

EDITORIAL COMMENT

Coronary Revascularization Before Noncardiac Vascular Surgery

One More Step Forward in Understanding Its Role*

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Epidemiologic studies have shown that up to 60% of patients with peripheral arterial disease have underlying clinical or subclinical coronary artery disease (1) and that the presence of peripheral arterial disease is associated with a 6.6-fold increase in relative risk of death from coronary heart disease (2). In addition to this strong relationship between peripheral arterial disease and cardiovascular mortality, numerous studies have shown a high risk of morbidity and mortality in patients with peripheral arterial disease undergoing surgical procedures, and in particular in patients undergoing open vascular surgical procedures. Angina pectoris, prior myocardial infarction (MI), prior heart failure, severe renal insufficiency, poor functional capacity (3,4), severe valvular heart disease, and myocardial ischemia on non-invasive testing are today recognized markers for increased risk (3). Although over the past 2 decades we have learned how to identify patients with peripheral arterial disease at increased risk of complication following surgical procedures, effective interventions aimed toward reducing such risk remain somewhat elusive.

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Aggressive medical management and myocardial protection with beta-blockers, statins, and antiplatelet agents currently play key roles in the perioperative management of patients undergoing vascular surgery (5–7). In particular, the use of beta-blockers in the perioperative state has been found to be associated with a significant reduction in the

incidence of perioperative ischemia, nonfatal MI, and death from cardiac cause (5) and with a lower mortality at short- and long-term follow-up following the index procedure (6).

The role of preoperative coronary revascularization in this patient population has been in part clarified by the recent CARP (Coronary Artery Revascularization Prophylaxis) trial (8). In the CARP trial, patients with stable coronary artery disease scheduled to undergo elective vascular operations were randomized to coronary revascularization or to optimal medical therapy. Medical therapy was optimized in both groups. Patients with left main stenosis >50%, left ventricular ejection fraction <20%, and severe aortic stenosis were excluded. The majority of patients enrolled had single- or 2-vessel disease. Following vascular surgery, there were no differences between the 2 groups in the incidence of MI or in-hospital mortality. At a median follow-up time of 2.7 years, the mortality rate was 22% in the revascularization group and 23% in the no-revascularization group. A non-significant trend toward a benefit of revascularization was identified in a small group of high-risk patients. Thus, although underpowered to detect differences in event rates in high-risk subgroups, the CARP trial suggested that if vascular surgery candidates are carefully screened and patients with unstable coronary symptoms, left main disease, aortic stenosis, or severe left ventricular dysfunction are excluded, revascularization does not appear to provide additional benefit in reducing the incidence of perioperative death or MI when compared with optimal perioperative medical treatment (9). Thus, the CARP trial provided us with an answer to the critical question regarding revascularization therapy, but left unsettled the questions regarding screening of patients and revascularization in high-risk patients.

In this issue of the *Journal*, Poldermans et al. (10) report the result of the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo Study Group)-V pilot study, a small randomized pilot study designed to test the safety and efficacy of 2 different treatment strategies in patients undergoing major vascular surgery. The population included patients scheduled to undergo abdominal aortic aneurysm repair or infrainguinal peripheral bypass surgery. Patients with 3 or more cardiovascular risk factors were evaluated with either dobutamine stress echocardiography or stress nuclear imaging. Those with extensive stress-induced ischemia were then randomized to either cardiac catheterization followed by coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or to medical therapy. All patients received beta-blockers, and anti-platelet therapy was continued in the perioperative period. The primary end point was a composite all-cause mortality and nonfatal MI at 30 days, and the secondary end point was a composite all-cause mortality and nonfatal MI at 1 year. A total of 1,880 patients were screened and, of these, 430 patients were identified as being at high risk (>3 risk factors). Of the 430 high-risk patients, 101 (23%) showed extensive ischemia and

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were randomly assigned to revascularization ($n = 49$) or no revascularization ($n = 52$). At 30-day follow-up, the incidence of the composite end point was 43% and 33% in the revascularization and no-revascularization group, respectively (odds ratio [OR] 1.4, 95% confidence interval [CI] 0.7 to 2.8, $p = 0.30$). No benefit with revascularization was observed at 1-year follow-up (event rates 49% vs. 44%, OR 1.2, 95% CI 0.7 to 2.3, $p = 0.48$). Importantly, 2 patients died after revascularization but before the operation because of a ruptured aneurysm.

The results of this study should be evaluated taking into account several factors. First, as stated by the authors in their introduction, the purpose of the study was "to assess the feasibility, and to obtain initial efficacy and safety estimates for the design of an adequately powered randomized controlled clinical trial in these patients." Thus, the trial was not powered to show a difference between optimal medical therapy and revascularization in high-risk patients. On the basis of the results obtained in this pilot study, the authors estimate that it would be safe to design such trials, and that in order to show that coronary revascularization is superior to medical therapy in improving postoperative outcome in high-risk patients by 20% (relative risk), more than 300 patients per arm would be required. Such a sample size would also require screening 9,000 major vascular surgery patients, of whom 2,000 would have 3 or more cardiac risk factors at screening. In addition, in the CARP trial, there was a nonsignificant trend toward a benefit of revascularization in a small group of patients with high-risk clinical features and objective evidence of ischemia (adjusted OR 4.0, 95% CI 0.8 to 19). In contrast, no such trend was observed in the current study, which specifically addressed high-risk patients. All this taken into account, the equivalence between medical therapy alone and revascularization plus medical therapy in high-risk patients is far from being proven.

Second, although the CARP trial addressed the issue of treatment following screening, in the current study, patients who were already identified as high risk were randomized to an invasive approach plus revascularization and optimal medical therapy versus optimal medical therapy alone. None of the patients randomized to optimal medical therapy alone underwent diagnostic cardiac catheterization, thus suggesting that effective beta-blockade and medical therapy might be sufficient and raising the question whether stable patients scheduled for major vascular surgery should even be screened with stress testing.

Third, 2 patients in the revascularization group died after revascularization but before operation because of a ruptured aneurysm, consistent with the fact that urgent or emergency vascular surgery in unstable patients should not be delayed by revascularization.

Finally, despite full optimization of medical therapy, the event rate in both treatment groups was still very high,

raising the additional question of how we can further reduce adverse events in these high-risk patients.

The lack of benefit from revascularization in the perioperative period observed both in this trial and in the CARP trial can be reconciled on the basis of histopathologic studies, which have shown that the pathophysiology surrounding fatal MI in the perioperative period after noncardiac surgery often includes unstable plaque and plaque disruption (11). Thus, it is possible that revascularization of stable coronary artery stenosis might not add significantly to the effect of optimal medical therapy, similar to what has been shown for other low-risk patients with stable coronary artery disease.

All that said, the debate on screening and revascularization for patients with peripheral arterial disease and scheduled for major vascular surgery continues to be far from settled. The importance of the DECREASE-V pilot trial is that it provides us with supporting evidence on safety and with the needed sample size for a larger trial that could help in settling this issue. It is now time to move forward with such a trial.

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