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Long-term Results of a Randomized Controlled Trial Analyzing the Role of Systematic Pre-operative Coronary Angiography before Elective Carotid Endarterectomy in Patients with Asymptomatic Coronary Artery Disease☆

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WHAT THIS PAPER ADDS

This study demonstrates that systematic pre-operative coronary angiography, followed by selective myocardial revascularization prior to carotid endarterectomy (CEA), reduces the incidence of late myocardial infarction and increases the survival rate in patients without any previous history of coronary artery disease. Therefore in the future, routine coronary screening should be considered as part of the standard pre-operative cardiac workup for CEA candidates. In addition, considering not only the potential risk of myocardial infarction in these patients but also the opportunity cost entailed, a possibly less invasive screening test with pre-operative thallium scanning or coronary CT should be thoroughly investigated.

Objectives: To evaluate the potential benefit of systematic preoperative coronary-artery angiography followed by selective coronary-artery revascularization on the incidence of myocardial infarction (MI) in patients undergoing carotid endarterectomy (CEA) without a previous history of coronary artery disease (CAD).

Methods: We randomised 426 patients who were candidates for CEA, with no history of CAD, a normal electrocardiogram (ECG), and a normal cardiac ultrasound. In group A (n = 216) all patients underwent coronary angiography before CEA. In group B (n = 210) CEA was performed without coronary angiography. Patients were not blinded for relevant assessments during follow-up. Primary end-point was the occurrence of MI at 3.5 years. The secondary end-point was the overall survival rate. Median length of follow-up was 6.2 years.

Results: In group A, coronary angiography revealed significant coronary artery stenosis in 68 patients (31.5%). Among them, 66 underwent percutaneous Intervention (PCI) prior to CEA and 2 received combined CEA and coronary-artery bypass grafting (CABG). Postoperatively, no MI was observed in group A, whereas 6 MI occurred in group B, one of which was fatal ($p = .01$).

During the study period, 3 MI occurred in group A (1.4%) and 33 were observed in group B (15.7%), 6 of which were fatal. The Cox model demonstrated a reduced risk of MI for patients in group A receiving coronary angiography (HR,.078; 95% CI, 0.024-0.256; $p < .001$). In addition, patients with diabetes and patients <70 years presented with an increased risk of MI. Survival analysis at 6 years by Kaplan-Meier estimates was 95.6 ± 3.2% in Group A and 89.7 ± 3.7% in group B (Log Rank = 6.54, p = .01).

Conclusions: In asymptomatic coronary-artery patients, systematic coronary angiography prior to CEA followed by selective PCI or CABG significantly reduces the incidence of late MI and increases long-term survival. **(*ClinicalTrials.gov number, NCT02260453*).**

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INTRODUCTION

The prevalence of coronary artery disease (CAD) among patients undergoing elective vascular surgery has been reported to be between 46% and 71%[1,2] with post-operative coronary complications observed in around 20% of cases[3] and an incidence of cardiac death at 1 year between 6 to 10%.[4–7] In addition, a large retrospective study[8] has shown that coronary artery bypass grafting (CABG) before peripheral vascular surgery improves long-term outcomes.

Panels of experts have recommended CABG before peripheral vascular surgery in patients with unstable angina for whom CABG offers long-term survival benefit.[9] But despite the existence of consensus guidelines, the optimal strategy for pre-operative cardiac risk management among patients scheduled for peripheral vascular surgery remains controversial with the likelihood of discordance between two cardiologists around 54%, and a 26% chance that recommendations for coronary revascularization will be directly contradictory.[10] While some studies have demonstrated the efficacy of coronary angiography or thallium scanning followed by selective coronary revascularization in the prevention of post-operative myocardial ischemia,[11–13] other studies have not only failed to show any substantial benefit but also raised concern about the risk of peri-operative bleeding in conjunction with the dual antiplatelet regimen required after pre-operative percutaneous intervention (PCI).[14–16]

In a previous data analysis, it was demonstrated that systematic pre-operative angiography, followed by selective coronary revascularization, significantly reduced the incidence of post-operative MI after carotid endarterectomy (CEA) in patients without clinical evidence of CAD.[17] We are reporting in the present study, the long-term follow up of this trial to assess whether the systematic use of pre-operative coronary angiography followed by selective coronary artery revascularization significantly reduces occurrence of late MI and improves survival in patients without a previous history of CAD at the time of carotid surgery.

MATERIAL AND METHODS

Study design

This randomized controlled trial (RCT) was conducted between January 2005 and December 2008 at two academic surgical centers and one affiliated surgical service. 426 patients were enrolled in the study. Among them, 216 were randomized to undergo pre-operative coronary angiography (group A) prior to CEA, and 210 underwent CEA without prior coronary angiography (group B) The trial was registered (ClinicalTrials.gov number, NCT02260453) and supported by a grant from the University of Rome. The institutional review board of the University approved the trial protocol and all patients provided written informed consent.

Randomization

Random assignment of patients to the two treatment groups was done independently of participating centers in a one to one ratio. The randomization sequence was generated by a computer program and centralized. The time of randomization was considered as time 0.

Eligibility criteria

The indication for CEA included carotid artery stenosis $>$ 60% according to the NASCET criteria.[18] As previously reported,[17] patients referred for CEA were enrolled in the study if they had no evidence of CAD, defined as the absence of any clinical sign or history of ischaemic cardiac disease, no electrical signs of cardiac ischemia at rest and a left ventricular ejection fraction $>$ 50% on transthoracic echocardiogram. In order to measure functional capacity (METS-metabolic equivalent), the cardiologists included a questionnaire on physical activity following the International Physical Activity Questionnaire (IPQ), the Physical Activity Scale for the Elderly (PASE), and the Metabolic Equivalent Task Scale (METS) with careful investigation of any clinical metabolic impairment before randomization. The items included were (a) classification of effort dyspnea during daily activity, (b) cycling (if adequate), (c) climbing a flight of stairs, (d) walking 4 mph, (e) yard work and other physical activity corresponding to a functional capacity classification of 4—7 METS. All patients presenting with doubtful clinical status and a functional capacity below 4 METS despite a normal left ventricular ejection fraction (LVEF) were excluded from randomization and received a complete coronary workup. Randomized patients had a median METS of 5.8 (4.5—7.6).

In addition, the initial METS classes of patients with positive coronary angiography in group A or without coronary angiography (group B) but presenting with a MI during follow up were not different from those of patients with negative coronary angiography and/or uneventful coronary follow up. As shown in the CONSORT flowchart (Fig. 1) patients were randomized in two groups. In group A, coronary artery stenosis was considered significant if $>$ 75% in diameter reduction as seen on coronary angiography, with the help of intravascular ultrasound in nine doubtful cases. Significant stenosis was treated either by PCI or by CABG according to current treatment standards. After coronary angiography and PCI all patients had ECG monitoring and their serum troponin level was assessed at 4, 8, 12, and 24 hours after the procedure. Periprocedural MI was defined as electrical changes associated with rise of troponin levels (Table 1). In group B ($n = 210$) patients received CEA without any further cardiac evaluation.

Study endpoint

The primary endpoint of the study was the occurrence of MI at 3.5 years. The secondary endpoint was overall survival and freedom from stroke, along with any complication related to coronary angiography and PCI. These endpoints were evaluated at 30 days and at 6 years from randomization.

Sample size

As previously reported in the CARP (Coronary Artery Revascularization Prophylaxis) trial,[3] MI was observed in approximately 20% of patients after major peripheral vascular surgery. In this study two groups of $>$ 200 patients