Long-term prognosis of patients with peripheral arterial disease with or without polyvascular atherosclerotic disease

Jan-Peter van Kuijk[1], Willem-Jan Flu[2], Gijs M.J.M. Welten[1], Sanne E. Hoeks[2], Michel Chonchol[3], Radosav Vidakovic[1], Hence J.M. Verhagen[1], Jeroen J. Bax[4], and Don Poldermans[1]*

[1]Department of Vascular Surgery, Erasmus Medical Center, 's Gravendijkwal 230, Room H-805, Rotterdam 3015 CE, The Netherlands; [2]Department of Anesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands; [3]Division of Renal Diseases and Hypertension, University of Colorado Health Sciences Center, Denver, CO, USA; and [4]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

Aims	Patients with peripheral atherosclerotic disease often have multiple affected vascular beds (AVB), however, data on long-term follow-up and medical therapy are scarce. We assessed the prevalence and prognostic implications of polyvascular disease on long-term outcome in symptomatic peripheral arterial disease (PAD) patients.
Methods and results	Two thousand nine hundred and thirty-three consecutive patients were screened prior to surgery for concomitant documented cerebrovascular disease and coronary artery disease. The number of AVB was determined. Cardiovascular medication as recommended by guidelines was noted at discharge. Single, two, and three AVB were detected in 1369 (46%), 1249 (43%), and 315 (11%) patients, respectively. During a median follow-up of 6 years, 1398 (48%) patients died, of which 54% secondary to cardiovascular cause. After adjustment for baseline cardiac risk factors and discharge-medication, the presence of 2-AVB or 3-AVB was associated with all-cause mortality (HR 1.3 95% CI 1.2–1.5; HR 1.8 95% CI 1.5–2.2) and cardiovascular mortality (HR 1.5 95% CI 1.2–1.7; HR 2.0 95% CI 1.6–2.5) during long-term follow-up, respectively. Patients with 2- and 3-AVB received extended medical treatment compared with 1-AVB at the time of discharge.
Conclusion	Polyvascular atherosclerotic disease in PAD patients is independently associated with an increased risk for all-cause and cardiovascular mortality during long-term follow-up.
Keywords	Peripheral arterial disease • Atherosclerosis • Polyvascular disease • Long-term • Prognosis

Introduction

Peripheral arterial disease (PAD) is a multifactorial syndrome that most commonly affects people over 60 years of age.[1] As population age increases, the prevalence of atherosclerotic disease and its associated adverse outcomes will increase. Cardiovascular risk profiles have been established in several large studies, showing an equal risk factor distribution among all populations and across age groups and gender.[2,3] It has to be noted that the process of established atherothrombosis is not limited to a single arterial location. The Reduction of Atherothrombosis for

Continued Health (REACH) registry showed that one of six patients with PAD, cerebrovascular disease (CVD), or coronary artery disease (CAD) had involvement of one or two other arterial beds.[1,4] The REACH registry also demonstrated a substantial gap between recommended clinical guidelines and actual clinical practices in the care of patients with or at risk for atherothrombosis. A pattern of underutilization of established medical therapies and lifestyle interventions was shown throughout all geographic regions studies and vascular disease subtypes.[1] Consequently, patients with PAD have a three- to six-fold increased risk for the occurrence of cardiovascular mortality compared with patients

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without PAD.[5,6] Therefore, the importance of risk factor reduction in patients with PAD has resulted in universally recommended atherothrombotic risk factor reduction, with the objective of decreasing the high incidence of heart disease and CVD associated with PAD.[7,8]

However, although these large studies have identified the risk factor profiles and treatment protocols of atherosclerotic patients, most data are based on the screening of polyvascular disease, especially in the primary care setting. Therefore, the aim of the current study was to assess (i) the prevalence and number of affected vascular beds (AVB) and (ii) the prognostic implications of polyvascular disease on short- and long-term mortality in high-risk vascular surgery patients with symptomatic PAD.

Methods

Study design and population

This retrospective single-centre study comprised a population of 2933 consecutive patients with PAD, referred for elective major vascular surgery. All patients underwent a major vascular surgery procedure during the time period 1990–2008, and included lower extremity revascularization, abdominal aortic surgery (dilatating or stenotic), or carotid surgery. From 1990 until 2001, standard pre-operative screening included a detailed cardiac history, physical examination, electrocardiogram (ECG) standard laboratory measurements, and additional (stress)-testing if indicated. After 2002, standard pre-operative echocardiography was added to the screening program. The study complies the Declaration of Helsinki. Patient enrolment was performed after approval of the hospital's Ethics Committee and after informed consent of all patients (or their guardians) at time of inclusion.

Patient data

At baseline, all medical records were reviewed to determine the presence of documented CAD and CVD. Patients undergoing lower extremity revascularization or abdominal aortic surgery were screened for the concomitant presence of documented CAD and CVD. Patients undergoing carotid surgery were screened for CAD and PAD. Coronary artery disease was defined as a documented history of ischaemic heart disease [composite of angina pectoris, myocardial infarction (MI), percutaneous coronary intervention, or coronary artery bypass grafting], using myocardial stress testing (ergometry, stress echocardiography, or CT scan) or coronary angiogram. Patients with stable or unstable angina pectoris were classified as having documented CAD according to the ESC guidelines.[9] The presence of coronary ischaemia was established by one of the following techniques: exercise ECG [horizontal or down-sloping ST-segment depression or elevation (≥ 1 mm (0.1 mV) for ≥ 60–80 ms after the end of the QRS complex)] or exercise testing with echocardiography, CT scan ($\geq 50\%$ stenosis in one or more of the coronary arteries).[10] The presence of documented CVD was defined as a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA). Cerebrovascular accidents had to be confirmed by a CT-scanning report. The diagnosis of TIA had to be confirmed by a neurologist report. Lower extremity arterial disease was defined as current intermittent claudication with ankle-brachial index <0.9 or a history of intermittent claudication with a previous intervention, such as angioplasty, stenting, atherectomy, peripheral arterial bypass graft, or other vascular intervention including amputation. Polyvascular disease was defined as the presence of 2- or 3-AVB. One-AVB included: PAD, 2-AVB: PAD and CAD or CVD, 3-AVB: PAD and CAD and CVD.

Finally, the use of the following medication was recorded at discharge: aspirin, statins, beta-blockers, diuretics, angiotensin-converting enzyme (ACE)-inhibitors, angiotensin receptor blockers, oral anticoagulants, and ticlopidines. Treatment goals were defined according to the current guidelines and included low-dose aspirin (75–325 mg daily) and statins (low-intermediate risk patients: target LDL level <100 mg/dL, high-risk patients <70 mg/dL) for patients with PAD, and if necessary combined with antihypertensive drugs to receive a target blood pressure below 140/90 mmHg.[7] Additionally, PAD patients with diabetes should receive ACE-inhibitors to a target blood pressure less than 130/80 mmHg.[7] Patients with CAD should be treated with aspirin, statins (target LDL <100 mg/dL), and beta-blockers, and additionally with ACE-inhibitors or angiotensin receptor blockers in case of diabetes mellitus and/or heart failure.[11]

Risk factors

All cardiac risk factors were determined at baseline, including age, gender, body mass index, smoking status, hypertension (defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg in non-diabetics, systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 80 mmHg in diabetics or the use of antihypertensive medication), diabetes mellitus (fasting blood glucose ≥ 7.0 mmol/L or requirement for insulin and/or oral anti-diabetic medication), hypercholesterolaemia (LDL cholesterol >135 mg/dL and/or the requirement of lipid-lowering medication), chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseases (GOLD) classification[12]) and chronic renal insufficiency (serum creatinine >2.0 mg/dL). The cardiac risk score was calculated according to the adapted Lee cardiac index which assigns 1 point for each of the following characteristics: high-risk surgery, ischaemic heart disease, heart failure, CVD, chronic renal insufficiency, and diabetes mellitus.[13]

Follow-up and endpoints

The median follow-up of all patients was 6 years (inter-quartile range 2–9). Primary study endpoint was the occurrence of all-cause mortality. Survival status was assessed by reviewing the municipal civil registries. Cause of death was ascertained by examining death certificates, and otherwise by reviewing medical records. Cause of death was further classified as either cardiovascular or non-cardiovascular death. Cardiovascular death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and includes death 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 event or transient ischaemic attack), and surgery-related bleeding complications (only a post-operative cause of death). Sudden unexpected death was classified as a cardiovascular death.

Statistics

Continuous data were compared using analysis of variance and are expressed as mean $\pm$ SD. Categorical data are presented as percentage frequencies and compared using χ^2 tests. Analyses for trends in all baseline characteristics (including age) between the number AVB were performed with linear-by-linear association. Logistic regression analysis was used to determine the association between polyvascular disease (2- and 3-AVB compared with 1-AVB) and short-term mortality (30 days). Cumulative survival of patients with 1-, 2-, or 3-AVB was determined by the Kaplan–Meier method and compared using the log-rank test. Univariable and multivariable Cox regression models were used to investigate the association between AVB

(patients with 1-AVB as reference group) and mortality during long-term follow-up. All multivariable analyses were primarily adjusted for demographics (age and gender) and cardiovascular risk factors (smoking, hypertension, diabetes mellitus, hypercholesterolaemia, renal dysfunction, heart failure, and COPD). Secondary adjustments were made for medications usage recommended by the ESC/ACC guidelines in patients with PAD, including aspirin, statins, beta-blockers in case of prior MI, and ACE-inhibitors in case of heart failure.[7] Finally, adjustment was made for pre-operative haemoglobin levels. To evaluate the effect of medication use (aspirin, statins, beta-blockers, and ACE-inhibitors) on long-term outcome, multivariate Cox regression analyses were performed with propensity score adjustment for each medication. Separate propensity scores were developed with logistic regression analyses for each type of medication. Variables included in the propensity score model were demographics (age and gender), cardiovascular risk factors (smoking, hypertension, diabetes mellitus, hypercholesterolaemia, renal dysfunction, heart failure, and COPD), medication use, and haemoglobin. Statistical analyses were performed using SPSS software (SPSS version 15.0; SPSS, Inc., Chicago, IL, USA). Hazard ratios (HR) were calculated from these models along with their 95% confidence intervals (CI). A *P*-value of <0.05 (two-sided) was considered statistically significant.

Results

Description of the study population

The study population consisted of 2933 consecutive patients with PAD referred for elective major vascular surgery. Lower extremity revascularization was performed in 1031 (35%) patients, abdominal aortic surgery in 1170 (40%) patients, and carotid surgery in 732 (25%) patients, respectively. Coronary artery disease and CVD were detected in 1248 (43%) and 1037 (35%) patients, respectively. In patients referred for lower extremity revascularization, 454 (44%) and 144 (14%) patients had concomitant documented CAD and CVD, respectively. Coronary artery disease and CVD were present in 575 (49%) and 166 (14%) of the patients referred for abdominal aortic surgery. Patients referred for carotid surgery, 219 (30%) and 79 (11%) patients had concomitant CAD and PAD. The number of AVB was determined at baseline, and one-vessel disease (1-AVB), two-vessel disease (2-AVB), and three-vessel (3-AVB) disease were detected in 1369 (46%), 1249 (43%), and 315 (11%) patients, respectively (*Figure 1*).

Lee cardiac index and number of affected vessels

Baseline characteristics of the study population were compared between the groups with different number of AVB and included demographic parameters and cardiovascular risk factors. A significant trend for an increased number of cardiovascular risk factors was present in patients with 2- or 3-AVB, compared with 1-AVB. Additionally, risk factor patterns were calculated following the Lee cardiac index and showed a relationship with the number of affected vessels. A Lee risk score of ≥3 was only present in 5% of patients with 1-AVB, whereas 252 (80%) patients had a Lee risk score of ≥3 in patients with 3-AVB (*P* < 0.001) (*Figure 2*).
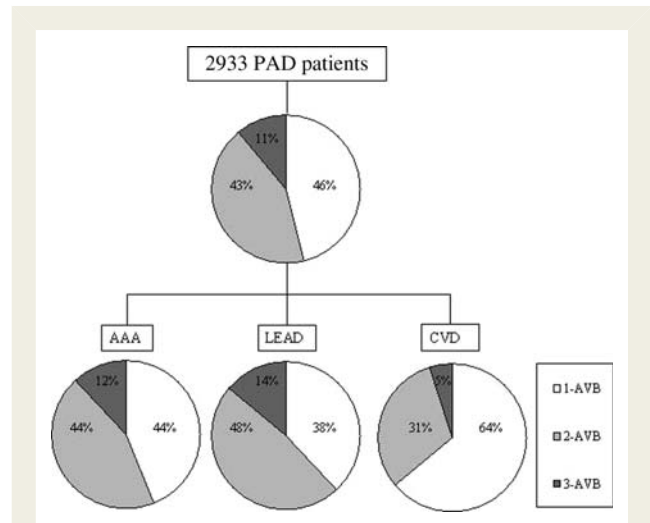

Figure 1 Number of affected vascular beds in the total study population and subdivided for type of surgery. PAD: peripheral arterial disease, AAA: abdominal aortic aneurysm, LEAD: lower extremity arterial disease, CVD: cerebrovascular disease, AVB: affected vascular beds.
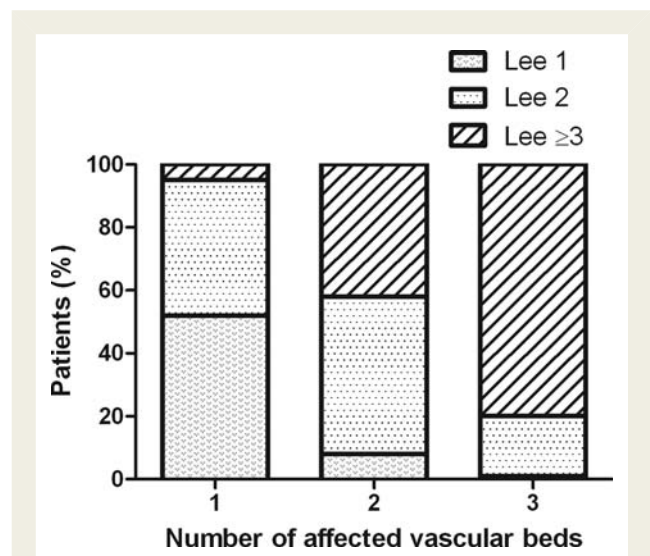

Figure 2 Distribution of the Lee cardiac index according to the number of affected vascular beds.

Medication use and number of affected vessels

Medication use at time of hospital discharge was registered and compared between the different patient groups (*Table 1*). Aspirin, statins, beta-blockers, and ACE-inhibitors were used by 1502 (51%), 1131 (39%), 1293 (44%), and 740 (25%) patients, respectively. There was a clear relationship between the year of surgery and medical treatment intensity after surgery (*Figure 3*). Importantly, aspirin was used in ≥50% of the patients from 1996, whereas statins and beta-blockers were prescribed in

Table 1 Baseline characteristics of the study population

	Total (*n* = 2933)	1-AVB (*n* = 1369)	2-AVB (*n* = 1249)	3-AVB (*n* = 315)	*P*-value
Demographics					
Age (year), mean ± SD	66 (11)	66 (12)	67 (11)	68 (10)	<0.001
Male (%)	2189 (75)	958 (70)	974 (78)	257 (82)	<0.001
Year of surgery					0.001
<1992	429 (15)	187 (14)	205 (16)	37 (12)	
1993–1995	653 (22)	323 (24)	270 (22)	60 (19)	
1996–1998	586 (20)	303 (22)	228 (18)	55 (18)	
1999–2001	353 (12)	177 (13)	150 (12)	26 (8)	
2002–2004	249 (9)	96 (7)	112 (9)	41 (13)	
2005–2008	663 (23)	283 (21)	285 (23)	314 (11)	
Cardiovascular risk factors					
Smoking					<0.001
No	1139 (39)	585 (43)	456 (37)	98 (31)	
Current	1092 (37)	490 (36)	471 (38)	131 (42)	
History	702 (24)	294 (22)	322 (26)	86 (27)	
Hypertension	1514 (52)	594 (43)	706 (57)	214 (68)	<0.001
Diabetes mellitus	491 (17)	161 (12)	263 (21)	67 (21)	<0.001
Hypercholesterolaemia	798 (27)	289 (21)	392 (31)	117 (37)	<0.001
Renal dysfunction	297 (10)	95 (7)	146 (10)	56 (18)	<0.001
Chronic heart failure	206 (7)	24 (2)	126 (10)	56 (18)	<0.001
COPD	557 (19)	201 (15)	271 (22)	85 (27)	<0.001
Medication at discharge					
Aspirin	1502 (51)	726 (53)	610 (49)	166 (53)	0.25
Statin	1131 (39)	463 (34)	506 (41)	162 (51)	<0.001
Beta-blocking agents	1293 (44)	506 (37)	599 (48)	188 (60)	<0.001
Diuretics	696 (24)	244 (18)	340 (27)	112 (36)	<0.001
ACE-inhibitors	740 (25)	260 (19)	335 (28)	125 (40)	<0.001
Calcium Antagonists	711 (24)	265 (19)	360 (29)	86 (27)	<0.001
AT- II antagonists	157 (5)	61 (5)	71 (6)	25 (8)	0.01
Oral anticoagulants	1108 (38)	463 (34)	505 (40)	140 (44)	<0.001
Ticlopidines	132 (5)	45 (3)	60 (5)	27 (9)	<0.001

AVB, affected vascular beds; COPD, chronic obstructive pulmonary disease; ACE-inhibitors, angiotensin converting enzyme-inhibitors; AT-II antagonists, angiotensin II antagonists.

≥50% of the patients from 2002. The number of AVB (1- vs. 2- vs. 3-AVB) showed a relationship with the use of statins (34% vs. 41% vs. 51%, *P* < 0.001), beta-blockers (37% vs. 48% vs. 60%, *P* < 0.001), and ACE-inhibitors (19% vs. 28% vs. 40%, *P* < 0.001). In contrast, there was no significant relationship between the number of AVB and aspirin use (53% vs. 49% vs. 53%, *P* = 0.25).

Short-term outcome

During the first 30 post-operative days, 112 (3.8%) patients died, of which 90 (80%) patients died secondary to a cardiovascular cause. Using univariable analysis, patients with 2- or 3-AVB had a significant increased mortality risk compared with patients with 1-AVB (2-AVB: OR 1.9 95% CI 1.22–2.88, 3-AVB: OR 2.5 95% CI 1.42–4.50), respectively (*Table 2*). This increased risk was present for the occurrence of cardiovascular death as well (2-AVB: OR 1.9 95% CI 1.16–3.00, 3-AVB: OR 2.2 95% CI

1.16–4.30). In multivariable analysis, 2- and 3-AVB were independently associated with all-cause mortality (2-AVB: OR 1.7 95% CI 1.03–2.63, 3-AVB: OR 2.5 95% CI 1.29–4.71). However, cardiovascular mortality was not longer significantly associated with polyvascular disease during short-term follow-up.

Long-term outcome

After 1-year follow-up, 308 (11%) patients died, of which 227 (74%) and 71 (26%) secondary to a cardiovascular or non-cardiovascular cause, respectively. Patients with 2- or 3-AVB had an increased risk for the occurrence of 1-year all-cause mortality (2-AVB: HR 1.3 95% CI 1.03–1.7; 3-AVB: 1.6 95% CI 1.1–2.3) and cardiovascular mortality (2-AVB: HR 1.7 95% CI 1.2–2.2; 3-AVB: 1.7 95% CI 1.1–2.6), compared with patients with 1-AVB, respectively. During long-term follow-up, 1389 (47%) patients reached the primary endpoint of all-cause mortality. A
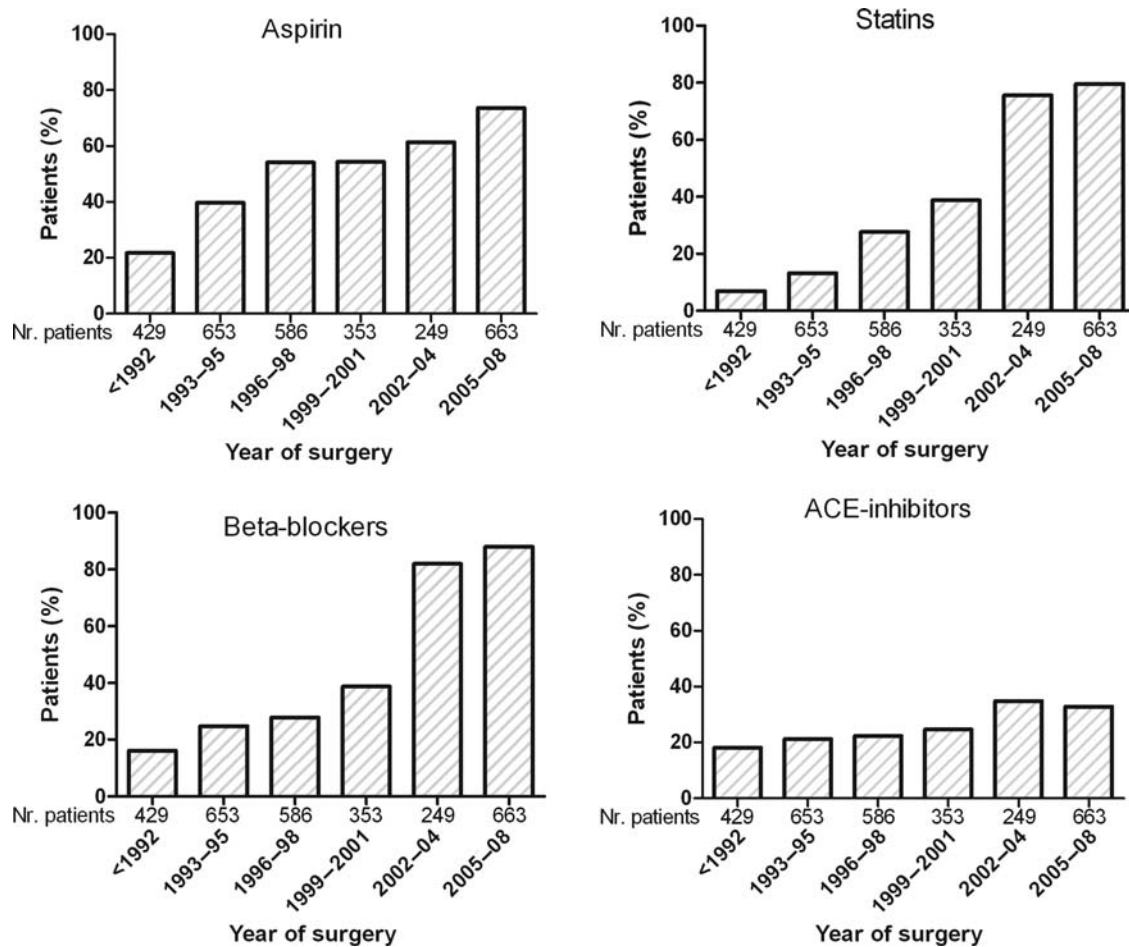
Figure 3 Post-operative prescription of aspirin, statins, beta-blockers, and ACE-inhibitors stratified according to the year of surgery.

Table 2 Short-term (30 days) survival

	Events	Univariate		Multivariate (1)		Multivariate (2)	
	n (%)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
All cause mortality							
One-vessel disease (n = 1369)	36 (3)	—		—		—	
Two-vessel disease (n = 1249)	57 (5)	1.87	1.22–2.88	1.59	1.01–2.50	1.65	1.03–2.63
Three-vessel disease (n = 315)	19 (6)	2.53	1.42–4.50	1.76	0.95–3.27	2.46	1.29–4.71
Cardiovascular mortality							
One-vessel disease (n = 1369)	29 (3)	—		—		—	
Two-vessel disease (n = 1249)	47 (5)	1.87	1.16–3.00	1.52	0.93–2.50	1.56	0.94–2.60
Three-vessel disease (n = 315)	14 (7)	2.23	1.16–4.30	1.44	0.72–2.89	1.94	0.94–4.02

Multivariate (1): adjustment for age, gender, smoking, hypertension, diabetes mellitus, hypercholesterolaemia, renal dysfunction, heart failure, chronic obstructive pulmonary disease, haemoglobin. Multivariate (2): adjustment for age, gender, smoking, hypertension, diabetes mellitus, hypercholesterolaemia, renal dysfunction, heart failure, chronic obstructive pulmonary disease, haemoglobin + medication use. Including: aspirin, statins, beta-blockers, and ACE-inhibitors.

cardiovascular or non-cardiovascular cause of death was detected in 849 (61%) and 434 (31%) patients, respectively. In the remaining 106 (3.6%) patients, no specific cause of death could be determined. The occurrence of all-cause mortality showed a significant relationship with the number of AVB (1-AVB 43%, 2-AVB 50%, 3-AVB 54%, $P < 0.001$). Kaplan–Meier estimates for long-

term mortality stratified according to the number of AVB showed that patients with 2- or 3-AVB had lower survival compared with patients with 1-AVB (*Figure 4*). At 1-year follow-up, survival rates in patients with 1-, 2-, and 3-AVB were 91.4, 87.9, and 83.6, respectively. Furthermore, at 10-year follow-up, survival rates in 1-, 2-, and 3-AVB were 48.0, 40.6, and 29.2, respectively. Log-rank test compared cumulative survival between 1- and 2-AVB and 2- and 3-AVB and showed a significant difference in survival between both comparisons ($P < 0.001$). After multivariable regression analysis, adjusted for baseline demographic and risk factors, a strong relationship between the number of AVB and the risk of all-cause and cardiovascular mortality was detected at both 1 and 10 years of follow-up (*Table 3*). During long-term follow-up, patients with 2- or 3-AVB had an increased risk for the occurrence of all-cause mortality (2-AVB: HR 1.3 95% CI 1.15–1.45; 3-AVB: HR 1.8 95% CI 1.50–2.15), and also for the occurrence of cardiovascular mortality (2-AVB: HR 1.5 95% CI

1.24–1.68; 3-AVB: HR 2.0 95% CI 1.60–2.51), compared with patients with 1-AVB, respectively.

Optimal medical therapy according to the ESC/ACC guidelines was 57% in the patient group that underwent surgery between 2002 and 2008. During this period, aspirin (HR 0.52 95% CI 0.37–0.72), statins (HR 0.38 95% CI 0.27–0.53), and ACE-inhibitors (HR 0.32 95% CI 0.11–0.94) were significantly associated with lower mortality rates in propensity adjusted analysis. Of note, over 90% of the patients who underwent surgery after 2002 were on perioperative beta-blocker therapy.

Discussion

To our knowledge, the current study is the first to show a strong relationship between the number of affected vessel beds and long-term prognosis in patients with known symptomatic PAD. When compared with 1-AVB, patients with 2- or 3-AVB had significantly higher rates of all-cause and cardiovascular mortality during long-term follow-up after major vascular surgery. The process of atherosclerotic vascular disease is a diffuse progressive condition that usually affects multiple vascular territories concomitantly. All manifestations of arterial diseases are preceded by atherosclerotic plaques formation in the arterial wall. The presence of risk factors like hypertension, diabetes mellitus, smoking, and hypercholesterolaemia make patients prone for the development of atherosclerotic plaques. Therefore, lifestyle modification and medical treatment are strongly recommended for patients with atherosclerotic disease.[7,8]

Until now, most data regarding the prevalence and long-term prognosis of patients with polyvascular disease included determination of polyvascular disease in the primary care setting, while follow-up was generally limited to 1-year.[4,14] In most studies and registries, data on the prevalence of polyvascular disease were mainly on the presence of risk factors, symptoms, and medical treatment. Hirsch *et al.*[1,15] found a prevalence of polyvascular disease (PAD and CVD) of 16% in the primary care setting, which was observed by the REACH registry as well. Recent data
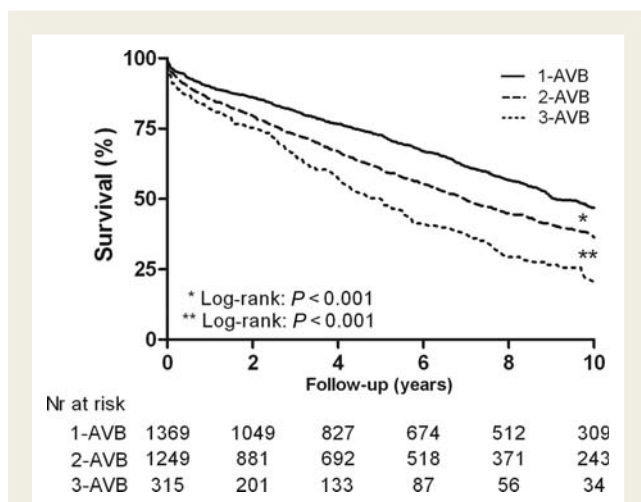

Figure 4 Kaplan–Meier estimates for long-term all-cause mortality, stratified according to the number of affected vascular beds.

Table 3 Long-term survival

	Events	Univariate		Multivariate (1)		Multivariate (2)	
	n (%)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
All cause mortality							
One-vessel disease (*n* = 1369)	558 (43)	—		—		—	
Two-vessel disease (*n* = 1249)	630 (50)	1.32	1.18–1.48	1.27	1.13–1.43	1.29	1.15–1.45
Three-vessel disease (*n* = 315)	171 (54)	1.87	1.57–2.22	1.62	1.36–1.94	1.79	1.50–2.15
Cardiovascular mortality							
One-vessel disease (*n* = 1369)	334 (24)	—		—		—	
Two-vessel disease (*n* = 1249)	401 (32)	1.5	1.29–1.73	1.42	1.22–1.65	1.45	1.24–1.68
Three-vessel disease (*n* = 315)	114 (36)	2.14	1.73–2.65	1.81	1.45–2.27	2	1.60–2.51

Multivariate (1): adjustment for age, gender, smoking, hypertension, diabetes mellitus, hypercholesterolaemia, renal dysfunction, heart failure, chronic obstructive pulmonary disease, haemoglobin. Multivariate (2): adjustment for age, gender, smoking, hypertension, diabetes mellitus, hypercholesterolaemia, renal dysfunction, heart failure, chronic obstructive pulmonary disease, haemoglobin + medication use. Including: aspirin, statins, beta-blockers, and ACE-inhibitors.

from the CRUSCADE investigators in patients presenting with non-ST-segment elevation acute coronary syndrome, reported a prevalence of 12% established PAD, 10% documented CVD, and 43% prior CAD.[16] Objective determination of polyvascular disease by screening and/or additional testing was performed primary by Hertzer *et al.*[17] who observed a prevalence of CAD in 44, 30, and 33% of the PAD patients, respectively. Analysis of the REACH registry showed that 2- or 3-AVB is present in 48 or 14% of PAD patients, respectively.[4] We demonstrated in the current study of patients with known PAD, a documented prevalence of 2- and 3-AVB of 43 and 11%, respectively. The slightly higher prevalence of polyvascular disease in the PAD subset of REACH patients is likely due to the inclusion of patients with ≥3 atherothrombotic risk factors without symptomatic vascular disease, in the REACH registry.

The current study showed a significant association between the presence of multiple risk factors and the presence of polyvascular disease, which was in line with the previous studies that focused on the prevalence of risk factors in several atherosclerotic populations.[14,15,18] Atherothrombotic risk factor reduction is universally recommended for patients with PAD to reduce their high incidence of heart disease and stroke.[7,8,19–21] Although we found that patients with 2- or 3-AVB received better medical treatment compared with patients with lone PAD, there was still a underutilization of medication. In this study, aspirin use was observed in more than 50% of the patients included after 1996 and was associated with increased survival rates, which is in line with the recent meta-analyses.[22] The underutilization of optimal medical therapy is strongly related to the implementation of the guidelines on PAD after 2003, as before the implementation of guidelines only a minority of patients received a combination of aspirin, statins, ACE-inhibitors, and in cases of ischaemic heart disease additional beta-blockers was used.[7] Thereafter, the use of statins and beta-blockers has strongly increased, and 57% of the patients included in this cohort received optimal medical therapy. As reported by others, aspirin, statins, and ACE-inhibitor use were all significantly associated with increased survival rates.[22] The gap between guideline recommendations and clinical practice in PAD patients remains a concerning and significant problem. Potential reasons for this undertreatment could be related to (i) low perception of the risk associated with PAD compared with CAD and CVD and (ii) the absence of healthcare campaigns directed at providing information to individuals with PAD, especially during the previous decade.

Data regarding the perioperative outcome in the polyvascular patient population are scarce, as most studies are directed at 1-year mortality rates. Our study showed that patients with 2- or 3-AVB had higher perioperative mortality rates compared with patients with 1-AVB (5 and 6% vs. 3% $P < 0.001$, respectively). Cardiovascular mortality was present in 75% of the patients that died within the first 30-days after major vascular surgery. In multivariable analyses, polyvascular disease was significantly associated with increased all-cause mortality rates. Our data are in keeping with others reporting 30-day mortality rates up to 6%, of which 76% are due to cardiovascular cause in major vascular surgery patients.[18] Bhatt *et al.*[16] reported a 30-day all-cause mortality rate of 7.3% in patients presenting with non-ST-elevation acute

coronary syndrome and concomitant 3-AVB. In this study, only 3-AVB was significantly associated with increased all-cause mortality (OR 1.25 95% CI 1.02–1.54) in multivariable analysis.

After 1-year follow-up, 11% of the patients died of which 74% secondary to a cardiovascular cause. A significant association between the number of AVB and the occurrence of all-cause and cardiovascular mortality was observed. Mortality rates increased from 8% in 1-AVB to 16% in 3-AVB. These findings are in keeping with others, as in the REACH registry 1-year all-cause and cardiovascular mortality rates were approximately doubled in patients with polyvascular disease, compared with single arterial disease.[14] Furthermore, the Polyvascular Atherothrombosis Observational Survey (PATHOS) found that patients with acute MI or stroke and concomitant PAD had an increased mortality risk (OR 2.05 95% CI 1.31–3.22) compared with patients without PAD.[23] These findings support the need for increased awareness of the cross-risk that is related to the overlap between the various arterial locations of atherothrombosis.

No prior large studies investigated the long-term prognosis of patients with polyvascular atherosclerotic disease up to 10 years. The current study found that after a follow-up period of 5 years, 50% of the patients with 3-AVB had already died, pointing at the grave prognosis of polyvascular disease. Criqui *et al.*[5] performed the first long-term outcome study in 565 patients with large-vessel PAD and detected an increased relative risk for cardiovascular mortality (RR 5.9 95% CI 3.0–11.4) after 10-years follow-up, compared with patients without PAD. Eagle *et al.*[24] and Sutton *et al.*[25] observed that during 10-year follow-up, CAD patients with concomitant PAD had a 25% greater likelihood of mortality compared with CAD patients without PAD at any point in time. Recently, Welten *et al.*[18] performed a propensity-matched study in PAD and CAD patients, showing that during a mean follow-up of 6 ± 4 years, patients with PAD had a significantly worse long-term prognosis compared with patients with CAD (unadjusted HR 2.4 95% CI 2.18–2.65). Hence, patients with combined PAD, CAD and/or CVD have the worst prognosis. Therefore, early objective detection and treatment of asymptomatic concomitant cardiovascular risk factors in patients with PAD is recommended and strongly emphasized by the current guidelines.[7,8]

Limitations

Potential limitations of the current study merit consideration. First, this study has the disadvantage of a retrospective design. Second, the standardized protocol for pre-operative screening did not include echocardiography before 2002; therefore, there could be an underestimation of subclinical atherosclerosis in patients undergoing surgery before this date. In addition, diagnostic methods and accuracy have changed over time, which could have influenced the criteria for the presence of documented CAD or CVD. Third, a specific cause of death could not be established in 3.6% of the patients that died during the follow-up period. One year after, the last patient had been included, mortality rates were verified according to the civil registries, however, reviewing the death certificates or contacting the treating general practitioner could not establish cause of death. Therefore, we performed two additional analyses in which patients for whom cause of death was unknown

were regarded either as cardiovascular or non-cardiovascular deaths. These analyses found similar results with no influence on the significance of the outcome parameters. Finally, although this study detected significant associations between medical treatment and increased survival rates, these results need to be interpreted with some caution as this study only included medical treatment at discharge and no evaluation of treatment adherence during follow-up was available.

Conclusion

Polyvascular atherosclerotic disease in PAD patients scheduled for elective major vascular surgery is independently associated with an increased risk for all-cause and cardiovascular mortality during long-term follow-up. Peripheral arterial disease patients with polyvascular disease have more atherosclerotic risk factors and receive extended medical treatment, mainly as a result of the implementation of guidelines. However, as PAD patients with polyvascular disease still receive sub-optimal cardioprotective medication, more attention should be given to optimization of lifestyle modification and medical treatment.

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