, Martin O'Donnell, Patrick J Commerford, Dragos Vinereanu, Nana Pogasova, Lars Ryden, Keith A A Fox, Deepak L Bhatt, Frank Misselwitz, John D Vargias, 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

Lancet 2018; 391: 219-29

PAD: Hx peripheral bypass, PTA, amputation, claudication, CAD with ABI:<0.90
Carotid AD: Carotid revasc, Asymptomatic >50% stenosis
Recent Trials: Rivaroxaban in PAD Efficacy

- Low-dose rivaroxaban (2.5 mg BD) + Aspirin (100 mg OD) group
- Rivaroxaban alone (5 mg BD)
- Aspirin (100 mg OD) alone

Superior to Aspirin: Low Rivaroxaban+Aspirin
Less: composite end point, limb events
## Recent Trials: Rivaroxaban in PAD

### Safety

<table>
<thead>
<tr>
<th></th>
<th>Low-dose rivaroxaban alone group (n=2474)</th>
<th>Rivaroxaban alone group (n=2504)</th>
<th>Aspirin alone group (n=2904)</th>
<th>Low-dose rivaroxaban plus aspirin versus aspirin alone</th>
<th>Rivaroxaban alone versus aspirin alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fatal bleeding</td>
<td>4 (&lt;1%)</td>
<td>5 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
<td>1.61 (1.12-2.31) 0.0089</td>
<td>1.68 (1.17-2.40) 0.0043</td>
</tr>
<tr>
<td>Non-fatal symptomatic intracranial haemorrhage</td>
<td>4 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
<td>8 (&lt;1%)</td>
<td>1.55 (0.64-3.74) 0.33</td>
<td>2.15 (0.94-4.96) 0.065</td>
</tr>
<tr>
<td>Non-fatal, non-intracranial haemorrhage symptomatic bleeding into a critical organ</td>
<td>13 (1%)</td>
<td>18 (1%)</td>
<td>8 (&lt;1%)</td>
<td>1.94 (1.24-3.04) 0.0031</td>
<td>1.86 (1.18-2.92) 0.0064</td>
</tr>
<tr>
<td>Other major bleeding (surgical site bleeding requiring reoperation or bleeding leading to hospitalisation)</td>
<td>56 (2%)</td>
<td>53 (2%)</td>
<td>29 (1%)</td>
<td>1.10 (0.59-2.05)</td>
<td>1.39 (0.89-3.09)</td>
</tr>
<tr>
<td>Fatal or symptomatic bleeding into a critical organ</td>
<td>21 (1%)</td>
<td>26 (1%)</td>
<td>19 (1%)</td>
<td>1.13 (0.64-2.01)</td>
<td>1.34 (0.77-2.52)</td>
</tr>
<tr>
<td>Fatal or symptomatic bleeding into a critical organ or surgical site bleeding leading to re-operation</td>
<td>25 (1%)</td>
<td>29 (1%)</td>
<td>22 (1%)</td>
<td>1.61 (1.08-2.39)</td>
<td>1.34 (0.89-2.02)</td>
</tr>
<tr>
<td>ISTH major bleeding</td>
<td>64 (3%)</td>
<td>53 (2%)</td>
<td>40 (2%)</td>
<td></td>
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</tr>
<tr>
<td><strong>Sites of bleeding</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Gastrointestinal</td>
<td>41 (2%)</td>
<td>26 (1%)</td>
<td>18 (1%)</td>
<td>2.28 (1.31-3.96) 0.0027</td>
<td>1.46 (0.80-2.66) 0.22</td>
</tr>
<tr>
<td>Intracranial</td>
<td>5 (&lt;1%)</td>
<td>6 (&lt;1%)</td>
<td>9 (&lt;1%)</td>
<td>0.56 (0.19-1.66)</td>
<td>0.68 (0.24-1.91)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>3 (&lt;1%)</td>
<td>14 (1%)</td>
<td>2 (&lt;1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular</td>
<td>7 (&lt;1%)</td>
<td>8 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>5 (&lt;1%)</td>
<td>6 (&lt;1%)</td>
<td>8 (&lt;1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>4 (&lt;1%)</td>
<td>4 (&lt;1%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>15 (1%)</td>
<td>15 (1%)</td>
<td>10 (&lt;1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>198 (8%)</td>
<td>170 (7%)</td>
<td>141 (6%)</td>
<td>1.43 (1.15-1.77) 0.0011</td>
<td>1.23 (0.98-1.54) 0.069</td>
</tr>
<tr>
<td><strong>Net benefit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death, myocardial infarction, stroke, and critical organ or fatal bleeding†</td>
<td>140 (6%)</td>
<td>168 (7%)</td>
<td>185 (7%)</td>
<td>0.75 (0.60-0.94) 0.011</td>
<td>0.92 (0.75-1.13) 0.43</td>
</tr>
<tr>
<td>Cardiovascular death, myocardial infarction, stroke or major adverse limb events, major amputation, or fatal or critical organ bleeding</td>
<td>169 (7%)</td>
<td>207 (8%)</td>
<td>234 (9%)</td>
<td>0.72 (0.59-0.87) 0.0008</td>
<td>0.89 (0.74-1.07) 0.23</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise indicated. HR=hazard ratio. ISTH=International Society of Thrombosis and Hemostasis. *Includes four components of prespecified major bleeding definition summarised hierarchically. †Prespecified net clinical benefit outcome.

Table 3: Safety outcomes and net benefit for patients with peripheral artery disease.
Use of Rivaroxaban in pts with stable peripheral artery disease

• The combination of low dose rivaroxaban bd plus Aspirin could replace Aspirin alone in such pts who are not at high risk of bleeding.
**Overall Summary**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Confirm patient has peripheral artery disease (PAD) by vascular testing or history of prior lower extremity revascularization</td>
</tr>
<tr>
<td>2</td>
<td>Assess if patient has PAD-associated limb symptoms</td>
</tr>
<tr>
<td>3</td>
<td>Determine if patient has clinically manifest coronary artery disease (CAD) or cerebrovascular disease and if the patient has had an acute coronary syndrome or percutaneous coronary intervention within the past 12 mo or an acute cerebrovascular ischemic event</td>
</tr>
<tr>
<td>4</td>
<td>Select antithrombotic management</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PAD alone without clinically manifest CAD or cerebrovascular disease</th>
<th>PAD with clinically manifest CAD or cerebrovascular disease</th>
<th>Acute coronary syndrome or percutaneous coronary intervention within the past 12 mo or an acute cerebrovascular ischemic event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asymptomatic PAD</strong></td>
<td></td>
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</tr>
<tr>
<td>Do not initiate antithrombotic therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manage cardiovascular disease risk factors as indicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PAD-associated limb symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANTITHROMBOTIC THERAPY FOR PAD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel or ticagrelor monotherapy to prevent MACE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence suggests clopidogrel is more effective than aspirin; ticagrelor is an acceptable alternative in patients known to be poor metabolizers of clopidogrel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For patients with lower extremity revascularization, evidence supports aspirin monotherapy to maintain procedural patency</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANTITHROMBOTIC THERAPY FOR STABLE CARDIOVASCULAR DISEASE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombotic therapy, such as aspirin and/or oral P2Y12 inhibitor, according to current guidelines for treatment of stable CAD or cerebrovascular disease</td>
<td></td>
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</tr>
<tr>
<td><strong>ANTITHROMBOTIC THERAPY FOR ACUTE CARDIOVASCULAR EVENT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow current guidelines for antithrombotic treatment of acute cardiovascular event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (or clopidogrel if aspirin is contraindicated) to prevent MACE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For patients taking aspirin and at high risk of cardiac and ischemic limb events, consider adding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticagrelor if prior (&gt;12 mo ago) myocardial infarction to prevent MACE and MALE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-dose rivaroxaban if patient has concomitant CAD to prevent MACE and MALE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For patients at high risk of ischemic limb events, consider adding vorapaxar to aspirin or clopidogrel to prevent MALE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MACE indicates major adverse cardiac events (myocardial infarction, ischemic stroke, or cardiovascular death); MALE, major adverse limb events (acute limb ischemia or major amputation).

a Patients with PAD at highest risk for ischemic limb events are those with a prior history of lower extremity revascularization or more severe disease (ankle-brachial index ≤0.60).

b Rivaroxaban 2.5 mg twice daily for this indication is under review by the Food and Drug Administration but is not yet available in the United States.
Ongoing/Upcoming Clinical Trials

• **VOYAGER** (Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects with Symptomatic PAD Undergoing Revascularisation Procedure)
  – 1:1 RCT, rivaroxaban 2.5 mg BD vs placebo on a background of aspirin 100 mg after peripheral surgical and/or endovascular revascularization

• **BEST-CLI** (Best endovascular versus Best Surgical Therapy in Patient With Critical Limb Ischemia)
  – Open-label RCT comparing best surgical revascularisation against best endovascular revascularisation
  – In addition to RCT, a concurrent registry is planned and will capture real-world antithrombotic therapy in Critical Limb Ischemia patients
15ο Ετήσιο Συνέδριο Ελληνικού Κολλεγίου Καρδιολογίας

Cardio-Cath Meeting 2019
Live Demonstration Course

27-29 Ιούνιου / June 2019

Ένοικοστέρι Du Lac, 
ΙΟΑΝΝΙΝΑ
Hotel Du Lac, 
ΙΟΑΝΝΙΝΑ, Greece
Recent Trials: General Remarks

• More potent antiplatelet monotherapy (i.e. EUCLID Trial) does not lead to improved CV outcomes

• Subgroup of studies with DAPT vs SAPT show an unclear overall benefit (i.e. CHARISMA and PEGASUS trials), no mortality benefit, and a bleeding hazard

• Dual pathways inhibition with antiplatelet and low-dose anticoagulant targets compared to SAPT (i.e. COMPASS trial) may provide the most significant CV and limb protection for PAD patients