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REVIEW

Non-coronary atherosclerosis

Augusto Gallino[1,2†‡*], Victor Aboyans[3,4,5†], Curt Diehm[6], Francesco Cosentino[7], Hans Stricker[1,2], Erling Falk[8], Olaf Schouten[9], John Lekakis[10], Beatrice Amann-Vesti[11], Francesco Siclari[12], Pavel Poredos[13], Salvatore Novo[14], Marianne Brodmann[15], Karl-Ludwig Schulte[16], Charalambos Vlachopoulos[17], Raffaele De Caterina[18], Peter Libby[19], and Iris Baumgartner[20], On behalf of the European Society of Cardiology Working Group on Peripheral Circulation

[1]Division of Vascular Medicine, Ospedale San Giovanni, 6500 Bellinzona, Switzerland; [2]University of Zürich, Zürich, Switzerland; [3]Department of Cardiology, Dupuytren University Hospital, Limoges, France; [4]INSERM 1094, Limoges, France; [5]Faculté de Médecine, Inserm U1064 Neuroépidémiologie Tropicale, F-87025, Limoges, France; [6] Department of Internal Medicine, SRH Klinikum Karlsbad, 76307 Karlsbad, Germany; [7]Division of Cardiology, Osp. S. Andrea-University Sapienza, 00189 Rome, Italy; [8]Department of Cardiology, Aarhus University Hospital, 8200 Aarhus, Denmark; [9]Erasmus University Hospital, 2593GT Den Haag, Netherlands; [10]Cardiology Department, Attikon University Hospital, Athens, Greece; [11]Angiology Department, University Hospital, 8091 Zurich, Switzerland; [12]Cardiosurgery Department, Cardiocentro CCT, 6900 Lugano, Switzerland; [13]Department of Vascular Medicine, University Medical Centre Ljubljana, 1525 Ljubljana, Slovenia; [14]Department of Cardiology, University Hospital Palermo, 90144 Palermo, Italy; [15]Department of Angiology, University Hospital Graz, 8036 Graz, Austria; [16]Vascular Center Berlin, Ev. Hospital KEH, Academic Teaching Hospital Charité, 10365 Berlin, Germany; [17]Cardiology Department, Athens University Medical School, Athens, Greece; [18]Institute of Cardiology Department, 'G. d'Annunzio' University-Chieti, Ospedale SS.Annunziata, 66013 Chieti, Italy; [19]Cardiovascular Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, MA 02115, USA; and [20]Angiology Dep., University Hospital Berne (Inselspital), 3000 Berne, Switzerland

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During the last decades, the clinical and research interest in atherosclerosis has been mostly focused on coronary arteries. After the publications of the European Society Guidelines and AHA/ACC Guidelines on Peripheral artery diseases, and of the Registry REduction in Atherothrombosis for Continued Health Registry, there has been an increased interest in atherosclerosis of the lower extremity arteries and its presence in multifocal disease. However, awareness in the general population and the medical community of non-coronary artery diseases, and of its major prognostic implications remain relatively low. The aim of this general review stemming out of an ESC Working Group on Peripheral Circulation meeting in 2011 is to enhance awareness of this complex disease highlighting the importance of the involvement of atherosclerosis at different levels with respect to clinical presentation, diagnosis, and co-existence of the disease in the distinct arterial territories. We also emphasize the need of an interdisciplinary approach to face the broad and complex spectrum of multifocal disease, and try to propose a series of tentative recommendations and measures to be implemented in non-coronary atherosclerosis.

Keywords Peripheral artery circulation • Atherosclerosis

Introduction

There is an increased interest among the medical community for non-coronary atherosclerosis. The most important recent initiatives in this field have been the new ESC Guidelines on the diagnosis and treatment of peripheral artery diseases,[1] the ACC/AHA Practice Guidelines in management of patients with peripheral artery disease,[2,3] the Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC I and II),[4,5] which all have established important educational, clinical, and research goals for the near future.

The pivotal results of several epidemiological studies—among others—the Basel, and the Ankle-Brachial Index Collaboration study[6,7] have also highlighted this interest, with the former demonstrating as early as the 60s the poor prognosis of patients with lower extremity artery disease (LEAD). More recently, the GetABI and the Registry Reduction in Atherothrombosis for Continued Health Registry (REACH)[8,9] have highlighted the role of atherosclerosis as a systemic disease with manifestations in multiple vascular beds, and indicated that these patients have a poorer prognosis than patients with just one territory affected[9] (*Figure 1*). The ability by a simple diagnostic tool as the measurement of the ankle-brachial

† These authors contributed equally.

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* Corresponding author. Tel: +41 91 811 91 07, Fax: +4191 811 91 69, Email: agallino@bluewin.ch

index (ABI), a surrogate and objective equivalent of the presence of LEAD, to anticipate overall cardiovascular prognosis and apply prevention strategies has increased the attention for this field.[8,10–12] (*Figure* 2) Cardiologists in fact—as elegantly demonstrated by the initial career as specialist in vascular medicine of Andreas Gruentzig and his invention of angioplasty[13]—have always been aware of the need of a multifocal diagnostic and therapeutic approach because atherosclerosis has a common pathogenesis, and simultaneously affects multiple circulatory regions.

This review has been conceived following an ESC Working Group on Peripheral Circulation meeting held in Zürich in 2011 convening 20 cardiovascular specialists in peripheral circulation and atherosclerosis together with leading European and American cardiologists who considered appropriate, 3 years after publication of the ESC guidelines, to reinforce this relevant problem since its knowledge in cardiology community tends to be low. It focuses the attention on atherosclerosis affecting the different non-coronary arterial territories, from the upper limbs arteries, the extra-cranial carotid through the thoracic and abdominal aorta, the mesenteric, renal, and lower limbs arteries, and emphasizes the growing and often unrecognized burden of vascular disease. Special attention is given to the issue of multifocal atherosclerosis, and the need for an interdisciplinary management. Given the vast extension of the topic, all facets of vascular diseases cannot be covered in detail, and some aspects go beyond the scope of the paper, i.e. therapeutic strategies, and will not be covered in this review. Finally, practical suggestions for clinicians and policy makers to increase awareness on this important item, also highlighting some areas of uncertainties in this field, are proposed.

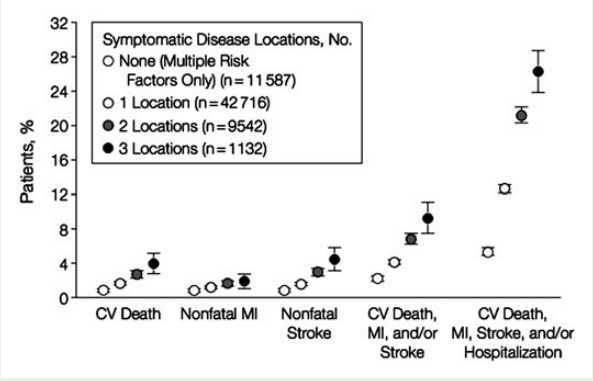

Figure 1 One-year cardiovascular event rates as a function of number of symptomatic disease locations. All *P*-values < 0.001. CV, cardiovascular; MI, myocardial infarction. Patients with at least three factors but no symptoms are counted as 0, even in the presence of asymptomatic carotid plaque or reduced ankle brachial index. Error bars represent 95% confidence intervals (adapted from Steg *et al.*[9] with permission by the publisher).

Upper extremity arteries

In contrast to many other territories, overt atherosclerosis of the upper limb arteries, including the case for the thoracic artery is relatively rare since 3–4% of the general public have a subclavian stenosis and 15–20% of patients with LEAD have it.[14] Conversely, it is intriguing to see how the upper extremity arteries (i.e. the brachial arteries) are the more convenient territory to assess non-invasively the endothelial dysfunction, one powerful early indicator of subclinical atherosclerosis. Endothelial dysfunction assessed by ultrasound measurement of the brachial artery flow-mediated dilation (FMD) after reactive hyperaemia or cold pressor test may provide prognostic information even in the absence of overt atherosclerosis, anticipating progression of the atherosclerotic lesions in patients with coronary artery disease, and in patients with LEAD.[15] Measurement of endothelial function has been of paramount importance for the understanding of pathophysiology of early and late manifestations of atherosclerosis and its complications, for determining the importance of traditional and emerging risk factors of atherosclerosis as well

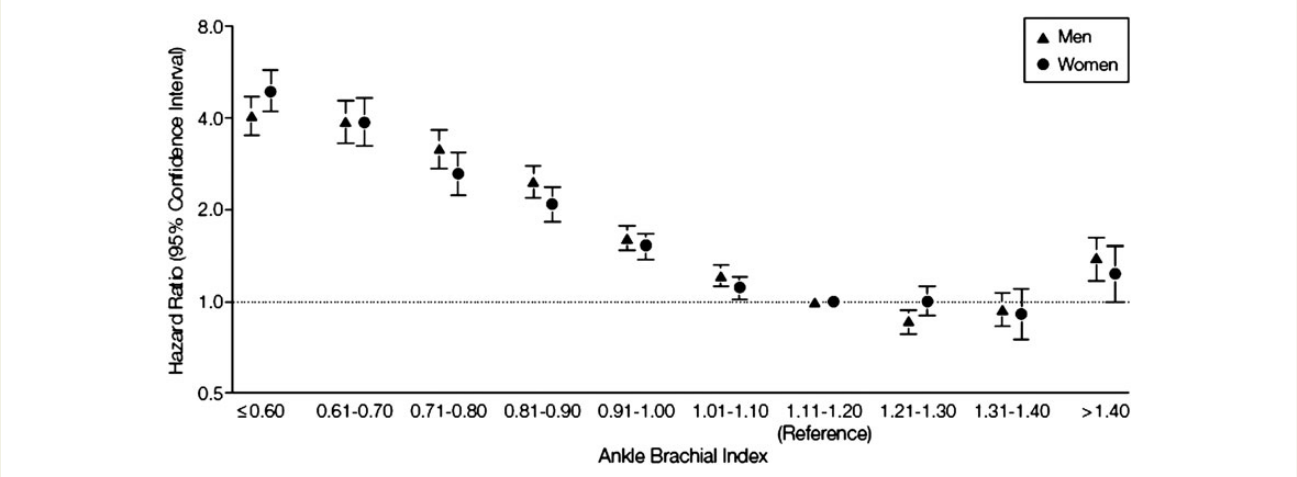

Figure 2 Hazard ratios for total mortality in men and women by ankle-brachial index at baseline for all studies combined in the ABI Collaboration (adapted from Aboyans *et al.*[12] with permission by the author and the publisher).

as for the comprehension of the mechanisms of action of several drug families and lifestyle changes crucial for the prevention as well as treatment of atherosclerosis, i.e. ACE inhibitors, and statins. A low brachial artery FMD is an independent predictor of cardiovascular risk.[16] Overall, the clinical relevance of upper limb atherosclerosis, and the use of FMD in the clinical arena remain relatively low, since the latter—in spite of its valid proof of concept—has not reached sufficient clinical utility.

Carotid arteries

The relevance of extra-cranial cerebral artery atherosclerosis is two-fold. From a clinical standpoint, carotid atherosclerosis is responsible for ~25% of strokes with major impact on disability of the growing older population.[17–19] From a clinical research standpoint, carotid atherosclerosis represents an extraordinary window to study *in vivo* early and late manifestations of atherosclerosis.[20,21] The earliest visible manifestation of carotid artery disease is the thickening of the intima-media which is detectable with high-resolution B-mode carotid ultrasonography (Duplex US),[22] a marker of early subclinical atherosclerosis which correlates with incident vascular outcomes, i.e. stroke and coronary heart disease. A recent meta-analysis by Lorenz et al. showed the strong predictive value of carotid intima-media thickness for the occurrence of cardiovascular events.[20] The morphological presentation of atherosclerotic plaques at the level of carotid arteries with a lipid core and fibrous cap is similar but not exactly the same than those found in other vascular areas.[23,24] Carotid atherosclerotic plaques are associated with embolization of superimposed thrombotic material,[2,4,24,25] a phenomenon which is clinically relatively less relevant at the level of coronary arteries or lower limbs arteries.[1–5] It has been assumed that the risk of embolization or complications of carotid plaques increases in parallel with the degree of obstruction although the complexity of the plaque probably plays an even more important role.[25] The annual risk of stroke in patients with asymptomatic carotid stenosis (between 50 and 99%) is 1.0–3.3% with the higher incidence in those with the more severe stenosis and more rapid progression of stenosis.[2,4,25] Patients with symptomatic carotid artery stenosis with previous stroke have an annual recurrent stroke risk of between 10 and 43%.[23,25] However, it should be emphasized that most of these studies[22,23] have been performed before the widespread use of statins, which may induce stabilization or reduction in carotid atherosclerotic plaque.[2,26] Duplex US is the standard tool in clinical practice for detection and estimates the degree of severity of carotid atherosclerosis.[27] Duplex US allows to estimate not only the degree of stenosis but also the extension and complexity of the plaque lesion; echogenicity detected by Duplex US ultrasound has been proposed to identify lesions at higher risk of spontaneous complication or following invasive treatment (i.e. carotid surgery or stenting).[28] Contrast-enhanced Duplex US is another emerging application of ultrasound imaging which may allow the identification of intraplaque neovascularisation, a further potential predictor of plaque vulnerability.[29]

Spiral CT, and particularly MRI plaque imaging may add important information on plaques composition and vulnerability-detecting plaque rupture, intraplaque haemorrhage, and the presence of thrombus.[21,30–32] Recently, PET/CT-scan and hybrid techniques prototypes using PET/CT and MRI seem to be promising research tools for identifying inflammatory component of atherosclerotic plaques.[32] However, so far the use of these techniques is proposed only to investigational purpose and are not used clinically.

Thoracic and abdominal aorta

The pathology of the aorta has several peculiar aspects. Atherosclerotic involvement of the thoracic ascending aorta and of the aortic arch has been recognized as a significant source of 'spontaneous' cerebral and peripheral thromboembolism and may represent a dangerous source of atherothrombotic embolism during diagnostic and invasive procedures (PCI, on-pump cardiac surgery).[33] Transesophageal echocardiography is one of the most powerful tools to detect mobile and complex plaques at the level of the aortic arch and of the descending aorta.[33,34]

A clinically distinct feature is the athero-embolic syndrome associated with severe aortic atherosclerosis and embolization from ulcerated plaques. Hallmark of this syndrome is renal insufficiency, skin lesions, blue toe(s), caused by micro-emboli associated with transient eosinophilia.[35] It can occur spontaneously, but frequently results from arterial manipulation, such as catheter intervention and aortotomy.[36] Prognosis is poor with 1-year mortality rates between 60 and 81%, although this high mortality may reflect selection bias due to the fact that these figures derive from autopsy studies. Over 70% of patients with athero-embolic syndrome present renal function impairment and over 40% of these patients end-up with severe renal failure needing dialysis.[35,36]

Aortic aneurysms have been traditionally considered a special form of atherosclerosis, because this disorder is almost always associated with severe atherosclerotic damage of the aortic wall, and because it shares many of the same risk factors as obstructive atherosclerosis. However, this conventional view has been challenged in recent years: basic and clinical research studies indicate that aneurysms arise through pathogenic mechanisms that are distinct from those responsible for athero-occlusive disease.[37,38]

Renal arteries

Haemodynamically significant renal artery stenosis (RAS) is associated with hypo-perfusion of the renal parenchyma which induces a series of (patho)-physiological responses, including upregulation of the renin–angiotensin–aldosterone system followed by fluid retention, reduced natriuresis, and vasoconstriction which may end-up with perpetuation of arterial hypertension , renal fibrosis, and renal function impairment.[39,40] The recent refinement and increasing use of diagnostic procedures such as Duplex US ultrasound,[41] angio-CT, and magnetic resonance[42] in the older population with diffuse atherosclerosis undergoing invasive diagnostic procedures (i.e. coronary angiography) have changed the spectrum of clinical presentation of RAS. Cardiologists face relatively frequently the management of patients with multi-morbid poly-vascular patients with uni- (or bilateral) atherosclerotic obstructive disease of the renal arteries. These patients may present with renal with resistant arterial hypertension, renal function deterioration, 'flash' pulmonary oedema, and unstable angina.[43]

Mesenteric artery

The prevalence of acute and chronic mesenteric ischaemia is low, but its clinical relevance is high since ischaemia may be often fatal particularly in cases of acute presentation.[1–5] Mesenteric ischaemia may be caused by atherosclerosis, arterial emboli, or thrombosis as well as several other rare pathologies affecting the mesenteric arteries (fibro muscular dysplasia, arterial infection, aneurysms, or dissections). Acute mesenteric ischaemia is often a result of cardio-embolic events or due to embolization following endovascular procedures. Other causes are arterial thrombosis based on a pre-existent stenotic lesion, acute aortic dissection, or hypercoagulability states. Patients with acute mesenteric ischaemia often present with abdominal pain out of proportion to physical findings associated with leukocytosis and lactic acidosis, and have frequently a history of cardiovascular disease or a recent history of cardiovascular intervention.[2,44] Computer tomography is the diagnostic tool to identify thrombosis of the proximal intestinal arteries and its consequences (intestinal wall thickening, distension, abdominal fluid, or perforation). Chronic intestinal ischaemia affects predominantly women. Patients often present with postprandial abdominal pain frequently associated with weight loss, although the absence of the typical postprandial discomfort is not infrequent, making this diagnosis very challenging.[44] While Duplex US is often the first row imaging method, CT (and/or MRI) are the most adequate investigations to detect the affected vessels causing ischaemia and its consequences. The sensitivity and specificity for detection of mesenteric ischaemia with newer multidetector CT and magnetic are for both >90%.[45,46]

Lower extremity arteries

One of the most recently re-discovered aspects of non-coronary atherosclerosis is the major prognostic impact of the presence of a symptomatic or asymptomatic atherosclerotic involvement of the peripheral arteries of the lower limbs (LEAD).[1–5,8,47,48] The prevalence of LEAD is high especially, in subjects over the age of 65 (*Figure 3*).The life expectancy of a patient with severe claudication is <80% at 5 years follow-up, and an additional 20% of patients suffer of non-fatal cardiovascular events.[5,48] Patients with more moderate symptoms or asymptomatic LEAD are also at significant higher risk to die because of cardio- or cerebrovascular complications.[1–5,8,47,48] (*Figure 1*) In spite of this poor survival prognosis, patients with LEAD have received until recently scant public attention, half of claudicants being not recognized as such.[1–5,9,11,49,50] Once diagnosed, patients with LEAD have significantly less chance of receiving appropriate risk factor modification, statins, and antithrombotic treatment than patients with coronary or cerebrovascular disease.[9,11,11,50]

Awareness of this condition should be promoted by the use of simple diagnostic tools such as measurement of the ABI, in order to detect a larger population of high-risk patients who should receive appropriate cardiovascular treatment.[1–5,9,11] The poor general prognosis of these patients contrasts with the relatively benign course of the local disease, only 25% of patients experience symptomatic deterioration, and 2–6% eventually lose the involved leg within 5 years.[1–5]

Critical limb ischaemia (CLI) deserves a special place in the spectrum of LEAD since it is a hallmark of dismal prognosis in terms of survival (up to 45% mortality within 1 year) and limb loss.[51] It is clinically defined by the presence of rest pain or gangrene associated with chronic ischaemia, and is usually associated with an ankle pressure ≤50 mmHg. It may develop slowly or occur with acute onset of symptoms in patients following distal athero-embolisation or in patients with multisegmental atherothrombosis.[1–5] It should be clearly differentiated from acute limb ischaemia, although the latter is also associated with risk of amputation: it follows acute arterial embolism and is accompanied by acute onset of symptoms with an obvious embolic source (atrial fibrillation, left ventricular aneurysm, atheromatous plaque in the aorta, or mural thrombus of arterial aneurysm), absence of previous claudication, and the presence of normal arterial pulses and Doppler systolic blood pressures in the contralateral extremity.[1–5,51]

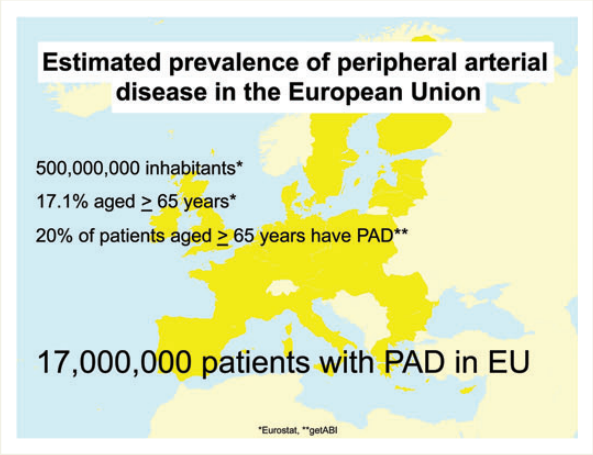

Figure 3 Estimated prevalence of peripheral arterial disease in the European Union. Estimation obtained through http://europa.eu.int/en/comm/eurostat/eurostat.html and estimation form GetABI study* (adapted from Diehm and Baumgartner[38])**.

From the clinical research standpoint, atherosclerosis of the lower extremities still remains an important model to study *'in vivo'* pathophysiology of atherosclerosis such as the study of arterial remodelling [52,53] and new treatment strategies as it was the case for angioplasty which was first introduced by A. Gruentzig to treat non-coronary atherosclerotic obstructions at the level of the lower limb arteries before being applied to the coronary arteries.[13]

A further example of how peripheral vascular medicine may be relevant to explore new cardiovascular revascularization strategies is angiogenesis. Intensive research in this field undertaken by J. Isner, another cardiologist interested in peripheral artery disease, allowed new insight into the complex issue of CLI, microcirculation and potential treatment modalities which have been relevant also for other territories (i.e. myocardium).[54,55] Through the emphasis on the importance of a global view of multisite atherosclerosis, and a close contact among internationalists in distinct arterial fields, there is a steady increasing mutual influence between coronary and non-coronary vascular specialists.

Multifocal atherosclerosis

The REACH registry has clearly confirmed that the presence of multifocal atherosclerosis has a major clinical and prognostic impact

(*Figures 1* and *2*).[1–5,9] The co-coexistence of coronary artery disease plays obviously a major prognostic role in terms of mortality.[1,6] Apart from the deemed spontaneous prognosis this may be important in those patients scheduled and undergoing vascular revascularization procedures, although the conclusions of a recent multicentre trial in patients scheduled for major vascular interventions did not show a significant benefit in patients undergoing preoperative coronary evaluation and revascularization (*Table 1* and *2*).[56]

The cause of the different prevalence of atherosclerosis at the level of distinct territories is complex. Loco-regional hemodynamic and rheological factors as a turbulent flow at bifurcations or side branches are also important mechanisms predisposing and favouring the progression of atherosclerotic lesions.[2,4] The distribution, predominance, and co-existence of atherosclerosis at different localizations of the arterial tree remain however frequently elusive, although some clues of distribution emerge from epidemiological series. Genetic, traditional, and/or emerging risk factors, inflammatory markers, environmental and socio-economic factors all may play an important role.[1–5,57–59] The different prevalence of classic risk factors in the various territories are important for both predominance and prognosis: smoking is three times more likely to cause LEAD than coronary artery disease.[60] Conversely, the association of hypertension with LEAD is lower than the association of hypertension with coronary artery disease or cerebrovascular disease.[61] Indeed, patients with carotid atherosclerosis present a stronger relationship with arterial hypertension (and benefit more of antihypertensive treatment) than patients with coronary atherosclerosis.[62]

Multifocal atherosclerosis in patients with lower extremity artery disease as primary manifestation of disease

Patients with LEAD have a poor prognosis as this disease is associated with two- to six-fold risk of coronary and cerebrovascular disease, when compared with the normal population.[1–5,63–71] In fact, the presence of LEAD in itself constitutes a very potent risk factor equivalent. The severity of LEAD goes hand in hand with an increased cardio- and cerebrovascular morbidity and mortality. Patients with more severe claudication present a higher prevalence of CAD and CVD than those with mild symptoms, and patients presenting with CLI, i.e. with rest pain or gangrene, will have the highest associated cardiovascular morbidity and mortality (up to 90% incidence of CAD and 1-year mortality ranging from 25 to 50%).[1–5,51] Cardiologists should better be aware of these figures while treating patients with LEAD not only because of the deemed spontaneous prognosis but also when estimating the risk of a surgical intervention. The presence of LEAD stratify the patient into a higher risk group. One-third of patients with LEAD present coronary artery disease on the basis of history and electrocardiogram two-thirds on the basis of an abnormal stress test and up to 70% present at least single vessel disease at coronary angiography. Whether a silent concomitant CAD should be confirmed and treated by an invasive procedure depends at the end upon the cardiac indication to coronary angiography and revascularisation.[56]

The risk of stroke in male patients with LEAD has been reported four to five times higher than in patients without LEAD.[71] Approximately 20% of patients with LEAD have a significant carotid stenosis detected at Duplex US ultrasound.[1–5,65,66] The severity of LEAD seems to correlate with the severity of carotid artery stenosis.[67] The presence of carotid bruits in LEAD patients should foster the search of carotid internal stenosis, i.e. by Duplex US: subsequent diagnostic and therapeutic strategies are driven again by the clinical presentation and the degree of the concomitant carotid stenosis.

Multifocal involvement in patients presenting with carotid arteries atherosclerosis

Patients with significant carotid artery disease (i.e. stenosis > 70–80%) are more prone to die following acute coronary syndrome than cerebrovascular events, pointing to the high prevalence of concomitant coronary artery disease.[72] Thus, patients with carotid artery disease should undergo aggressive medical treatment of their risk factors in analogy to patients with 'lone' coronary artery disease.

Patients with symptomatic carotid artery atherosclerosis have per se a 30% and 20% co-prevalence of CAD and LEAD respectively.[1–3,58]

Table 1 Non-coronary atherosclerosis: co-prevalence in other territories

Affected territory	Carotid arteries			Aorta			Renal arteries
Clinical presentation	ICA < 60% asymptomatic	ICA > 60% asymptomatic	ICA > 70% symptomatic	Athero-embolism	Thoracic aneurysm	Abdominal aneurysm	Hypertension or renal failure
Associated atherosclerosis							
CAD	up to 25%		up to 35%	>50%	up to 40%	>50%	up to 90%
CVD				>50%	up to 20%	>50%	up to 60%
PAD	up to 10%		up to 20%	>50%	up to 30%	>50%	up to 60%

CAD, coronary artery disease; CVD, cerebro-vascular disease; ICA, internal carotid artery stenosis; PAD, lower limb artery disease.
Co-prevalence estimated according: Circulation 2006;113:e463–e465; Dormandy and Rutherford[4]; Tendera *et al.*[1]; J Vasc Surg 1994;19:668–74; Circulation 2006.

Table 2 Lower limb artery disease: co-prevalence in other territories

Affected territory	Lower limb arteries				
Clinical presentation	**Asymptomatic ABI <0.9**	**Intermittent claudication**	**Acute limb ischaemia**	**Chronic CLI**	**Aneurysm**
Associated atherosclerosis					
CAD	Up to 50%		AF frequent	Up to 90%	Up to 50%
CVD	Up to 20%		>50%	Up to 60%	Up to 20%

ABI, ankle-brachial index; AF, atrial fibrillation, CAD, coronary artery disease; CVD, cerebrovascular disease.
Co-prevalence estimated according: J Vasc Surg 1994;19:668–74; Tendera *et al.*[1]; Circulation 2006;113:e463–e465; Dormandy and Rutherford[4].

Recent studies indicate that patients with cerebrovascular atherosclerosis also have simultaneous subclinical LEAD as detected by Duplex US and the ABI.[73,74] Whether and how a patient with significant carotid artery disease should be screened for the concomitancy of CAD remains a question of debate even in case of a planned invasive surgical carotid revascularization procedure.[1–3] The bottom line remains that, in the presence of cerebrovascular atherosclerosis, the concomitant involvement of other territories is not infrequent, and in case of clinical suspicion should be actively searched by non-invasive methods.

Patients presenting with aortic aneurysms as primary manifestation of disease

It is well known that patients with aortic aneurysms present with higher prevalence of smoking, hypertension which are associated with diffuse atherosclerosis with high cardiac and vascular co-morbidities, i.e. coronary artery disease, heart failure, and carotid artery, and/or LEAD. The presence of concomitant coronary atherosclerosis in patients undergoing abdominal (or thoracic) aneurysm repair has been extensively studied and its prevalence depends on the screening method (up to 50% according to the method of detection).[2,3,75] The high concomitant cardiovascular co-morbidity is a matter of major concern especially in patients needing open aortic repair who have symptomatic coronary artery disease or decompensated heart failure.[1–5,76] Conversely, in patients with stable coronary artery disease, the risk of cardiovascular events during aortic repair seems nowadays relatively low, obviating the need of preventive coronary revascularization.[56]

Patients presenting with renal atherosclerosis

Patients with unilateral and—most importantly—with bilateral renal artery atherosclerotic obstructions have a dismal prognosis because they probably represent a marker of the burden of global atherosclerosis.[40] Renal function impairment in these cases seems to perpetuate and accelerate the process of systemic atherosclerosis which is associated in patients with chronic kidney disease with a cardiovascular mortality of 30–50%.[1,40,43,77]

Comprehensive approach

Given the broad spectrum of non-coronary atherosclerosis, there is a need for a comprehensive approach. When facing a patient with non-coronary artery disease, one has to keep in mind the frequent systemic feature of the disease, i.e. the potential involvement of other territories, i.e. coronary or cerebrovascular arteries making the cardiologist a natural player in the management of these pathologies. This may especially be relevant not only for prognostic purposes but, most importantly, in cases where revascularisation is needed in order to plan and prioritize which territory should be firstly treated (concomitant or staged procedures). As recently underscored by the 2011 ESC guidelines on Peripheral Artery Diseases and by the NHLBI, a multidisciplinary team including specialists in cardiovascular medicine, vascular surgery, radiology and even sometimes other fields according to the organs involved should take care of these patients. Recently, an EU division in vascular medicine has been officially recognized by the UE regulatory agency (UEMS)* in Europe, and a National Institute of Health (NIH) fellowship in clinical vascular medicine has been advocated in the USA**. This speciality/fellowship includes a 2- to 3-year training period with intensive teaching in basic, clinical, pathophysiology, non-invasive and invasive diagnostic, prevention and therapeutic strategies in vascular medicine.

Multidisciplinary boards, pending upon the local situation, may be more efficient when these organization models are integrated preferably into a broad cardiovascular concept, i.e. within cardiovascular centres. Major efforts in this direction should be pursued in order to better achieve a global management of patients with non-coronary and coronary atherosclerosis.

*UEMS—European Union of Medical Specialists http://www.uems.net/EU—Division of Angiology

**NHLBI Vascular Medicine Training Programme Working Group Executive Summary http://www.nhlbi.nih.gov/Meetings/workshops/vascular-med.htm

Economical impact of non-coronary atherosclerosis

The results of *REACH Registry*—a large, international, prospective study of stable outpatient population with either established symptomatic atherothrombosis (CAD, cerebrovascular disease, or

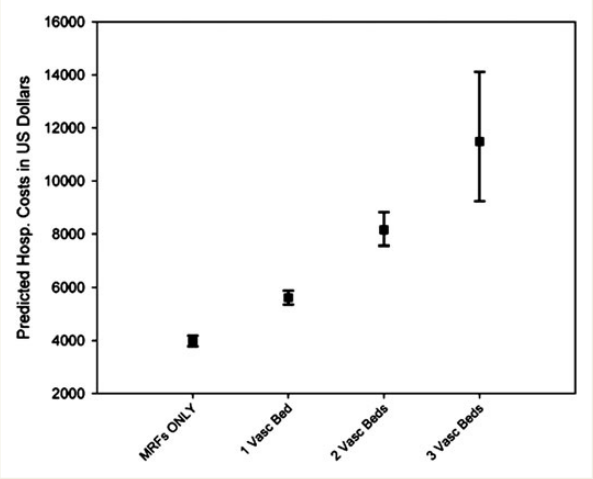

Figure 4 Data from the One-Year Costs in Patients With a History of or at Risk for Atherothrombosis in the United States Costs across patient subgroups defined according to specific arterial bed(s) affected and the number of affected arterial beds. Total costs per patient (mean, with 95% confidence interval) adjusted for covariates by presence of multiple risk factors only and number of diseased vascular beds (cerebrovascular, coronary, and peripheral). Hosp, hospitalization; MRFs, multiple risk factors. There is a consistent increase in costs with each additional diseased arterial bed. (Adapted from Circulation Outcomes 2008;1: 38–45).[79]

Table 3 Key messages by the panelists

Key messages
Prevalence of LEAD in subjects >60 years is higher than actually perceived by the medical community
Prognosis in LEAD (independent of symptoms) is poor
Multivascular atherosclerosis is frequent in the presence of LEAD and is associated with high morbidity and mortality
Patients with LEAD and multivascular disease receive insufficient primary and secondary prevention

Table 4 Measures to be implemented in non-coronary atherosclerosis

Measures to be implemented in non-coronary atherosclerosis
Further increase awareness in the cardiology community and in the public of the clinical and prognostic relevance of LEAD
Increase awareness of the importance of multivascular disease
Females with LEAD should receive more attention
The use of ABI as a diagnostic and prognostic tool should be encouraged among GPs and specialists
RCTs and Surveys on LEAD and multisite atherosclerosis are needed

LEAD)—have clearly indicated that symptomatic LEAD is associated with the greatest costs when compared with coronary artery disease and cerebrovascular disease.[78,79] (*Figure 4*) In this registry, the authors compared the rates of associated costs in the USA with LEAD across patient subgroups as well as the incidence of vascular-related hospitalizations. Patients with symptomatic LEAD at enrolment were defined on the basis of presence of intermittent claudication with an ABI < 0.90 or a history of previous lower limb revascularization (or amputation). Asymptomatic LEAD was defined when ABI < 0.90 in the absence of symptoms. A total of 2396 (9.3%) had symptomatic and 213 (0.8%) had asymptomatic LEAD at baseline were considered for the cost analysis. Based on the results of the American REACH cohort and of the 2004 US census data, the total annual costs associated with vascular hospitalizations in patients with LEAD would excess $21 billion. Similar results and cost extrapolations have been observed in several European cohorts of the REACH Registry where 2-year hospitalization costs were highest for patients with LEAD.[80] These data emphasize the need for an early and aggressive identification, prevention, and treatment of LEAD which is clearly underdiagnosed and undertreated. Several further studies have underlined how LEAD is responsible of a major proportion of the burden on healthcare systems beyond from indirect costs, as those related to lost productivity.[81] All these costs could potentially be reduced, i.e. through long-term prevention, when the disease would be recognized at an earlier stage, although such long-term prevention is expensive on its own.[82] Therefore, there is a need for further prospective studies on cost efficacy of long-term preventions strategies in the setting of non-coronary atherosclerosis, and in patients with LEAD which may allow to draw more solid cost-efficacy conclusions. The same holds also true in the field of cost–benefit analysis of revascularization procedures in LEAD where there is also a need of prospective studies including long-term standardized evaluation of patient-centric results, and re-intervention outcomes as reported in a recent a systematic review of the Mayo clinic on economic evaluation of LEAD revascularization procedures.[83]

Areas of uncertainty

Compared with CAD where a huge amount of prospective data based on RCTs has been generated during the last three decades on diagnostic-, preventive-, and therapeutic strategies, clinical research in non-coronary and multisite atherosclerosis—as reported in *Table 3* and *4*—has suffered of a relatively limited interest, and large RCTs are generally lacking. This may be related to the frequent involvement of multiple arterial districts preventing to focus in detail on each arterial area. Thus, several data on management of LEAD and on carotid artery disease are frequently extrapolated from results derived from CAD. Although the relevance of traditional risk factors has been evaluated in patients with LEAD, the role of emergent risk factors and of drug prevention has been limited studied in large prospective studies. We also have poor data on the causes of different behaviour in progression of atherosclerosis among the distinct arterial sites.

Data regarding multisite atherosclerosis are lacking: the usefulness of carotid revascularization in asymptomatic patients with >80%

Table 5 Measures to increase awareness for non-coronary atherosclerosis

Targets	Measures to increase awareness
Public	Public campaigns in analogy to NIH, VDF campaigns at European-national-, regional-community levels
General practioners	Spread the message that LEAD and multivessel disease are more prevalent than actually perceived by the medical community Organize ABI courses Reimbursement for ABI measurement by GPs
Cardiologists	Enhance graduate and postgraduate teaching in non-coronary atherosclerosis Spread existent Guidelines on LEAD Promote RCTs and survey on management of LEAD at European level
Industry	Involvement in public, GPs and specialists awareness and prevention campaigns

VDF, vascular diseases foundation.

internal carotid stenosis before CABG remains uncertain. The optimal timing (staged or synchronous), and the method for carotid revascularization (carotid endarterectomy or stenting) in patients undergoing CABG have not yet been clearly identified.

Conclusions

Non-coronary atherosclerosis includes a large spectrum of disease with distinct manifestations at different vascular locations; it may occur in isolated form or—more frequently—simultaneously at various sites. Associated CAD is frequent especially in the case of lower limb atherosclerosis, which is a powerful predictor of mortality, hospitalizations, and costs. Awareness of the disease and active screening for non-coronary atherosclerosis using simple diagnostic tools are essentials for the detection of disease. Once diagnosed efforts should be made for a holistic management aiming at treating and preventing the whole spectrum of the disease and their complications.[2]

This review by the ESC Working Group on Peripheral Circulation and by the panellists of the 2011 Zürich meeting suggest some tentative strategies (*Table 3, 4, 5*) in order to further improve management, and to increase visibility of non-coronary atherosclerosis. The panellists propose several tentative measures to be implemented in the field non-coronary atherosclerosis and to increase awareness of this disease complex (*Tables 4* and *5*). The use of ABI as a diagnostic and prognostic tool should be more encouraged among GPs and specialists; females with LEAD should receive more attention; randomized clinical trials, surveys, and registries on LEAD and multisite atherosclerosis should also be encouraged. Awareness of the disease should be increased through public campaigns at European, national, and community levels. The medical communities should be sensitized through the existing guidelines on peripheral arteries,[1–5] and more emphasis on LEAD during graduate and postgraduate teaching.

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