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Panvascular disease – Diagnosis and management

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SOUHRN

Panvaskulární postižení (panvascular disease, PVD) významně zvyšuje riziko kardiovaskulárních příhod (infarkt myokardu, cévní mozková příhoda a úmrtí z kardiovaskulárních příčin); čím více míst je postiženo, tím vyšší je riziko závažné kardiovaskulární příhody. Přes vysokou incidenci PVD a vysoce nepříznivou prognózu pacientů z hlediska kardiovaskulárního systému je poznatků o tomto postižení stále ještě nedostatek. Při počátečním screeningu a stanovování diagnózy je naprosto nezbytné odebrat anamnézu rizikových faktorů a přidružených onemocnění a současně provést důkladné fyzikální vyšetření. Diagnóza aterosklerózy postihující různá cévní řečiště se stanovuje na základě hodnot indexu kotník-paže a výsledků různých neinvazivních zobrazovacích metod, jako jsou duplexní ultrazvuk, výpočetní tomografie nebo MR angiografie, zatímco digitální subtrakční angiografie se v současnosti používá téměř výhradně v souvislosti s endovaskulárními výkony. Vhodnost použití každé z uvedených metod uvádějí mezinárodní doporučené postupy a každý konkrétní případ projednává multidisciplinární tým.

Léčba pacientů s PVD může být velmi náročná. Ke snížení nadměrného kardiovaskulárního rizika je nutno přijmout opatření sekundární prevence a vést agresivní farmakoterapii. Dosud není známo, zda rutinní screening na případnou přítomnost aterosklerózy na různých místech tepenného stromu u všech nebo pouze u vybraných pacientů může změnit způsob léčby natolik, aby se zlepšil výsledný stav těchto pacientů. V nepřítomnosti „tvrdých" důkazů je nutno rozhodovat o každém případu individuálně formou spolupráce řady odborností v rámci multidisciplinárního přístupu. Obecně lze konstatovat, že nejdříve je nutno věnovat pozornost lézím s více symptomy nebo lézím s nejzávažnějším dopadem na prognózu. Ve vybraných případech lze provádět kombinované výkony. Vzhledem k tomu, že u pacientů s PVD často dochází k perioperačním kardiovaskulárním komplikacím, je vhodný předoperační cílený screening.

Cílem dalších klinických studií bude stanovit účinnější postupy v diagnostice a léčbě uvedených pacientů. Dosud jediná studie neprokázala nutnost screeningu na přítomnost PVD u pacientů se závažnou ischemickou chorobou srdeční. V současnosti je k optimalizaci krátkodobé a dlouhodobé prognózy často nutno spoléhat na rozhodnutí multidisciplinárního týmu.

ABSTRACT

Panvascular disease (PVD) increases significantly the risk for cardiovascular events (myocardial infarction, stroke and cardiovascular death); the more sites affected, the greater the risk of a major cardiac event. Despite its high incidence and severe cardiovascular prognosis, PVD has still not been well studied. History of risk factors and co-morbidities, as well as a detailed physical examination, are mandatory in the initial screening and diagnostic work-up. The ankle-brachial index and various non-invasive imaging methods such as duplex ultrasound, computed tomography or magnetic resonance angiography are used for the diagnosis of atherosclerosis in various vascular beds, while digital subtraction angiography is currently used almost

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exclusively in association with endovascular procedures. Appropriate utilization of techniques is based on international guidelines and a multidisciplinary discussion for each case.

Management of a patient diagnosed with PVD can be very complex. Secondary preventive measures and aggressive medical treatment are needed to reduce excess cardiovascular risk. Whether routine screening for atherosclerosis at various sites in the arterial tree in all or selected patients may alter treatment to improve outcome in these patients has not been shown.

In the lack of hard evidence, individualized decision-making is needed with the collaboration of many specialties in a multidisciplinary approach. In general, the more symptomatic lesion or the lesion with the strongest prognostic impact should be treated first. In selected cases combined interventions can be done. Perioperative cardiovascular complications are common in patients with PVD, thus preoperative targeted screening may be needed.

Clinical studies are needed to identify more effective approaches to diagnose and treat these patients. A single trial performed so far failed to demonstrate a panvascular screening in patients with severe coronary artery disease. Meanwhile, a multidisciplinary team is often needed to optimize short- and long-term prognosis.

Keywords:
Ankle-brachial index
Carotid artery disease
Computed tomography angiography
Diagnosis
Magnetic resonance angiography
Panvascular disease
Peripheral artery disease
Treatment

Diagnosis

Panvascular disease (PVD) or multisite artery disease is defined as the simultaneous presence of clinically relevant atherosclerotic lesions in at least two major vascular territories [1]. The diagnosis of PVD, especially in patients with proven atherosclerosis at one site, is primarily based on a thorough medical history and a detailed clinical examination including blood pressure measurement in the arms and legs to derive ankle-brachial index (ABI) [1,2]. In case of clinical suspicion, focused non-invasive imaging using ultrasound as a first-line method and then computed tomography or magnetic resonance angiography as second-line methods may follow (Table 1) [3].

Medical history should include all known cardiovascular (CV) risk factors and co-morbidities. All types of symptoms suggestive of vascular disease should be systematically sought [1,2]. These may be:

- chest pain or other symptoms (e.g. shortness of breath) suggesting angina (on exertion or at rest);
- any walking impairment, e.g. fatigue, aching, cramping, or pain localized anywhere in the lower limb from the buttock to the thigh, calf, or foot, particularly when symptoms are quickly relieved at rest;
- any pain at rest localized to the lower leg or foot and its association with the upright or recumbent position;
- any poorly healing wounds of the extremities;
- exertional pain in the upper extremity, particularly if associated with dizziness or vertigo;
- any transient or permanent neurological symptoms;
- post-prandial abdominal pain and diarrhoea, particularly if related to eating and associated with weight loss;
- erectile dysfunction;
- renal impairment or hypertension.

In the general population, only 10% of patients with lower extremity arterial disease (LEAD) have the classic symptom of intermittent claudication [4]. About 50% have various leg symptoms different from classic claudication, whereas the remaining 40% do not complain of any leg pain.

A thorough CV examination should involve auscultation and palpation of all relevant arteries, inspection of the feet, and record of the colour, temperature, quality and integrity of the skin and hairs, as well as the presence of ulcerations or any poorly healing wounds of the extremities [2]. Measurement of blood pressure in both arms is essential; an inter-arm difference >10 mmHg is indicative of significant vascular disease and should prompt further investigation [5].

The ABI is both a diagnostic tool for LEAD [1] and a prognostic tool of future CV events [6]. ABI is calculated as the ratio of the ankle to brachial systolic blood pressure; blood pressure in the lower limbs is normally higher than in the upper limbs and normal ABI values range from 1.10 to 1.40 [7]. ABI values <0.90 indicate the presence of flow-limiting arterial stenoses along the course of the arterial beds studied with a high specificity and a positive predictive value. Supranormal ABI values (i.e. >1.40) are found in patients with generalized blood vessel stiffening and advanced medial calcification, which is most commonly seen in patients with diabetes mellitus and chronic kidney disease. ABI can be measured easily, rapidly, non-invasively, safely and at very low cost. While it may identify a large number of patients with previously unrecognized LEAD, abnormal ABI values are consistent with a rather advanced stage of the atherosclerotic disease. Low ABI values <0.90 are also predictive of atherosclerosis at other sites, such as CAD and carotid artery disease. The ABI has also been shown in many large epidemiological studies to have a strong prognostic role. A U-shaped association between ABI and CV events has been demonstrated with a significantly increased risk for all-cause mortality and CV events in both low (<0.90) and high (>1.40) ABI groups [6].

Advances in imaging technology have improved the ability to diagnose and quantify atherosclerosis in multiple different vascular beds. Many different imaging techniques are being used today for the identification of PVD and each one has advantages and limitations [3]. Current guidelines offer guidance on the appropriate implementation of each technique while a multidisciplinary approach will probably be needed for each patient [1].

Ultrasonography is a non-invasive, widely available examination that can be safely used for screening and diagnosis of vascular lesions in practically all extra-cardiac vascular sites: abdominal aorta, renal arteries, carotid, upper and lower limb arteries. All modes of echocardiography (B-mode, pulsed-wave Doppler, color Doppler and power Doppler) should be used to detect and localize

vascular lesions and quantify their extent and severity. In most of the cases, Duplex ultrasound is used as the first-line diagnostic method due to its availability, great safety, high diagnostic capacity and low cost [3].

Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are used as second-line diagnostic methods in extra-cardiac vascular disease. CTA offers many advantages such as wide availability, high sensitivity and specificity although stenoses may be over- or under-estimated with CT [3]. The use of multidetector CT has offered advantages such as shortened examination time, reduced motion and respiration artefacts and simultaneous imaging of vessels and organs. Cost, use of radiation, need for contrast agents with potential nephrotoxicity and risk for allergy are the main limitations of CT. Indeed, CTA should be performed with caution and previous preparation with hydration in patients with estimated glomerular filtration rate <60 ml/min, a common phenomenon in elderly individuals with PVD. No studies have so far shown a benefit from screening with CTA for PVD.

MRA offers high-resolution scanning with a high signal-noise ratio, fast acquisition and no radiation exposure [1,3]. Absolute contraindications to MRA remain today cardiac pacemakers, implantable cardioverter defibrillators, neurostimulators, cochlear implants, first-trimester pregnancy, and severe renal failure. MRA should not be performed in patients with estimated glomerular filtration rate <30 ml/min/1,73 m^2 because of the risk for nephrogenic sclerosis. Claustrophobia, metallic foreign objects, and second- or third-trimester pregnancy are regarded as relative contraindications, while new MRI-compatible pacemakers have been developed. For vascular imaging, time-of-flight angiography and phase-contrast angiography, without intravenous contrast, can be used. Development of novel MRA imaging techniques such as the 'Angiosurf' and 'Bodysurf' techniques allows a whole-body approach with depiction of the head, thoracic, and all peripheral arteries from the carotids to the ankles that may prove ideal for detection of PVD. Prospective studies are needed to prove its value in management and prognosis of PVD.

Finally, digital subtraction angiography used to be the gold standard of vascular imaging, but nowadays it is used almost exclusively today during endovascular procedures as part of the treatment [1]. The invasive nature of this investigation and its potential associated complications along with the great advances in non-invasive imaging led to the replacement of this method by other, safer, non-invasive diagnostic modalities.

Management

Despite the relatively high incidence and excess CV risk of PVD, PVD patients have not still attracted great attention.

Table 1 – Non-invasive methods to detect atherosclerosis.

Imaging technology	Component detected	Relation to disease	Advantages	Limitations
Ankle-brachial index	Difference in upper and lower limb blood pressures because of significant atherosclerotic plaque	Presence of significant atherosclerotic stenosis Predictor of cardiovascular events	Easy Rapid Reproducible Relatively cheap	Cannot identify location of stenosis
Ultrasound	Intima media thickness Plaque extension Plaque composition: – Echolucency – Plaque-vascularization	Non-coronary arteries Pre-clinical atherosclerosis Plaque burden Plaque vulnerability	No radiation Bedside Cheap	Poor acoustic window (calcified lesions) Operator-dependent
Electron beam computed tomography	Coronary artery calcification	Coronary plaque burden Predictors of coronary events	Easy Rapid Automated Reproducible Relatively cheap	Low-dose radiation
Multidetector computed tomography	Coronary artery anatomy Plaque composition	High negative predictive value (high-risk plaque)	Relatively easy Rapid Reproducible	High-dose radiation Renal failure (contrast medium) High costs
Magnetic resonance	Plaque burden Remodeling Plaque composition (coronary anatomy)	Atherosclerosis extension Plaque burden High-risk plaque	No radiation Reproducible	Cumbersome High costs Renal failure (contrast medium)
Positron emission tomography	Macrophages Uptake proportional to the number of macrophage in inflammatory plaques	Association between embolic events distal to FDG PET-positive carotid stenoses	Highly reproducible	Nonspecific uptake by cells other than inflammatory cells Very high radiation

Modified from reference [3].

Almost no randomized clinical trials have been performed to compare diagnostic or treatment strategies in PVD patients [1,8]. Management of these patients lies on personal experience, knowledge that comes from registries or subgroup analyses of trials designed for other purposes, and mainly extrapolation from data accumulated on CAD and LEAD. The latter data may produce conflicting results because of small numbers of patients recruited and great variability in clinical presentations. PVD, involving multiple arterial sites, may create many various clinical scenarios that are difficult to address systematically, leading thus to many answered clinical questions. However, great efforts to increase physicians' awareness of extra-cardiac vascular disease have recently been made, especially after the reductions in CAD-related morbidity and mortality, achieved in the developed world with aggressive treatment of acute coronary syndromes (ACS), primary and secondary CV prevention.

Towards that aim, guidelines have been published to provide guidance on diagnosis and treatment of these patients. In 2010, the ESC/European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization included for the first time specific recommendations for the management of patients with CAD associated with carotid artery disease, renal artery disease, or LEAD [9]. In 2011, the ESC guidelines on the diagnosis and treatment of peripheral artery diseases included a section on multisite artery disease emphasizing its effect on CV prognosis and provided guidance on the diagnosis and management of the most clinically relevant combinations of multisite atherosclerotic disease [10]. This was updated and further enhanced in the most recent ESC guidelines [1]. Of interest, the majority of recommendations in the section of polyvascular disease are still classified as level of evidence (LOE) C (i.e. based on consensus of opinion of the experts and/or small studies, retrospective studies, registries) and few of them are in the LOE B category (i.e. data derived from a single randomized clinical trial or large non-randomized studies).

Undoubtedly, all PVD patients will benefit from a greater adherence to secondary prevention strategies aiming to reduce long-term CV events. Risk factor modification and aggressive medical therapy are particularly important in patients with manifest PVD, especially since it is well known from the REACH registry that in patients with LEAD, risk factors are not as well controlled compared to patients without LEAD [11]. In short, smoking cessation must be strongly advised in all patients who smoke. Statins are recommended in all patients with vascular disease at any site [1]. LDL cholesterol should be lowered to <1.8 mmol/L (70 mg/dL) or ≥ 50% if baseline values are 1.8–3.5 mmol/L (70–135 mg/dL). Blood pressure should be controlled to ≤140/90 mmHg and ACEIs or ARBs should be considered as first-line therapy. Beta-blockers should not be contraindicated in patients with PVD, especially those with peripheral vasodilatory properties, and in contrast should be considered in concomitant CAD and/or heart failure. In patients with diabetes mellitus, the HbA_{1c} level should be kept at <7% in the presence of increased age and multiple co-morbidities as these patients usually have. Antiplatelet therapy should be initiated promptly if not already administered. A post hoc analysis of the CHARISMA trial [12] showed that patients with PVD had markedly higher event rates and indicated a potentially large benefit of dual antiplatelet therapy in this cohort. In patients with CAD, the co-existence of LEAD may have a direct impact on the duration and type of antiplatelet therapy, especially when there is a prior history of coronary stenting or ACS; prolonged double antiplatelet therapy may be encouraged [1]. In the PEGASUS trial which examined the effect of prolonged (3 years) dual antiplatelet therapy (aspirin plus ticagrelor) versus aspirin alone in patients with prior myocardial infarction, the benefit in the dual antiplatelet therapy arm was more pronounced when PAD was present (absolute risk reduction of major adverse CV events 4.1% for PAD vs 1.0% when no PAD was present) [13].

Despite all the above, most studies show that patients with PAD are still less frequently treated with optimal medical therapies such as statins or antiplatelet agents. This may be attributed to a low patient adherence to medications but also the difficulties to coordinate a multidisciplinary approach for these patients. Data from the CRUSADE registry in high-risk non-ST elevation ACS patients showed that PVD patients were less treated with important guideline-recommended, evidence-based therapies despite their higher-risk profiles and the absence of contraindications [14]. This under-treatment of patients with LEAD who present with ACS, despite their greater extent of CAD, left ventricular dysfunction and myocardial ischemia, may partly contribute to their worse outcome. In the future, research should aim to provide knowledge on the optimal management of this complex group of patients. PVD patients may represent an appealing population for controlled trials due to their high event rates and the enormous cost of complications [15].

Given the high incidence of CAD and any PAD in the general population and the markedly higher risk for CV events in the presence of both, two important clinical questions arise: whether screening of any extra-cardiac vascular disease should be performed routinely in patients with CAD and whether screening for CAD should be routinely performed in patients diagnosed with PAD. If PVD is diagnosed, these patients are at great need for secondary prevention with aggressive medical treatment. Beyond that, it has not been proven yet that routine screening for atherosclerosis in multiple locations and subsequent local interventions to treat that may reduce the excess risk associated with PVD.

Screening for carotid artery disease

Although screening for carotid artery disease can be performed easily using carotid artery duplex ultrasonography, the available data regarding the prevalence of severe carotid stenosis in patients with CAD and the lack of evidence of any beneficial effect on clinical outcomes lead to the conclusion that carotid screening is not indicated in patients with CAD other than in candidates for CABG [1]. However, the rationale of screening with the aim to perform prophylactic carotid revascularization before or during the CABG operation remains an important issue in everyday clinical practice as the presence of severe CAS in this group of patients may increase the risk of a peri-operative stroke.

In the latest ESC guidelines [1], in patients undergoing CABG, DUS is recommended (I-B recommendation) in patients with a recent (<6 months) history of TIA/stroke. Among patients undergoing planned CABG and no recent (<6 months) history of TIA/stroke, the presence of risk factors such as carotid bruits, older age >75 years, presence of LEAD or multi-vessel CAD may identify a high-risk subset of patients suitable for CAS screening (IIb-B recommendation) [16,17]. In contrast, screening for CAS is not indicated in patients with unstable CAD who require emergent CABG with no recent stroke/TIA (III-C recommendation).

Apart from screening and diagnosis, issues such as the indication for prophylactic carotid revascularization, the optimal revascularization method and the preferred timing in relation to the CABG procedure (synchronous or staged) remain largely unclear, and according to the latest ESC guidelines [1], these issues should be discussed within a multidisciplinary team, including a neurologist (I-C recommendation). Indeed, the occurrence of stroke after CABG is multifactorial; embolization with atherothrombotic debris from the aortic arch is the most frequent cause, while atrial fibrillation, low cardiac output, and hypercoagulation states from tissue injury may also contribute. Indeed, the presence of CAS in patients undergoing CABG has been considered to be a marker of high risk for CABG-related stroke rather than its cause.

In CABG candidates with asymptomatic CAS, evidence of the benefits of prophylactic revascularization to reduce perioperative stroke is lacking. The decision to perform revascularization with either carotid endarterectomy (CEA) or carotid stenting in these patients should be made by a multidisciplinary team. It may be reasonable to restrict prophylactic carotid revascularization to patients at highest risk of postoperative stroke [1], i.e. patients with severe bilateral lesions (both 70–99% or unilateral 70–99% and contralateral occlusion) (IIb-B recommendation) [18] or in patients with a 70–99% carotid stenosis in the presence of one or more characteristics that may be associated with an increased risk of ipsilateral stroke (IIb-C recommendation). In CABG candidates with symptomatic carotid stenoses (i.e. a recent <6 months TIA/stroke), carotid revascularization should be considered only in patients with 50–99% carotid stenosis and CEA should be considered as the first choice for revascularization [19,20].

Regarding the timing and modality of carotid revascularization (CEA or carotid stenting), there are many controversial issues and decisions should be individualized based on clinical presentation, level of emergency and severity of carotid and coronary artery diseases [1]. No specific strategy has been proven to be clearly safer so far. The two-staged CEA strategies provide higher risk of periprocedural MI if the carotid artery is revascularized first and a trend towards increased cerebral risk if CABG is performed first.

Two problems need to be considered regarding carotid stenting that looks more appealing as a less invasive approach. First, the higher risk of cerebral embolization from aortic arch plaques may explain why CAS is not associated with lower procedural risks. The second problem is the need for antiplatelet treatment in carotid stenting and the associated bleeding. If carotid stenting is performed before elective CABG (staged approach), the need for double antiplatelet therapy is expected to delay CABG for about 5 weeks, increasing thus the risk of MI in the meantime [1]. The staged approach of carotid stenting performed within 90 days before elective CABG, has been recently associated with more favourable early and importantly late outcomes [21]; however, the risk of bleeding during CABG that will affect long-term prognosis needs to be considered.

In general, the diagnosis of CAD and CAS in the same patients should alert treating physicians on various aspects of treatment. The presence of severe atherosclerosis in both the carotid and the coronary arteries indicates a high risk for widespread atherosclerotic lesions, also involving the aorta and its arch. These could be a source of stroke during manipulation or catheterization of the aorta. Carotid artery stenting should also be performed with great care in these patients as there is a high risk of stroke during carotid artery catheterization.

Screening for renal artery disease (RAD)

Routine screening for RAD in patients planned for invasive coronary angiography, is not recommended. Apart from the use of ionized contrast agents, longer exposure to irradiation, and increased cost, a systematic screening for RAD is not expected to affect the medical or invasive management of the patient; proof for benefit of renal artery stenting is lacking in atherosclerotic RAD [1, 22–24].

RAD is frequently discovered incidentally during imaging for LEAD as it shares the same risk factors. Whether atherosclerotic RAD could be a marker of worse CV prognosis in LEAD remains unclear. The only study that looked also at limb outcomes showed no change in prognosis in the case of RAD [25]. However, since routine treatment of RAD with stenting has no proven therapeutic value, systematic screening for RAD in patients with LEAD cannot be recommended [1].

Screening for LEAD

LEAD often coexists with CAD; left main coronary artery stenosis and multivessel CAD were independent predictors. Patients with LEAD exhibit more extensive, calcified and progressive coronary atherosclerosis [26]. LEAD is often under-recognized in the presence of CAD as patients with angina on exertion do not exercise to a degree insufficient to evoke intermittent claudication.

The co-existence of LEAD and CAD, although undiagnosed in most patients, is known to dramatically deteriorate the prognosis of patients, almost doubling the risk of events in CAD patients (especially in the context of an ACS) if diagnosed with LEAD [13,27–28]. Diagnosis of LEAD (clinical or subclinical) has also been associated with worse outcome in patients undergoing CABG [29,30].

However, whether routine screening for LEAD in patients with CAD or other vascular disease is a valid strategy is not known still today as there are no data to suggest that this would significantly modify the management of the patient. The diagnosis of concomitant LEAD in patients with CAD should lead to closer attention of the patient, more aggressive use of all secondary preventive treatments and stricter control of risk factors. A combination

of clopidogrel and aspirin in these high-risk patients has also been advocated on the basis of a post-hoc analysis of the CHARISMA trial that showed a significant decrease in non-fatal MI with aspirin and clopidogrel vs aspirin alone, at the cost of increased minor bleeding [12]. Randomized studies need to confirm this benefit of double antiplatelet therapy in this population.

In CAD patients who require coronary revascularization and are also diagnosed with LEAD, treatment of CAD almost always comes first except in cases of critical limb ischemia [1]. Whether PCI or CABG is preferable in this group is unclear [31,32]. In the case of PCI, radial artery access should be favored [33]. If the femoral approach is necessary, pre-interventional assessment of the iliac and common femoral arteries should be performed to minimize the risk of peri-procedural complications.

In patients with LEAD undergoing CABG, practical issues related mainly to the use of saphenous vein grafts are clarified. In such patients, sparing the autologous great saphenous vein for potential future use for surgical peripheral revascularization should be considered. In these patients, the use of venous bypass has also been associated with impaired wound healing; this justifies the screening for LEAD prior to use of the saphenous vein as bypass material, at least by clinical examination and/or ABI.

Finally, the recent ESC guidelines acknowledged the strong prognostic role of ABI demonstrated in multiple studies [1] and suggested that a systematic screening approach with ABI measurement in patients with CAD may be considered for improved risk stratification (IIb-B).

Screening for CAD

The value of systematic screening for asymptomatic CAD in patients with carotid artery disease has not been extensively investigated, although the co-existence of CAD in these patients is thought to be high (40–60% of total patients) and mostly in the absence of cardiac symptoms [34,35].

An important clinical question certainly arises when patients with severe CAS need to undergo revascularization. In the case of severe CAS and CAD, which site will be revascularized first will be decided according to the patient's clinical status and the severity of carotid and coronary disease. Carotid revascularization should be performed first only in the case of unstable neurological symptoms; while asymptomatic carotid stenosis should be treated if appropriate, but following CAD revascularization. The value of pre-operative coronary angiography (and subsequent revascularization if needed) in patients with planned CEA but without history, symptoms or signs of CAD was tested in a randomised controlled trial. A significant benefit both in early (decrease in post-operative MI) and late outcomes (decrease in MI and death at 6 years) without an increase in strokes or bleeding was found [36,37]. Given these data, the latest ESC guidelines [1] recommend that preoperative CAD screening, including coronary angiography, may be considered in patients undergoing elective CEA (IIb-B recommendation).

The high frequency of co-existence of LEAD with CAD is well recognised; 25% to 70% of patients with LEAD also have CAD depending on the population studied and the method used [1]. The prevalence of CAD is 2- to 4-fold

Table 2 – Indication for screening of associated atherosclerotic disease in additional vascular territories.

Leading disease \ Screened disease	CAD	LEAD	Carotid	Renal
CAD				
Scheduled for CABG		IIa[a]	I[b] / IIb[c]	U
Not scheduled for CABG		IIb	NR	U
LEAD				
Scheduled for CABG	I[d]		NR	U
Not scheduled for CABG	NR		NR	U
Carotid stenosis				
Scheduled for CEA/CAS	IIb	NR		U
Not scheduled for CEA/CAS	NR	NR		U

Modified from reference [1].
CABG – coronary artery bypass grafting; CAD – coronary artery disease; CAS – carotid artery stenting; CEA – coronary endarterectomy; CKD – chronic kidney disease; ECG – electrocardiogram; LEAD – lower extremity artery disease; NR – no recommendation (not enough evidence to support systematic screening); TIA – transient ischaemic attack; U – uncertain.
[a] Especially when venous harvesting is planned for bypass.
[b] In patients with symptomatic cerebrovascular disease.
[c] In patients with asymptomatic carotid disease and: age ≥ 70 years, multivessel CAD, associated LEAD or carotid bruit.
[d] Screening with ECG is recommended in all patients and with imaging stress testing in patients with poor functional capacity and more than two of the following: history of CAD, heart failure, stroke or TIA, CKD, diabetes mellitus requiring insulin therapy.

higher in patients with LEAD vs. those without. The prevalence of associated CAD is related to the severity of LEAD; CAD is found in up to 90% of patients presenting with critical limb ischemia.

Patients with atherosclerotic disease at both sites have a worse overall prognosis with increased (more than double) mortality and major cardiac events compared to isolated LEAD [38]. Routine screening of patients with known LEAD for the presence of asymptomatic CAD would enable identification of patients with a poor long--term prognosis; whether such identification may alter treatment strategy (either conservative and or invasive) and improve clinical outcomes in patients who are already in secondary prevention program has not been shown so far. Prognostic improvement using prophylactic coronary revascularization has not been proven in asymptomatic CAD patients in the COURAGE trial [39]. However, the trial did not include stable patients with a low ejection fraction and those with left main stenosis >50%, in whom revascularization was considered necessary. Such patients are frequently encountered among patients with severe and diffuse LEAD and PVD. Moreover, in the REACH registry, annual mortality rate was as high as 3.8% [40,41], whereas patients with non-obstructive coronary plaques have an annual mortality rate of only 0.63%. According, to the recent European stable CAD guidelines, these CAD patients with an annual mortality risk >3%, such as the ones with PVD, are candidates for coronary revascularization [42]. Nevertheless, since no solid evidence occurs, there is no recommendation on whether to screen and how (stress testing or coronary CTA) and the decision to screen for CAD in LEAD patients should be individualized. It is important to emphasize that in LEAD patients, secondary prevention medications such as statins, antiplatelet agent and antihypertensives if needed, should be initiated immediately after diagnosis (irrespective of the presence of CAD) to improve long-term CV prognosis [1].

The need of screening for asymptomatic CAD arises when PAD patients need to undergo surgery, and especially vascular surgery that is considered to have high-risk for cardiac complications (expected 30-day major adverse cardiac event rate >5%) [43]. Peri-operative CV complications are common in LEAD patients and result in significant morbidity following non-cardiac surgery.

In case of any emergency surgery, this should be performed without delay, while all appropriate CV medications are administered. In case of an elective surgical procedure in a stable LEAD patient, pre-operative screening is required to quantify and limit peri-operative and long--term risk if possible. Whether screening for CAD will be performed, how this will be done and whether or how its results will modify patient management needs to be decided. This complex matter should be based on the latest ESC guidelines on non-cardiac surgery [43].

In summary, all indications for screening of atherosclerosis in other vascular sites have been included in a comprehensive Table in the latest ESC guidelines [1] (Table 2). In only a few clinical situations, the identification of asymptomatic lesions may affect management [1]:

- Patients undergoing CABG; ABI may be considered, especially when saphenous vein harvesting is planned.
- Selected patients undergoing planned CABG; carotid screening should be considered. Prophylactic revascularization should be decided based on severity of carotid disease, recent symptoms and/or multidisciplinary discussions.
- Patients planned for carotid artery revascularization; pre-operative coronary angiography for the detection and revascularization of CAD may be considered.

Conclusion

The management of patients diagnosed with PVD is very complex. These patients are at high CV risk with multiple CV risk factors and co-morbidities and usually present late in a poor clinical status. There are many lesions in different vascular sites that need to be treated with various isolated and inter-related technical problems. In most such patients, it is very difficult to base decisions on hard evidence and individualized decision-making is mandatory with the collaboration of many specialties. The multidisciplinary, skilled and experienced team that is needed to assess these patients may extend from the basic cardiovascular specialties (cardiologists, vascular surgeons, radiologists cardiothoracic surgeons) but involve also neurologists or nephrologists.

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Ethical statement
Authors state that the research was conducted according to ethical standards.

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