Online version at http://www.minervamedica.it

International Angiology 2021 February;40(1):29-41
DOI: 10.23736/S0392-9590.20.04518-6

GUIDELINES

PERIPHERAL ARTERIAL DISEASE

EDITOR'S CHOICE

How to manage patients with polyvascular atherosclerotic disease

Position paper of the International Union of Angiology

Pavel POREDOS [1] *, Ales BLINC [1, 2], Salvatore NOVO [3], Pier L. ANTIGNANI [4]

[1]Department of Vascular Diseases, University Medical Center Ljubljana, Ljubljana, Slovenia; [2]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; [3]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (ProMISE), University of Palermo, Palermo, Italy; [4]Nuova Villa Claudia Vascular Center, Rome, Italy

*Corresponding author: Pavel Poredos, Department of Vascular Diseases, University Medical Center Ljubljana, Zaloska 7, 1000 Ljubljana, Slovenia. E-mail: pavel.poredos@kclj.si

ABSTRACT

Atherosclerosis is a systemic disease affecting multiple arterial territories. Patients with clinical atherosclerotic disease in one vascular bed are likely to have asymptomatic or symptomatic atherosclerotic lesions in other vascular beds. Specifically, peripheral arterial disease (PAD) often coexists with coronary and carotid disease. With progression of atherosclerotic disease in one vascular bed, the risk of clinical manifestations in other territories increases and the incidence of adverse cardiovascular events increases substantially with the number of affected vascular beds. Classical risk factors are associated with the development of polyvascular atherosclerotic disease (PVD) in different territories; however, to a different extent. Risk modification represents basic treatment of patients with PVD. All modifiable risk factors should be aggressively controlled by lifestyle modification and medication. Particular attention should be directed to patients with PAD who are often undertreated in spite of the proven benefits of guideline-based approach. There is currently no proof that identification of asymptomatic atherosclerosis and PVD improves clinical outcomes in patients who are already in prevention programs. Revascularization should be performed only in symptomatic vascular beds, using the least aggressive method according to consensual decision of a multidisciplinary vascular team.

(*Cite this article as:* Poredos P, Blinc A, Novo S, Antignani PL. How to manage patients with polyvascular atherosclerotic disease. Position paper of the International Union of Angiology. Int Angiol 2021;40:29-41. DOI: 10.23736/S0392-9590.20.04518-6)

Key words: Atherosclerosis; Diagnostic techniques and procedures; Risk factors.

Atherothrombosis is a leading cause of morbidity and mortality.[1] The frequent co-existence of atherothrombotic disease in different vascular beds is well established.[2] Therefore, atherosclerosis is a systemic disease and by the definition, polyvascular disease (PVD) indicates the simultaneous presence of clinically relevant atherosclerotic lesions in at least two major vascular territories: coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral arterial disease (PAD) and renal artery disease.[3] In the CAPRIE study, atherosclerotic vascular disease in at least two vascular beds was found in a quarter of patients with atherosclerotic vascular disease.[4, 5] The CRUSADE Registry found that 13% patients with acute coronary syndromes had PVD.[6] Major cardiovascular event rates are approximately doubled in patients with PVD compared with patients with a single symptomatic arterial bed, and the event rate increases proportionally to the number of symptomatic atherosclerotic vascular beds.[7, 8] Coronary patients with atherosclerotic involvement of all three major arterial beds have worse short-term and intermediate-term outcomes compared with dual vascular bed involvement, whereas those with coronary bed involvement alone have the lowest risk.[8] The probability for PVD is greater in patients with PAD than in patients with CAD because PAD indicates an extensive and severe degree of systemic atherosclerosis and carries the worst prognosis.[9]

Predictors of PVD are: age over 70 years, renal failure, male sex and increased Body Mass Index.[10] The coexistence of PAD and CAD is probably more frequent than it is recognized, because PAD is often asymptomatic or masked by symptoms of angina or dyspnea in patients with concomitant CAD.[11]

Despite the severity of PVD and its grave prognosis, the data on management of this entity are scanty. Therefore, the aim of this review was to increase the awareness of this neglected clinical entity.

Relationship between peripheral arterial and coronary artery disease

As with other manifestations of atherosclerosis, PAD which is defined as occlusive disease of arteries distal to the aortic bifurcation, usually presents after the age of 50 years, with an exponential increase after the age of 65 years.[12, 13] The prevalence of PAD reaches approximately 20% by the age of 80 years.[12, 14] In high-income countries, symptomatic PAD is somewhat more frequent in men, although the difference practically disappears in the elderly.[12, 13] In low- and middle-income countries, the prevalence of PAD is higher in women than in men, especially at younger ages: 6.3% (95% confidence interval [CI]: 4.9-8.1%) *vs*. 2.9% (CI: 2.0-4.1%).[13] The prevalence of asymptomatic PAD is much higher than that of symptomatic disease, and the prevalence of PAD is somewhat dependent on the diagnostic methods used. Preclinical and clinical PAD are most commonly diagnosed by reduced ankle brachial index (ABI<0.9). PAD is common in patients with CAD, with a prevalence of 22-42%.[15, 16] In the study of Poredoš and Jug, a total of 42% of patients with CAD had PAD.[15] Also, asymptomatic PAD was strongly associated with CAD, even after adjustment for age, gender and other risk factors. In patients with CAD and associated PAD, the superficial femoral artery was most frequently affected.[17] The CAPRIE Study demonstrated that approximately 41% of patients with PAD had concurrent coronary artery or cerebrovascular disease and 8.6% had disease in all three vascular beds.[4, 18] Similarly, the Trans-Atlantic Consensus Document collected data from all the available studies and concluded that almost 60% patients with PAD have significant CAD or CVD, while about 40% of patients with CAD also have PAD.[14, 19]

Patients with acute coronary syndrome and concomitant PAD have more extensive coronary artery disease and poorer outcomes. In a study involving geriatric patients, CAD was present in more than 2/3 of patients who had PAD.[20] In an acute coronary syndrome registry, in-hospital mortality, acute heart failure and recurrent ischemic events were up to 5-times higher in patients with PAD.[8] Concomitant PAD (clinical or sub-clinical) is also associated with worse outcome in patients undergoing CABG.[21]

Morbidity and mortality of patients with PAD is high because of accompanying cardiovascular complications, particularly those related to CAD. Several studies indicated that decreased ABI is an independent risk factor for cardiovascular adverse events. ABI<0.9 was found to be associated with 2.4-times higher total mortality than normal ABI in diabetics.[22] Even a slightly reduced ABI implied a grave prognosis.[22] Similarly, in the Cardiovascular Health Study, subclinical PAD detected by reduced ABI involved a greater risk of developing cardiovascular complications than absence of PAD with normal values of ABI.[23] Further, reduced ABI combined with the Framingham Risk Score improves the accuracy of cardio-vascular risk prediction.[24] On the other hand, elevated ABI>1.40, indicating non-compressible calf arteries, is also associated with coronary and cerebral-vascular disease.[24, 25]

It is unknown whether in PAD the increased risk of cardiovascular events is associated with common risk factors such as hypertension or dyslipidemia, or with more specific factors such as lack of physical activity, cardiac insufficiency, impaired endothelial function and systemic inflammation.[26]

Relationship between peripheral arterial disease and carotid atherosclerosis

Similarly, as PAD and CAD, PAD and CVD are closely interrelated. Already a borderline decrease of ABI has a strong predictive value for CVD, and the risk of cardiovascular events and mortality increases with the severity of PAD.[27, 28] The SMART (second manifestation of arterial disease) study showed that in patients with PAD, carotid stenosis was present in 14% overall, while in patients who had additional risk factors the prevalence of carotid stenosis increased to as much as 50%.[29] In the Limburg-PAOD study, the prevalence of CVD in asymptomatic PAD patients was even 2-times higher than in symptomatic PAD patients.[30] Studies also showed an interrelationship between preclinical PAD and intima-media thickness (IMT). Individuals with decreased ABI had significantly thicker carotid IMT and were twice as likely to have preclinical carotid plaques than patients with normal ABI.[27] The Rotterdam Study showed significant inverse association between common carotid artery IMT and ABI.[31] An increase of IMT for 0.1 mm was associated with reduction of ABI by 0.26.[31] The prevalence of symptomatic or asymptomatic PAD was strongly increased among subjects with IMT>0.89 mm.[31] Concomitant carotid and lower limb extremity atherosclerosis significantly increases the risk for cardio-cerebrovascular events.[32]

Coronary and carotid arterial disease

Preclinical carotid lesions (increased intima-media thickness and asymptomatic atherosclerotic plaques) or symptomatic plaques are associated with the presence of CAD.[33]

Several studies indicated a close relationship between CAD and CVD. In 315 patients with previous myocardial infarction or symptomatic angina, who were asymptomatic for claudication and cerebral ischemic disease, the prevalence of carotid or peripheral artery atherosclerosis (stenosis >30% in carotid or peripheral arteries) was 23% in all patients and 32% in patients with triple coronary disease >50%.[33] Increased number of affected coronary vessels was associated with a higher prevalence of carotid and peripheral asymptomatic plaques.[34]

Preclinical carotid atherosclerosis is a strong marker of cardiovascular events. In subjects with predicted total cardiovascular risk <20%, the prevalence of events was 8% with normal carotid ultrasound findings, 13% with increased IMT and 15% in patients with carotid atherosclerotic plaques. Therefore, the identification of preclinical atherosclerosis of carotid arteries should be considered a strong predictor of future cardiovascular events.[35] In a study of 558 asymptomatic patients, risk factors for atherosclerosis were assessed and the 10-year-risk was calculated. Doppler ultrasound of carotid arteries identified the presence of IMT greater than 0.9 mm in 183 patients (33%) and carotid plaques in 147 patients (26%). In multivariate analysis the incidence of cardiovascular events was significantly influenced by the presence of asymptomatic carotid lesions.[36] Similar results were shown in a more recent study in which the algorithm of risk of Framingham, Euroscore and of the Italian Progetto Cuore and the impact of baseline asymptomatic carotid plaque on future cardiovascular events in a ten years follow-up was compared.[37] In a population of 529 asymptomatic patients, divided into two groups, with and without metabolic syndrome and with a follow-up of 20 years there were 242 cardiovascular events: 144 among patients with metabolic syndrome and 98 among healthy controls (59.5% *vs*. 40.5%; P<0.0001).[38] Patients without atherosclerotic lesions of the carotid arteries had significantly less events than patients with preclinical atherosclerosis (26.1% *vs*. 73.9%; P<0.0001). Therefore, already preclinical carotid atherosclerosis leads to an increased risk of cardiovascular events, especially if it is associated with metabolic syndrome.[38, 39] Similarly, in a recent study including 1007 patients who underwent coronary angiography and ultrasound examination of carotid arteries, a close association between carotid and coronary atherosclerosis was demonstrated.[40] In a study of preclinical carotid atherosclerosis and cardiovascular events, 668 subjects were divided in 3 groups according to the results of carotid examination: normal IMT (<0.9 mm), IMT between 0.9 and 1.5 mm, and patients with asymptomatic carotid plaques.[41] Total ischemic cardiovascular events were 9%, 19.5% and 30%, respectively.[41] Events occurred mainly in the coronary arteries, followed by the cerebral and the peripheral arteries of the lower limbs. The results show that carotid atherosclerosis is a predictor of multifocal disease.[41]

Multifocal atherosclerosis and cardiovascular or cerebrovascular morbidity and mortality

Numerous studies indicated high morbidity and mortality of patients with PVD, which are significantly higher than in single territory vascular disease. Multivariate analysis showed that besides classical risk factors, multifocal atherosclerosis was independently associated with fatal and non-fatal events in patients with ischemic heart disease.[42, 43] In accordance with this, a reduction of ABI influences the incidence of cerebrovascular and cardiovascular events and deaths.[44] In a sub-analysis of the HOPE study,

a progressive increase of all cardiovascular events was related to a decrease of ABI during the follow-up of 4.5 years.[45] In the Get-ABI study, 6880 patients were evaluated for ABI and followed-up for 5 years. At the end of the follow-up, the incidence of all-cause mortality was 24.1% in patients with symptomatic PAD, 19.2% in asymptomatic patients with ABI<0.90, and 9.5% in controls.[46]

A multicenter, cross-sectional database of patients with myocardial infarction throughout France (The Alliance project) included 9783 patients hospitalized for acute coronary syndrome.[47] Mortality of patients with PVD (CAD and/or PAD) was consistently higher than in those with CAD alone, regardless of age. Both PAD and CVD were independent predictors of hospital mortality in comparison to patients with CAD alone. A substantial number among patients with acute coronary syndrome had PVD and were at increased risk of death, yet they were managed less aggressively than patients with CAD alone.[47] In another study of patients with acute coronary syndrome, PVD was associated with worse in-hospital outcomes and all-cause mortality, even after adjusting for baseline covariates.[48] The EUCLID (examining use of ticagrelor in PAD) trial enrolled 13,885 patients with PAD alone, PAD and CAD, PAD and CAD and CVD.[49] The study demonstrated an increased composite endpoint of cardiovascular deaths, myocardial infarction or ischemic stroke with multiple vascular bed involvement.[49] In the CRUSADE registry (can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines) cardiovascular outcomes in older patients with non ST-segment elevation myocardial infarction were studied in relation to PVD.[8, 50] 34,205 patients with CAD were classified into 4 groups according the presence of concomitant atherosclerotic disease.[8, 50] Compared with CAD alone, patients with PVD had greater morbidities and the 3-year mortality increased with the number of affected arterial beds.[8, 50] The risk of long-term composite ischemic events was the highest among patients with symptomatic involvement of all three vascular beds.[8, 50] In the study of Zhang *et al*., which included 5440 participants with asymptomatic intra- or extracranial and renal arterial stenosis, the adjusted hazard ratio for death increased from 1.53 with single artery involvement to 2.22 with preclinical PVD.[51] Results of all these studies indicate that atherosclerosis is often multifocal and that coronary arteries are most frequently involved, followed by the carotid arteries and then the peripheral circulation. The more vascular beds are involved, the worse is the outcome of patients.

Diagnostic approach to patients with suspected polyvascular atherosclerotic disease

Screening for polyvascular disease in asymptomatic patients

There are two reasons, why screening for asymptomatic PVD has attracted a lot of attention. Firstly, the majority of coronary events occur in patients without previously known CAD,[52] and secondly, patients with more than one vascular bed affected by atherosclerotic disease have significantly increased risk of major cardiovascular events and worse outcomes regardless of the presentation site.[12, 51] Computed tomography for coronary calcium scoring and myocardial perfusion scintigraphy are useful in identifying, among apparently intermediate-risk subjects, those who have a high probability for developing future cardiac events.[52] Several other tests and conditions have been shown to predict cardiovascular morbidity and mortality beyond classical risk factors and prediction models: arterial stiffness, wave reflections indices, pulse wave velocity, central blood pressure, ankle-brachial index, carotid intima-media thickness, as well as vasculogenic erectile dysfunction.[53] There is a general consensus that patients at high risk and very high risk for cardiovascular disease should receive comprehensive prevention, including lifestyle counselling and preventive medication.[54] However, there is no proof that identification of asymptomatic atherosclerosis and multi-site atherosclerotic disease improves clinical outcomes in patients who are already in prevention programs.[12, 52]

Screening for polyvascular disease in symptomatic patients

Patients with symptomatic PVD, *i.e.* clinically relevant atherosclerotic lesions in at least two major vascular territories, who develop worsening symptoms in either vascular bed, have worse clinical outcomes than patients with single-site atherosclerotic disease.[12] However, in patients with one symptomatic vascular bed, screening for atherosclerotic disease in other vascular beds with the intention of intensifying medical treatment and possibly offering revascularization, has so far not been proven beneficial.[12] In the only randomized clinical trial conducted so far, systematic screening for multisite atherosclerotic disease in patients with high-risk coronary disease did not improve outcomes.[55] Proactive strategy combining ankle-brachial index determination, carotid ultrasound, lower extremity artery and renal artery duplex ultrasound identified mul-

tisite atherosclerotic disease in 21.7% of patients, but revascularization of non-coronary arteries was performed in only 3.6% of patients.[55] After 2 years, the primary endpoint of ischemic event leading to re-hospitalization, any organ failure or death occurred in 44.9% of patients in the pro-active group and 43.0% of patients in the conventional treatment group (hazard ratio [HR] 1.03; 95% confidence interval (CI): 0.80 to 1.34).[55]

In the real world, there is no danger of over-diagnosing and over-treating patients with symptomatic multisite atherosclerotic disease, but quite the contrary. Among 44157 patients entered into the Swiss prospective acute coronary syndrome registry between the years 1999-2016, multisite atherosclerotic disease was identified in 4544 patients and those patients were significantly less likely to receive coronary angiography and PCI than patients with coronary artery disease only.[56]

Patients presenting with lower extremity artery disease

The management of coronary artery disease in patients requiring vascular surgery PAD should be based on the 2014 ESC/ESA guidelines on non-cardiac surgery.[57] Patients with PAD requiring vascular surgery should be clinically assessed for ischemic heart disease if more than two clinical risk factors are present among the following: angina pectoris/previous myocardial infarction, heart failure, previous stroke /transient ischemic attack, renal dysfunction with creatinine clearance <60 mL/min, or diabetes mellitus requiring insulin therapy.[57] Those patients should be considered for preoperative nuclear medicine stress testing or coronary imaging.[57] However, prophylactic coronary revascularization before vascular surgery on arteries of the lower limbs or abdominal aorta did not improve clinical outcomes.[58]

Due to the high prevalence of carotid disease in patients with PAD, preoperative carotid artery duplex ultrasound may be considered in patients undergoing vascular surgery.[57]

For patients with symptomatic PAD who do not require revascularization, recommended optimal medical treatment and lifestyle measures are very similar to those of patients with stable coronary artery disease, *i.e.* chronic coronary syndrome.[54, 59] There is no evidence that the presence of coronary artery disease directly influences limb outcomes, but mortality remains higher in patients with concomitant symptomatic PAD and coronary artery disease.[12]

Optimal medical treatment is also vital for PAD patients after revascularization since they are at increased risk for repeated major adverse limb events in the early period after revascularization and at steadily increased risk for coronary events.[60]

Patients presenting with coronary artery disease

In patients with coronary artery disease, screening for PAD by ABI determination may be considered for risk stratification.[12] In patients with coronary artery disease and concomitant PAD, radial artery access is recommended as the first option for coronary angiography/intervention.[12]

In patients scheduled for coronary artery bypass grafting, screening for PAD should be considered with the intention of sparing the autologous great saphenous vein for potential future use in surgical peripheral revascularization.[12]

Screening for carotid disease by duplex ultrasound in patients scheduled for coronary artery bypass grafting is recommended in subjects with a recent (within 6 months) history of transient ischemic attack or stroke, and may be considered also in patients older than 70 years, those with multivessel coronary artery disease, concomitant PAD or a carotid bruit.[12]

Patients presenting with carotid artery disease

Due to the high prevalence of high-grade coronary artery stenosis among patients scheduled for elective carotid endarterectomy, preoperative coronary artery disease screening, including coronary angiography, may be considered.[12]

Risk factors management in PVD: present reality and how aggressive should it be?

Cardiovascular risk factors contribute to the development of multifocal atherosclerotic disease in different arterial territories, although to a different extent.[61] Several studies have shown that patients with PAD patients with PVD receive less aggressive therapy and risk factor modification than patients with CAD alone in spite of their worse prognosis.[62] Evidenced-based treatment was less frequently used in patients with combined acute coronary syndrome and PAD than in patients with CAD alone.[56]

Contemporary guidelines on prevention and management of atherosclerotic disease agree on the basic life-style recommendations and principles of pharmacological treatment.[12, 54, 63, 64]

Smoking cessation is recommended to all smokers and patients with atherosclerosis should avoid passive smoking.[12, 54, 63, 64]

Healthy diet and physical activity are recommended.

Patients with PAD and symptoms of intermittent claudication benefit from exercise therapy, usually performed as walking in intervals.[12] In patients with chronic limb threatening ischemia revascularization and healing of ulcers must be achieved before exercise therapy may be advised.[12]

Lipid-lowering with statins is recommended to all patients with atherosclerosis unless there is a clear contraindication. The ESC guidelines on prevention of cardiovascular disease in clinical practice, the ESVM guidelines on conservative treatment of PAD and the ESVS guidelines on management of atherosclerotic carotid and vertebral disease recommend reducing LDL-cholesterol to <1.8 mmol/L (70 mg/dL) or decreasing it by ≥50% if baseline values are 1.8-3.5 mmol/L (70-135 mg/dL).[54, 63, 64] The 2019 ESC guidelines for the management of dyslipidemia go even further with the goal of LDL reduction in patients with atherosclerotic disease by >50% and an LDL cholesterol level of <1.4 mmol/L (<55 mg/dL).[65] For patients with atherosclerotic vascular disease who experience a second vascular event within 2 years, not necessarily of the same type as the first event, while taking maximally tolerated statin-based therapy, an LDL cholesterol goal of <1.0 mmol/L (<40 mg/dL) may be considered.[65] If the LDL cholesterol goal is not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.[65] As the next step, in patients with atherosclerotic vascular disease who do not reach the LDL cholesterol goal with statin and ezetimibe, a PCSK9 inhibitor is recommended.[66] In the FOURIER trial, the anti-PCSK9 monoclonal antibody evolucumab reduced cardiovascular events in patients with atherosclerotic cardiovascular disease by about 15% after three years of treatment[66] and the benefit of patients with peripheral arterial disease was even greater: an about 20% reduction of composite events and a significant reduction in adverse limb events – acute limb ischemia, major amputation, or urgent peripheral revascularization.[67] Similarly, alirocumab resulted in greater absolute risk reduction in patients with PVD than in patients with isolated CAD.[68] Patients with cardiovascular disease and mild to moderate hypertriglyceridemia benefit from eicosapentaenoic acid, a long chain omega-3-polyunsaturated fatty acid, 2 g *b.i.d.* on top of statin treatment, by an about 25% reduction of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.[69]

In patients with atherosclerotic disease it is recommended to control blood pressure reduce to cardiovascular risk.[12, 54, 63, 64] The first objective is to lower office blood pressure to <140/90 mmHg in all patients, and if treatment is well tolerated, the goal should be set to 130/80 mmHg, but never lower than 120 mmHg of systolic pressure.[70] A target blood pressure of just below 130/80 mmHg seems safe in patients with coronary artery disease.[70] Angioplasty-converting enzyme inhibitors or angiotensin receptor blockers should be considered as first-line therapy in patients with PAD.[63, 70] In patients with tight carotid stenosis, especially bilateral, a cautious and pragmatic approach to treating arterial hypertension is recommended.[70]

In diabetic patients, strict glycemic control is recommended with a target glycated hemoglobin (HbA1c) <7% (<53 mmol/L) with the goal of decreasing microvascular and macrovascular complications, although the data on reducing macrovascular complications by glycemic control is less compelling.[71] Two classes of newer glucose-lowering drugs have shown promise in reducing major adverse cardiovascular events: glucagon-like peptide-1 (GLP1) receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors.[71] The GLP1 receptor agonists liraglutide, semaglutide and to a lesser extent exenatide reduce the risk of major adverse cardiovascular events, overall, by about 12%.[71] The SGLT2 inhibitors empagliflozin, canagliflozin, and to a lesser extent dapagliflozin reduce major adverse cardiovascular events by about 14%, mainly related to a strong reduction in heart failure-related events.[71] In retrospective subgroup analyses, empagliflozin reduced the incidence of amputations in patients with PAD, while canagliflozin increased the rate of minor amputations and is therefore not recommended in diabetic patients with PAD.[63]

Antiplatelet therapy is recommended to all patients with symptomatic atherosclerotic disease, as it has been shown to reduce the combined outcome of acute myocardial infarction, stroke or vascular death by about 20-25%.[72] Low-dose aspirin is the most often prescribed antiplatelet drug.[72] Clopidogrel was slightly more effective than aspirin in patients with atherosclerotic cardiovascular disease, mainly due to its effectiveness in patients with peripheral arterial disease.[4]

In a sub-analysis of the CHARISMA trial, the combination of aspirin and clopidogrel was more effective than aspirin alone in preventing stroke, myocardial infarction or cardiovascular death among patents with prior cardiovascular disease, but at the cost of increased major bleeding and fatal bleeding.[73] In the population of patients with prior myocardial infarction, prolonged administration of ticagrelor 60 mg *b.i.d.* or 90 mg *b.i.d.* plus aspirin was more effective than aspirin alone in preventing major car-

diovascular adverse events, but again at the cost of increased major bleeding.[74] Similarly, the combination of aspirin and ticagrelor has been more effective then aspirin alone in preventing recurrent ischemic stroke in conservatively treated patients but caused more bleeding.[75]

Due to the crosstalk between the pathways of platelet aggregation and fibrin formation, the concept of combined antiplatelet and anticoagulant treatment has been introduced for prevention of atherothrombotic events. In the APPRAISE-2 trial the addition of apixaban to antiplatelet treatment did not affect the primary outcome of cardiovascular death, but significantly increased major bleeding.[76] In this trial, apixaban was used in the same dose to treat patients with venous thrombosis (5 mg *b.i.d.*).[76] In the ATLAS-ACS 2-TIMI 51 trial, low doses of rivaroxaban (2.5 or 5 mg *b.i.d.*) were used. The 2.5 mg *b.i.d.* significantly reduced cardiovascular deaths compared with standard antiplatelet therapy alone, whereas the higher dose intriguingly did not have this effect.[77] In the COMPASS trial, patients with stable atherosclerotic vascular disease were randomized regarding antithrombotic treatment to receive rivaroxaban 2.5 mg *b.i.d.* plus aspirin 100 mg once daily, rivaroxaban alone 5 mg *b.i.d.*, or aspirin alone 100 mg once daily.[78] The superiority of rivaroxaban plus aspirin was demonstrated in comparison to aspirin after a median follow-up of only 23 months with a 24% reduction of cardiovascular death, stroke, or myocardial infarction.[78] More major bleeding events occurred in the rivaroxaban-plus-aspirin group, but there was no significant difference in intracranial or fatal bleeding.[78] Among the 27,395 enrolled patients in the COMPASS study, there were 7470 patients with PADs, *i.e.* 4129 patients with symptomatic lower extremity artery disease, 1422 patients with coronary disease and Ankle-Bronchial Index <0.90, and 1919 patients with >50% carotid artery stenosis or prior carotid revascularization.[79] In the PADs subgroup, rivaroxaban-plus-aspirin in comparison to aspirin alone reduced the HR for the primary outcome to 0.72 (CI: 0.57-0.90), P=0.005, reduced the HR for major adverse limb events to 0.54 (CI: 0.35-0.84), P=0.005, and reduced the HR for major amputation to 0.30 (CI: 0.11-0.80), P=0.01. Major bleeding was increased, but not fatal or intracranial bleeding, so there was a net clinical benefit with a combined HR of an adverse event in comparison to aspirin alone of 0.72 (CI: 0.59-0.87), P=0.0008.[79] According to the ESVM guidelines on management of PAD, aspirin in combination with low-dose rivaroxaban should be considered in PAD patients without a high risk of bleeding or other contraindications.[63] In patients with chronic coronary syndromes, adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered if there is no elevated bleeding risk, but there is a high risk of ischemic events: diffuse multivessel CAD with at least one of the following: diabetes mellitus requiring medication, recurrent myocardial infarction, PAD, or chronic kidney disease with estimated glomerular filtration rate 15- 59 mL/min/1.73 m^2.[59] Adding clopidogrel 75 mg/d, ticagrelor 60 mg *b.i.d.* or rivaroxaban 2.5 mg *b.i.d.* are the most widely used options in patients with chronic coronary syndromes.[59] In patients with diabetes mellitus and chronic symptomatic PAD without high bleeding risk, a combination of low-dose rivaroxaban and aspirin should be considered.[71]

Recently, the combination of low-dose rivaroxaban and aspirin has been shown superior to aspirin alone after infrainguinal percutaneous or surgical revascularization for disabling claudication.[80]

Proof of concept that anti-inflammatory drugs benefit patients with previous myocardial infarction, some of them with PVD, has been demonstrated for the first time with canakinumab, an interleukin-1β-inhibiting monoclonal antibody.[81] Canakinumab led to an about 15% lower rate nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death after 4 years of follow-up.[81] There were more cases of sepsis with canakinumab than with placebo, but cancer mortality was significantly lower with canakinumab.[81] Canakinumab is not registered for clinical use in atherosclerotic CVD. Among patients with a recent myocardial infarction, colchicine 0.5 mg daily on top of standard treatment led to an about 23% reduction of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization.[82] Colchicine is also not registered for clinical use in atherosclerotic CVD.

Evidence-based management of patients with PAD, many of whom had polyvascular atherosclerotic disease, brings good results even without the latest additions of PCSK9-inhibitors and dual low-dose antithrombotic treatment. Canadian authors compared propensity-matched patients with PAD undergoing systematic assessment of vascular risk with patients undergoing usual care.[83] Systematic attention to antiplatelet agents, statins, angiotensin-converting enzyme inhibitors, blood pressure control, lipid control, diabetic glycemic control, smoking cessation and target Body Mass Index resulted after 7-year follow-up in a significantly lower HR of 0.63 for the composite primary outcome of death, myocardial infarction or ischemic

stroke.[83] Also, the systematically treated patients were less likely to undergo major amputation of the lower limb, minor amputation, peripheral bypass surgery, or hospitalization due to heart failure.[83] Austrian authors have demonstrated the benefits of meticulous tertiary-centre care for patients with PAD, who had a more than 90% 5-year survival in comparison to 66% 5-year survival of the usual-care group with similar baseline characteristics.[84] Slovenian authors have studied the fate of patients with moderate PAD, 24% of whom had coronary disease and 16% had carotid disease or a history of stroke, receiving meticulous secondary prevention in primary care settings.[85] The overall mortality was 15% after 5 years, but cardiovascular events were no longer the leading cause of death.[85]

Priorities in revascularization of polyvascular atherosclerotic disease

Lower extremity artery revascularization in polyvascular patients

Patients with PVD, who have claudication symptoms, are usually managed conservatively due to their high periprocedural risk.[11] With chronic limb-threatening ischemia, revascularization becomes necessary, but is often problematic, since a severely threatened limb often coexists with high complexity of anatomical vascular lesions and high peri-procedural risk.[12, 86]

For aortoiliac lesions not extending to the common femoral artery, endovascular treatment may be best suited for patients with high surgical risk, whereas fitter patients with occlusion of the aortic bifurcation may be best served by open aorto-bi-iliac bypass.[12] When the common femoral artery is affected in addition to the aortoiliac segment, hybrid procedures – combining thromboendarterectomy of the common femoral artery and endovascular revascularization of the iliac arteries and possibly of the aortic bifurcation – are suitable for high-risk patients with chronic limb-threatening ischemia.[12, 87]

For infrainguinal limb-threatening ischemia, manifested by rest pain, ulceration or gangrene, the BASIL trial reported no differences in amputation-free survival and overall survival between endovascular-first or bypass-surgery-first revascularization strategies.[88] Extensive research of the literature performed by the writing group of the 2019 global vascular guidelines on the management of chronic limb-threatening ischemia reached similar conclusions.[86] Mortality, amputation, and amputation-free survival rates were similar at 1 year in patients with infrainguinal chronic limb-threatening ischemia regardless whether they were revascularized by endovascular procedures or by bypass surgery.[86] However, beyond 1 year there was improved patency for bypasses using autologous vein compared with endovascular interventions or prosthetic bypass grafts.[86] Evidence-based recommendations on revascularization thus favor vein bypass for average-risk patients with advanced threat to the limb and high complexity disease, while for patients with less complex lesion anatomy, intermediate severity of limb threat, or high operating risk, endovascular intervention is preferred.[86] To further clarify the dilemma between endovascular-first and bypass surgery-first revascularization strategies in the modern setting, the results of two ongoing randomized clinical trials, BASIL-2 and BESTCLI, are awaited.[89, 90]

When the common femoral artery is involved together with the femoropopliteal segment, hybrid treatment is an option for high-risk patients.[12, 86, 87]

In below-the-knee arterial disease with limb-threatening ischemia, drug-eluting balloons have not shown superiority over plain balloon angioplasty regarding all-cause mortality, major amputation, and repeated revascularization at 1 and 5 years,[91, 92] but there was also no signal of increased all-cause mortality with use of paclitaxel.[92]

Whenever possible, multidisciplinary vascular teams should make decisions on revascularization strategies in patients with peripheral arterial disease.[12] All patients with chronic limb threatening ischemia should receive best medical therapy including antithrombotic, lipid-lowering, antihypertensive, and in case of diabetes glycemic control medication, as well as counseling on smoking cessation, diet, exercise, and preventive foot care.[12, 86] Following revascularization, long-term limb surveillance is advised.[12, 86]

Coronary revascularization in patients with PAD

In patients with symptomatic PAD and symptomatic CAD, coronary revascularization takes priority, except in limb threatening ischemia.[12]

In a study that validated anatomical and clinical characteristics of patients with CAD in order to guide the decision between coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI), the presence of PAD worsened the outcomes of CABG and PCI to an equal degree.[93] Among propensity-matched patients with multi-vessel coronary artery disease, mortality was lower with CABG than with PCI, and this effect was intensified by the presence of PAD.[94] According to the 2017 ESC guidelines on peripheral arterial disease, it remains

controversial, whether PCI or CABG should be favored to treat coronary artery disease in patients with PAD.[12]

In patients with PAD and symptomatic coronary artery disease, radial artery access is preferred for percutaneous coronary intervention.[12] If femoral access is needed, preinterventional assessment of the iliac and common femoral arteries is recommended to minimize the risk of ischemia due to embolization.[12] The presence of PAD is a risk factor for femoral vascular access complications of coronary procedures, regardless whether arterial closure devices or manual compression are used.[95]

In patients with advanced PAD, who are scheduled for coronary artery bypass grafting, the great saphenous vein should be spared whenever possible for later peripheral vascular revascularization.[12, 96]Also, wound healing may be delayed after saphenous vein harvesting in patients with advanced PAD.[12]

Carotid revascularization in patients with coronary artery disease

In patients with carotid disease and symptomatic coronary artery disease, revascularization priority should be assigned according to the patient's clinical status and to the severity of carotid and coronary disease.[12] Carotid revascularization should be performed first only in patients with a recent history of stroke or transient ischemic attack, while asymptomatic carotid stenosis should be treated following coronary revascularization.[12]

In patients with carotid disease, who are scheduled for CABG, the indication, method and timing of carotid revascularization should be individualized after discussion with a multidisciplinary team, including a neurologist.[12] In patients with a symptomatic carotid stenosis, *i.e.* transient ischemic attack or stroke within the last 6 months, carotid revascularization should be considered in patients with 50-99% carotid stenosis, with carotid thromboendarterectomy as the first choice.[12] Prophylactic carotid revascularization is not recommended in asymptomatic unilateral carotid stenosis but may be considered in bilateral 70-99% stenosis or unilateral 70-99% stenosis with contra lateral occlusion.[12] In asymptomatic unilateral 70-99% stenosis, revascularization may be considered in the presence of one or more characteristics that increase the risk of ipsilateral stroke: ipsilateral silent infarctions, stenosis progression, spontaneous embolization on transcranial Doppler, impaired cerebral vascular reserve, large plaques, echo-lucent plaques on ultrasound, increased juxta-luminal echolucent area on ultrasound, intra-plaque hemorrhage or lipid rich necrotic core on magnetic resonance imaging.[12]

The issue, whether CABG and carotid thromboendarterectomy should be performed synchronously or by staged approach has not been completely resolved, since a meta-analysis of observational studies suggested comparable outcomes of the synchronous and staged approach.[97] A randomized study comparing simultaneous carotid thromboendarterectomy – of high grade (≥80%) asymptomatic carotid stenosis – and CABG with isolated CABG found no significant differences between the two approaches.[98] However, there were only 129 patients randomized, and the rate of stroke and death was twice as high with the simultaneous approach as with isolated CABG (12/65 *vs.* 6/62 patients, P=0.12), casting doubt on the merit of revascularizing asymptomatic carotid stenosis in the context of CABG.[98]

Conclusions

In conclusion, atherosclerosis is a systemic disease affecting multiple vascular beds. There is a close relationship between CAD, PAD and CVD. The presence of more than one concurrently affected vascular bed has a huge negative impact on cardiovascular morbidity and mortality. Particularly PAD is an indicator of an advanced atherosclerotic process and is frequently associated with preclinical or clinical atherosclerosis in other territories. Consequently, patients with PAD most frequently die because of accompanied CAD. Cardiovascular risk factors contribute to the development of multifocal atherosclerotic disease in different arterial territories. All too often, patients with PAD and PVD receive less aggressive secondary prevention therapy and risk factor modification than patients with CAD alone, although the benefits of guideline-based treatment have been proven. However, there is currently no proof that identification of asymptomatic atherosclerosis and multi-site atherosclerotic disease improves clinical outcomes in patients who are already in prevention programs. Revascularization should be performed only in symptomatic vascular beds, using the least aggressive methods according to consensual decisions of multidisciplinary vascular teams.

References

1. Steg PG, Bhatt DL, Wilson PW, D'Agostino R Sr, Ohman EM, Röther J, *et al.*; REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA 2007;297:1197–206.

2. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, *et al.*; American Association for Vascular Surgery; Society for Vascular Surgery; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society of Interventional Radiol-

ogy; ACC/AHA Task Force on Practice Guidelines Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease; American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; Vascular Disease Foundation. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006;113:e463–654.

3. De Carlo M. Multsite artery disease. In: Camm AJ, Lüscher TF, Maurer G, Serruys PW, editors. ESC CardioMed. Third edition. Oxford: Oxford University Press; 2018.

4. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329–39.

5. Hirsh J, Bhatt DL. Comparative benefits of clopidogrel and aspirin in high-risk patient populations: lessons from the CAPRIE and CURE studies. Arch Intern Med 2004;164:2106–10.

6. Bhatt DL, Roe MT, Peterson ED, Li Y, Chen AY, Harrington RA, *et al.*; CRUSADE Investigators. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. JAMA 2004;292:2096–104.

7. Alberts MJ, Bhatt DL, Mas JL, Ohman EM, Hirsch AT, Röther J, *et al.*; REduction of Atherothrombosis for Continued Health Registry Investigators. Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry. Eur Heart J 2009;30:2318–26.

8. Subherwal S, Bhatt DL, Li S, Wang TY, Thomas L, Alexander KP, *et al.* Polyvascular disease and long-term cardiovascular outcomes in older patients with non-ST-segment-elevation myocardial infarction. Circ Cardiovasc Qual Outcomes 2012;5:541–9.

9. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, *et al.*; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006;295:180–9.

10. Vidakovic R, Schouten O, Kuiper R, Hoeks SE, Flu WJ, van Kuijk JP, *et al.* The prevalence of polyvascular disease in patients referred for peripheral arterial disease. Eur J Vasc Endovasc Surg 2009;38:435–40.

11. Imori Y, Akasaka T, Ochiai T, Oyama K, Tobita K, Shishido K, *et al.* Co-existence of carotid artery disease, renal artery stenosis, and lower extremity peripheral arterial disease in patients with coronary artery disease. Am J Cardiol 2014;113:30–5.

12. Aboyans V, Ricco JB, Bartelink ME, Björck M, Brodmann M, Cohnert T, *et al.*; ESC Scientific Document Group. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)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). Eur Heart J 2018;39:763–816.

13. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, *et al.* Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet 2013;382:1329–40.

14. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45(Suppl S):S5–67.

15. Poredos P, Jug B. The prevalence of peripheral arterial disease in high risk subjects and coronary or cerebrovascular patients. Angiology 2007;58:309–15.

16. Dieter RS, Tomasson J, Gudjonsson T, Brown RL, Vitcenda M, Einerson J, *et al.* Lower extremity peripheral arterial disease in hospitalized patients with coronary artery disease. Vasc Med 2003;8:233–6.

17. Taimur SD, Chowdhury MZ, Hakim E. Correlation between peripheral arterial disease and coronary artery disease in Bangladeshi population: a five years retrospective study. University Heart Journal 2015;11:79–83.

18. Creager MA. Results of the CAPRIE trial: efficacy and safety of clopidogrel. Clopidogrel versus aspirin in patients at risk of ischaemic events. Vasc Med 1998;3:257–60.

19. McAllister FF. The fate of patients with intermittent claudication managed nonoperatively. Am J Surg 1976;132:593–5.

20. Veeranna V, Froehlich J, Eagle KA. Treatment approach to pateinets with combined peripheral and coronary disease. Vasc Dis Manag 2010;7:e135–41.

21. Aboyans V, Lacroix P, Postil A, Guilloux J, Rollé F, Cornu E, *et al.* Subclinical peripheral arterial disease and incompressible ankle arteries are both long-term prognostic factors in patients undergoing coronary artery bypass grafting. J Am Coll Cardiol 2005;46:815–20.

22. Pang XH, Han J, Ye WL, Sun X, Ding Y, Huang WJ, *et al.* Lower Extremity Peripheral Arterial Disease Is an Independent Predictor of Coronary Heart Disease and Stroke Risks in Patients with Type 2 Diabetes Mellitus in China. Int J Endocrinol 2017;2017:9620513.

23. Kennedy M, Solomon C, Manolio TA, Criqui MH, Newman AB, Polak JF, *et al.* Risk factors for declining ankle-brachial index in men and women 65 years or older: the Cardiovascular Health Study. Arch Intern Med 2005;165:1896–902.

24. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, *et al.*; American Heart Association Council on Peripheral Vascular Disease; Council on Epidemiology and Prevention; Council on Clinical Cardiology; Council on Cardiovascular Nursing; Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation 2012;126:2890–909.

25. Li Q, Zeng H, Liu F, Shen J, Li L, Zhao J, *et al.* High ankle-brachial index indicates cardiovascular and peripheral arterial disease in patients with type 2 diabetes. Angiology 2015;66:918–24.

26. Grenon SM, Vittinghoff E, Owens CD, Conte MS, Whooley M, Cohen BE. Peripheral artery disease and risk of cardiovascular events in patients with coronary artery disease: insights from the Heart and Soul Study. Vasc Med 2013;18:176–84.

27. Zheng ZJ, Sharrett AR, Chambless LE, Rosamond WD, Nieto FJ, Sheps DS, *et al.* Associations of ankle-brachial index with clinical coronary heart disease, stroke and preclinical carotid and popliteal atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study. Atherosclerosis 1997;131:115–25.

28. Poredoš P, Golob M, Jensterle M. Interrelationship between peripheral arterial occlusive disease, carotid atherosclerosis and flow mediated dilation of the brachial artery. Int Angiol 2003;22:83–7.

29. Sprengers RW, Janssen KJ, Moll FL, Verhaar MC, van der Graaf Y; SMART Study Group. Prediction rule for cardiovascular events and mortality in peripheral arterial disease patients: data from the prospective Second Manifestations of ARTerial disease (SMART) cohort study. J Vasc Surg 2009;50:1369–76.

30. Hooi JD, Stoffers HE, Kester AD, Rinkens PE, Kaiser V, van Ree JW, *et al.* Risk factors and cardiovascular diseases associated with asymptomatic peripheral arterial occlusive disease. The Limburg PAOD Study. Peripheral Arterial Occlusive Disease. Scand J Prim Health Care 1998;16:177–82.

31. Bots ML, Hofman A, Grobbee DE. Common carotid intima-media

thickness and lower extremity arterial atherosclerosis. The Rotterdam Study. Arterioscler Thromb 1994;14:1885–91.

32. Li MF, Zhao CC, Li TT, Tu YF, Lu JX, Zhang R, *et al.* The coexistence of carotid and lower extremity atherosclerosis further increases cardio-cerebrovascular risk in type 2 diabetes. Cardiovasc Diabetol 2016;15:43.

33. Novo S, Corrado E. Asymptomatic carotid lesion as a marker of future cerebrovascular and cardiovascular events. Acta Chir Belg 2003;103:262–9.

34. Ciccone M, Di Noia D, Di Michele L, Corriero F, Di Biase M, Biasco MG, *et al.* The incidence of asymptomatic extracoronary atherosclerosis in patients with coronary atherosclerosis. Int Angiol 1993;12:25–8.

35. Novo S, Carità P, Corrado E, Muratori I, Pernice C, Tantillo R, *et al.* Preclinical carotid atherosclerosis enhances the global cardiovascular risk and increases the rate of cerebro- and cardiovascular events in a five-year follow-up. Atherosclerosis 2010;211:287–90.

36. Novo S, Visconti CL, Amoroso GR, Corrado E, Fazio G, Muratori I, *et al.* Asymptomatic carotid lesions add to cardiovascular risk prediction. Eur J Cardiovasc Prev Rehabil 2010;17:514–8.

37. Novo S, Carità P, Lo Voi A, Muratori I, Tantillo R, Corrado E, *et al.* Impact of preclinical carotid atherosclerosis on global cardiovascular risk stratification and events in a 10-year follow-up: comparison between the algorithms of the Framingham Heart Study, the European SCORE and the Italian 'Progetto Cuore'. J Cardiovasc Med (Hagerstown) 2019;20:91–6.

38. Novo S, Peritore A, Trovato RL, Guarneri FP, Di Lisi D, Muratori I, *et al.* Preclinical atherosclerosis and metabolic syndrome increase cardio- and cerebrovascular events rate: a 20-year follow up. Cardiovasc Diabetol 2013;12:155.

39. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, *et al.*; International Diabetes Federation Task Force on Epidemiology and Prevention; Hational Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–5.

40. Levantino P, Polizzi G, Evola S, Leone G, Evola G, Novo G, *et al.* Close association between carotid and coronary atherosclerosis analyzed through SYNTAX score. Vasc Investig Ther 2019;2:1–7.

41. Corrado E, Rizzo M, Tantillo R, Muratori I, Bonura F, Vitale G, *et al.* Markers of inflammation and infection influence the outcome of patients with baseline asymptomatic carotid lesions: a 5-year follow-up study. Stroke 2006;37:482–6.

42. Romano G, Corrado E, Muratori I, Novo G, Andolina G, Cospite V, *et al.* Carotid and peripheral atherosclerosis in patients who underwent primary percutaneous coronary intervention and outcome associated with multifocal atherosclerosis. Int Angiol 2006;25:389–94.

43. Pipitone S, Corrado E, Muratori I, Novo G, Evola S, Fabbiano A, *et al.* Extracoronary atherosclerosis in patients with chronic ischemic heart disease: relationship with risk factors and the severity of coronary artery disease. Int Angiol 2007;26:346–52.

44. Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. BMJ 1996;313:1440–4.

45. Ostergren J, Sleight P, Dagenais G, Danisa K, Bosch J, Qilong Y, *et al.*; HOPE study investigators. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. Eur Heart J 2004;25:17–24.

46. Diehm C, Allenberg JR, Pittrow D, Mahn M, Tepohl G, Haberl RL, *et al.*; German Epidemiological Trial on Ankle Brachial Index Study Group. Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. Circulation 2009;120:2053–61.

47. Meizels A, Zeitoun DM, Bataille V, Cambou JP, Collet JP, Cottin Y, *et al.*; ALLIANCE investigators on behalf of the working group on Epidemiology of the French Society of Cardiology. Impact of polyvascular disease on baseline characteristics, management and mortality in acute myocardial infarction. The Alliance project. Arch Cardiovasc Dis 2010;103:207–14.

48. Al Thani H, El-Menyar A, Alhabib KF, Al-Motarreb A, Hersi A, Al-faleh H, *et al.* Polyvascular disease in patients presenting with acute coronary syndrome: its predictors and outcomes. ScientificWorldJournal 2012;2012:284851.

49. Gutierrez JA, Mulder H, Jones WS, Rockhold FW, Baumgartner I, Berger JS, *et al.* Polyvascular Disease and Risk of Major Adverse Cardiovascular Events in Peripheral Artery Disease: A Secondary Analysis of the EUCLID Trial. JAMA Netw Open 2018;1:e185239.

50. Bhatt DL, Peterson ED, Harrington RA, Ou FS, Cannon CP, Gibson CM, *et al.*; CRUSADE Investigators. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. Eur Heart J 2009;30:1195–202.

51. Zhang Q, Wang A, Zhang S, Li N, Chen S, Zhang Y, *et al.* Asymptomatic polyvascular disease and the risks of cardiovascular events and all-cause death. Atherosclerosis 2017;262:1–7.

52. Perrone-Filardi P, Achenbach S, Möhlenkamp S, Reiner Z, Sambuceti G, Schuijf JD, *et al.* Cardiac computed tomography and myocardial perfusion scintigraphy for risk stratification in asymptomatic individuals without known cardiovascular disease: a position statement of the Working Group on Nuclear Cardiology and Cardiac CT of the European Society of Cardiology. Eur Heart J 2011;32:1986–93, 1993a, 1993b.

53. Vlachopoulos C, Terentes-Printzios D, Stefanadis C. How to identify subjects with poly-vascular disease? Curr Vasc Pharmacol 2012;10:728–30.

54. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, *et al.*; ESC Scientific Document Group. 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). Eur Heart J 2016;37:2315–81.

55. Collet JP, Cayla G, Ennezat PV, Leclercq F, Cuisset T, Elhadad S, *et al.*; AMERICA Investigators. Systematic detection of polyvascular disease combined with aggressive secondary prevention in patients presenting with severe coronary artery disease: the randomized AMERICA Study. Int J Cardiol 2018;254:36–42.

56. Roffi M, Radovanovic D, Iglesias JF, Eberli FR, Urban P, Pedrazzini GB, *et al.* Multisite vascular disease in acute coronary syndromes: increased in-hospital mortality and no improvement over time. Eur Heart J Acute Cardiovasc Care 2018;2048872618814708.

57. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, De Hert S, *et al.*; Authors/Task Force Members. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur J Anaesthesiol 2014;31:517–73.

58. McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, *et al.* Coronary-artery revascularization before elective major vascular surgery. N Engl J Med 2004;351:2795–804.

59. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, *et al.*; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407–77.

60. Hess CN, Wang TY, Weleski Fu J, Gundrum J, Allen LaPointe NM, Rogers RK, *et al.* Long-term outcomes and associations with major adverse limb events after peripheral artery revascularization. J Am Coll Cardiol 2020;75:498–508.

61. Paraskevas KI, Bessias N, Papas TT, Gekas CD, Andrikopoulos V, Mikhailidis DP. Do different vascular risk factors affect all arteries equally? Angiology 2008;59:397–401.

62. Ferreira-González I, Permanyer Miralda G, Heras M, Ribera A, Marsal JR, Cascant P, *et al.*; Investigadores del Estudio MASCARA. Prognosis and management of patients with acute coronary syndrome and polyvascular disease. Rev Esp Cardiol 2009;62:1012–21.

63. Frank U, Nikol S, Belch J. Conservative treatment for PAD – rsik factor management. Vasa 2019;48.

64. Naylor AR, Ricco JB, de Borst GJ, Debus S, de Haro J, Halliday A, *et al.*; Esvs Guidelines Committee; Esvs Guideline Reviewers. Editor's Choice - Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2018;55:3–81.

65. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, *et al.*; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41:111–88.

66. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, *et al.*; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–22.

67. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, *et al.* Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). Circulation 2018;137:338–50.

68. Jukema JW, Szarek M, Zijlstra LE, de Silva HA, Bhatt DL, Bittner VA, *et al.*; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab in Patients With Polyvascular Disease and Recent Acute Coronary Syndrome: ODYSSEY OUTCOMES Trial. J Am Coll Cardiol 2019;74:1167–76.

69. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, *et al.*; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11–22.

70. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, *et al.*; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021–104.

71. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, *et al.*; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2020;41:255–323.

72. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71–86.

73. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, *et al.*; CHARISMA Investigators. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol 2007;49:1982–8.

74. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, *et al.*; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372:1791–800.

75. Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S, *et al.*; THALES Investigators. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. N Engl J Med 2020;383:207–17.

76. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, *et al.*; APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med 2011;365:699–708.

77. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, *et al.*; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012;366:9–19.

78. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, *et al.*; COMPASS Investigators. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 2017;377:1319–30.

79. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, *et al.*; COMPASS Investigators. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet 2018;391:219–29.

80. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, *et al.* Rivaroxaban in peripheral artery disease after revascularization. N Engl J Med 2020;382:1994–2004.

81. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, *et al.*; CANTOS Trial Group. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med 2017;377:1119–31.

82. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, *et al.* Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med 2019;381:2497–505.

83. Hussain MA, Al-Omran M, Mamdani M, Eisenberg N, Premji A, Saldanha L, *et al.* Efficacy of a Guideline-Recommended Risk-Reduction Program to Improve Cardiovascular and Limb Outcomes in Patients With Peripheral Arterial Disease. JAMA Surg 2016;151:742–50.

84. Höbaus C, Herz CT, Obendorf F, Howanietz MT, Wrba T, Koppensteiner R, *et al.* Center-based patient care enhances survival of elderly patients suffering from peripheral arterial disease. Ann Med 2017;49:291–8.

85. Blinc A, Kozak M, Šabovič M, Božič Mijovski M, Stegnar M, Poredoš P, *et al.* Survival and event-free survival of patients with peripheral arterial disease undergoing prevention of cardiovascular disease. Int Angiol 2017;36:216–27. https://10.23736/S0392-9590.16.03731-7

86. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, *et al.*; GVG Writing Group. Global vascular guidelines on the management of chronic limb-threatening ischemia. J Vasc Surg 2019;69(6S):3S–125S, e40.

87. Murakami A. Hybrid Operations in Patients with Peripheral Arterial Disease. Ann Vasc Dis 2018;11:57–65.

88. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, *et al.*; BASIL trial Participants. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: an intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. J Vasc Surg 2010;51(Suppl):5S–17S.

89. Popplewell MA, Davies H, Jarrett H, Bate G, Grant M, Patel S, *et al.*; BASIL-2 Trial Investigators. Bypass versus angio plasty in severe ischaemia of the leg - 2 (BASIL-2) trial: study protocol for a randomised controlled trial. Trials 2016;17:11.

90. Menard MT, Farber A. The BEST-CLI trial: a multidisciplinary effort to assess whether surgical or endovascular therapy is better for patients with critical limb ischemia. Semin Vasc Surg 2014;27:82–4.

91. Zeller T, Baumgartner I, Scheinert D, Brodmann M, Bosiers M, Micari A, *et al.*; IN.PACT DEEP Trial Investigators. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. J Am Coll Cardiol 2014;64:1568–76.

92. Zeller T, Micari A, Scheinert D, Baumgartner I, Bosiers M, Vermassen FE, *et al.*; IN.PACT DEEP Trial Investigators. The IN.PACT DEEP Clinical Drug-Coated Balloon Trial: 5-Year Outcomes. JACC Cardiovasc Interv 2020;13:431–43.

93. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, *et al.* Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;381:639–50.

94. Hlatky MA, Boothroyd DB, Baker L, Kazi DS, Solomon MD, Chang TI, *et al.* Comparative effectiveness of multivessel coronary bypass surgery and multivessel percutaneous coronary intervention: a cohort study. Ann Intern Med 2013;158:727–34.

95. Dencker D, Pedersen F, Engstrøm T, Køber L, Højberg S, Nielsen MB, *et al.* Major femoral vascular access complications after coronary diagnostic and interventional procedures: A Danish register study. Int J Cardiol 2016;202:604–8.

96. Neufang A, Dorweiler B, Espinola-Klein C, Savvidis S, Doemland M, Schotten S, *et al.* Outcomes of complex femorodistal sequential autologous vein and biologic prosthesis composite bypass grafts. J Vasc Surg 2014;60:1543–53.

97. Sharma V, Deo SV, Park SJ, Joyce LD. Meta-analysis of staged versus combined carotid endarterectomy and coronary artery bypass grafting. Ann Thorac Surg 2014;97:102–9.

98. Weimar C, Bilbilis K, Rekowski J, Holst T, Beyersdorf F, Breuer M, *et al.*; CABACS Trial Investigators. Safety of Simultaneous Coronary Artery Bypass Grafting and Carotid Endarterectomy Versus Isolated Coronary Artery Bypass Grafting: A Randomized Clinical Trial. Stroke 2017;48:2769–75.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—All authors read and approved the final version of the manuscript.

History.—Article first published online: September 7, 2020. - Manuscript accepted: August 12, 2020. - Manuscript received: July 24, 2020.