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Long-Term Prognosis of Patients With Peripheral Arterial Disease

A Comparison in Patients With Coronary Artery Disease

Gijs M. J. M. Welten, MD,* Olaf Schouten, MD,* Sanne E. Hoeks, MSc,† Michel Chonchol, MD,§
Radosav Vidakovic, MD,* Ron T. van Domburg, PhD,† Jeroen J. Bax, MD,‖
Marc R. H. M. van Sambeek, MD,* Don Poldermans, MD‡

Rotterdam and Leiden, the Netherlands; and Denver, Colorado

Objectives This study was designed to compare the long-term outcomes of patients with peripheral arterial disease (PAD) with a risk factor matched population of coronary artery disease (CAD) patients, but without PAD.

Background The PAD is considered to be a risk factor for adverse late outcome.

Methods A total of 2,730 PAD patients undergoing vascular surgery were categorized into groups: 1) carotid endarterectomy (n = 560); 2) elective abdominal aortic surgery (AAA) (n = 923); 3) acute AAA surgery (r-AAA) (n = 200), and 4) lower limb reconstruction procedures (n = 1,047). All patients were matched using the propensity score, with 2,730 CAD patients who underwent coronary angioplasty. Survival status of all patients was obtained. In addition, the cause of death and complications after surgery in PAD patients were noted. The Kaplan-Meier method was used to compare survival between the matched PAD and CAD population and the different operation groups. Prognostic risk factors and perioperative complications were identified with the Cox proportional hazards regression model.

Results The PAD patients had a worse long-term prognosis (hazard ratio 2.40, 95% confidence interval 2.18 to 2.65) and received less medication (beta-blockers, statins, angiotensin-converting enzyme inhibitors, aspirin, nitrates, and calcium antagonists) than CAD patients did ($p < 0.001$). Cerebro-cardiovascular complications were the major cause of long-term death (46%). Importantly, no significant difference in long-term survival was observed between the AAA and lower limb reconstruction groups (log rank $p = 0.70$). After vascular surgery, perioperative cardiac complications were associated with long-term cardiac death, and noncardiac complications were associated with all-cause death.

Conclusions Long-term prognosis of vascular surgery patients is significantly worse than for patients with CAD. The vascular surgery patients receive less cardiac medication than CAD patients do, and cerebro-cardiovascular events are the major cause of late death. (J Am Coll Cardiol 2008;51:1588–96) © 2008 by the American College of Cardiology Foundation

Atherosclerosis is a systemic disease affecting numerous vascular beds. In patients with peripheral arterial disease (PAD), coronary artery disease (CAD) has a prevalence of 46% to 71% (1,2). Post-operative and long-term prognosis after vascular surgery is predominantly determined by underlying CAD (3). Furthermore, cardiac death accounts for approximately 40% of 30-day mortality, and the 1-year mortality has been estimated at 6% to 10% (4–7). To improve outcomes of patients with PAD requiring surgery, assessment and aggressive therapy of atherosclerotic risk factors is recommended. Hence, the secondary prevention for subjects with PAD is similar to the measures for patients with CAD (8,9). However, data are scarce about the survival and treatment of patients with PAD compared with patients with CAD.

In addition, long-term outcomes in vascular surgery patients with PAD are ill-defined and often not considered in the immediate pre-operative workup. To provide information on long-term prognosis after open vascular surgery repairs among an entire stratum of procedures, it would be

From the Departments of *Vascular Surgery, †Cardiology, and ‡Anesthesiology, Erasmus Medical Center, Rotterdam, the Netherlands; ‖Department of Cardiology, Leiden University, Leiden, the Netherlands; and the §Division of Renal Diseases and Hypertension, University of Colorado Health Sciences Center, Denver, Colorado. Dr. Schouten is supported by an unrestricted research grant from the Netherlands Organization of Health Research and Development (ZonMW), the Hague, the Netherlands. Drs. Vidakovic and Hoeks are supported by an unrestricted research grant from Lijf and Leven Foundation, Rotterdam, the Netherlands. Emile Mohler, MD, served as Guest Editor for this article.

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important to understand the relationship between preoperative characteristics and nonfatal perioperative complications with long-term all-cause mortality and cardiac events in a large cohort of patients with PAD. Therefore, in this analysis, we compared survival and treatment of patients with PAD scheduled for open vascular surgery procedures with a risk factor matched large cohort of patients with documented severe myocardial ischemia referred for coronary angioplasty in the same clinical setting, without signs or symptoms of PAD.

Methods

Study design and patient selection. Between January 1993 and June 2006, 2,730 PAD patients underwent major vascular surgery at the Erasmus Medical Center, Rotterdam, the Netherlands, and were entered into a computerized database. All patients underwent open surgery and were categorized into 4 groups, respectively: 1) carotid endarterectomy (CEA); 2) elective infrarenal abdominal aortic surgery (AAA); 3) acute infrarenal AAA surgery (r-AAA), and 4) lower limb arterial reconstruction procedures (LLR). The medical ethics committee of the Erasmus Medical Center was informed about the study protocol, and per institutional practice, no official approval was requested.

Operation groups. Patients in the CEA group underwent an elective reconstruction or desobstruction of the carotid artery. The AAA group underwent open infrarenal AAA repair (aortic-to-aortic or aortic-bifurcation prostheses procedures, removal of infected prostheses, and other operations of the abdominal aorta). Those with a rupture of the infrarenal abdominal aorta were classified as r-AAA. Finally, patients of the LLR group underwent iliac-femoral, femoral-popliteal, or femoral-tibial artery bypass procedures; removal of infected prostheses; peripheral desobstruction; and other elective peripheral arterial surgical reconstructions.

Propensity score risk factor matched CAD population. To compare the risk of underlying vascular disease (PAD or CAD) on long-term mortality, we compared the prognosis of patients undergoing vascular surgery (PAD patients) with the survival of a separate group of 15,993 patients diagnosed with severe myocardial ischemia (CAD patients), who were referred to the Erasmus Medical Center in the same period (1993 to 2006) for coronary angioplasty without signs or symptoms of PAD obtained from review of medical records. Because of the differences in baseline characteristics between the PAD and CAD populations, propensity score methodology was used to identify comparable patients with the same risk. First, a propensity score for each patient was constructed, providing an estimate of the propensity toward belonging to 1 patient group versus the other using multivariate logistic regression with the type of population as end point (PAD coded as 0, CAD coded as 1). Included in the analysis were the following available cardiovascular risk factors: age, gender, year of operation, hypertension, diabetes mellitus, smoking status, prior percutaneous coronary intervention, prior coronary artery bypass graft, and prior myocardial infarction (MI). Then, each PAD patient was matched with 1 CAD patient with the same propensity score, rounded off at 2 deciles. The graphical method of examination by box plots showed a balance of the estimated propensity score between PAD and CAD patients within each decile of the propensity score. As a result, the matched CAD population resembled the PAD cohort after matching for cardiovascular risk factors (Table 1). Finally, a total of 2,730 PAD patients were matched with 2,730 CAD patients.

In addition, medication use (statins, beta-blockers, angiotensin-converting enzyme inhibitors (ACE inhibitors), aspirin, nitrates, and calcium antagonists) of the CAD

Abbreviations and Acronyms

AAA = elective infrarenal abdominal aortic surgery

ACE = angiotensin-converting enzyme

CAD = coronary artery disease

CCV = cerebro-cardiovascular

CEA = carotid endarterectomy

LLR = lower limb arterial reconstruction procedures

MI = myocardial infarction

PAD = peripheral arterial disease

r-AAA = acute infrarenal abdominal aortic surgery

Table 1 Propensity Score Risk Factor Matched PAD and CAD Population

	Before Matching			After Matching*		
Baseline Risk Factors (%)	PAD (n = 2,730)	CAD (n = 15,993)	p Value	PAD (n = 2,730)	CAD (n = 2,730)	p Value
Age, yrs (± SD)	66 (11)	61 (13)	<0.001	66 (11)	66 (12)	1.0
Males	75	72	<0.001	75	75	1.0
Hypertension	45	33	<0.001	44	45	0.9
Diabetes mellitus	15	11	<0.001	14	12	0.8
Smoking	23	24	0.008	23	21	0.8
Prior PCI	10	11	0.02	10	11	0.9
Prior CABG	19	27	<0.001	19	22	0.4
Prior MI	25	38	<0.001	25	25	1.0

*Matched for age, gender, year of operation, hypertension, diabetes mellitus, smoking status, and prior PCI.
CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention.

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population was recorded to attempt to explain differences in survival between the PAD and CAD populations.

Patients' characteristics. For all PAD patients, we recorded age, gender, hypertension (defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, and/or use of antihypertensive medication), diabetes mellitus (the presence of a fasting blood glucose ≥140 mg/dl or requirement for insulin or oral hypoglycemic agents), smoking status, hypercholesterolemia (total cholesterol of >200 mg/dl and/or the requirement of lipid-lowering medication), chronic obstructive pulmonary disease according to symptoms and pulmonary function tests (i.e., forced expiratory volume in 1 s <70% of maximal age and gender predictive value), body mass index, renal dysfunction (baseline serum creatinine >1.5 mg/dl), the presence of ischemic heart disease (prior MI, prior coronary revascularization (coronary artery bypass graft or percutaneous coronary intervention) and angina pectoris), heart failure (defined according the New York Heart Association functional classification), and medication (statins, diuretics, ACE inhibitors, calcium antagonists, nitrates, beta-blockers, aspirin, and anticoagulants). All prescription and over-the-counter medications were noted on the day of admission.

Clinical follow-up and end points. Post-operative clinical information was retrieved from an electronic database of patients followed in our hospital. On occasion, missing data were abstracted retrospectively by reviewing patients' medical records. Routinely, all vascular surgery patients are screened for adverse post-operative outcome by repeated cardiac isoenzyme measurements and electrocardiographic recording. Additional tests are performed at the discretion of the attending physician. After surgery, patients visit the outpatient clinic regularly and are screened for late cardiac events. From the municipal civil registries, we obtained the survival status. At the reference date, January 2007, follow-up was complete in 99.3% of cases. The mean follow-up of the PAD patients was 6.37 ± 4.08 years, the mean follow-up of the CAD patients was 9.17 ± 4.14 years. The primary end point was long-term all-cause mortality in the PAD and CAD populations. The secondary end point was the composite of perioperative mortality and nonfatal events in the PAD population.

Perioperative and long-term mortality. Perioperative all-cause mortality was defined as death occurring during 30-day in-hospital stay or as death occurring after hospital discharge but within the first 30 days after surgery. Cardiac death was defined as death secondary to MI, heart failure, or arrhythmias. Long-term all-cause mortality was defined as death beyond 30 days after surgery; deaths that occurred in the 30-day period were thus excluded from the long-term period.

The cause of death in the PAD population was grouped into a cerebro-cardiovascular (CCV), a non-CCV, and an

Table 2 Baseline Characteristics of All Patients With PAD, According to Type of Operation

	All Patients n = 2,730 (100%)	CEA n = 560 (21%)	AAA n = 923 (34%)	r-AAA n = 100 (7%)	LLR n = 1,047 (38%)	p Value
Demographics						
Mean age (± SD)	66 (11)	65 (10)	66 (11)	71 (9)	65 (12)	<0.001
Male (%)	75	73	78	88	72	<0.001
Cardiovascular risk factor (%)						
Body mass index (± SD)	25.0 (5)	25.8 (3)	24.9 (5)	25.4 (3)	24.7 (4)	0.006
Current smoker	24	11	28	14	29	<0.001
Hypertension	45	34	53	43	46	<0.001
Diabetes mellitus	15	10	13	10	20	<0.001
Hypercholesterolemia	29	28	37	33	26	<0.001
COPD	18	7	26	20	17	<0.001
Renal dysfunction*	12	5	13	20	14	<0.001
Disease history (%)						
Angina	15	7	17	14	19	<0.001
MI	24	9	30	27	31	0.01
Coronary revascularization	24	19	26	20	28	<0.001
Heart failure	5	1	6	5	7	<0.001
Medication use (%)						
Statins	26	26	33	19	23	<0.001
Diuretics	18	10	18	19	23	<0.001
ACE inhibitors	31	21	35	25	34	<0.001
Calcium antagonists	34	27	43	22	32	<0.001
Nitrates	19	13	21	14	20	<0.001
Beta-blockers	33	26	45	22	29	<0.001
Aspirin	40	73	33	28	32	<0.001
Anticoagulation	20	6	17	10	33	<0.001

*Baseline serum creatinine >1.5 mg/dl.

AAA = elective infrarenal abdominal aortic surgery; ACE = angiotensin-converting enzyme; CEA = carotid endarterectomy; COPD = chronic obstructive pulmonary disease; LLR = lower limb arterial reconstruction procedures; r-AAA = acute infrarenal abdominal aortic surgery; other abbreviations as in Table 1.

unknown cause of death. A CCV death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and included deaths following MI, serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), congestive heart failure, stroke (cerebrovascular accident or transient ischemic attack), surgery-related bleeding complications (only a post-operative cause of death), and others. Sudden unexpected death was classified as a CCV death. An MI was defined as the presence of 2 out of the following 3 criteria: 1) typical chest pain complaints; 2) electrocardiographic changes including acute ST-segment elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 h, or new ST-segment depression that persisted >24 h; and 3) a positive troponin T (i.e., >0.10 ng/ml) or peak creatinine phosphokinase myocardial band ≥8% of an elevated total creatinine phosphokinase with characteristic rise and fall (10). Non-CCV death was defined as any death with a principal non-CCV cause, including infection, malignancy, respiratory insufficiency, and others. The cause of death was ascertained by reviewing medical records, the computerized hospital database, autopsy reports, or by contacting the referring physician or general practitioner.

Nonfatal perioperative events in the PAD population. We recorded the following nonfatal complications within 30 days after surgery: infection (such as wound infection, pneumonia, sepsis, and urinary tract infection), MI, arrhythmias, heart failure, stroke, reoperation (percutaneous revascularization or bypass surgery to a vessel that has been treated during the index procedure), hemorrhage (arterial bleeding leading to hypotension (systolic pressure of <100 mm Hg) requiring blood transfusion), thrombectomy, amputation (excluded toe amputation), perioperative renal dysfunction (peak post-operative serum creatinine >+0.5 mg/dl within 3 days after surgery compared with pre-operative serum creatinine), and the requirement of hemodialysis (excluding pre-operative hemodialysis).

Statistical analysis. Continuous data are described as mean values and standard deviations, and dichotomous data are described as percentage frequencies. The chi-square test was used for categorical variables, and the analysis of variance test was used for continuous variables.

Kaplan-Meier survival analysis was used to compare survival times between the PAD and CAD patients and the 4 PAD subgroups, stratified by type of surgery. To test for differences between the resulting curves, the log-rank test was used. For the long-term survival analysis using the Kaplan-Meier method, we included those who died within 30 days after surgery.

A univariate Cox proportional hazard regression model was used to explore the association of underlying vascular disease on long-term survival. We used univariate and not multivariate analysis because we matched all PAD and CAD patients for the available baseline cardiovascular risk factors. For this long-term analysis, we included all survivors within 30 days after vascular surgery.

Multivariate logistic regression and Cox proportional hazard regression models were used to explore the relationship of major baseline risk factors of all PAD patients undergoing vascular surgery and perioperative all-cause and cardiac death, respectively. Risk factors entered in the risk model were type of operation, age >70 years, gender, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, smoking status, hypercholesterolemia, prior MI, prior heart failure, prior coronary revascularization, prior angina, and renal dysfunction. For the long-term all-cause and cardiac mortality, multivariate Cox proportional hazards regression analysis was performed and included also all nonfatal perioperative complications.

All univariate risk factors with a p value of <0.10 were entered in the perioperative and long-term multivariate analysis, resulting in an adjusted significant odds and hazard ratios (ORs and HRs) or as not significant. Unadjusted and adjusted ORs and HRs were reported with corresponding 95% confidence intervals (CIs). A p value of <0.05 was considered to be significant. All computations were performed with SPSS software version 12.0.1 (SPSS Inc., Chicago, Illinois), running under Windows 2000 Professional (Microsoft, Redmond, Washington).

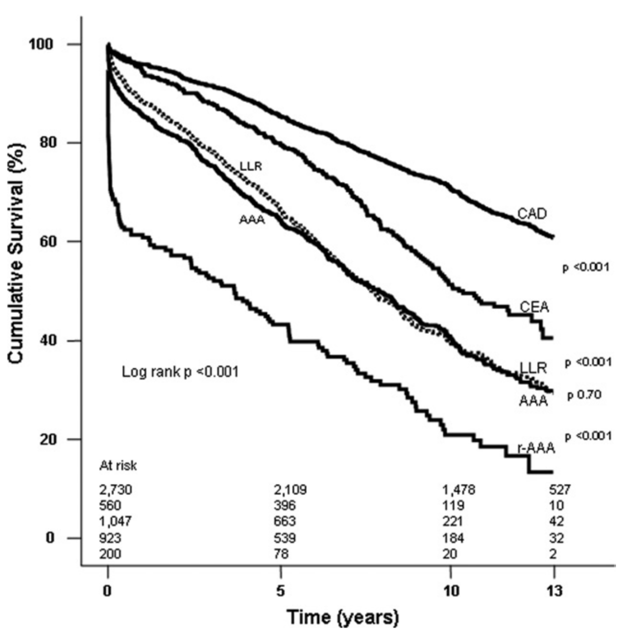

Figure 1 **Kaplan-Meier Estimate of Long-Term Survival of CAD and Different Types of Peripheral Surgical Patients**

To test for differences between the resulting curves, the log-rank test was used. AAA = elective infrarenal abdominal aortic surgery; CAD = coronary artery disease; CEA = carotid endarterectomy; LLR = lower limb arterial reconstruction; r-AAA = acute infrarenal AAA.

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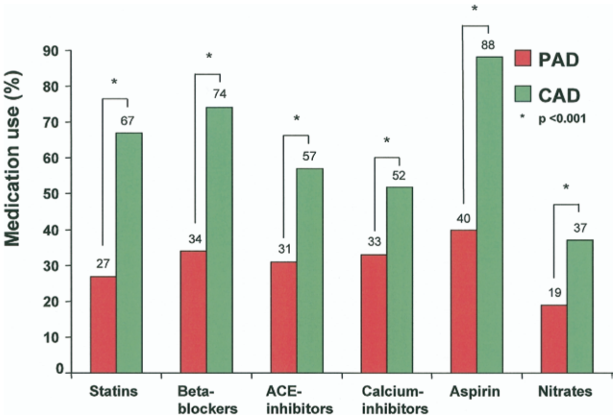

Figure 2 **Medication Use According to PAD and CAD Patients**

ACE = angiotensin-converting enzyme;
PAD = peripheral arterial disease; other abbreviation as in Figure 1.

Results

Patient characteristics. The mean age of all patients with PAD (n = 2,730) was 64 ± 16 years and 76% were male. A total of 560 patients (20%) underwent CEA surgery; 923 patients (34%) underwent AAA surgery (aortic-to-aortic n = 206, aortic bifurcation n = 624, infected prostheses n = 51, and others n = 42); 200 patients (7%) had a r-AAA; and 1,047 patients (38%) underwent LLR surgery (iliac-femoral n = 208, femoral-popliteal n =6 03, femoral-tibial n = 203, and infected prostheses n = 33). Patient's characteristics are presented in Table 2.

Primary end point. Compared with CAD patients, patients with PAD had a significantly worse long-term prognosis (unadjusted HR 2.40, 95% CI 2.18 to 2.65) (Fig. 1). Annual mortality rates of the PAD and CAD populations were 5.7% and 3.0% per year ($p < 0.001$). Importantly, patients with CAD received more cardiac medications than the PAD patients did (beta-blockers 74% vs. 34%, calcium antagonists 52% vs. 33%, aspirin 88% vs. 40%, nitrates 37% vs. 19%, statins 67% vs. 29%, and ACE inhibitors 57% vs. 31%, respectively) (Fig. 2).

Secondary end point. Within 30 days after surgery, a total of 153 PAD patients (5.6%) died. The overall mortality of the CEA, AAA, r-AAA, and LLR groups was 8 (1.4%), 58 (6.3%), 57 (28.5%), and 30 (2.9%) ($p < 0.001$), respectively. The leading causes of death were CCV events (76%) (Table 3). Specified according to the type of surgery, the leading cause of death at 30 days for CEA patients was stroke (38%), for

Table 3 **Cause of Death During the Perioperative and Long-Term Period**

	All Patients n = 2,730 (100%)	CEA n = 560 (21%)	AAA n = 923 (34%)	r-AAA n = 200 (7%)	LLR n = 1,047 (38%)	p Value
Perioperative mortality	153 (6)	8 (1)	58 (6)	57 (29)	30 (3)	
Total CCV death n (%)	116 (76)	6 (75)	45 (78)	46 (81)	19 (63)	0.3
MI	28 (18)	2 (25)	14 (24)	6 (11)	6 (20)	0.3
Congestive heart failure	15 (10)	0 (0)	7 (12)	4 (7)	4 (13)	0.5
Arrhythmia	15 (10)	0 (0)	4 (7)	7 (12)	4 (13)	0.5
Stroke	9 (6)	3 (38)	3 (5)	3 (5)	1 (3)	0.001
Fatal bleeding	40 (26)	1 (13)	13 (22)	23 (40)	3 (10)	0.01
Other	9 (6)	0 (0)	5 (9)	3 (5)	1 (3)	0.6
Total n-CCV death n (%)	37 (24)	2 (25)	13 (22)	11 (19)	11 (37)	0.3
Infection	22 (14)	0 (0)	4 (7)	8 (14)	10 (33)	0.005
Malignancy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Respiratory insufficiency	9 (6)	2 (25)	4 (7)	2 (4)	1 (3)	0.1
Others	6 (4)	0 (0)	5 (9)	1 (2)	0 (0)	0.1
Unknown n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Long-term mortality*	1,353 (53)	216 (39)	470 (54)	87 (61)	580 (57)	
Total CCV death n (%)	625 (46)	91 (42)	203 (43)	36 (41)	295 (51)	0.03
MI	250 (19)	31 (14)	85 (18)	15 (17)	119 (21)	0.2
Congestive heart failure	168 (12)	28 (13)	41 (9)	10 (12)	89 (15)	0.01
Arrhythmia	26 (2)	2 (1)	11 (2)	3 (3)	10 (2)	0.4
Stroke	96 (7)	22 (10)	33 (7)	5 (7)	35 (6)	0.2
Others	85 (6)	8 (4)	33 (7)	2 (2)	42 (7)	0.1
Total n-CCV death n (%)	412 (31)	66 (31)	150 (32)	30 (35)	166 (29)	0.6
Infection	78 (6)	4 (2)	26 (6)	7 (8)	41 (7)	0.03
Malignancy	153 (11)	32 (15)	54 (12)	7 (8)	60 (10)	0.2
Respiratory insufficiency	85 (6)	9 (4)	31 (7)	10 (12)	35 (6)	0.1
Others	96 (7)	21 (10)	39 (8)	6 (7)	30 (5)	0.09
Unknown n (%)	316 (23)	59 (27)	117 (25)	21 (24)	119 (21)	0.2

*Excluding those patients who died within the post-operative period (n = 153).
CCV = cerebro-cardiovascular; n-CCV = noncerebro-cardiovascular; other abbreviations as in Table 2.

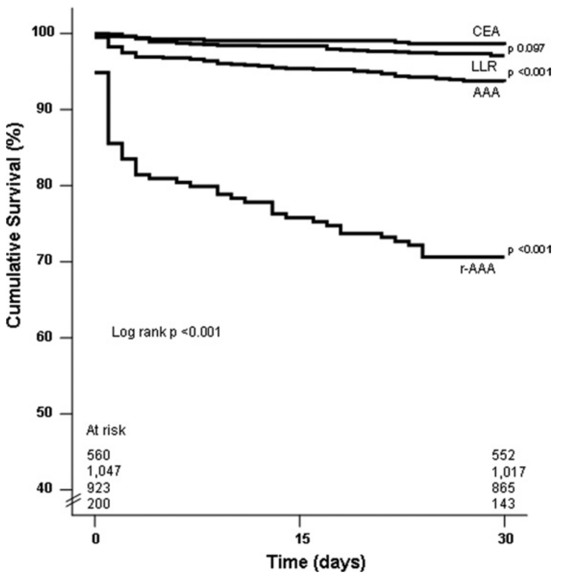

Figure 3 **Kaplan-Meier Estimate of Overall Perioperative (30-Day) Survival of Different Types of Surgical Patients**

To test for differences between the resulting curves, the log-rank test was used. Abbreviations as in Figure 1.

AAA was MI (24%), for r-AAA was fatal bleeding (40%), and for LLR was infection (40%). Outcomes at 30 days of patients undergoing CEA or LLR were superior to patients undergoing AAA surgery (Fig. 3). Patients scheduled for r-AAA surgery had the worst 30-day outcome. Also, in the multivariate Cox proportional hazards regression analysis, the type of operation was an important independent risk factor for perioperative all-cause mortality and cardiac events (Table 4).

A total of 1,353 (52.5%) patients with PAD died during 6.37 ± 4.08 years of follow-up, excluding the 153 patients who died within 30 days post-operatively. Mortality rates among the different surgical procedures were 216 (39.1%), 470 (54.3%), 87 (60.8%), and 580 (57.0%) for CEA, AAA, r-AAA, and LLR, respectively. Annual mortality rates of CEA, AAA, LLR, and r-AAA are 5.0%, 5.9%, 5.9%, and 6.8% per year (log rank $p < 0.001$), respectively. The leading cause of death was CCV (46%). Myocardial infarction accounts for 19% of all causes of long-term mortality. During long-term follow-up, patients of the LLR group had a similar prognosis compared with the AAA group (log rank $p = 0.70$), but patients of the r-AAA group had the worst outcome (Fig. 1). However, the multivariate Cox proportional hazards regression analysis illustrated that, converse to the perioperative outcome, the type of surgery was not related to outcome during long-term follow-up (Table 5). The proportional hazards assumptions were tested by constructing interaction terms between the variables and time to each end point. The Cox proportional hazards regression analyses showed no statistically significant interaction with time (each p value >0.05).

Long-term all-cause outcome was affected by age, smoking, chronic obstructive pulmonary disease, MI, renal dysfunction, and noncardiac complications (infection, stroke, and amputation). Pre-operative cardiac risk factors (age >70 years, diabetes mellitus, prior MI, coronary revascularization, heart failure) and perioperative nonfatal cardiac complications (MI, heart failure, arrhythmia) were the primary determinants of long-term adverse cardiac outcome.

Table 4 **Multivariate Associations of Baseline Characteristics With All-Cause and Cardiac Mortality in the Perioperative Period**

	Perioperative All-Cause Mortality		Perioperative Cardiac Death*	
Risk Factor	**OR Univariate (95% CI)**	**OR Multivariate (95% CI)**	**OR Univariate (95% CI)**	**OR Multivariate (95% CI)**
Operation group				
LLR (reference)	1.0	1.0	1.0	1.0
r-AAA	13.51 (8.40–21.74)	12.22 (7.46–20.04)	6.86 (3.32–14.15)	6.21 (2.94–13.12)
AAA	2.27 (1.45–3.57)	2.00 (1.27–3.16)	2.05 (1.06–3.97)	1.89 (1.01–3.68)
CEA	0.49 (0.22–1.07)	NS	0.26 (0.06–1.17)	NS
Gender	1.19 (0.80–1.77)	NS	1.40 (0.72–2.72)	NS
Age >70 yrs	2.31 (1.66–3.21)	1.55 (1.09–2.21)	2.57 (1.50–4.39)	1.95 (1.12–3.39)
Hypertension	1.50 (1.08–2.09)	1.55 (1.08–2.22)	1.72 (1.02–2.92)	NS
COPD	2.39 (1.68–3.40)	2.05 (1.40–3.01)	2.06 (1.17–3.62)	NS
Diabetes mellitus	1.13 (0.73–1.76)	NS	1.20 (0.60–2.40)	NS
Hypercholesterolemia	0.71 (0.40–1.23)	NS	0.83 (0.36–1.96)	NS
Current smoker	1.10 (0.73–1.68)	NS	0.88 (0.43–1.81)	NS
MI	1.22 (0.80–1.89)	NS	1.41 (0.80–2.47)	NS
Coronary revascularization	0.54 (0.34–0.84)	NS	0.65 (0.33–1.28)	NS
Heart failure	1.26 (0.65–2.34)	NS	2.50 (1.12–5.61)	NS
Angina	1.11 (0.60–2.03)	NS	1.27 (0.55–2.96)	NS
Renal dysfunction†	2.61 (1.77–3.84)	2.09 (1.38–3.18)	2.88 (1.60–5.19)	2.11 (1.15–3.88)

*Death because of MI, heart failure, and arrhythmia. †Baseline serum creatinine >1.5 mg/dl.
CI = confidence interval; NS = not significant; OR = odds ratio; other abbreviations as in Table 2.

Table 5 Multivariate Associations of Baseline Characteristics and Nonfatal Perioperative Complications With Long-Term All-Cause and Cardiac Mortality

Risk Factor	Long-Term All-Cause Mortality		Long-Term Cardiac Death*	
	HR Univariate (95% CI)	HR Multivariate (95% CI)	HR Univariate (95% CI)	HR Multivariate (95% CI)
Baseline risk factors				
Operation group				
LLR (reference)	1.0	1.0	1.0	1.0
r-AAA	1.29 (1.03–1.62)	NS	1.11 (0.75–1.64)	NS
AAA	0.97 (0.86–1.09)	NS	0.75 (0.61–0.93)	NS
CEA	0.66 (0.57–0.78)	NS	0.50 (0.38–0.67)	NS
Gender	1.15 (1.01–1.30)	NS	1.13 (0.91–1.41)	NS
Age >70 yrs	2.18 (1.96–2.43)	2.11 (1.88–2.36)	2.00 (1.65–2.41)	2.02 (1.66–2.47)
Hypertension	1.15 (1.03–1.28)	NS	1.18 (0.98–1.42)	NS
COPD	1.60 (1.41–1.81)	1.49 (1.29–1.71)	1.29 (1.02–1.63)	NS
Diabetes mellitus	1.32 (1.14–1.52)	NS	1.87 (1.50–2.34)	1.47 (1.16–1.87)
Hypercholesterolemia	1.06 (0.93–1.22)	NS	1.38 (1.10–1.72)	NS
Current smoker	1.30 (1.16–1.46)	1.20 (1.06–1.36)	1.44 (1.18–1.76)	NS
MI	1.43 (1.28–1.62)	NS	2.59 (2.15–3.13)	1.59 (1.26–2.01)
Coronary revascularization	1.08 (0.96–1.22)	NS	2.17 (1.80–2.62)	1.61 (1.30–1.99)
Heart failure	1.74 (1.41–2.14)	NS	2.94 (2.19–3.94)	1.45 (1.04–2.01)
Angina	1.26 (1.10–1.45)	NS	2.22 (1.81–2.73)	1.21 (1.01–1.59)
Renal dysfunction†	2.23 (1.83–2.47)	1.72 (1.47–2.02)	2.31 (1.80–2.96)	1.60 (1.22–2.09)
Post-operative complications				
Nonfatal MI	1.45 (1.19–1.76)	NS	4.07 (2.17–7.63)	2.22 (1.15–4.28)
Heart failure	2.20 (1.47–3.29)	NS	3.36 (1.89–5.96)	1.86 (1.01–3.43)
Arrhythmia	2.04 (1.41–2.98)	1.65 (1.12–2.43)	2.41 (1.33–4.40)	1.86 (1.00–3.52)
Infection	1.75 (1.52–2.02)	1.51 (1.31–1.76)	1.51 (1.17–1.96)	NS
Stroke	2.05 (1.55–2.72)	1.98 (1.47–2.67)	1.57 (0.90–2.73)	NS
Amputation	2.03 (1.58–2.61)	1.74 (1.33–2.29)	1.50 (0.84–2.68)	NS
Hemorrhage	1.24 (0.99–1.57)	NS	0.95 (0.60–1.50)	NS
Thrombectomy	1.14 (0.87–1.48)	NS	1.45 (0.96–2.19)	NS
Reoperation	1.30 (0.98–1.74)	NS	1.49 (0.93–2.39)	NS
Acute renal failure‡	1.81 (1.54–2.12)	1.44 (1.21–1.73)	1.73 (1.31–2.29)	1.39 (1.01–1.92)
Hemodialysis§	2.95 (1.98–4.38)	1.67 (1.06–2.63)	3.13 (1.61–6.06)	NS

*Death because of MI, heart failure, and arrhythmia. †Baseline serum creatinine >1.5 mg/dl. ‡Peak post-operative serum creatinine >+0.5 mg/dl (>44 μmol/l) within 3 days after surgery compared with pre-operative serum creatinine. §Excluding patients who were on pre-operative dialysis.
HR = hazard ratio; other abbreviations as in Table 2.

Discussion

Our main finding of this study is that patients with PAD, compared with a matched population for cardiac risk factors and year of treatment with CAD, are at increased risk for long-term mortality. In addition, PAD patients receive less cardiovascular medical therapy (e.g., beta-blockers, statins, ACE inhibitors, calcium antagonists, nitrates, and aspirin) than CAD patients do.

Furthermore, we conclude that CCV death is the major cause of perioperative and long-term mortality among vascular surgical patients with PAD (76% and 46%, respectively). Cardiac risk factors and perioperative cardiac complications are associated with long-term cardiac death, but noncardiac complications including infection, stroke, amputation, acute renal failure, and dialysis dependency are mainly related with all-cause mortality. The type of vascular surgery was found to be an independent risk factor for an adverse outcome in the perioperative period but not during the long-term follow-up. The long-term prognosis of patients undergoing acute repair of the ruptured abdominal aorta is similar to patients undergoing elective AAA surgery, contrary to the perioperative period. Similar results were observed by Soisalon-Soininen et al. (11) among 1,070 patients undergoing repair of ruptured and nonruptured abdominal aorta aneurysms.

Aggressive treatment of atherosclerotic risk factors (i.e., hypertension, diabetes mellitus, smoking, and hypercholesterolemia) and usage of cardioprotective medications (i.e., beta-blockers, statins, aspirin, and ACE inhibitors) are recommended for PAD patients, because they are associated with improved long-term survival (12–14). However, in our matched PAD and CAD population for cardiovascular risk factors, we clearly observed an underuse of cardiac medication among patients with PAD. McDermott et al. (8) reported that patients with CAD, compared with PAD patients, are treated more frequently with aspirin and lipid-lowering medication (82% vs. 37% and 56% vs. 40%, respectively). Overall, the undertreatment of PAD patients can explain their worse long-term outcome when compared with CAD patients.

Peripheral atherosclerotic disease is becoming an increasingly important health issue in Western society; it affects between 8 to 12 million adults (15). The introduction of endovascular repair has the potential to improve the outcome for PAD patients undergoing noncardiac surgery because of its reduced perioperative myocardial stress (16). This technique is currently considered as a promising alternative, especially in high-risk cardiac patients. In addition, new cardioprotective strategies, including medical therapy (17) and prophylactic coronary interventions (18), are currently being evaluated in these patients. Though the preliminary results of endovascular repair are promising and associated with improved immediate post-operative outcome, the beneficial effect on long-term survival remains controversial (3,19,20). We described the results of open surgery in a tertiary hospital in relation to long-term outcome of patients undergoing different types of vascular surgery. The results of this study will provide useful information to compare long-term outcome between open and endovascular surgery.

We do think that propensity matching is appropriate in this study setting. In this study, we deal with patients with the same underlying disease, namely generalized atherosclerosis. However, patients with PAD present themselves with different clinical symptoms (e.g., claudication), compared with the more cardiac-related complications (e.g., angina) observed in CAD patients. We used the propensity score to compare survival of patients with generalized atherosclerosis with the same risk profile with 2 different treatments (PAD or CAD).

Study limitations. First, the study is not a randomized clinical trial but an observational study of a propensity-matched cohort. Despite using propensity to adjust as much as possible for the bias inherent in the decision about being PAD or CAD patients, we cannot exclude the possibility of residual confounding. As can be seen in Table 1, the PAD and CAD populations differed significantly, and by using the propensity score matching procedure, the resulting matched CAD cohort ultimately reassembled the PAD cohort. We did not match the PAD and CAD database with the risk factor hypercholesterolemia, because of the inconsistency of the CAD database regarding the reporting of hypercholesterolemia during the early stage of our study period. Second, although data were prospectively collected, this analysis is retrospective. Because of the acute setting of r-AAA patients, not all the baseline characteristics were completely recorded in the admission data, which might result in an underdiagnosis of some risk factors. Third, changes in the perioperative management have evolved markedly over time and were not taken into account in our analysis. These include multiple factors ranging from preoperative management, such as drug therapy, to anesthesiological and surgical techniques to intensive post-surgical care management. We tried to adjust for this confounding by adding the year of operation in our multivariate analysis (as a categorical variable per 2 years). We did not investigate our results across different time periods, because we did not observe different perioperative (30-day) outcomes in the PAD database over time. Finally, in our cohort, we found a remarkably low incidence of diabetes mellitus (15%). The diagnosis of diabetes mellitus was based on the requirement for insulin therapy, hypoglycemic agents, or as fasting blood glucose ≥140 mg/dl. In patients qualified as nondiabetics with PAD, fasting glucose levels may be normal, and the diagnosis of diabetes is only made after a glucose loading test. Unfortunately, we did not routinely perform a loading test for patients with a normal fasting glucose. Therefore, the number of diabetics might be underestimated.

Reprint requests and correspondence: Prof. Dr. Don Poldermans, Department of Anesthesiology, Erasmus MC, Gravendijkwal 230, 3015 CE Rotterdam, the Netherlands. E-mail: d.poldermans@erasmusmc.nl.

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