Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 49, No. 17, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2006.11.052

A Clinical Randomized Trial to Evaluate the Safety of a Noninvasive Approach in High-Risk Patients Undergoing Major Vascular Surgery

The DECREASE-V Pilot Study

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Objectives The purpose of this research was to perform a feasibility study of prophylactic coronary revascularization in patients with preoperative extensive stress-induced ischemia.

Background Prophylactic coronary revascularization in vascular surgery patients with coronary artery disease does not improve postoperative outcome. If a beneficial effect is to be expected, then at least those with extensive coronary artery disease should benefit from this strategy.

Methods One thousand eight hundred eighty patients were screened, and those with ≥3 risk factors underwent cardiac testing using dobutamine echocardiography (17-segment model) or stress nuclear imaging (6-wall model). Those with extensive stress-induced ischemia (≥5 segments or ≥3 walls) were randomly assigned for additional revascularization. All received beta-blockers aiming at a heart rate of 60 to 65 beats/min, and antiplatelet therapy was continued during surgery. The end points were the composite of all-cause death or myocardial infarction at 30 days and during 1-year follow-up.

Results Of 430 high-risk patients, 101 (23%) showed extensive ischemia and were randomly assigned to revascularization (n = 49) or no revascularization. Coronary angiography showed 2-vessel disease in 12 (24%), 3-vessel disease in 33 (67%), and left main in 4 (8%). Two patients died after revascularization, but before operation, because of a ruptured aneurysm. Revascularization did not improve 30-day outcome; the incidence of the composite end point was 43% versus 33% (odds ratio 1.4, 95% confidence interval 0.7 to 2.8; p = 0.30). Also, no benefit during 1-year follow-up was observed after coronary revascularization (49% vs. 44%, odds ratio 1.2, 95% confidence interval 0.7 to 2.3; p = 0.48).

Conclusions In this randomized pilot study, designed to obtain efficacy and safety estimates, preoperative coronary revascularization in high-risk patients was not associated with an improved outcome. (J Am Coll Cardiol 2007;49:1763–9) © 2007 by the American College of Cardiology Foundation

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Patients with multiple cardiac risk factors scheduled for major vascular surgery are at increased risk of perioperative cardiac complications. According to the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA), it is highly recommended to refer these patients for noninvasive cardiac stress testing before surgery (1). The guidelines also recommend coronary angiography for patients with high-risk

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Manuscript received July 19, 2006; revised manuscript received October 31, 2006, accepted November 2, 2006.

Abbreviations and Acronyms

ACC = American College of Cardiology
AHA = American Heart Association
CABG = coronary artery bypass graft
CI = confidence interval
LVEF = left ventricular ejection fraction
OR = odds ratio
PCI = percutaneous coronary intervention

noninvasive test results, and myocardial revascularization in patients with prognostic high-risk anatomy in whom long-term outcome is likely to be improved.

However, noninvasive testing may delay surgery and run the risk of aortic aneurismal rupture or exacerbation of critical limb ischemia. Furthermore, coronary revascularization is commonly performed by percutaneous coronary intervention (PCI) with stent placement instead of bypass surgery (CABG). Although this approach prevents further delay of the index surgical procedure, it necessitates the prolonged use of extensive antiplatelet therapy, which may aggravate the risk of perioperative bleeding complications. But temporary discontinuation of antiplatelet therapy is potentially harmful, as it may lead to in-stent thrombosis (2,3).

The current ACC/AHA recommendations are based on small observational, noncontrolled studies and expert opinion (4,5). The usefulness of the strategy of prophylactic revascularization was not confirmed by the recently completed CARP (Coronary Artery Revascularization Prophylaxis) randomized trial (6). In this trial, the incidence of perioperative myocardial infarction was similar in patients allocated to prophylactic revascularization versus those allocated to optimal medical therapy (12% vs. 14% events). There was also no beneficial effect observed during long-term follow-up. However, it should be realized that the vast majority of patients included in the CARP trial had single- or 2-vessel disease with a preserved left ventricular function. Indeed, based on previous research from our group, sufficient cardioprotection by medical therapy can be expected in these patients, which may explain the CARP trial findings (7). In contrast, patients with multiple cardiac risk factors and extensive stress-induced myocardial ischemia are insufficiently protected (7).

Hence, if a beneficial effect of the invasive strategy of prophylactic revascularization is to be expected, then at least patients with extensive coronary artery disease should benefit from this strategy. We therefore undertook the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo)-V pilot study 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.

Methods

Patients. This study was conducted during 2000 to 2005 in 6 hospitals in Belgium (until 2001), Brazil (until 2001), the Netherlands, Italy, Serbia, and Montenegro. The early cessation in participation to the study of 2 centers was due to logistic reasons. A total of 1,880 consecutive patients undergoing elective open abdominal aortic or infrainguinal arterial reconstruction were screened for the prevalence of cardiac risk factors (Fig. 1). These included age over 70 years, angina pectoris, prior myocardial infarction on the basis of history or a finding of pathologic Q waves on electrocardiography, compensated congestive heart failure or a history of congestive heart failure, drug therapy for diabetes mellitus, renal dysfunction (serum creatinine >160 μmol/l), and prior stroke or transient ischemic attack (7). Patients with at least 3 risk factors underwent cardiac stress testing before surgery. All patients who experienced extensive stress-induced ischemia were enrolled in the DECREASE-V pilot study.

All patients provided informed consent, and the study was approved by the Erasmus Medical Center Medical Ethics Committee and local research ethics committees.

Cardiac testing. Left ventricular ejection fraction (LVEF) was measured from resting echocardiographic images using the biplane Simpson's rule. Cardiac stress testing was performed by dobutamine echocardiography or dobutamine or dipyridamole perfusion scintigraphy, as previously described (8,9). Test results were scored by the extent of stress-induced ischemia using a 17-segment model in dobutamine echocardiography and a 6-wall model in stress perfusion scintigraphy. Limited ischemia was defined by the presence of 1 to 4 ischemic segments or 1 to 2 ischemic walls, whereas extensive ischemia was defined by $\geq$5 ischemic segments or $\geq$3 ischemic walls.

Allocated treatment. Perioperative beta-blocker therapy was installed in all patients at the screening visit, regardless of test results. A computer algorithm was used at each center to assign patients with extensive stress-induced ischemia randomly, in a 1:1 ratio, to 1 of the 2 strategies. The sealed envelope method was used to conceal treatment allocation, and it was assured that envelopes were opened in consecutive order. Patients were randomized to either an invasive approach followed by revascularization or a noninvasive approach. Quantitative analysis of all coronary angiographies was reviewed centrally at Erasmus Medical Center, Rotterdam, the Netherlands, by 2 experienced cardiologists. They assessed independently the number of affected vessels. The mode of revascularization, CABG or PCI with stenting, was decided by the treating physicians, based on coronary anatomy and the possible delay of the index surgical procedure. Patients allocated to the medical-only strategy were referred for surgery without further delay.

Beta-blocker therapy. Patients on chronic beta-blocker therapy continued their medication. Patients without beta-blockers started with bisoprolol 2.5 mg once a day at the screening visit. Beta-blocker dose was adjusted in all patients at admission to the hospital and on the day before surgery to achieve a resting heart frequency of 60 to 65 beats/min. The same dose of beta-blockers was continued postoperatively except in patients who were unable to take medication orally or by nasogastric tube postoperatively. In

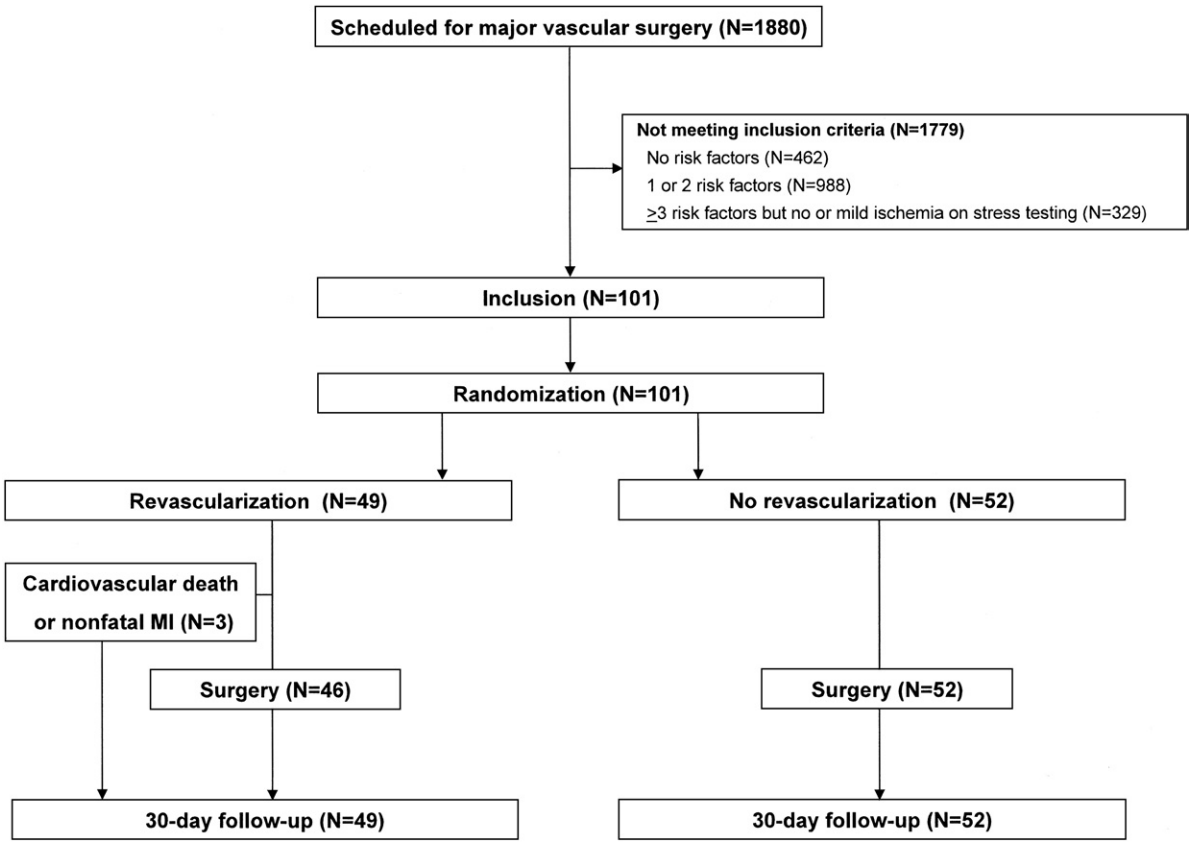

Figure 1 **Flowchart of the Study**

Cardiac risk factors included age over 70 years, angina pectoris, prior myocardial infarction (MI) on the basis of history or a finding of pathologic Q waves on electrocardiography, compensated congestive heart failure or a history of congestive heart failure, current treatment for diabetes mellitus, renal dysfunction (serum creatinine >160 μmol/l), and prior stroke or transient ischemic attack. Patients with >3 risk factors and extensive ischemia were randomly (1:1) assigned to coronary revascularization.

these patients, the heart rate was monitored continuously at the intensive care unit or hourly at the ward, and intravenous metoprolol was administered at a dose sufficient to keep the heart rate between 60 to 65 beats/min. The heart rate and blood pressure were measured immediately before each scheduled dose of beta-blockers. Beta-blockers were withheld if the heart rate was <50 beats/min or the systolic blood pressure was <100 mm Hg. After discharge, patients continued beta-blocker therapy, and dose adjustments were carried out during outpatient visits to achieve a resting heart frequency of 60 to 65 beats/min.

Perioperative management. Anesthetic management, monitoring, and other aspects of perioperative management were at the discretion of the attending physician. Results of preoperative testing and coronary revascularization were discussed with the attending physicians, and hemodynamic management was implemented accordingly. Anticoagulant and antiplatelet therapy was continued after PCI and during the index surgical procedure. Intraoperative ischemia was treated at the discretion of attending physicians, and additional beta-blockers were permitted.

End point definition. All patients were monitored for cardiac events after screening. Twelve-lead electrocardiogram (ECG) and serum troponin-T level were systematically determined 1, 3, 7, and 30 days after surgery. Outpatient follow-up was performed at 30 days if a patient had been discharged from the hospital. At the outpatient clinic, all patients were screened at 3-month intervals for cardiac events by clinical history and 12-lead ECG. All data were collected by the participating centers and evaluated in a blinded fashion by members of the adverse-events committee. The primary end point was the composite of all-cause death and nonfatal myocardial infarction that occurred between screening and 30-days after the index surgical procedure. Patients were followed-up during at least 1 year after surgery, and the composite of all-cause death and nonfatal myocardial infarction during this period was considered as secondary end point. Myocardial infarction within 48 h after CABG was defined as a creatine kinase (CK)-MB rise above 5× the local upper limit of normal. Myocardial infarction within 48 h after PCI was defined as a CK-MB rise above 3× the upper limit of normal.

Myocardial infarction within 30 days after the index surgical procedure was defined as a positive troponin-T level in combination with new Q waves on the ECG lasting more than 0.03 s. In all other situations, myocardial infarctions were defined by new Q waves lasting more than 0.03 s.

Sample size. The purpose of this pilot study was to assess the feasibility of prophylactic revascularization in high-risk patients scheduled for major vascular surgery, and to obtain initial efficacy and safety estimates needed for the design of an adequately powered randomized controlled clinical trial. We aimed for the enrollment of 100 patients, 50 in each strategy. Based on the DECREASE-I study (7), an incidence of 33% of the primary end point was expected in the patients allocated to optimal medical therapy only. It was recognized a priori that a modest, but clinically relevant, risk reduction by prophylactic revascularization would not be detectable given this sample size. However, if the beneficial effect of revascularization was similar to the observations in the CASS (Coronary Artery Surgery Study) registry (85% risk reduction associated with prior CABG in vascular surgery), then our study has 93% power (type II error of 7%), based on a 2-sided test with a type I error of 5%.

Statistical analysis. All analyses were based on the intention-to-treat principle. Continuous data are presented as median values and corresponding 25th and 75th percentiles, whereas dichotomous data are presented as percentages. Differences in clinical and surgical characteristics between patients allocated to revascularization or no revascularization were evaluated by Wilcoxon nonparametric tests, chi-square tests, or Fisher exact tests, as appropriate. Differences in the incidence of the end points were evaluated by a chi-square test. The incidence of events over time was further examined by the Kaplan-Meier method, whereas a log-rank test was applied to evaluate differences between the allocated treatment strategies. Analyses were performed according to the intention-to-treat principle. All statistical tests were 2-sided, and a p value <0.05 was considered significant.

Results

Characteristics of patients. A total of 1,880 vascular surgery patients were enrolled and screened for cardiac risk factors (Fig. 1), and 430 (23%) were classified as high risk, who were referred for cardiac testing. Testing showed extensive ischemia in 101 (22%). Dobutamine echocardiography was performed in 88 (88%), and stress scanning in 13 (13%). No serious side effects occurred during stress testing. Of 101 patients with extensive stress-induced ischemia, 49 patients were randomized for coronary revascularization. A reduced LVEF (<35%) was observed in 43 (43%) patients. No patient had significant valve disease such as aortic stenosis or mitral valve regurgitance. Coronary angiography, performed in patients allocated to the invasive strategy, showed 2-vessel disease in 12 (24%), 3-vessel disease in 33 (67%), and left main disease in 4 (8%). A PCI was performed in 32 patients, using a drug-eluting stent in 30 and a bare-metal stent in 2, and bypass surgery in 17. There were no differences in the presence of ischemic heart disease (i.e., previous myocardial infarction and angina pectoris) or other baseline characteristics between the randomized groups (Table 1). Complete revascularization was achieved in 42 (86%). Incomplete revascularization occurred in 7 (15%) patients initially scheduled for a percutaneous intervention. Bypass surgery was considered not feasible in these patients as the index procedure could not be further delayed. The median duration of revascularization to operation was 29 (13 to 65) days in the 17 patients undergoing bypass surgery and 31 (19 to 39) days in the 32 patients undergoing a percutaneous intervention.

Table 1 Baseline Characteristics

	Revascularization	No Revascularization
Number of patients	49	52
Age (yrs)	71 (64, 74)	70 (63, 75)
Men	42 (86%)	47 (90%)
History of diabetes	18 (37%)	15 (29%)
Current angina pectoris	25 (51%)	22 (42%)
History of myocardial infarction	49 (100%)	50 (96%)
History of congestive heart failure	23 (47%)	24 (46%)
History of cerebrovascular accident	20 (41%)	13 (25%)
History of renal failure	9 (18%)	11 (21%)
Aspirin use	37 (76%)	30 (58%)
Beta-blocker use	34 (70%)	36 (69%)
ACE inhibitor use	28 (57%)	22 (42%)
Statin use	34 (69%)	30 (58%)
Type of surgery		
Thoraco-abdominal	5 (10%)	5 (10%)
Tube graft	11 (22%)	14 (27%)
Bifurcated graft	10 (20%)	15 (29%)
Femoro-popliteal	23 (47%)	18 (35%)
Right coronary artery disease	39 (80%)	—
Left artery descending	46 (94%)	—
Left circumflex artery	37 (76%)	—
Number of diseased vessels		—
1	0	—
2	12 (24%)	—
3	33 (67%)	—
Left main disease (%)	4 (8%)	—

ACE = angiotensin-converting enzyme.

Antiplatelet therapy, using aspirin and clopidogrel, was continued during surgery in all patients who underwent a PCI. The median perioperative blood transfusion requirement in patients with and without antiplatelet therapy was similar: 2 versus 3 U (p value = 0.25).

Perioperative cardiac events. Two patients died before vascular surgery because of a ruptured aneurysm after successful bypass surgery. Their aortic diameters were, respectively, 62 and 73 mm. In 1 patient, a myocardial infarction occurred after an incomplete coronary revascularization. This precluded the proceeding of the scheduled vascular surgery. Revascularization did not improve

Table 2 Patient Outcome

	Revascularization n (%)	No Revascularization n (%)	HR (95% CI)	p Value
Number of patients	49	52		
Events before surgery				
All-cause mortality	2 (4.1)	0	—	0.23
Myocardial infarction	1 (2.1)	0	—	
Composite	3 (6.1)	0	—	0.11
Events up to 30 days after surgery				
All-cause mortality	11 (22.5)	6 (11.5)	2.2 (0.74–6.6)	0.14
Myocardial infarction	17 (34.7)	16 (30.8)	—	
Composite	21 (42.9)	17 (32.7)	1.4 (0.73–2.8)	0.30
Events up to 365 days after surgery				
All-cause mortality	13 (26.5)	12 (23.1)	1.3 (0.55–2.9)	0.58
Myocardial infarction	18 (36.7)	19 (36.5)		
Composite	24 (49.0)	23 (44.2)	1.2 (0.68–2.3)	0.48

CI = confidence interval; HR = hazard ratio.

30-day outcome after vascular surgery. Troponin elevation was found in 38.8% in the noninvasive group versus 34.7% in the invasive group. The incidence of all-cause death or nonfatal myocardial infarction for patients with preoperative revascularization or medical treatment only was 43% versus 33%, respectively (odds ratio [OR] 1.4, 95% confidence interval [CI] 0.7 to 2.8; p = 0.30) (Table 2). Also, no difference was observed in the incidence of perioperative cardiac events between patients treated by prophylactic bypass surgery or percutaneous intervention (41.1% vs. 43.8%, respectively).

Late cardiac events. The incidence of the 1-year end point all-cause death or nonfatal myocardial infarction in high-risk patients was 47%. In high-risk patients, no long-term benefit was observed after coronary revascularization; respectively, 49% versus 44% of patients with preoperative revascularization or medical treatment only died or experienced a nonfatal myocardial infarction (OR 1.2, 95% CI 0.7 to 2.3; p = 0.48) (Fig. 2). No patients initially randomized for medical therapy underwent revascularization within 1 year of follow-up. One patient randomized to the invasive strategy underwent a redo PCI because of myocardial infarction in the first year of follow-up.

Implications for a study design. Assuming that the event rates in the 101 studied patients are representative of what would occur in the planned study, the required sample size for a randomized study to establish definitively that coronary revascularization is superior to medical therapy to

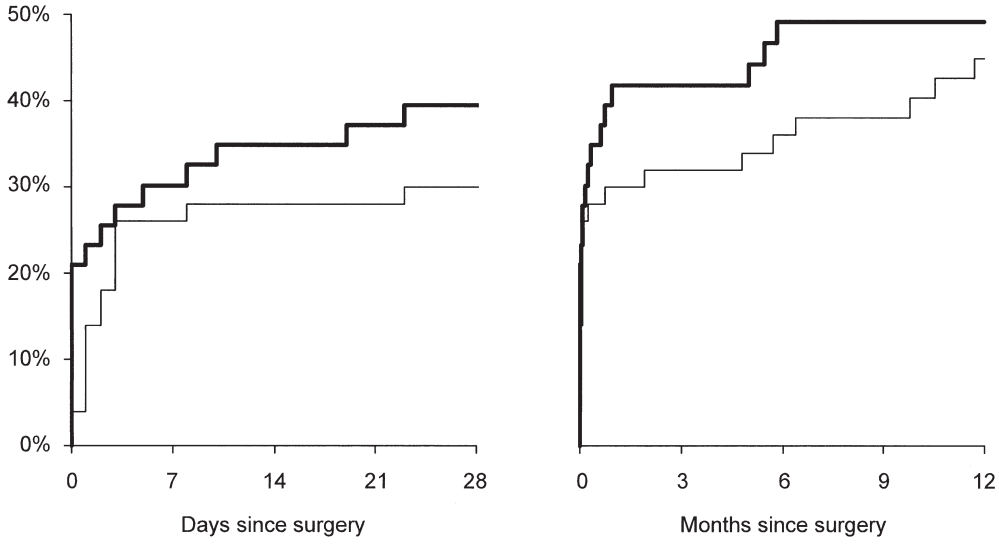

Figure 2 Incidence of All-Cause Death or Myocardial Infarction During 1-Year Follow-Up According to the Allocated Strategy in Patients With 3 or More Cardiac Risk Factors With Extensive Stress-Induced Ischemia

Light line = best medical treatment only; **dark line** = best medical treatment and prophylactic revascularization.

improve postoperative outcome in high-risk patients by 20% (relative risk) compared to optimal medical therapy would be over 300 patients per arm. This would require a sample size of 9,000 major vascular surgery patients, of which 2,000 patients have 3 or more cardiac risk factors at screening.

Discussion

The concept of a beneficial effect of prophylactic coronary revascularization before major vascular surgery is based on the assumption that perioperative myocardial infarctions arise at locations in coronary arteries with hemodynamically critical stenosis, elicited by the stress of surgery. Preoperative coronary revascularization might prevent this devastating event and, in addition, improve long-term outcome. This hypothesis was supported by the CASS study that showed a reduced incidence of nonfatal myocardial infarctions after previous bypass surgery among vascular surgery patients compared with those treated medically (8.5% vs. 0.6%, p = 0.001) (4). More recently, the data from the BARI (Bypass Angioplasty Revascularization Investigation) trial showed that bypass surgery and PCI had similar low rates of postoperative cardiac events in noncardiac surgery (5). However, these studies were not designed to assign the optimal strategy in severely ill patients with extensive coronary artery disease immediately before major vascular surgery. In addition, these studies could not address the concern of delaying the vascular surgical procedure because of testing, revascularization, and initiation of antiplatelet therapy since the time between revascularization and noncardiac surgery in these studies was, respectively, 4.1 and 2.4 years.

The randomized CARP trial was the first study that addressed the strategy of prophylactic revascularization compared with optimal medical therapy in patients with clinically stable coronary artery disease who were scheduled for major vascular surgery (6). This trial showed that prophylactic revascularization was safe but did not improve perioperative or long-term outcome. The long-term mortality was 22% in patients allocated to prophylactic coronary revascularization, compared with 23% in the medical only strategy (p = 0.92). Also, the incidence of perioperative nonfatal myocardial infarction was similar, respectively, 12% and 14% (p = 0.37). In the present study, the effect of prophylactic revascularization was comparable to the effect reported by McFalls et al. (6), although the study population is different. The current study population consisted of 12% women, 43% of the patients had a reduced left ventricular function (LVEF <35%), and the vast majority of patients, 75%, had 3-vessel or left main disease compared with 33% in the CARP trial. In a subgroup of 37 comparable patients of the CARP trial (i.e., 3 or more cardiac risk factors and extensive stress-induced ischemia assessed by noninvasive testing), prophylactic coronary revascularization was associated with a favorable, nonsignificant trend for long-term survival (OR 4.0, 95% CI 0.8 to 19). If a beneficial effect of revascularization was to be expected, this should have occurred in the selected population with high-risk anatomy. However, this was not observed, although the current study was not powered to test this strategy. A study to establish the effect of coronary revascularization would require, based on the findings of this pilot study, a screening population of 9,000 patients, of which 2,000 would have 3 or more risk factors, and of these 600 would have extensive stress-induced ischemia during cardiac testing and be eligible for randomization to revascularization. Our findings support the current guidelines of the ACC/AHA on perioperative management in high-risk patients to reserve revascularization only for cardiac unstable patients. After successful vascular surgery, these patients should be regularly screened for the presence of ischemic complaints, and aggressive anti-ischemic therapy, both medical and invasive, should be considered. As shown in Figure 2, a trend was observed for a "catch up" of late cardiac events in patients treated medically. In these patients at high risk scheduled for major vascular surgery, prophylactic revascularization might be switched to late revascularization, preventing the delay of surgery.

The apparent lack of benefit of coronary revascularization of the present study is not fully understood. Most likely, patients with stress-induced ischemia not only suffer from a blood flow-limiting coronary lesion but also from (multiple) nonsignificant lesions that are vulnerable to rupture due to the stress of surgery (10). The perioperative stress response, which includes a cytokine response, catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation, and consequent hypercoagulability, triggers coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion (11,12). Autopsy results have shown that this mechanism is responsible for at least half of all perioperative infarctions (10,12). These findings are in line with dobutamine echocardiography results that show a correlation between the assessment of the preoperative culprit coronary lesion and the location of the perioperative myocardial infarction in only half of all cases (13). Surgical or percutaneous treatment of the culprit coronary lesion(s) apparently provides insufficient protection for rupture of these instable lesions.

The optimal perioperative evaluation and management of patients with multiple risk factors and extensive stress-induced ischemia remains controversial. Success will depend on careful collaboration between cardiologists, anesthesiologists, and surgeons. In patients with aortic aneurysms, a surgical repair is performed to reduce the chance of aneurysm-related death. It might be hypothesized that abdominal aortic aneurysm repair should not be performed in this high-risk group. As the current trial shows, open repair poses an unacceptable 30-day cardiac event rate of approximately 30%, whereas the chance of aneurysm rupture is around 9 per 100 person-years. Endovascular treatment modalities may be an alternative for these high-risk

patients. Although the EVAR (Endovascular Aneurysm Repair)-2 trial showed no benefit of elective endovascular repair in patients deemed unfit for open repair because of comorbidities (14), these findings were not confirmed in the recently conducted study by the Society for Vascular Surgery Outcomes Committee. In a group of 565 high-risk patients, matched for the EVAR-2 inclusion criteria, undergoing endovascular repair, perioperative mortality was 2.9%. These promising results need to be confirmed in a large study population. Importantly, in all cases, an individualized strategy should be performed, weighing the chances of future aneurysms rupture or limb salvage instead of amputation and short-term perioperative events.

Conclusions

In this small randomized pilot study, designed to obtain initial efficacy and safety estimates for the design of an adequately powered randomized controlled clinical trial, preoperative coronary revascularization in high-risk vascular surgery patients with extensive stress-induced ischemia was not associated with an improved postoperative and long-term outcome.

Acknowledgment

The authors are indebted to Margaret van Nierop for the outstanding care of blood sample collections of the study patients.

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APPENDIX

For a list of DECREASE Study Group members and participating institutions, please see the online version of this article.