Key recommendations on antithrombotic and lipid lowering therapy from the 2017 guidelines of the European Society of Cardiology

Univ.-Prof. Dr. med. Christine Espinola-Klein

Department of Angiology
Center of Cardiology / Cardiology I
University Medical Center Mainz
Potential conflicts of interest

Scientific support:
Berlin Chemie-Menarini, Abbott Vascular GmbH

Advisory board, speaker fee:
Amgen GmbH, Bayer Health Care, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, MSD Sharp & Dohme, Pfizer Pharma GmbH, Sanofi-Aventis GmbH
2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)

The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS)

Endorsed by the European Stroke Organization (ESO)

ESC Chairperson: Victor Aboyans (France).
Co-Chairperson: Jean-Baptiste Ricco1 (France).

Authors/Task Force Members: Marie-Louise EL Bartelink (The Netherlands), Martin Björck1 (Sweden), Marianne Brodmann (Austria), Tina Cohnert1 (Austria), Jean-Philippe Collet (France), Martin Czerny (Germany), Marco De Carlo (Italy), Sebastian Debus1 (Germany), Christine Espinola-Klein (Germany), Thomas Kahan (Sweden), Serge Kownator (France), Lucia Mazzolai (Switzerland), A. Ross Naylor1 (UK), Marco Roffi (Switzerland), Joachim Röther2 (Germany), Muriel Sprynger (Belgium), Michal Tendera (Poland), Gunnar Tepe (Germany), Maarit Venermo1 (Finland), Charalambos Vlachopoulos (Greece), Ileana Desormais (France).
Atherosclerosis

- Aorta disease

- Coronary Artery Disease (CAD)

Peripheral Arterial Diseases (PADs)

- Cerebrovascular diseases:
  - Carotid artery disease
  - Vertebrobasilar artery disease

- Upper-Extremity Artery Disease (UEAD)

- Mesenteric artery disease

- Renal Artery Disease (RAD)

- Lower-Extremity Artery Disease (LEAD)

Presentations

- Stroke, Transient Ischaemic Attack (TIA), acute monocular blindness

- Subclavian steal syndrome, pain on exertion, digital symptoms, acute ischaemia

- Chronic Mesenteric Ischaemia (CMI)
  Acute Mesenteric Ischaemia (AMI)

- Hypertension, renal failure

- Typical claudication, atypical symptoms, Chronic Limb-Threatening Ischaemia (CLTI), Acute Limb Ischaemia (ALI)

Multi-vascular atherosclerosis

Espinola-Klein C. et al., Internist 2011; 52:549-60
Asymptomatic PAD

Aspirin for Asymptomatic Atherosclerosis Trial

N = 3350 (ABI < 0.95), FU 8.2 years

Double-blind, randomized: 100 mg Aspirin or placebo

Endpoint:
Cardiovascular events (cv death, infarction, stroke revascularization)

Major bleeding:
A=2.0% vs. P=1.2%

Fowkeas et al. JAMA 2010; 3003: 841-848.
**BOA: The Dutch Bypass Oral anticoagulants or Aspirin Study**

N=2690; Infrainguinal Bypass, VKA (INR 3-4,5) vs. 80 mg ASS

- **Occlusion venous grafts**
  - Hazard Ratio (95% KI)
  - ASS vs. VKA = 0.69 (0.54-0.88)
  - NNT (VKA) = 17

- **Occlusion allografts**
  - Hazard Ratio (95% KI)
  - ASS vs. VKA = 1.26 (1.03-1.55)
  - NNT (ASS) = 15

---

**VKA:** Bleeding 4.7% (intracranial: 0.8%)

**ASS:** Bleeding 2.5% (intracranial: 0.1%)

BOA Study Group; Lancet 2000; 355: 346-351
Management of antiplatelet therapy in patients with LEAD not requiring anticoagulation

**Asymptomatic**
- No SAPT
  - Class III A

**Symptomatic**
- SAPT
  - A or C
  - Class I A

**Revascularization**
- Percutaneous
  - DAPT A + C
    - Class IIa C
- Surgery
  - SAPT A or C
    - Class IIb B

**Time delay**
- 0
- 1 mo.
- 1 year
- Long term

**Antithrombotic management**

**Asymptomatic**
- No SAPT
  - Aspirin 75-100 mg/day
- SAPT A or C
  - Class I A

**Symptomatic**
- SAPT A or C
  - Class IIa C

**Revascularization**
- Percutaneous
  - DAPT A + C
    - Class IIa C
- Surgery
  - SAPT A or C
    - Class IIb B
  - VKA
    - 75 mg/day
  - Oral Anticoagulation

www.escardio.org/guidelines

2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with ESVS (European Heart Journal 2017; doi:10.1093/eurheartj/ehx095)
Key Recommendations
Antithrombotic therapy in LEAD

- Long-term SAPT is recommended in **symptomatic** patients, clopidogrel may be preferred over aspirin.

- SAPT is recommended after **infra-inguinal bypass surgery**. Vitamin K antagonists may be considered after autologous vein infrainguinal bypass. DAPT with aspirin and clopidogrel may be considered in below-knee bypass with prosthetic graft.

- DAPT with aspirin and clopidogrel for at least one month should be considered after **infra-inguinal stent implantation**.

- Antiplatelet therapy is not routinely indicated in patients with isolated **asymptomatic** LEAD.

LEAD in patients requiring long-term oral anticoagulation

(A)symptomatic

Surgery

Percutaneous intervention

Bleeding risk low

OAC Monotherapy

Class I

Bleeding risk high

OAC Monotherapy

Class IIa

OAC Monotherapy

Class IIa

Time delay

0

1 mo.

1 year

Long term

OAC Monotherapy

Class IIb

Asymptomatic

Surgery

Percutaneous intervention

Bleeding risk low

OAC Monotherapy

Class I

Bleeding risk high

OAC Monotherapy

Class IIa

OAC Monotherapy

Class IIb

www.escardio.org/guidelines

2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with ESVS (European Heart Journal 2017; doi:10.1093/eurheartj/ehx095)
4.2.2 Lipid-lowering drugs

All patients with PADs should have their serum low-density lipoprotein cholesterol (LDL-C) reduced to <1.8 mmol/L (<70 mg/dL) or decreased by >50% if the initial LDL-C level is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL). In observational studies and limited randomized clinical trials (RCTs) in patients with LEAD (from asymptomatic to severe cases), statin therapy has been shown to cause reductions in all-cause mortality and CV events. In the Reduction of Atherothrombosis for Continued Health (REACH) registry, among patients with LEAD, statin use was associated with a 17% decrease in adverse CV events rates. Even in the most advanced stages of disease, statin therapy is associated with lower 1-year rates of mortality and major CV adverse events. Combination treatment with ezetimibe in selected patients is also beneficial. In a randomized trial, bezafibrate showed no benefit over placebo to reduce coronary and cerebrovascular events in patients with LEAD. In those with CAD, statins reduce the stroke risk. Recently the Fourier trial demonstrated the additional benefits of evolocumab, a monoclonal antibody inhibiting the proprotein convertase subtilisin/kexin type 9 to reduce CV events in patients with atherosclerotic disease over statins alone. The results were consistent in the subgroup of 1505 patients with LEAD alone. Further results are awaited.
2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)

Authors/Task Force Members: Massimo F. Piepoli* (Chairperson) (Italy), Arno W. Hoes* (Co-Chairperson) (The Netherlands), Stefan Agewall (Norway)¹, Christian Albus (Germany)², Carlos Brotons (Spain)³, Alberico L. Catapano (Italy)⁴, Marie-Therese Cooney (Ireland)⁵, Ugo Corrà (Italy)⁶, Bernard Cosyns (Belgium)⁷, Christi Deaton (UK)⁸, Ian Graham (Ireland)⁹, Michael Stephen Hall (UK)¹⁰, F. D. Richard Hobbs (UK)¹¹, Maja-Lisa Løchen (Norway)¹², Herbert Löllgen (Germany)¹³, Pedro Marques-Vidal (Switzerland)¹⁴, Joep Perk (Sweden)¹⁵, Eva Prescott (Denmark)¹⁶, Josep Redon (Spain)¹⁷, Dimitrios J. Richter (Greece)¹⁸, Naveed Sattar (UK)¹⁹, Yvo Smulders (The Netherlands)²⁰, Monica Tiberi (Italy)²¹, H. Bart van der Worp (The Netherlands)²², Ineke van Dis (The Netherlands)²³, W. M. Monique Verschuren (The Netherlands)²⁴

Piepoli ME et al. European Heart Journal 2016; 37: 2315-2381
### Table 5  Risk categories

#### Very high-risk
- Subjects with any of the following:
  - Documented CVD, clinical or unequivocal on imaging.
  - Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm, and PAD.
  - Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery.
  - DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension.
  - Severe CKD (GFR <30 mL/min/1.73 m²).
  - A calculated SCORE ≥10%.

#### High-risk
- Subjects with:
  - Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g., in familial hypercholesterolaemia) or BP ≥180/110 mmHg.
  - Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk).
  - Moderate CKD (GFR 30–59 mL/min/1.73 m²).
  - A calculated SCORE ≥5% and <10%.

#### Moderate-risk
- SCORE ≥1% and <5% at 10 years. Many middle-aged subjects belong to this category.

#### Low-risk
- SCORE <1%.

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BP = blood pressure; CKD = chronic kidney disease; DM = diabetes mellitus; GFR = glomerular filtration rate; PAD = peripheral artery disease; SCORE = systematic coronary risk estimation; TIA = transient ischaemic attack.
2016 ESC Guidelines
Cardiovascular Prevention

Recommendations for lipid control

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients at VERY HIGH CV risk, an LDL-C goal &lt;1.8 mmol/L (&lt;70 mg/dL), or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.</td>
<td>I</td>
<td>B</td>
<td>350-353</td>
</tr>
<tr>
<td>In patients at HIGH CV risk, an LDL-C goal &lt;2.6 mmol/L (&lt;100 mg/dL), or a reduction of at least 50% if the baseline is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) is recommended.</td>
<td>I</td>
<td>B</td>
<td>350-353</td>
</tr>
<tr>
<td>In the remaining patients on LDL-C lowering treatment, an LDL-C goal &lt;3.0 mmol/L (&lt;115 mg/dL) should be considered.</td>
<td>IIa</td>
<td>C</td>
<td>350-353</td>
</tr>
</tbody>
</table>

CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

*aClass of recommendation.

*bLevel of evidence.

*cReference(s) supporting recommendations.

*Non-HDL-C is a reasonable and practical alternative target because it does not require fasting. Non-HDL-C secondary targets of <2.6, <3.3 and <3.8 mmol/L (<100, <130 and <145 mg/dL) are recommended for very high, high and low to moderate risk subjects, respectively. See section 3a.7.10 for more details.

*A view was expressed that primary care physicians might prefer a single LDL-C goal of 2.6 mmol/L (100 mg/dL). While accepting the simplicity of this approach and that it could be useful in some settings, there is better scientific support for the three targets matched to level of risk.

*This is the general recommendation for those at very high-risk. It should be noted that the evidence for patients with CKD is less strong.

Piepoli ME et al.
European Heart Journal 2016; 37: 2315-2381
## Heart Protection Study

<table>
<thead>
<tr>
<th>Major vascular event &amp; prior disease group</th>
<th>Simvastatin-allocated (10,269)</th>
<th>Placebo-allocated (10,267)</th>
<th>Event rate ratio (95% CI)</th>
<th>Heterogeneity p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>369 (10.9%)</td>
<td>465 (13.8%)</td>
<td>0.73 (0.67 - 0.79)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>No PAD</td>
<td>529 (7.7%)</td>
<td>747 (10.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal: coronary</td>
<td>898 (8.7%)</td>
<td>1212 (11.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strokes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>179 (5.3%)</td>
<td>242 (7.2%)</td>
<td>0.75 (0.66 - 0.85)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>No PAD</td>
<td>265 (3.8%)</td>
<td>343 (5.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal: stroke</td>
<td>444 (4.3%)</td>
<td>585 (5.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularisations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>466 (13.8%)</td>
<td>603 (17.9%)</td>
<td>0.76 (0.70 - 0.83)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>No PAD</td>
<td>473 (6.9%)</td>
<td>602 (8.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal: revascularisation</td>
<td>939 (9.1%)</td>
<td>1205 (11.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAJOR VASCULAR EVENTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>895 (26.4%)</td>
<td>1101 (32.7%)</td>
<td>0.76 (0.72 - 0.81)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>No PAD</td>
<td>1138 (16.5%)</td>
<td>1484 (21.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heart Protection Study Collaborative Group, J Vasc Surg 2007; 45: 645-54
Statin therapy in LEAD
(N=5861), 4 years follow-up

Kumbhani DJ et al. (REACH), Eur Heart J 2014; 35: 2864-2872
Ezetimib + Statin

**IMPROVE-IT** N=18144 patients with acute coronary syndrome
Simvastatin (40 mg) + Ezetimib (10 mg) vs. Simvastatin (40 mg) + Placebo

### Recommendation Diagnostics

#### Routine tests

Fasting serum lipid profile:
- total cholesterol,
- triglycerides,
- high-density lipoprotein cholesterol,
- low-density lipoprotein cholesterol.

Lipoprotein(a) if there is a family history of premature cardiovascular disease.
### 2017 ESC Guidelines
Peripheral Arterial Diseases

#### Recommendation therapy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins are recommended in all patients with PADs.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients with PADs, it is recommended to reduce LDL-C to $&lt;1.8$ mmol/L (70 mg/dL) or decrease it by $\geq 50%$ if baseline values are 1.8-3.5 mmol/L (70-135 mg/dL).</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>On top of general prevention, statins are indicated to improve walking distance.</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

B CV Death, MI or Stroke in Patients with and without PAD

<table>
<thead>
<tr>
<th>Days from Randomization</th>
<th>Placebo PAD</th>
<th>Evolocumab PAD</th>
<th>Placebo no PAD</th>
<th>Evolocumab no PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1784</td>
<td>1858</td>
<td>11996</td>
<td>11926</td>
</tr>
<tr>
<td>90</td>
<td>1756</td>
<td>1834</td>
<td>11861</td>
<td>11802</td>
</tr>
<tr>
<td>180</td>
<td>1721</td>
<td>1806</td>
<td>11732</td>
<td>11699</td>
</tr>
<tr>
<td>270</td>
<td>1685</td>
<td>1774</td>
<td>11606</td>
<td>11583</td>
</tr>
<tr>
<td>360</td>
<td>1654</td>
<td>1758</td>
<td>11494</td>
<td>11490</td>
</tr>
<tr>
<td>450</td>
<td>1632</td>
<td>1740</td>
<td>11375</td>
<td>11397</td>
</tr>
<tr>
<td>540</td>
<td>1587</td>
<td>1692</td>
<td>10767</td>
<td>10828</td>
</tr>
<tr>
<td>630</td>
<td>1332</td>
<td>1427</td>
<td>9099</td>
<td>9138</td>
</tr>
<tr>
<td>720</td>
<td>1014</td>
<td>1091</td>
<td>7167</td>
<td>7258</td>
</tr>
<tr>
<td>810</td>
<td>729</td>
<td>779</td>
<td>5429</td>
<td>5474</td>
</tr>
<tr>
<td>900</td>
<td>452</td>
<td>480</td>
<td>3636</td>
<td>3649</td>
</tr>
</tbody>
</table>

HR 0.73
95% CI (0.59 – 0.91)
P=0.0040

HR 0.81
95% CI (0.73 – 0.90)
P<0.001

p-interaction = 0.41

PAD 3.5% ARR
NNT 29

No PAD 1.4% ARR
NNT 72

Bonaca MP. et al. Circulation 2017; 137:00–00. DOI: 10.1161/CIRCULATIONAHA.117.032235
Thank you for your attention!
Management of antithrombotic treatment in patients with carotid artery stenosis

Management of antiplatelet therapy in carotid artery stenosis

- **Asymptomatic**
  - SAPT (A or C)
    - **Class IIa C**

- **Carotid Artery Stenting**
  - DAPT (A + C)
    - **Class I A**

- **Carotid Surgery**
  - SAPT (A or C)
    - **Class I A**

**Time delay**
- 0
- 1 mo.
- 1 year
- Long term

- **SAPT**
  - **Class IIa C**

**Antithrombotic Therapy**
- **Aspirin**
  - 75-100 mg/day
- **Clopidogrel**
  - 75 mg/day

---

www.escardio.org/guidelines

2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with ESVS
(European Heart Journal 2017; doi:10.1093/eurheartj/ehx095)