Multisite Atherosclerotic Disease: State of Art and Review of Literature
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Abstract
Multisite artery disease, defined by the simultaneous presence of atherosclerotic lesions in at least two major vascular territories, denotes an aggressive manifestation of the disease and leads to a deterioration of cardiac prognosis. The therapeutical strategy of multisite artery disease is not standardized and it is influenced by increased risk for both vascular and coronary surgery.

Percutaneous treatments should be considered as an alternative to surgical revascularization in patients at high surgical risk. Simultaneous percutaneous intervention involving coronary and peripheral arteries seems to represent a promising strategy of treatment.

Keywords: Atherosclerosis; Carotid; Concomitant coronary artery disease (CAD)

Introduction
Atherosclerosis is a progressive disease with a multifactorial pathogenesis, which involves both large and mid-size arteries of different districts, causing stenosis of some vessels and ectasia in others. The clinical manifestations of the disease are different depending on the affected district (ischemic heart disease, ischemic stroke, peripheral artery diseases).

Atherosclerosis represents the leading cause of death and disability in Europe and USA (about 52%) [1] and it is predicted to become the main cause of mortality and disability worldwide [2,3].

The simultaneous presence of atherosclerotic lesions in at least two major vascular territories is defined “multisite” artery disease [4]. The prevalence in the population of atherosclerotic multisite disease is very high, because of common pathophysiology and risk factors (smoking, diabetes, hyperlipidemia, hypertension, and elevated C-reactive protein).

The presence of atherosclerosis in multiple vascular districts denotes an aggressive manifestation of the disease and leads to a deterioration of cardiac prognosis. The concomitant coronary artery disease (CAD) in patients with peripheral artery disease (PAD) influences the treatment and the risk associated with the surgical treatment and general anaesthesia is greater in the presence of ischemic heart disease.

So, the therapeutical strategy (conservative, surgical or endovascular) of combined CAD and PAD is not standardized and depends on the opinion of attending physicians and the preference of patients, due to lack of randomized trials.

Epidemiology of Multi-Site Atherosclerotic Disease
The prevalence of combined CAD and PAD (cerebrovascular disease, CVD and lower extremity vascular disease, LEAD) has been confirmed in two international studies: CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trial [5] and Aronow & Ahn trial [6].

Relevant CAD was demonstrated in 16-35% of patients with atherosclerosis or three or more risk factors [7].

As shown by the Reduction of Atherothrombosis for Continued Health (REACH) Registry [8], a substantial percentage of patients with chronic CAD have associated CVD, LEAD, or both. In particular 60% of patients affected by LEAD, 25% of patients affected by CAD and 40% of patients with CVD had multisite disease.

Coronary artery disease in at least one vessel was diagnosed in 40% of patients with extracranial carotid arteries disease [9-11] and 60% of patients with severe lower limb disease [12,13].

Prognostic Implications
Peripheral artery disease and cardiac prognosis
The presence of atherosclerosis in peripheral districts suggests an aggressive manifestation of disease, increases risk of recurrent symptoms and complications and worsens cardiac and global prognosis. Clinical manifestations of non-coronary forms of atherosclerotic disease (peripheral arterial disease and carotid artery disease with transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery), are considered as a coronary heart disease (CHD) risk equivalent by the guidelines of the Adult Treatment Panel III (ATP III) [14].

Carotid disease and cardiovascular events: The presence of severe carotid stenosis correlates with the severity of coronary artery disease [15]. In particular, the values of carotid artery intima-media (IMT) wall thickness was associated with a high rate of cerebrovascular and cardiovascular events, as confirmed in Cardiovascular Health Study (CHS) [16], the Rotterdam Study [17] and the Atherosclerosis Risk in Communities (ARIC) [18]. The Global Registry of Acute Coronary Events (GRACE) [19] showed that patients with acute coronary syndrome (ACS) and previous stroke had higher-in-hospital mortality than patients with CAD alone.

Lower limb disease and cardiovascular events: LEAD is associated with higher risk of multivessel coronary disease and it’s an important predictor of mortality: patients with peripheral arterial disease had
a higher rate of multi-vessel coronary artery disease and a higher concentration of C-reactive protein, a marker of systemic inflammation [20].

The risk of death from all causes increases threefold in patients with stable coronary artery disease and peripheral vascular disease, while the risk of cardiac death increases six-fold, compared to patients without vascular disease [21].

In the REACH registry [8], 1-year risk of cardiovascular death, myocardial infarction (MI), stroke or hospitalization for atherothrombosis was 23.1% in presence of combined CAD and PAD and 13-17% in either disease alone; this risk increased with the number of districts affected by symptomatic disease.

Data from Global Registry of Acute Coronary Events (GRACE) [19] showed an increase of in-hospital mortality from 4.5 to 7.2% and 6-month mortality from 3.9 to 8.8% in patients with LEAD.

Ankle-brachial index (ABI), which correlates with LEAD severity, is a strong marker of cardiovascular disease and it is predictive of cardiovascular events and mortality [22,23].

**Multisite artery disease and myocardial revascularization:** Several trials have shown that patients with LEAD or cerebrovascular disease undergoing percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG) for CAD had higher procedural failure rates, in-hospital system complication rates and long term rates of MI, target vessel revascularization and cardiac mortality [24-30].

The extra cardiac arteriopathy (any or more of the following: claudication, carotid occlusion or > 50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries, or carotids) is one of parameters considered in the EuroScore risk model to predict in-hospital mortality for patients undergoing open-heart surgery; extra cardiac arteriopathy is significantly associated with the occurrence of operative mortality (Odds ratio 1.9, P value 0.001) [31].

The important relationship between carotid artery disease and coronary artery disease (CAD) is expressed by the high incidence of stroke following CABG [4,32].

**Coronary Artery Disease In Patients Undergoing Vascular Surgery**

Coronary artery disease is the leading cause of death in patients with peripheral artery disease.

Postoperative and long-term prognosis of vascular surgery is strongly influenced by the presence of ischemic heart disease. Cardiovascular death is the major cause of peri-operative and long-term mortality among vascular surgical patients with PAD [33-35]; cardiac risk is more than 5% [36].

The risk of perioperative complications is related to patient's conditions before surgery, presence of comorbidity and the nature, duration and urgency of surgery. In severe cases, the presence of CAD prevents surgery, due to this risk.

Guidelines on the diagnosis and treatment of peripheral artery diseases [4] and guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery [36] recommend a careful evaluation of the patient according to clinical risk factors, results of imaging studies and the surgical stress, to obtain a preoperative cardiac risk assessment and to select the most appropriate intervention. Prophylactic coronary revascularization before surgery shows no advantage in terms of all-cause death or MI [37,38]. However, Monaco et al. suggested that systematic prophylactic coronary angiography and myocardial revascularization in medium-high-risk patients improves long-term outcome after major vascular surgery [39].

**Treatment of Patients with Multi-Site Atherosclerotic Disease**

The best management of patients with multisite artery disease is not standardized, due to lack of randomized trials.

A global evaluation not only of the specific treatment options for the management of lesion sites, but also of the clinical status of the patient is mandatory. So, the treatment strategy suggested by current guidelines for the management of atherosclerotic disease involving specific districts should be adapted on an individual basis.

**Treatment of carotid disease in patients with coronary artery disease**

The benefits of surgical carotid artery revascularization (carotid endarterectomy, CEA) over medical management have been clearly established in several randomized trials, including the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [40], Asymptomatic Carotid Atherosclerosis Study (ACAS) [41], Asymptomatic Carotid Surgery Trial (ACST) [42] and European Carotid Surgery Trial (ECST) [43]. Nevertheless, the risks of CEA (stroke, TIA, MI, cranial nerve palsy, hypertension, hypotension, haemorrhage, venous thromboembolism, restenosis, infection, death) are higher in patients with CAD.

The Stenting and Angioplasty with Protection in Patients with High Risk for Endarterectomy (SAPPHIRE) study [44] and the randomized multicentre Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) trial [45] demonstrated that carotid artery stenting (CAS) with use of embolic protection devices (distal filters and proximal protection) should be considered as an alternative to surgical revascularization in symptomatic patients at high surgical risk [46,47].

**Treatment of Lower Limb Disease in Patients with Coronary Artery Disease**

While revascularization is mandatory in patients with critical limb ischemia (CLI) [4], the evidence of long-term benefit of prophylactic revascularization over supervised exercise and best medical treatment is inconclusive [48]. Revascularization is indicated in patients with lifestyle-limiting claudication when clinical features suggest a reasonable likelihood of symptomatic improvement and there has been an inadequate response to conservative therapy.

The selection of the most appropriate revascularization strategy is based on comorbidities, anatomical suitability, according to the Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) [49].

A primary endovascular approach may be considered in complex lesions (TASC D) in patients with severe comorbidities, if done by an experienced team [49]. Endovascular treatment offers several advantages: lesser invasivity, local anesthesia, short hospitalization time, no preclusion to subsequent surgery and possibility to repeat intervention if necessary.

**Multi-Site Percutaneous Revascularization**

It's important to consider a global therapeutic approach of
Endovascular treatment of coronary and carotid disease

In 2001, Kiesz et al. [50] published the first case of treatment with PCI and bilateral internal carotid artery stenting.

In the recent clinical trial FRIENDS [54], patients with ACS (ST-Elevation Myocardial Infarction STEMI, Non-ST elevation myocardial infarction NSTEMI, unstable angina) and asymptomatic carotid disease were divided into three groups of treatment: surgical (CABG and CEA), endovascular (PCI and carotid Percutaneous Transluminal Angioplasty, PTA) and hybrid (CABG and carotid PTA or PCI and TEA).

The trial showed lower incidence of primary endpoints (death, MI, ischemic stroke) in patients treated by combined PCI and carotid PTA, compared to patients treated with surgical coronary and carotid revascularization: in particular, the endovascular group had a lower incidence of mortality and myocardial infarction, but higher of stroke and bleeding.

In May 2011, a prospective study [55], enrolling 239 patients affected by carotid obstructive disease and concomitant coronary disease undergoing PCI and carotid artery stenting, was published. The primary endpoints (major adverse cardiac and cerebrovascular events, MACCE) within 30 days occurred in 4.2% of patients, the mortality rate was 4.2%, the incidence of MI and stroke was 2.1% and 3.8% respectively.

According to these data, a combined percutaneous treatment seems to be comparable to previous surgical experiences, in terms of cardiac and cerebrovascular events, especially for patients considered at high surgical risk.

Endovascular treatment of coronary and lower limb disease

The first cases of combined PCI and PTA for LEAD were described by Baruah et al. [51] and Movahed et al. [53].

Bartuś et al. coordinated the most significant studies. In patients with non-ST elevation ACS and chronic LEAD, treated by PCI and PTA, this group documented a promising long-term follow-up [56]. In another trial, Bartuś et al. assessed long-term (12-month) safety and efficacy of coronary and peripheral endovascular procedures in patients with multi-vessel CAD, in comparison to patients with a single-vessel CAD [57]. Generally, patients with multi-vessel CAD had a worse cardiovascular prognosis due to comorbidity and risk factors of atherosclerosis. These patients, when treated by PCI and PTA for LEAD, had a similar prognosis compared to those with single-vessel CAD.

According to a recent study [58], a combined “global” revascularization of coronary and lower extremities districts could be associated to a better outcome. A total number of 245 patients with NSTEMI or unstable angina and LEAD (intermittent claudication for at least 3 months prior to the event) were enrolled; 125 patients underwent PCI and PTA procedures, 120 patients PCI alone. Primary endpoints (MACCE: death, MI, ischemic stroke/TIA, urgent PCI or CABG) occurred in 3.2% of patients treated with PCI and PTA and in 15% of patients treated with PCI alone (p = 0.029); secondary endpoints (major adverse peripheral events: rePTA, ischemic stroke/TIA, lower limb amputation) were more frequently in the group of patients treated with PCI and PTA (6.4% vs 3.3%, p = 0.19).

Conclusions

The prevalence of multisite vascular disease is increasing and influences the prognosis and the possible strategies of treatment.

Endovascular techniques have rapidly developed as an alternative to surgery for patients at high cardiac risk and offer promising long-term outcome.

References


