Eur J Vasc Endovasc Surg (2018) 55, 529–536

FOR DEBATE

Ten Year Mortality in Different Peripheral Arterial Disease Stages: A Population Based Observational Study on Outcome☆

Fredrik Sartipy [a,*], **Birgitta Sigvant** [b], **Fredrik Lundin** [c], **Eric Wahlberg** [d]

[a] Section of Vascular Surgery, Department of Clinical Science and Education, Karolinska Institutet at Södersjukhuset, Stockholm, Sweden
[b] Department of Surgical Sciences, Uppsala University, Uppsala, Sweden
[c] Centre of Clinical Research, County Council of Värmland, Karlstad, Sweden
[d] Department of Medicine and Health, Linköping University, Linkoping University Hospital, Linköping, Sweden

WHAT THIS PAPER ADDS

This cohort study provides up to date long-term follow-up data on mortality for different PAD stages in a population based setting. Age adjusted risks for cardiovascular and all cause mortality are presented separately for subjects with different PAD stages and compared with a reference population. PAD subjects were still found to have a high mortality risk, similar to that presented almost two decades ago. Asymptomatic PAD (APAD) confers similar risk of cardiovascular death as symptomatic subjects. These findings highlight the need for awareness and preventive strategies for all PAD stages, including APAD subjects.

Objective: The aim was to determine long-term mortality rates and the underlying cause of death for subjects with different peripheral arterial disease (PAD) stages in a population based setting.
Methods: A randomly selected population sample of 5080 subjects was enrolled in the study in 2004–2005. Participants completed health state questionnaires and underwent ankle brachial index (ABI) measurements for classification into PAD severity stages and reference subjects. A follow-up was conducted by the end of 2015 using data from Swedish governmental national registers for cause of death, which was then compared with PAD stage determined at baseline in 2005.
Results: The 10 year all cause mortality was 27% for reference cases, 56% for asymptomatic PAD (APAD), 63% for intermittent claudication (IC), and 75% for severe limb ischaemia (SLI). Among all PAD subjects, cardiovascular (CV) causes were the most common main cause of death (45%) and a CV event was present as either the main or one of the three most common contributing causes of death in 64% of the cases. The age adjusted hazard ratios for a main cause of death by a CV event were 1.9 (95% CI 1.5–2.3) for APAD, 2.6 (95% CI 2.1–3.4) for IC, and 3.5 (95% CI 2.3–5.2) for SLI.
Conclusion: PAD subjects, including the APAD subjects, are still at high risk of CV death. The mortality risks are more than doubled in symptomatic PAD patients compared with reference subjects and increase by severity of PAD stage. Awareness and improved risk reduction management of PAD are still warranted.
© 2018 European Society for Vascular Surgery. Published by Elsevier Ltd. All rights reserved.
Article history: Received 10 September 2017, Accepted 23 January 2018, Available online 23 February 2018
Keywords: Peripheral arterial disease, Mortality, Cardiovascular death

INTRODUCTION

Peripheral arterial disease (PAD) is a major healthcare issue worldwide with a prevalence that increased by 23% between 2000 and 2010.[1] Patients with PAD have an increased risk of cardiovascular (CV) mortality.[2,3] Knowledge of PAD risk levels is mainly based on studies performed over 10 years ago,[4–6] with few being population based and covering all stages of PAD. Treatment of risk factors such as smoking, hypertension, diabetes, and dyslipidaemia has improved since then and there are recent reports suggesting that mortality rates for the comparable illnesses coronary artery disease (CAD) and stroke are declining.[7–9] Over the last two decades, in Sweden, CAD mortality has decreased by approximately two thirds,[8] mainly due to reduction in major risk factors such as high cholesterol.[10]

☆ The abstract of this original article (ESVS-569), was rated among the top 9 out of 602 submitted abstracts to the ESVS 31st Annual Meeting in Lyon, France, 2017 and was presented at the ESVS Prize Session, Wednesday, 20 September (14:00–16:00).

* Corresponding author. Kirurgkliniken, Sjukhusbacken 10, 118 83 Stockholm, Sweden.
E-mail address: fredrik.sartipy@sll.se (Fredrik Sartipy).

1078-5884/© 2018 European Society for Vascular Surgery. Published by Elsevier Ltd. All rights reserved.

https://doi.org/10.1016/j.ejvs.2018.01.019

Up to date information on morbidity and mortality rates in PAD is essential in decision making for vascular procedures and other treatments. From a societal perspective it is important for prioritisation and allocation of resources since PAD affects large populations for a long time period.[11] Accordingly, there is a need for updated information on the risks associated with PAD.

Besides being more reliable for assessing mortality from a societal perspective, prospective population based cohort studies have the advantage of enabling quantification and duration of risk factors influencing the variability of the disease. Such cohorts can also identify subgroups at risk that could benefit from improved prophylactic treatment. More widespread implementation of the latter is likely to result in better patient survival, but needs to be verified by epidemiological data.

The aim of this prospective population based observational study was to determine current mortality rates for all PAD stages. The hypothesis was that mortality for PAD has tended to decline compared with the rates reported from the 20th century.

METHODS

Study design

The study was conducted as a prospective observational population based cohort study using physical examinations and questionnaires at baseline, and register data at the end of the observation time 10 years later. The study was a long-term follow-up of the original cohort, published and described in 2007.[12]

Study population

The cohort was assembled between August 13, 2004, and January 13, 2005, through invitation of 8000 randomly selected men and women aged 60–90 years from the Swedish tax register from four different regions in Sweden. The sample had the same distribution of age and gender as the general population in this age group. Four regions were enrolled (Malmö, Karlstad, Älvkarleby, and Skellefteå) to obtain representation from urban, industrial, rural, and agricultural districts. In each region, 2000 subjects were invited and in total 5080 subjects agreed to participate and each provided written informed consent. The observation period ended in December 31, 2015, when individual patient register data from Swedish national registers covering 2004–2015 were retrieved, thus rendering an observation time of 10 years.

Data collection

In 2004 all subjects were invited to participate by a letter. Three self administered questionnaires that assessed risk factors for PAD, current pharmacological treatment, concomitant diseases, present and former smoking habits, leg symptoms, and walking ability were enclosed with the invitation. Walking ability covered the questions in the Rose's World Health Organisation (WHO) questionnaire and Walking Impairment Questionnaire (WIQ).[13,14] The participants were invited to a primary healthcare clinic where specially trained nurses performed bilateral ankle brachial index (ABI) measurements and assisted in completion of the questionnaires when necessary. The procedure has been described in detail previously.[12] The subjects were divided into the following subgroups by ABI and symptomatic severity stage of PAD: asymptomatic PAD (APAD), intermittent claudication (IC), or severe limb ischaemia (SLI). Subjects with normal ABI and no qualifying symptoms were classified as the reference group (Ref). SLI was used as a proxy for critical limb ischaemia,[12] which was difficult to assess in an epidemiological study of this kind which relied on questionnaire data. Subjects who were diagnosed and considered at risk of critical limb ischaemia or who had a brachial blood pressure above 180 mmHg were referred to their general practitioner, but no other intervention was made during the assessment period.

Definitions of PAD stages

APAD: subjects with an ABI <0.9 without qualifying answers in the questionnaire (i.e., no pain in the calf or thigh when walking).

IC: subjects with an ABI <0.9 and qualifying answers in the questionnaire (i.e., pain in calf or thigh when walking with relief at rest).

SLI: all subjects with lowest ankle blood pressure ≤ 70 mmHg.

Ref: subjects with an ABI ≥ 0.9 and no symptomatic qualifying answers.

Register data

Healthcare is mainly organised, administered, and funded by the government in Sweden, which also keeps a variety of mandatory healthcare registers. Every citizen has a unique personal registration number that makes it possible to follow each one over time and to cross link data. One of the registers is the National Patient Register (NPR), which includes all diagnoses recorded at Swedish hospitals covering all in and outpatient care since 2001. Beyond the primary discharge diagnosis, an unlimited number of secondary diagnoses can be recorded. The International Classification of Diseases, 10th revision (ICD-10), has been used for diagnosis coding since 1997. The NPR is updated once a year and covers $>99\%$ of all hospital discharges. Cases with a missing main diagnosis are around 1%. The NPR is regularly checked for quality and validity.[15]

The Cause of Death Register (CDR) contains data of all deaths in Sweden since 1961. The data collected include time of death, underlying and contributing causes of death, as well as 30 other variables. The use of CDR, in combination with NPR, has previously been demonstrated to provide highly accurate data in similar patient populations.[16]

Questionnaire data

Smoking habits, declarations of weight and height, and current pharmacological treatment were collected as self

reported information at the time of inclusion. Drugs were classified by their ATC codes (Anatomical Therapeutic Chemical Classification, WHO Collaborating Centre for Drug Statistics Methodology). Any antiplatelet, antihypertensive, or lipid lowering therapy was recorded. Changes in medication during the observation period were not covered.

Information on concomitant diseases such as angina pectoris (ICD-10 code, I20), myocardial infarction (I21), heart failure (I50), diabetes mellitus (E10—14), stroke (I60—I69), renal insufficiency (N17—19), and hypertension (I10—15) was achieved by cross linkage of self reported information and data from the NPR register of 2004—2005.

Definitions of outcome

The date and the cause of death was obtained from the CDR. The main cause of death was defined as the primary cause of death according to the CDR. The contributing causes of death were the secondary, tertiary, and quaternary reported relevant causes. The main and contributing causes of death were then categorised by disease area as either cardiovascular (CV) (ICD-10 codes, I10—15, I20—25, I50—51, I60—69, and I70—73), cancer (C00—D48), psychiatric (F00—99), neurological (G00—99), respiratory (J00—99), gastrointestinal (K00—93), or other (any other ICD code). Examples of common diagnoses covered by the other category are atrial fibrillation, trauma by falling, and aortic valve stenosis.

For a more sensitive coverage of CV associated death, additional analyses were performed for all non-CV main deaths that had a CV condition as one of the three closest contributing causes recorded in the register. The aggregated CV death was then defined by having either a CV main cause of death or a CV condition as one of the three closest contributing causes.

Statistical analysis

Baseline data are described as the mean ± standard deviation (SD) for continuous data or absolute and relative frequencies for nominal or ordinal data.

Overall mortality was analysed in each baseline group using Kaplan—Meier plots (both unadjusted and age adjusted). Cause specific mortality was described using the number of deaths, incidence proportion, incidence rate, defined as the number of events per 1000 person years (10 year mean incidence with 95% CI) and cumulative incidence plots.[17] A Cox proportional hazard model[18] was used to study the effect of PAD stage on mortality compared with the reference group. Both unadjusted and age adjusted analyses were employed. Separate analyses were made for death by cardiovascular causes (also separately for myocardial infarction and stroke), cancer, and psychiatric, neurological, respiratory, gastrointestinal, and other conditions. Regression results were reported as hazard ratios (HR) with 95% CI.

All statistical analyses were performed in Stata MP4 ver. 13 (StataCorp LLC, College Station, TX, USA) and all tests were two sided.

RESULTS

Population

At baseline, the cohort consisted of 5080 persons of whom 2779 were women. The median age was 71 years (IQR 13 years). One hundred and forty did not have their ABI measured, leaving a final cohort of 4940 participants (54.5% women). Overall PAD prevalence was 18% (95% CI 16.0—19.9), and APAD, IC, and SLI were diagnosed in 522 (11%), 295 (6%), and 65 (1%) of the subjects. Baseline characteristics are presented in Table 1. A total of 4926 subjects were eligible for follow-up in 2015. Fourteen participants were lost due to relocation.

Overall mortality

The all cause mortality rate after 10 years was 33% ($n = 1636$) in the entire cohort and for Ref, APAD, IC, and SLI subjects it was 27%, 56%, 63% and 75%, respectively (Table 2). The incidences varied between 28 events per 1000 person years for the Refs to 112 for the SLI group (Table 3). The same pattern was observed for HR and in the survival curves (Fig. 1).

For all PAD subjects, the main causes of death were cardiovascular (45%), other (22%), cancer (15%), psychiatric (6%), respiratory (6%), neurological (3%), and gastrointestinal (2%). Their cumulative mortality by different main causes of death is presented in Fig. 2. For the Refs, cancer was the main cause of death (34%), followed by cardiovascular (31%), other (17%), neurological (6%), psychiatric (5%), respiratory (5%), and gastrointestinal conditions (2%).

CV mortality

A CV main cause of death was the most frequent mortality cause in subjects with PAD and accounted for 45% of the deaths. Myocardial infarction was the most common CV diagnosis (28%, 162 cases) and almost as many died from stroke (26%, 152 cases). In the entire cohort, 258 subjects (16%) didn't having a CV main cause of death but a contributing CV cause of death. Accordingly, there were 335 (64%) aggregated CV deaths (Table 2).

Mortality and PAD stage

CV death increased by severity of PAD stage, and the Cox proportional hazard model revealed an almost doubled risk of CV death in the APAD group (HR 1.9) and a HR of 2.6 and 3.5 (Table 3) for subjects with IC and SLI, respectively.

Death due to cancer was more common in the APAD group than all other PAD groups (HR 1.38, $p = .025$, Table 3) while respiratory conditions were significantly more common among symptomatic PAD subjects.

DISCUSSION

One of the main findings in this study is the confirmation that the risk of CV mortality is approximately doubled in age adjusted PAD patients and increase by stage severity. Even APAD subjects face a substantially increased risk. The most

Table 1. Baseline characteristics.

	All subjects, *n* (%)	Reference, *n* (%)	Asymptomatic PAD, *n* (%)	Intermittent claudication, *n* (%)	Severe limb ischaemia, *n* (%)	All PAD stages, *n* (%)
Group size	4940 (100)	4058 (82.2)	522 (10.6)	295 (6.0)	65 (1.3)	882 (17.9)
Cohort mean (SD)						
Age	71.0 (7.9)	69.8 (7.5)	75.4 (8.0)	75.6 (7.9)	78.0 (6.8)	75.5 (8.0)
Women	2693 (54.5)	2169 (53.5)	327 (62.6)	152 (51.5)	45 (69.2)	479 (58.6)
ABI	1.0 (0.2)	1.1 (0.1)	0.8 (0.1)	0.7 (0.1)	0.4 (0.1)	0.8 (0.1)
WIQ walking index	78.0 (29.1)	81.8 (25.8)	75.5 (31.2)	47.4 (32.7)	41.4 (35.9)	65.3 (34.5)
Smoking habits, *n* (%)						
Never smoker	2348 (47.5)	1983 (48.9)	231 (44.3)	114 (38.6)	20 (30.8)	345 (42.2)
Less than 10 years	635 (12.9)	547 (13.5)	51 (9.8)	29 (9.8)	8 (12.3)	80 (9.8)
10—30 years	1024 (20.7)	871 (21.5)	86 (16.5)	49 (16.6)	18 (27.7)	135 (16.5)
More than 30 years	933 (18.9)	657 (16.2)	154 (29.5)	103 (34.9)	19 (29.2)	257 (31.5)
Comorbidity, *n* (%)						
Angina pectoris	702 (14.2)	486 (12.0)	88 (16.9)	98 (33.2)	30 (46.2)	186 (22.8)
Myocardial infarction	471 (9.5)	292 (7.2)	70 (13.4)	86 (29.2)	23 (35.4)	156 (19.1)
Heart failure	327 (6.6)	205 (5.1)	45 (8.6)	60 (20.3)	17 (26.2)	105 (12.9)
Diabetes mellitus	512 (10.4)	360 (8.9)	71 (13.6)	64 (21.7)	17 (26.2)	135 (16.5)
Stroke	380 (7.7)	247 (6.1)	72 (13.8)	51 (17.3)	10 (15.4)	123 (15.1)
Renal insufficiency	125 (2.5)	78 (1.9)	17 (3.3)	25 (8.5)	5 (7.7)	42 (5.1)
Joint disorder	1883 (38.1)	1507 (37.1)	181 (34.7)	165 (55.9)	30 (46.2)	346 (42.4)
Hypertension	1830 (37.0)	1412 (34.8)	221 (42.3)	168 (57.0)	29 (44.6)	389 (47.6)
Medication, *n* (%)						
Any antiplatelet	1346 (27.3)	954 (23.5)	193 (37.0)	154 (52.2)	45 (69.2)	347 (42.5)
Any antidyslipidaemic	831 (16.8)	622 (15.3)	93 (17.8)	86 (29.2)	30 (46.2)	179 (21.9)
Any antihypertensive	2038 (41.3)	1511 (37.2)	275 (52.7)	204 (69.2)	48 (73.9)	479 (58.6)

Table 2. Mortality by all cause, cardiovascular (CV) main cause of death and aggregated CV cause.

	All	Reference	Asymptomatic PAD	Intermittent Claudication	Severe limb ischaemia	All PAD
Group size at baseline (*n*) by 2005	4940	4058	522	295	65	882
All cause mortality by 2015 (*n*)	1636	1111	290	186	49	525
Percent (%)	33.1	27.4	55.6	63.1	75.4	59.5
CV main cause of death by 2015 (*n*)	582	348	121	87	26	234
Percent (%)	11.8	8.6	23.2	29.5	40	26.5
Percent of all cause mortality (%)	35.6	31.3	41.7	46.	53.1	44.6
CV contributing cause of death in non-CV main death (*n*)	258	157	51	41	9	101
Percent (%)	5.2	3.9	9.8	13.9	13.9	11.5
Percent of all cause mortality (%)	15.8	14.1	17.6	22.0	18.4	19.2
Aggregated CV cause of death (*n*)	840	505	172	128	35	335
Percent (%)	17	12.4	33.0	43.4	53.9	38.0
Percent of all cause mortality (%)	51.3	45.5	59.3	68.8	71.4	63.8

Note. The aggregated CV cause was defined by having either a CV main cause of death or a CV condition as one of the three closest contributing causes of death.

important cause of death for all PAD subjects is a CV event, in particular a myocardial infarction or stroke.

There is a clear and well known strong association between having PAD and mortality caused by CV events.[19,20] The magnitude of this association tends to differ between studies,[21] for example, the HR for CV mortality varies between 1.1 and 6.3 in PAD patients. Discrepancies in study methodology make comparisons between reports difficult. Composition of study populations, definitions of PAD stage groups, endpoints used, and ways of interpreting the ankle brachial blood pressure measurements vary greatly. Most cohort studies covering PAD are focused on IC and are not population based. In this study, a large, randomly selected cohort of inhabitants from different demographic areas with 10 years of follow-up was used to facilitate the interpretation of the results from a societal context. The results are similar to what was presented in a recently published systematic review and meta-analysis by Hajibandeh et al.,[2] where patients with ABI <0.9 were found to have a two to threefold increased risk for CV death compared with controls. Eberhardt et al.[22] likewise found a doubled risk in an APAD cohort followed for 10 years.

Over recent decades a reduction in CV death among subjects with atherosclerosis in other vascular beds has been demonstrated.[8,10] The decline in mortality among coronary heart disease patients is explained by improved treatment of acute myocardial infarction and increasing secondary prevention.[8,10] The stroke mortality reduction is multifactorial, including better care processes and prevention measures.[23]

Table 3. Mortality by incidence and hazard ratio (crude and age adjusted) divided by disease areas.

Disease area	PAD Stage group	Events n (%)	Incidence (events/1000 person years) (95% CI)	Crude hazard ratio	*p*	Age adjusted hazard ratio	*p*
All cause mortality	All	1636 (33.1)	34.6 (33.0,36.3)	–	–	–	–
	Ref	1111 (23.4)	27.6 (26.0,29.3)	1	–	1	–
	APAD	290 (55.6)	66.5 (59.3,74.6)	2.5 (2.2,2.9)	<.001	1.6 (1.4,1.8)	<.001
	IC	186 (63.1)	82.7 (71.7,95.5)	3.3 (2.8,3.8)	<.001	2.0 (1.7,2.3)	<.001
	SLI	49 (75.4)	112.4 (84.9148.7)	4.6 (3.5,6.1)	<.001	2.3 (1.8,3.1)	<.001
Cardiovascular mortality[a]	All	582 (11.8)	12.3 (11.3,13.3)	–	–	–	–
	Ref	348 (8.6)	8.6 (7.8,9.6)	1	–	1	–
	APAD	121 (23.2)	27.7 (23.2,33.2)	3.4 (2.7,4.1)	<.001	1.9 (1.5,2.3)	<.001
	IC	87 (29.5)	38.7 (31.4,47.8)	4.8 (3.8,6.1)	<.001	2.6 (2.1,3.4)	<.001
	SLI	26 (40)	59.6 (40.6,87.6)	7.7 (5.2,11.5)	<.001	3.5 (2.3,5.2)	<.001
Myocardial infarction[a]	All	155 (3.1)	3.3 (2.8,3.8)	–	–	–	–
	Ref	90 (2.2)	2.2 (1.8,2.8)	1	–	1	–
	APAD	32 (6.1)	7.3 (5.2,10.4)	3.4 (2.3,5.1)	<.001	2.0 (1.3,3.1)	.001
	IC	24 (8.1)	10.7 (7.2,15.9)	5.1 (3.2,8.0)	<.001	3.0 (1.9,4.7)	<.001
	SLI	9 (13.8)	20.6 (10.7,39.7)	10.1 (5.1,20.0)	<.001	5.1 (2.5,10.2)	<.001
Stroke	All	146 (3.0)	3.1 (2.6,3.6)	–	–	–	–
	Ref	96 (2.4)	2.4 (2.0,2.9)	1	–	1	–
	APAD	31 (5.9)	7.1 (5,1.1)	3.1 (2.11,4.6)	<.001	1.6 (1.1,2.5)	.022
	IC	17 (5.8)	7.6 (4.7,12.2)	3.4 (2.0,5.7)	<.001	1.7 (1.0,2.9)	.041
	SLI	2 (3.1)	4.6 (1.2,18.3)	2.1 (0.5,8.6)	.294	0.9 (0.2,3.7)	.879
Cancer	All	462 (9.4)	9.8 (8.9,10.7)	–	–	–	–
	Ref	381 (9.4)	9.5 (8.6,10.5)	1	–	1	–
	APAD	55 (10.5)	12.6 (9.7,16.4)	1.4 (1.0,1.8)	.025	1.0 (0.8,1.4)	.799
	IC	24 (8.1)	10.7 (7.2,15.9)	1.2 (0.8,1.8)	.399	0.9 (0.6,1.3)	.549
	SLI	2 (3.1)	4.6 (1.2,18.3)	0.5 (0.1,2.1)	.37	0.4 (0.1,1.4)	.14
Psychiatric condition	All	95 (1.9)	2.0 (1.6,2.5)	–	–	–	–
	Ref	61 (1.5)	1.5 (1.2,2.0)	1	–	1	–
	APAD	21 (4)	4.8 (3.1,7.4)	3.5 (2.1,5.7)	<.001	1.7 (01,2.8)	.051
	IC	9 (3.1)	4.0 (2.1,7.7)	3.1 (1.5,6.3)	.002	1.5 (0.7,3.0)	.293
	SLI	4 (6.2)	9.2 (3.4,24.4)	7.8 (2.8,21.6)	<.001	2.7 (1.0,7.6)	.054
Neurological condition	All	76 (1.5)	1.6 (1.3,2.0)	–	–	–	–
	Ref	62 (1.5)	1.5 (1.2,2.0)	1	–	1	–
	APAD	10 (1.9)	2.3 (1.2,4.3)	1.6 (.8,3.2)	.147	1.0 (.5,2.0)	.925
	IC	4 (1.4)	1.8 (0.7,4.7)	1.4 (.5,3.8)	.544	.8 (.3,2.3)	.746
	SLI	0	0	0	1	0	1
Respiratory condition	All	82 (1.7)	1.7 (1.4,2.2)	–	–	–	–
	Ref	50 (1.2)	1.2 (0.9,1.6)	1	–	1	–
	APAD	14 (2.7)	3.2 (1.9,5.4)	2.8 (1.5,5.0)	.001	1.7 (.9,3.1)	.093
	IC	14 (4.7)	6.2 (3.7,10.5)	5.6 (3.1,1.2)	<.001	3.3 (1.8,6.1)	<.001
	SLI	4 (6.2)	9.2 (3.4,24.4)	8.8 (3.2,24.3)	<.001	4.4 (1.6,12.)	.005
Gastrointestinal condition	All	35 (0.7)	0.7 (0.5,1.0)	–	–	–	–
	Ref	22 (.5)	0.6 (0.4,0.8)	1	–	1	–
	APAD	8 (1.5)	1.8 (0.9,3.7)	3.6 (1.6,8)	.002	2.4 (1.0,5.5)	.041
	IC	4 (1.4)	1.8 (0.7,4.7)	3.5 (1.2,1.3)	.02	2.3 (.8,7.0)	.127
	SLI	1 (1.5)	2.3 (0.3,16.3)	4.8 (.6,35.3)	.128	2.7 (.4,2.4)	.337
Other condition	All	304 (6.2)	6.4 (5.7,7.2)	–	–	–	–
	Reference	187 (4.6)	4.6 (4.2,5.4)	1	–	1	–
	APAD	61 (11.7)	14.0 (10.9,18.0)	3.2 (2.4,4.2)	<.001	1.8 (1.3,2.4)	<.001
	IC	44 (14.9)	19.6 (14.6,26.3)	4.6 (3.3,6.3)	<.001	2.5 (1.8,3.6)	<.001
	SLI	12 (18.5)	27.5 (15.6,48.5)	6.7 (3.7,11.9)	<.001	3.1 (1.7,5.6)	<.001

[a] The cardiovascular area is also presented with two subgroups: Myocardial infarction and Stroke. The PAD stage groups are abbreviated as follows Asymptomatic PAD (APAD), Intermittent Claudication (IC), Severe Limb Ischaemia (SLI) and the Reference (Ref).

In this study, PAD subjects still had a high mortality risk. The magnitude is similar to data presented almost two decades ago. Risks for CV mortality in PAD subjects was, for example, HR = 1.5,[4] RR = 1.62,[6] and RR = 4.14.[24] The reason for this stability in CV death is unknown but could be attributable to a lack of awareness of PAD and its risks and differences in secondary preventive medication management. Despite guideline recommendations,[25] recently published Swedish data showed that only 60% of surgical PAD patients were offered antiplatelet therapy and 40% statins 1 year after diagnosis. Corresponding figures for myocardial infarction patients were 91% and 78% respectively.[3] This pattern of

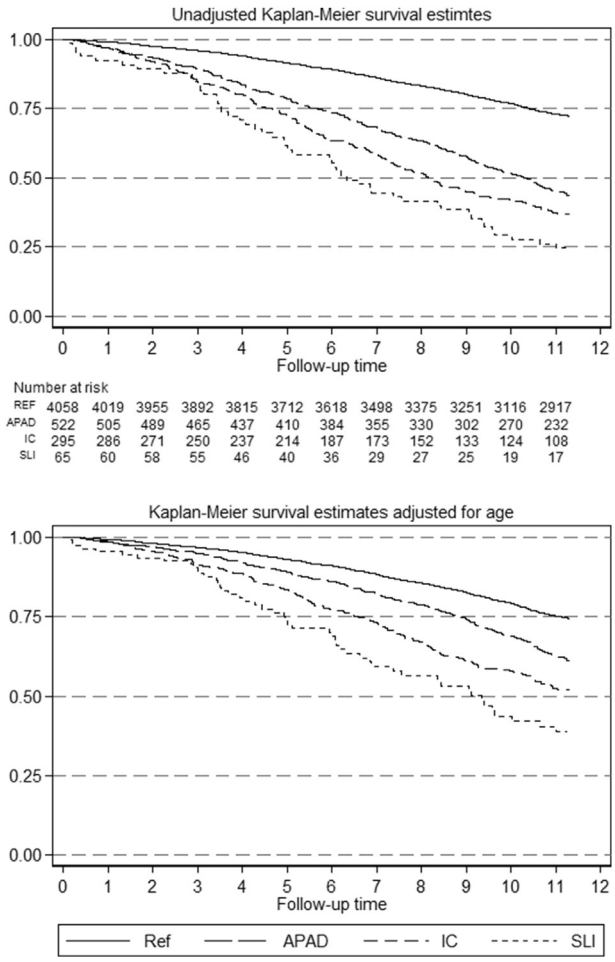


Figure 1. Unadjusted and age adjusted Kaplan—Meier survival curves separately for each PAD group. The maximum standard deviations of the survival curves are 0.008, 0.023, 0.029 and 0.062 respectively for the reference, APAD, IC, and SLI groups.

under treatment is also observed after revascularisation.[26,27] These findings show that PAD still is in the periphery and calls for increased awareness and attendance in society, and among policy makers and healthcare givers. Contributing explanations could also be a heavier arteriosclerotic burden in PAD than in CAD subjects,[28] but further analyses need to explain why PAD patients continue to have a CV mortality risk at this level, while CAD patients do not.

The most common cause of death for a PAD patient in this study was a CV event. For subjects with a non-CV event registered as the main cause of death, CV was present as one of the three most prominent contributing causes in another 16%. It could be expected that other causes of death common in PAD subjects are important for mortality in PAD.[29] Indeed, respiratory disease showed a similar HR pattern as CV in this study. About one fifth of all deaths in both PAD and Refs were classified as other. Considering that this disease area also covers atrial fibrillation, pulmonary embolism, and heart valve problems this is not surprising. The risks of psychiatric, neurological, and gastrointestinal conditions did not appear to be elevated in PAD or related to disease stage. One might suspect that some psychiatric diseases, such as dementia, would be higher in PAD subjects than in Refs, but the confidence intervals were quite wide for these diseases and could thus be an effect of minor risk increase, with too few PAD patients in the groups to assess it. Cancer mortality was not elevated in PAD patients, and lower in symptomatic groups than in Refs and APAD, possibly a consequence of competing risks.[30] Accordingly, PAD patients die from CV related causes, and sometimes from respiratory disease and preventive measures should be focused on these disease areas.

The results of this study imply a need for improved PAD risk reduction management. For symptomatic patients, this equates to better compliance and adherence to guideline regimens. There is also a need to further investigate whether

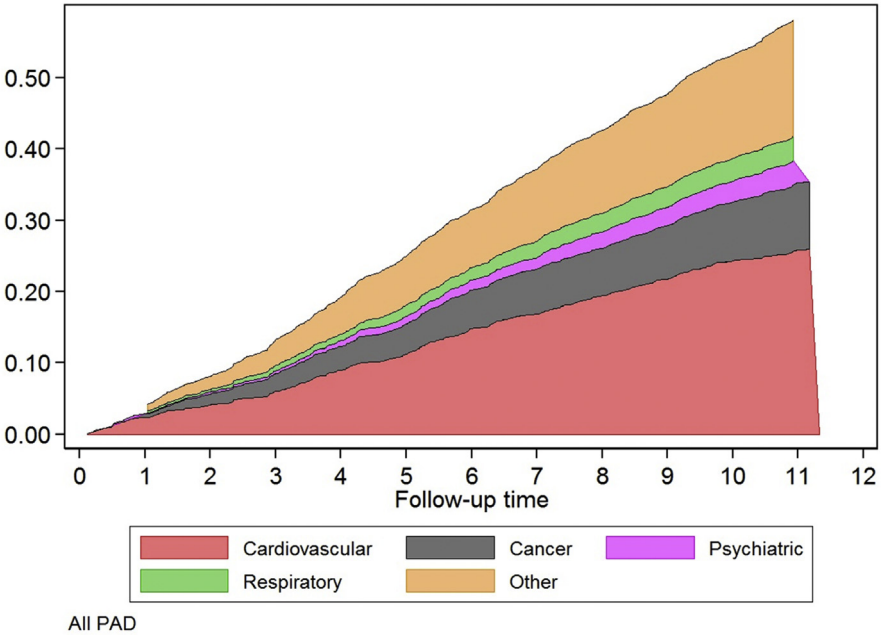


Figure 2. Cumulative mortality for all PAD subjects by disease area causing mortality. Follow-up time in years.

preventive treatment strategies for APAD will improve their outcome. They constitute a substantial part of the elderly population and certain subgroups among them could possibly benefit from improved health recommendations and possibly cardioprotective therapy. This could also benefit society.[31]

Limitations

In cohort studies, non-participation is a possible limitation, and so also in this study. While the participation rate was acceptable, the oldest and most ill subjects were in the majority among non-participants, which could have led to an under representation of PAD in the cohort. Registry data also depend on the quality and completeness of recorded data and coding errors, but the national registers used for outcome in this study are validated against medical records frequently and found reliable.[15] Finally, the SLI subgroup is not comparable to the clinical definition of CLI, and data for this group need to be generalised for CLI patients with caution.

CONCLUSION

The risk of CV mortality remains at least double in age adjusted PAD patients, and the risk increases by severity of PAD stage. Moreover, CV death is the main cause of death in PAD subjects, while cancer is more common among reference patients without PAD. APAD confers a similar risk of CV death as symptomatic subjects. Efforts to increase awareness of PAD are warranted and further studies on optimal management of certain risk groups especially within the APAD subgroup are needed.

ETHICAL APPROVAL

The study was approved by the local ethics committees in Stockholm (KI 03-538 and Dnr 2014/2070-32), Umeå University (Dnr 03-459), Lunds University (832-0), Uppsala University (Dnr 03-564) and Örebro (Dnr 374-03). Informed consent was obtained from each participant.

FUNDING

The original study was supported by unrestricted grants from The Swedish Heart-Lung Foundation, Värmland's County Research Council and Sanofi-Aventis.

REFERENCES

1 Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;**382**:1329—40.
2 Hajibandeh S, Hajibandeh S, Shah S, Child E, Antoniou GA, Torella F. Prognostic significance of ankle brachial pressure index: a systematic review and meta-analysis. *Vascular* 2017;**25**:208—24.
3 Sigvant B, Hasvold P, Kragsterman B, Falkenberg M, Johansson S, Thuresson M, et al. Cardiovascular outcomes in patients with peripheral arterial disease as an initial or subsequent manifestation of atherosclerotic disease: results from a Swedish nationwide study. *J Vasc Surg* 2017;**66**:507—514.e1.
4 Hooi JD, Kester AD, Stoffers HE, Rinkens PE, Knottnerus JA, van Ree JW. Asymptomatic peripheral arterial occlusive disease predicted cardiovascular morbidity and mortality in a 7-year follow-up study. *J Clin Epidemiol* 2004;**57**:294—300.
5 Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992;**326**:381—6.
6 Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the cardiovascular health study. The cardiovascular health study group. *Arterioscler Thromb Vasc Biol* 1999;**19**:538—45.
7 Herrington W, Lacey B, Sherliker P, Armitage J, Lewington S. Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. *Circ Res* 2016;**118**:535—46.
8 Berg J, Bjorck L, Lappas G, O'Flaherty M, Capewell S, Rosengren A. Continuing decrease in coronary heart disease mortality in Sweden. *BMC Cardiovasc Disord* 2014;**14**:9.
9 Muller-Nordhorn J, Binting S, Roll S, Willich SN. An update on regional variation in cardiovascular mortality within Europe. *Eur Heart J* 2008;**29**:1316—26.
10 Bjorck L, Rosengren A, Bennett K, Lappas G, Capewell S. Modelling the decreasing coronary heart disease mortality in Sweden between 1986 and 2002. *Eur Heart J* 2009;**30**:1046—56.
11 Hasvold P, Nordanstig J, Kragsterman B, Kristensen T, Falkenberg M, Johansson S, et al. Long-term cardiovascular outcome, use of resources, and healthcare costs in patients with peripheral artery disease: results from a nationwide Swedish study. *Eur Heart J Qual Care Clin Outcomes* 2018;**4**:10—7.
12 Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Andersson B, Persson E, et al. A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. *J Vasc Surg* 2007;**45**:1185—91.
13 Leng GC, Fowkes FG. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. *J Clin Epidemiol* 1992;**45**:1101—9.
14 Jain A, Liu K, Ferrucci L, Criqui MH, Tian L, Guralnik JM, et al. The Walking Impairment Questionnaire stair-climbing score predicts mortality in men and women with peripheral arterial disease. *J Vasc Surg* 2012;**55**:1662—73. e2.
15 Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;**11**:450.
16 Johansson LA, Westerling R. Comparing Swedish hospital discharge records with death certificates: implications for mortality statistics. *Int J Epidemiol* 2000;**29**:495—502.
17 Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med* 2007;**26**:2389—430.
18 Cox DR. Regression models and life-tables. *J R Stat Soc B (Methodological)* 1972;**34**:187—220.
19 Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res* 2015;**116**:1509—26.
20 Cacoub PP, Abola MT, Baumgartner I, Bhatt DL, Creager MA, Liau CS, et al. Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Atherosclerosis* 2009;**204**:e86—92.
21 Sigvant B, Lundin F, Wahlberg E. The risk of disease progression in peripheral arterial disease is higher than expected: a meta-analysis of mortality and disease progression in peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2016;**51**:395—403.
22 Eberhardt RT, Coffman JD. Cardiovascular morbidity and mortality in peripheral arterial disease. *Curr Drug Targets Cardiovasc Haematol Disord* 2004;**4**:209—17.

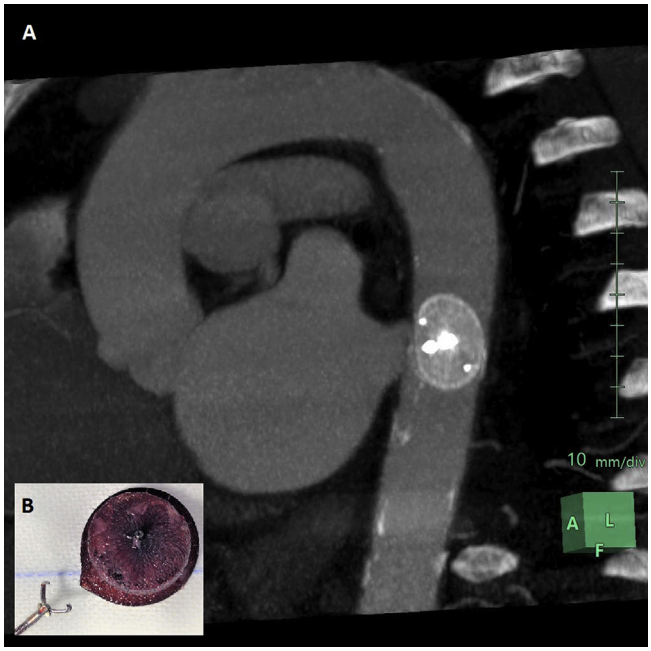
23 Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, et al. Factors influencing the decline in stroke mortality: a statement from the American heart association/American stroke association. *Stroke* 2014;**45**:315–53.
24 Kornitzer M, Dramaix M, Sobolski J, Degre S, De Backer G. Ankle/arm pressure index in asymptomatic middle-aged males: an independent predictor of ten-year coronary heart disease mortality. *Angiology* 1995;**46**:211–9.
25 Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. Editor's Choice – 2017 ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018;**55**:305–68.
26 Sigvant B, Kragsterman B, Falkenberg M, Hasvold P, Johansson S, Thuresson M, et al. Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization. *J Vasc Surg* 2016;**64**:1009–17. e3.
27 Subherwal S, Patel MR, Kober L, Peterson ED, Bhatt DL, Gislason GH, et al. Peripheral artery disease is a coronary heart disease risk equivalent among both men and women: results from a nationwide study. *Eur J Prev Cardiol* 2015;**22**:317–25.
28 Valentijn TM, Stolker RJ. Lessons from the REACH Registry in Europe. *Curr Vasc Pharmacol* 2012;**10**:725–7.
29 Pecci R, De La Fuente Aguado J, Sanjurjo Rivo AB, Sanchez Conde P, Corbacho Abelaira M. Peripheral arterial disease in patients with chronic obstructive pulmonary disease. *Int Angiol* 2012;**31**:444–53.
30 Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. *Br J Cancer* 2004;**91**:1229–35.
31 Chen YJ, Lin MS, Hsu KY, Chen CR, Chen CM, Chen W. Prevalence of asymptomatic peripheral arterial disease and related risk factors in younger and elderly patients in Taiwan. *Angiology* 2014;**65**:396–401.

Eur J Vasc Endovasc Surg (2018) 55, 536

COUP D'OEIL

Aortic Migration of a Septal Occluder

Gautier Haupert *, **Myriam Ammi**
University Hospital Center, Angers, France



A 75 year old man with atrial fibrillation and formal contraindication to oral anticoagulants underwent left atrial implantation of a 24 mm septal occluder (Amplatzer, AGA Medical Corporation). The procedure was performed through femoral venous access with trans-septal puncture under angiographic and trans-oesophageal echocardiographic controls. A 3 month computed tomography scan (A) highlighted asymptomatic migration of the prosthesis into the descending thoracic aorta. It was extracted through femoral access via a 24F introducer (Gore, DrySeal) with a special foreign body grasper (rat tooth, Endoflex, (B)). The patient recovered well. He was given aspirin, and has currently declined further interventions.

* Corresponding author.
E-mail address: ghaupert@gmail.com (Gautier Haupert).
1078-5884/© 2017 European Society for Vascular Surgery. Published by Elsevier Ltd. All rights reserved.
https://doi.org/10.1016/j.ejvs.2017.12.017