Systematic detection of polyvascular disease combined with aggressive secondary prevention in patients presenting with severe coronary artery disease: The randomized AMERICA Study☆☆☆

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Background: The prevalence and associated-risk of asymptomatic multisite artery disease (MSAD) in high risk coronary patients are unknown. Whether systematic identification and aggressive management of asymptomatic MSAD is clinically relevant in high risk coronary patients has not been evaluated.

Methods: We randomly assigned 521 high risk coronary patients defined by the presence of three-vessel coronary disease (n = 304) or recent acute coronary syndrome beyond the age of 75 years (n = 215) to either a strategy of systematic detection of asymptomatic MSAD combined with an aggressive secondary prevention (n = 263) or to a more conventional strategy based on treatment of coronary artery disease only with standard of care (n = 258). The primary end point was the time to first occurrence of death, any organ failure or ischemic event leading to re-hospitalization through two years of follow-up.

Results: The pro-active strategy identified asymptomatic MSAD in 21.7% of patients with few revascularizations (3.6%); the pro-active pharmacological secondary prevention was obtained in ~85% of patients and lifestyle changes in ~60% of patients. At 2-year follow-up, the primary end point occurred in 44.9% of patients in the pro-active group and 41.0% of patients in the conventional group (HR 1.03; 95% confidence interval [CI], 0.80 to 1.34). The rate of major bleeding did not differ significantly between groups (4.6% vs 5.0%; HR, 0.97; 95% CI, 0.40 to 1.91).

Conclusion: In high risk coronary patients, there is no apparent benefit of a systematic detection of asymptomatic extra-coronary atherothrombotic disease and intensified treatment over a 2-year follow-up period. (Fundied by the Academic Allies in Cardiovascular Trials Initiatives and Organized Networks and Institut de l’Atherothrombose; AMERICA ClinicalTrials.gov number, NCT00445835).

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Abbreviations: AMERICA, The Active detection and Management of the Extension of atherothrombosis in high Risk coronary patients In comparison with standard of Care for coronary Atherosclerosis, CAD, Coronary Artery Disease; CABG, Coronary Artery By-pass Graft; LEAD, Lower Extremity Artery Disease; MSAD, Multisite Artery Disease; PCI, Percutaneous Coronary Intervention.

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1. Introduction

Atherosclerosis is a slow-progressing systemic disease which can affect virtually any arterial territory [1–3] but is often detected at an advanced stage or after a cardiovascular event. At early stages, the most frequent subclinical location of atherothrombosis is ilio-femoral [4]. Extensive atherosclerosis is identified in up to one third of low-risk individuals suggesting a potential added value of noninvasive imaging for improving cardiovascular risk stratification. At later stages, the presence of significant vascular lesions in different arterial locations is common. The prevalence of multisite artery disease (MSAD) in patients with established coronary artery disease (CAD) is 5 to 10% for carotid artery disease and up to 40% for lower extremity artery disease (LEAD) [5].

In patients with symptomatic CAD, symptomatic MSAD is associated with increased mortality and more frequent major cardiovascular events [2,6]. Asymptomatic MSAD remains challenging given the paucity of data on its real prevalence, its relationship to ischemic events and the potential benefit of their treatment [7]. As for an example, asymptomatic severe carotid artery stenosis in multivessel CAD patients scheduled for CABG is identified in up to 10% and is associated with a three to five-fold increased risk of perioperative stroke [8–10]. However, whether a systematic identification of such asymptomatic lesions using noninvasive imaging is relevant in all comers not eligible for CABG surgery is unknown and a case by case decision making is recommended [11].

The active detection and Management of the Extension of atherothrombosis in high risk coronary patients In comparison with standard of Care for coronary Atherosclerosis (AMERICA) study evaluated a pro-active strategy of detection and management of the extension of atherothrombosis to territories other than coronary combined with an aggressive pharmacological secondary prevention strategy in a population with very high risks features of coronary disease (pro-active strategy) as compared with a conservative strategy based on a clinically-guided identification of MSAD and standard pharmacological treatment (conventional strategy).

2. Methods

2.1. Study patients

In this randomized, open-label study, we recruited high risk patients with recently (<6 months) diagnosed stable three-vessel CAD (profile 1) or recent (<1 month) acute coronary syndrome (ACS) occurring beyond the age of 75 (profile 2) at 25 centers in France. When patients qualified for both profiles, profile 1 was quoted. Main exclusion criteria were the absence of significant coronary lesions and/or a rise in troponin level related to a non-coronary cause (Online Table 1). This study was performed according to the Declaration of Helsinki and the study protocol was approved by the French National Institutional Ethical Review Board. Written informed consent was obtained from all patients. The study was coordinated by the ACTION Study Group (www.action-coeur.org) at Pitié-Salpêtrière Hospital in Paris, France.

2.2. Randomization and treatment strategies

Randomization was conducted centrally with the use of an interactive voice-response system. Eligible patients were randomly assigned to a strategy of active and systematic detection of asymptomatic MSAD combined with aggressive secondary prevention (pro-active group) or to a more conventional strategy based on treatment of CAD and known symptomatic MSAD only (conventional group) (Fig. 1). Stratification was by center and patient profile with random block size. Randomization was always performed after CAD was proven by angiography irrespective of the revascularization strategy but, always prior to CABG surgery if it was the chosen strategy.

In the pro-active treatment strategy, systematic detection of atherosclerosis was undertaken combining ankle-brachial index measurement and carotid, lower-extremities and renal vascular duplex ultrasound. Computed tomography angiography and/or magnetic resonance imaging were allowed according to local practice. Decisions of revascularization were left to the physicians in charge of the patients on the basis of the international recommendations (Online Table 2) [12]. The pro-active pharmacological program recommended lipid-lowering therapy with target LDL ≤ 70 mg/dl, a systematic use of angiotensin-converting enzyme (ACE) inhibitors at doses proven to be effective, prolonged dual antiplatelet therapy during the whole duration of follow-up and a systematic beta-blockade aiming at a rest heart rate of 60 bpm. Smoking cessation, blood pressure and blood glucose controls were also part of the pro-active program strategy. Predefined biomarkers were measured every 6 months to guide secondary prevention. In the conventional-treatment group, standard medical therapy and a selective symptom-guided detection of MSAD was recommended. Follow-up visits were performed every 6 months for all patients.

2.3. End points

The primary endpoint was a composite of death, any ischemic event leading to rehospitalization or any evidence of organ failure during the two-year follow-up period. Organ failure was defined as any episode of acute heart failure, new cognitive dysfunction, acute or worsening renal failure, new atrial or ventricular arrhythmia, and episode of malignant hypertension. The main secondary endpoint included the composite of all-cause death, myocardial infarction, stroke or any revascularization. Other prespecified end points were the prevalence of MSAD, each individual component of the primary end point, the number of hospitalizations. The main safety end point was major bleeding, according to the Thrombolysis In Myocardial Infarction definition. All definitions are described in the online supplement material. Independent predictors of asymptomatic MSAD were also identified.

![Fig. 1. Study flow chart.](image-url)
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