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CLINICAL RESEARCH | Clinical Trial

Systematic Strategy of Prophylactic Coronary Angiography Improves Long-Term Outcome After Major Vascular Surgery in Medium- to High-Risk Patients

A Prospective, Randomized Study

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Objectives This study was undertaken to determine the impact of a strategy of systematic coronary angiography on immediate- and long-term outcome of patients at medium-high risk who were undergoing surgical treatment of peripheral arterial disease.

Background Despite pre-operative risk stratification according to the current guidelines, vascular surgery patients still represent a high-risk population, as 30-day cardiovascular complications and mortality rates still remain as high as 15% to 20% and 3% to 5%, respectively.

Methods In all, 208 consecutive patients scheduled for elective surgical treatment of major vascular disease and with a revised cardiac risk index ≥2 were randomly allocated to either a "selective strategy" group (group A, n = 103), in whom coronary angiography was performed based on the results of noninvasive tests, or to a "systematic strategy" group (group B, n = 105), consisting of patients who systematically underwent pre-operative coronary angiography.

Results The 2 groups were similar with respect to baseline clinical characteristics, revised cardiac risk index, and type of vascular surgery performed. The myocardial revascularization rate in group B was higher than in group A (58.1% vs. 40.1%; p = 0.01). In-hospital major adverse cardiovascular event rate was not significantly lower in group B (p = 0.07). At 58 ± 17 months of follow-up, group B showed significantly better survival (p = 0.01) and freedom from death/cardiovascular events (p = 0.003).

Conclusions In this study, a strategy of routine coronary angiography positively impacted long-term outcome of peripheral arterial disease surgical patients at medium-high risk. This is the first such demonstration in a randomized, prospective trial. Multicenter trials to confirm this finding in a larger population are warranted. (J Am Coll Cardiol 2009;54:989–96) © 2009 by the American College of Cardiology Foundation

The extent and severity of atherosclerotic lesions in major peripheral artery vessels correlate with the extent and severity of coronary artery disease (CAD) (1–4). Among patients undergoing major surgery for peripheral artery disease (PAD), the prevalence of CAD ranges from 37% to 78%, and myocardial infarction (MI) is the main cause of perioperative death (5,6). As a consequence, it is thought by many that these patients should be outright considered candidates for coronary angiography and possible coronary revascularization. Indeed, coronary artery revascularization before elective major vascular surgery has been advocated to reduce perioperative mortality rate (7,8). However, this issue is still hotly debated, as 2 recent randomized studies have shown that, among patient candidates for major vascular surgery, coronary artery revascularization before vascular surgery was not associated with an improved outcome (9,10). In the American Heart Association (AHA)/American College of Cardiology (ACC) guideline update, coronary angiography is recommended only if the patient, after positive noninvasive testing, is considered at increased risk for perioperative cardiac complications (11).

See page 997

According to current guidelines, pre-operative coronary risk assessment is best achieved—in patients with 2 or more

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Abbreviations and Acronyms

AAA = abdominal aortic aneurysm

ACC = American College of Cardiology

AHA = American Heart Association

CABG = coronary artery bypass graft surgery

CAD = coronary artery disease

CCS = Canadian Cardiovascular Society

DSE = dobutamine stress echocardiography

dTS = dipyridamole-thallium scintigraphy

OPCABG = off-pump coronary artery bypass graft surgery

MACE = major adverse cardiovascular event

MI = myocardial infarction

NYHA = New York Heart Association

PAD = peripheral artery disease

RCRI = revised cardiac risk index

risk factors by Lee's revised cardiac risk index (RCRI)—by means of noninvasive testing (11,12). However, despite pre-operative risk stratification according to the guidelines, vascular surgery patients still represent a high-risk population, as 30-day cardiovascular complication rates and mortality rates still remain as high as 15% to 20% and 3% to 5%, respectively (13). Thus, current recommendations seem to underestimate the true incidence of CAD. Furthermore, it has long been held that pre-treatment with beta-blockers would dramatically reduce incidence of perioperative cardiac complications, thus making extensive pre-operative work-up unnecessary (14–16); however, this notion has recently been seriously challenged (17–20).

Therefore, we are left with little guidance on how to best manage these patients pre-operatively, and thus there is a need for an effective strategy to curb their risk of cardiac events.

With this aim, we designed a protocol to test whether for patients with RCRI ≥2 and in need of peripheral vascular angiography before major vascular surgery, a systematic strategy of routinely performed pre-operative coronary angiography would be more effective in reducing the occurrence of major adverse cardiovascular events (MACE) than a strategy based on selective coronary angiography guided by the results of noninvasive tests. Patients scheduled to undergo elective major vascular surgery were randomly and prospectively enrolled, and followed up for at least 3 years.

Methods

Study population. From January 2000 through December 2004, 672 consecutive patients were admitted for elective major vascular surgery, aortoiliac obstructive disease, or abdominal aortic aneurysm (AAA) repair. Diagnosis was made by echo-duplex scanner and/or spiral computed tomography. Surgical indications for AAA were dimension >5 cm, and for aortoiliac obstructive disease, the indication was a stenosis >75% of the aortic bifurcation and/or of the iliac arteries, not suitable to percutaneous repair. All patients were administered statins, beta-blockers, and low-molecular-weight heparin 1 week before admission, discontinuing antiplatelet therapy. The study was approved by the ethics committee of all institutions.

After a thorough medical and instrumental evaluation, 208 patients were found to have a RCRI ≥2 (12), and they form the basis of this trial. In all of these patients, the beta-blocker regimen was titrated to achieve a resting heart rate of ≤60 beats/min. After a detailed description of the procedure and having obtained written informed consent, patients were allocated through a computer-generated randomization list into 2 groups. The "selective strategy" group A consisted of 103 patients who eventually underwent coronary angiography at the time of peripheral angiography as a result of a positive stress test (see the following text for details), according to current guidelines (21). The "systematic strategy" group B consisted of 105 patients who underwent outright coronary angiography at the time of peripheral angiography, without a noninvasive test being performed.

Cardiac testing. Left ventricular ejection fraction was assessed by resting echocardiographic images using biplane Simpson's rule. Cardiac stress testing was performed by dipyridamole-thallium scintigraphy (dTS) or dobutamine stress echocardiography (DSE). All 103 group A patients underwent pre-operative testing during hospital admission. The DSE or dTS was performed according to availability: dTS was performed in 55 patients (56.3%), and DSE was performed in 48 (43.7%, $p = 0.4$). Positivity was considered to be the appearance of 1 or more reversible thallium-201 myocardial defects for dTS and the occurrence or worsening of wall motion abnormalities in at least 2 adjacent segments for DSE.

Angiographic strategy. Peripheral angiography was performed in all patients as part of a routine diagnostic workup before major vascular surgery to confirm vascular pre-operative noninvasive testing and/or to gain additional anatomical information (e.g., location of aneurysmal neck in AAA patients). In all patients for whom coronary angiography was indicated, coronary and peripheral vascular angiography were performed at the same time and by the same team. Stenoses of ≥70% of major epicardial vessels (≥50% for left main trunk) were considered significant. A patient was considered eligible for myocardial revascularization procedure if 1 or more major coronary vessels, suitable for revascularization, showed a significant stenosis.

Coronary revascularization strategy. A staged approach (myocardial revascularization followed by vascular surgery) was typically performed. Combined procedures (i.e., repair of AAA immediately after myocardial revascularization procedure in the same surgical session) were reserved only for patients with large aortic aneurysms (≥6 cm) and/or signs of impending rupture. Percutaneous coronary interventions were performed at the time of coronary angiography, using bare metal stents. Patients were then discharged on a double antiplatelet regimen of 75 mg/day clopidogrel or 250 mg/day ticlopidine, plus 100 mg/day aspirin, and were scheduled for vascular surgery within 30 to 60 days. Only clopidogrel or ticlopidine were withdrawn 7 days before surgery. When surgical revascularization was indicated,

Table 1 Definitions

Nonfatal myocardial infarction	Myocardial infarction after coronary artery bypass graft surgery or percutaneous coronary intervention was defined as a creatine kinase-MB rise >3 times the upper limit of normal. Myocardial infarction within 30 days after the index surgical procedure was defined as a troponin-T level >2 times the upper limit of normal, in combination with new Q waves on the electrocardiogram lasting >0.03 s. In all other situations, myocardial infarctions were defined by new Q waves lasting >0.03 s.
Cerebrovascular accident	Any new episode of transient ischemic attack or stroke.
Congestive heart failure	Left ventricular ejection fraction <0.4, with need for diuretic and/or angiotensin-converting enzyme inhibitor therapy, requiring hospitalization.
Need for new cardiac revascularization procedure	Any new surgical or percutaneous revascularization procedure on a treated vessel.

the off-pump coronary artery bypass graft (OPCABG) technique was always employed, and a 30- to 60-day interprocedure interval was observed.

Study end points. Patients were followed up for at least 3 years after surgery, and the primary end point was the MACE incidence at follow-up; the occurrence of a MACE between the screening and 30 days after the index surgical procedure was considered as the secondary end point. The MACE definitions are given in Table 1.

Follow-up. Follow-up data were obtained directly from the patients and/or their family physician by telephone call or by written questionnaire, at 30 days if a patient had been discharged from the hospital and every 6 months thereafter. Data collected included death, functional status according to New York Heart Association (NYHA) functional classification, and anginal status according to the Canadian Cardiovascular Society (CCS) classification, as well as any new MACE.

Statistical analysis. As previously reported, the CARP (Coronary Artery Revascularization Prophylaxis) trial (9) shows a mortality of 22% in the revascularization group and 23% in the no-revascularization group, at a median of 2.7 years after randomization, and an incidence of MACE can be observed in ≈20% of cases within 30 days after major vascular surgery. Therefore, our study enrolled a total sample of >200 patients to observe a 10% reduction in long-term and 30-day MACE rate, with a statistical power of ≥80% (1 − beta) to detect a probability of <0.05 (alpha error level). All variables are presented as mean and standard deviation. The chi-square test for categorical variables and the Mann-Whitney test for continuous data were used to assess statistical significance. Differences resulting in a p value <0.05 were considered significant. Intention-to-treat analyses provided information about survival from the time of randomization. If more than 1 end point occurred within the follow-up period, only the first event was considered. Kaplan-Meier analysis was used to study patient survival and event-free status, using the log-rank test (Cox-Mantel) to ascertain differences between groups. All data were analyzed using STATISTICA 6.0 (StatSoft Inc., Tulsa, Oklahoma).

Results

Patient population. In all, 672 consecutive patients were screened. An RCRI <2 was found in 464 patients and followed the published guidelines for pre-operative risk assessment (11). The remaining 208 patients, with an RCRI ≥2, were enrolled and randomly allocated to a selective strategy or a systematic strategy. The selective strategy group (group A = 103 patients) underwent a stress test followed by coronary angiography if the test was positive. The systematic strategy group (group B = 105 patients) was assigned to outright coronary angiography, without a previous noninvasive test. Carvedilol, a nonselective $beta_1$/$beta_2$-blocker with alpha-blocking activity, was used (12.5 to 25 mg twice daily) for all patients to obtain a resting heart rate of ≤60 beats/min (58.1 ± 3.8 beats/min and 57.5 ± 4.4 beats/min in group A and group B, respectively; p = 0.3): the target heart rate was achieved in 95.1% of group A patients and in 94.3% of group B patients (p = 0.8). Clinical and demographic characteristics are summarized in Table 2.

Early outcome. Table 3 summarizes 30-day outcome data for the 2 groups. In the selective strategy group A, the noninvasive test was positive in 47 (45.6%) patients; they underwent coronary angiography, which demonstrated sig-

Table 2 Characteristics of Patients Randomized to Selective (Group A) or Routine (Group B) Coronary Angiography

Clinical Variables	Group A (n = 103)	Group B (n = 105)	p Value
Age, yrs	73.1 ± 4.3	74.4 ± 5.3	NS
Men	82.6	75.0	NS
NYHA functional class III or IV	21 (20.4)	27 (25.7)	0.5
CCS class III or IV	23 (22.3)	26 (24.8)	0.8
Peripheral arterial disease			
Aortoiliac obstruction/stenosis	65 (63.1)	61 (58.1)	NS
Abdominal aortic aneurysm	38 (36.9)	44 (41.9)	NS
Diabetes mellitus	40 (38.8)	39 (37.1)	NS
Hypertension	72 (69.9)	70 (66.6)	NS
Ischemic heart disease	32 (31.1)	35 (33.3)	NS
Previous CABG	16 (15.5)	18 (17.4)	NS
Previous vascular surgery	13 (12.6)	14 (13.3)	NS
CVA	18 (17.5)	22 (20.9)	NS
Creatinine >1.7 mg/dl	35 (33.9)	36 (34.3)	NS
Chronic obstructive pulmonary disease	42 (40.1)	45 (42.8)	NS
RCRI score	3.2 ± 0.7	3.3 ± 0.6	NS
ASA score	1.7 ± 0.5	1.8 ± 0.4	NS

Values are mean ± SD or n (%).
ASA = American Society of Anesthesiologists; CABG = coronary artery bypass graft surgery; CCS = Canadian Cardiovascular Society; CVA = cerebrovascular accident; NS = not significant; NYHA = New York Heart Association; RCRI = revised cardiac risk index.

JACC Vol. 54, No. 11, 2009
September 8, 2009:989–96

Table 3 30-Day Outcome

	Group A (n = 103)	Group B (n = 105)	p Value	OR (95% CI)
Patients with CAD	46 (44.7)	65 (61.9)	0.02	2.07 (1.1–3.9)
Myocardial revascularization	42 (40.1)	61 (58.1)	0.01	2.01 (1.1–3.6)
Major vascular surgery	99 (96.1)	100 (95.2)	0.9	—
Previous myocardial revascularization*	38 (36.9)	56 (53.3)	0.02	0.5 (0.3–0.9)
Interprocedure lost patients*	4 (3.9)	4 (3.8)	0.8	—
Cardiac mortality	7 (6.8)	2 (1.9)	0.08	—
Myocardial revascularization related	1 (1.0)	1 (0.9)	0.7	—
Interprocedure	1 (1.0)	—	0.5	—
Vascular surgery related	5 (4.8)	1 (0.9)	0.1	—
MACE	5 (4.8)	3 (2.8)	0.7	—
Myocardial infarction	4 (3.9)	2 (1.9)	0.6	—
Cerebrovascular accident	1 (1.0)	1 (0.9)	0.5	—
MACE, including cardiac mortality	12 (11.7)	5 (4.8)	0.1	—
LOS, days	7.5 ± 2.5	6.8 ± 2.1	0.03	—

Values are mean ± SD or n (%). *See the section "Results: Early Outcome" for explanation.
CAD = coronary artery disease; CI = confidence interval; LOS = length of hospital stay; MACE = major adverse cardiovascular event; OR = odds ratio.

nificant coronary artery lesions in 46 (44.7%). Myocardial revascularization was performed in 42 (40.8%) such patients, either by percutaneous coronary intervention (n = 30, 29.1%) or by OPCABG (n = 12, 11.6%), as appropriate (22) (Table 4); it was staged in 37 (35.9%) patients and combined in 5 (4.9%), with an operative mortality of 2.4% (1 patient died of cardiogenic shock). Of the 41 surviving patients undergoing myocardial revascularization, 3 did not subsequently undergo vascular surgery: 1 patient died during the interprocedure interval of cardiac-related causes, and 2 declined surgery. Thirty-eight patients underwent the planned vascular operation within 2 months, with no operative mortality. The remaining 61 patients (56 with negative noninvasive tests, 1 with negative coronary angiography, and 4 with coronary anatomy not amenable to revascularization) directly underwent the planned vascular operation. In this subgroup, there were 5 operative deaths (5 of 61, 6.5%), all cardiac related.

Table 4 Coronary Angiography Results and Revascularization Procedures

	Group A (n = 42)	Group B (n = 61)	p Value
Number of diseased vessels			
1 vessel	11 (26.2)	17 (27.9)	0.9
LAD	9 (21.5)	13 (21.3)	
2 vessels	15 (35.7)	17 (27.9)	0.8
3 vessels or more	16 (38.1)	27 (44.3)	0.5
Left main disease	4 (9.5)	8 (13.1)	0.8
PCI	30 (71.4)	32 (52.5)	0.08
Complete revascularization	30 (100)	31 (96.8)	
OPCABG	12 (28.6)	29 (47.5)	0.08
Complete revascularization	11 (91.7)	29 (100)	

Values are n (%).
LAD = left anterior descending coronary artery; OPCABG = off-pump coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

Overall, of the 103 group A patients, 99 (96.5%) underwent vascular surgery with an intention-to-treat hospital mortality (including patients not undergoing vascular surgery or patients who died during the interprocedure interval) of 6.8% (7 of 103 patients).

In the systematic strategy group B, 65 (61.9%) patients showed significant coronary stenosis (p = 0.02; odds ratio: 2.07; 95% confidence interval: 1.1 to 3.9, vs. group A). No major complications related to coronary angiography were observed. Of the 65 patients with coronary angiography positive for CAD, 61 (58.1%) had indications for myocardial revascularization, either percutaneous coronary intervention (n = 42, 40.0%) or OPCABG (n = 19, 18.1%), as appropriate (22) (Table 4). Staged myocardial revascularization was performed in 50 (47.6%) patients, and a combined approach was carried out in 11 (10.5%). One in-hospital death was observed (1.6%). Forty-four patients (41.9%), 40 with absence of CAD at coronary angiography and 4 with CAD deemed unfit for myocardial revascularization, directly underwent the planned vascular operation. There were no hospital deaths. Four patients who had undergone prior myocardial revascularization did not subsequently undergo vascular surgery: 1 patient died during the interprocedure interval of cardiac-related causes, and 3 patients declined surgery. The remaining 56 patients underwent the planned vascular operation within 2 months, with no 30-day mortality.

Overall, of the 105 group B patients, 100 (94.3%) underwent vascular surgery with an intention-to-treat hospital mortality of 1.9% (2 of 105 patients, p = 0.08, vs. group A).

The overall incidence of MACE, including cardiac mortality, was higher in group A (n = 12) than in group B (n = 5, p = 0.1), although not reaching statistical significance, whereas the length of hospital stay was significantly higher in group A than in group B patients (p = 0.03).

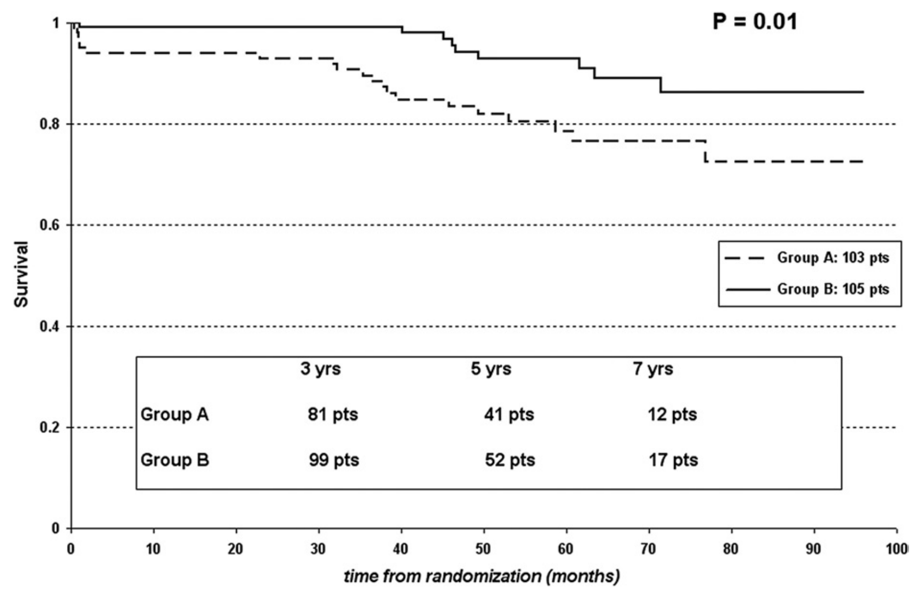

Figure 1 **Cumulative Survival**

Cumulative survival for patients (pts) of group A (**dashed line** [n = 103]) and group B (**solid line** [n = 105]), intention-to-treat.

Follow-up. Follow-up ranged from 36 to 95 months, with a mean of 58 ± 17 months. No patients were lost to follow-up. No difference was observed in functional status: 10 (10.6%) patients and 14 (14.1%) patients were in NYHA functional class III or IV in group A and B, respectively ($p = 0.6$); a significantly better outcome was observed with respect to CCS anginal class: there were 29 (30.8%) patients in group A and 17 (17.2%) patients in group B ($p = 0.03$) in CCS class >2.

Survival and freedom from any cardiac-related event, including mortality, are shown in Figures 1 and 2, respectively. At Kaplan-Meier survival analysis, there was a significant difference between group A and group B survival ($p = 0.01$) and freedom from any cardiac-related event

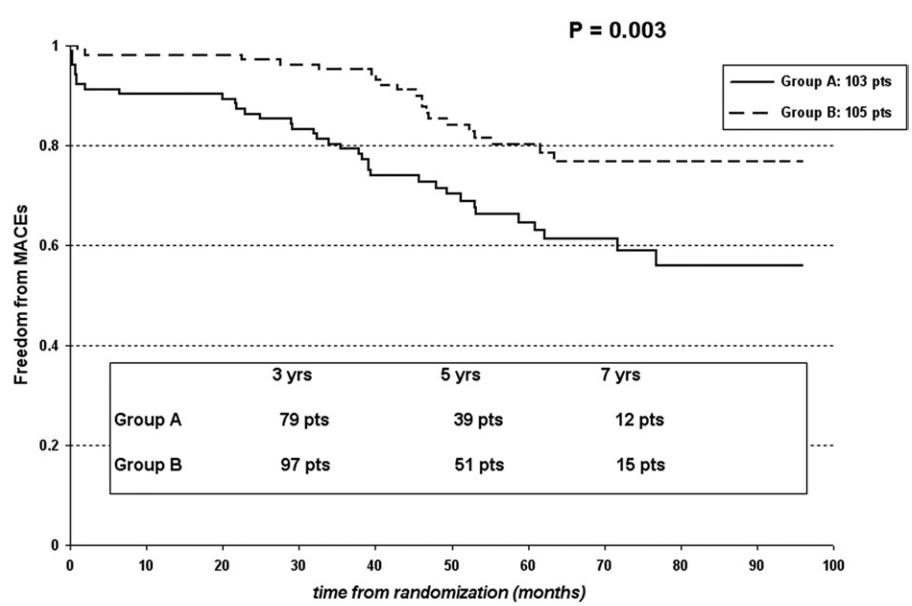

Figure 2 **Freedom From Major Cardiac Events**

Freedom from major adverse cardiac events (MACE) for patients (pts) of group A (**solid line** [n = 103]) and group B (**dashed line** [n = 105]), intention-to-treat.

including mortality (p = 0.003). For this end point, the 4-year freedom from events was 69.6 ± 4.7% for group A and 86.6 ± 3.6% for group B, with an absolute risk reduction of 16.7%, corresponding to a relative risk reduction of 59.4% (95% confidence interval: 1.4 to 6.8; p = 0.04); the 8-year freedom from events was 53.5 ± 6.3% for group A and 77.5 ± 4.8% for group B, with an absolute risk reduction of 19.8%, corresponding to a relative risk reduction of 53.6% (95% confidence interval: 1.4 to 5.7; p = 0.002).

Discussion

For patients in preparation for major vascular surgery, the present study shows that a strategy of "prophylactic" coronary artery angiography for all patients at medium-high risk, followed by coronary revascularization as needed, is more effective in curbing the rate of post-operative cardiac events and death than is a conservative strategy of coronary angiography and revascularization performed on the basis of a positive noninvasive test. Furthermore, the benefits of this systematic approach extended well beyond the perioperative phase, as the rate of cardiac events at late follow-up was one-half of that among patients for whom coronary angiography was performed only in selected cases.

There is general agreement that CAD remains the major cause of perioperative mortality after major vascular surgery (6,23–25). The pre-operative screening of patients in need of major vascular surgery is therefore of paramount importance to decrease surgical risk and obtain good long-term results. The RCRI discriminates patients with low probability (Class I and II, risk 0.4% and 0.9%) from those with high probability (Class III and IV, risk 6.6% and 11%) of major cardiac events (26). For such patients in Class III and IV, ACC/AHA guidelines recommend pre-operative noninvasive cardiac evaluation (21). However, the use of noninvasive tests in the pre-operative assessment of these patients may at times prove inaccurate. Bursi et al. (27) recently reported that, despite adherence to pre-operative risk stratification according to the ACC/AHA guidelines, patients undergoing elective major vascular surgery are still at high risk of MI and death; Back et al. (28) demonstrated that the presence of 3-vessel angiographic CAD was an independent predictor of cardiac morbidity, whereas inducible ischemia by stress imaging was not. Moreover, among some high-risk patients, namely, patients undergoing liver or kidney transplantation, a systematic coronary angiography approach may be of benefit (29,30).

A meta-analysis involving 8,008 subjects, showed a 0.5% of annualized event rate of MI or cardiac death and a 1.25% annualized event rate of myocardial revascularization or unstable angina after a normal myocardial perfusion stress test (31). Although myocardial perfusion testing provides accurate clinical information, there are instances in which potentially life-threatening CAD may be present, even though there are no significant abnormalities on the perfusion-imaging test (32). Diamond et al. (33) recently reported an incidence of 29% of significant CAD (9.1% left main and/or 3-vessel disease) among patients with normal myocardial perfusion test who subsequently underwent coronary angiography within 6 months from the stress test. Noninvasive testing as a tool to predict and reduce preoperative risk may rest with the relative suboptimal performance in particular population. Patients with 1-vessel CAD often exhibit negative stress tests (34). Furthermore, among the elderly, a negative and/or an equivocal noninvasive test does not necessarily exclude an important CAD involvement (35). Finally, vascular patients are often unable to perform adequate exercise, they may also have concomitant pulmonary morbidity that prevents executing stress echocardiography, and they are less likely to be left off drugs to undergo diagnostic testing. The results of the present study lend support to this interpretation as we observed that in the systematic strategy patients, a significantly greater proportion underwent coronary revascularization before vascular surgery compared with selective strategy patients. It is unlikely that we inadvertently selected 2 groups with significantly different prevalences of CAD, since patients were allocated to either strategy on a random basis, and since baseline characteristics were similar in the 2 groups; a more likely explanation is that noninvasive testing missed a substantial portion of patients with CAD.

Comparison with previous studies. In spite of the obvious clinical relevance of the issue, there is a relative paucity of data to precisely address the role of coronary angiography in preparation for a major vascular intervention. That aggressive treatment of CAD before vascular surgery may reduce the coronary risk and improves long-term outcomes has been suggested by several studies (7,8,36); however, they were retrospective, nonrandomized reports. In contrast, the CARP trial (9) randomized 510 patients, and showed that pre-operative coronary artery revascularization before an elective vascular operation does not improve long-term post-operative outcome. However, it should be noted that the vast majority of patients in the CARP trial had single-vessel or 2-vessel disease, with normal left ventricular ejection fraction. For these patients, adequate cardioprotection can be expected by medical therapy (37). Hence, the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo Study Group)-V randomized pilot study was more recently performed in patients with extensive stress-induced myocardial ischemia; in this study, also, pre-operative coronary revascularization was not associated with an improved outcome (10). This trial, however, considers as end points only cardiac death and MI and excludes all cardiovascular events (cerebrovascular accident, congestive heart failure) and repeated revascularization, and patients were followed up for only 1 year after surgery, whereas in our study, both survival and freedom from MACE curves start to diverge from 2 years. Furthermore, the DECREASE-V study randomized a highly selected group of patients, who underwent coronary revascularization without exception, and had an extremely high mortality and MI rate. Moreover, both the CARP study and the DECREASE-V trial recommended coronary angiography only on the basis of the presence of ischemia on a noninvasive stress imaging study: patients with CAD but negative or limited ischemia at stress testing may have been left out of coronary revascularization, thus reducing its possible benefits.

The issue is, therefore, still much debated to this very day (38–40). To our knowledge, ours is the first study that prospectively and randomly evaluates "all comers" for prophylactic coronary angiography, extending the observations into follow-up for several years.

Study limitations. The present study randomly allocated 208 patients, and therefore results cannot be immediately extended to the large population of patients at medium-high risk who need vascular surgery. As demonstrated by others (9), however, because of the obvious difficulties in randomizing this type of patient, it is not easy to recruit substantially larger populations. Another limitation is the lack of blinding of investigators that is inherent to the trial design, and the lack of an independent events adjudication committee. However, we believe that the choice of the end points of death and major cardiac events helps minimize this limitation.

Implications. In addition to the possibility of reducing perioperative risk, a strategy of systematic coronary angiography for patients at medium-high risk who are candidates for major vascular surgery may also have additional beneficial effects, thus improving the AHA/ACC guidelines. Coronary angiography precisely assesses coronary anatomy, allowing the physician to treat more effectively the underlying CAD as well as coronary risk factors, and that conceivably will translate into better long-term secondary prevention of cardiac events and into a patient's increased compliance with and adherence to life-long medical multitherapy. In addition, the reduced length of hospital stay connected with the vascular surgery procedure and the possibility of performing in the same session both coronary and vascular angiography may also help defray higher costs connected with performing more coronary angiographies; in this respect, one should also factor in the further cost-effectiveness advantage of not performing noninvasive evaluation.

Conclusions

Patients at medium-high risk of cardiovascular events scheduled to undergo major vascular surgery, and in whom coronary angiography was systematically performed as part of their pre-operative workup, scored significantly better than patients in whom coronary angiography was selectively performed only on the basis of positive noninvasive tests. Our data indicate that the advantages of such a systematic approach may significantly offset its disadvantages, and call for larger, multicenter trials to thoroughly investigate this important clinical issue.

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REFERENCES

1. Rohani M, Jogestrand T, Ekberg M, et al. Interrelation between the extent of atherosclerosis in the thoracic aorta, carotid intima-media thickness and the extent of coronary artery disease. Atherosclerosis 2005;79:311–6.
2. Sukhija R, Yalamanchili K, Aronow WS. Prevalence of left main coronary artery disease, of three- or four-vessel coronary artery disease, and of obstructive coronary disease in patients with and without peripheral arterial disease undergoing coronary angiography for suspected coronary artery disease. Am J Cardiol 2003;92:304–5.
3. Lekakis JP, Papamichael C, Papaioannou TG, et al. Intima-media thickness score from carotid and femoral arteries predicts the extent of coronary artery disease: intima-media thickness and CAD. Int J Cardiovasc Imag 2005;21:495–501.
4. Amanullah AM, Artel BJ, Grossman LB, Espioneza A, Chaudhry FA. Usefulness of complex atherosclerotic plaque in the ascending aorta and arch for predicting cardiovascular events. Am J Cardiol 2002;89:1423–6.
5. Zipes DP, Libby P, Bonow R, Braunwald E. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 7th edition. Philadelphia, PA: Saunders, 2004.
6. Golden MA, Whittemore AD, Donaldson MC, Mannick JA. Selective evaluation and management of coronary artery disease in patients undergoing repair of abdominal aortic aneurysms. A 16-year experience. Ann Surg 1990;212:415–20.
7. Hertzer NR, Young JR, Bevern EG, et al. Late results of coronary bypass in patients with peripheral vascular disease. II. Five year survival according to sex, hypertension, and diabetes. Cleve Clin J Med 1987;54:15–23.
8. Rihal CS, Eagle KA, Mickel MC, Foster ED, Sopko G, Gersh BJ. Surgical therapy for coronary artery disease among patients with combined coronary artery and peripheral vascular disease. Circulation 1995;91:46–53.
9. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. N Engl J Med 2004;351:2795–804.
10. Poldermans D, Schouten O, Vidakovic R, et al. 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. J Am Coll Cardiol 2007;49:1763–9.
11. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). J Am Coll Cardiol 2002;39:542–53.
12. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100:1043–9.
13. Hoeks SE, Bax JJ, Poldermans D. Should the ACC/AHA guidelines be changed in patients undergoing vascular surgery? Eur Heart J 2005;22:2358–60.
14. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 1996;335:1713–20.
15. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. N Engl J Med 1999;341:1789–94.
16. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. N Engl J Med 2005;353:349–61.
17. Devereaux PJ, Beattie WS, Choi PT, et al. How strong is the evidence for the use of perioperative beta blockers in non-cardiac surgery?

Systematic review and meta-analysis of randomised controlled trials. BMJ 2005;331:313–21.
18. Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR, for the POBBLE Trial Investigators. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. J Vasc Surg 2005;41:602–9.
19. Juul AB, Wetterslev J, Kofoed-Enevoldsen A, Callesen T, Jensen G, Gluud C. Randomized, blinded trial on perioperative metoprolol versus placebo for diabetic patients undergoing non-cardiac surgery. Circulation 2005;111:1725–8.
20. Devereaux PJ, Yang H, Yusuf S, et al., and the POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371:1839–47.
21. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). J Am Coll Cardiol 2007;50:1707–32.
22. Smith SC Jr., Feldman TE, Hirshfeld JW Jr., et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). J Am Coll Cardiol 2006;47:216–35.
23. Paty PS, Darling RC III, Chang BB, Lloyd WE, Kreienberg PB, Shah DM. Repair of large abdominal aortic aneurysm should be performed early after coronary artery bypass surgery. J Vasc Surg 2000;31:253–9.
24. Wattanakit K, Folsom AR, Chambless LE, Nieto FJ. Risk factors for cardiovascular event recurrence in the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J 2005;149:606–12.
25. Klinkert P, van der Steenhoven TJ, Vrancken Peeters MP, Breslau PJ. Mortality after peripheral bypass surgery: value of a mortality scoring system in evaluating the quality of care. Vascular 2004;12:121–5.
26. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. Am J Med 2005;118:1134–41.
27. Bursi F, Babuin L, Barbieri A, et al. Vascular surgery patients: perioperative and long-term risk according to the ACC/AHA guidelines, the additive role of post-operative troponin elevation. Eur Heart J 2005;26:2448–56.
28. Back MR, Schmacht DC, Bowser AN, et al. Critical appraisal of cardiac risk stratification before elective vascular surgery. Vasc Endovasc Surg 2003;37:387–97.
29. Tiukinhoy-Laing SD, Rossi JS, Bayram M, et al. Cardiac hemodynamic and coronary angiographic characteristics of patients being evaluated for liver transplantation. Am J Cardiol 2006;98:178–81.
30. Gowdak LH, de Paula FJ, César LA, et al. Screening for significant coronary artery disease in high-risk renal transplant candidates. Cor Artery Dis 2007;18:553–8.
31. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. J Am Coll Cardiol 2007;49:227–37.
32. Bateman TM. Clinical relevance of a normal myocardial perfusion scintigraphic study. American Society of Nuclear Cardiology. J Nucl Cardiol 1997;4:172–3.
33. Diamond JA, Makaryus AN, Sandler DA, Machac J, Henzlova MJ. Normal or near normal myocardial perfusion stress imaging in patients with severe coronary artery disease. J Cardiovasc Med 2008;9:820–5.
34. Kertai MD, Boersma E, Bax JJ, et al. A meta-analysis comparing the prognostic accuracy of six diagnostic tests for predicting perioperative cardiac risk in patients undergoing major vascular surgery. Heart 2003;89:1327–34.
35. Psirropoulos D, Efthimiadis A, Boudonas G, et al. Detection of myocardial ischemia in the elderly versus the young by stress thallium-201 scintigraphy and its relation to important coronary artery disease. Heart Vessels 2002;16:131–6.
36. Landesberg G, Berlatzky Y, Bocher M, et al. A clinical survival score predicts the likelihood to benefit from preoperative thallium scanning and coronary revascularization before major vascular surgery. Eur Heart J 2007;5:533–9.
37. Boersma E, Poldermans D, Bax JJ, et al., for the DECREASE Study Group. Predictors of cardiac events after major vascular surgery: role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. JAMA 2001;285:1865–73.
38. Landesberg G, Mosseri M. Preoperative coronary revascularization in high-risk patients undergoing vascular surgery. Anesth Analg 2008;106:759–63.
39. Garcia S, McFalls EO. Preoperative coronary revascularization in high-risk patients undergoing vascular surgery. Anesth Analg 2008;106:764–6.
40. Kertai MD. Preoperative coronary revascularization in high-risk patients undergoing vascular surgery: a core review. Anesth Analg 2008;106:751–8.

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