European Journal of Preventive Cardiology

Original scientific paper

European Journal of Preventive Cardiology
0(00) 1–10

DOI: 10.1177/2047487314566998
ejpc.sagepub.com

Cause-specific mortality and years of life lost in patients with different manifestations of vascular disease

Rob CM van Kruijsdijk[1], Yolanda van der Graaf[2], Hendrik Koffijberg[2], Gert Jan de Borst[3], Hendrik M Nathoe[4], L Jaap Kappelle[5], Frank LJ Visseren[1] and on behalf of the SMART study group

Abstract

Background: Patients with cardiovascular disease might be at increased risk of non-vascular mortality due to shared risk factors. Our aim was to evaluate causes of death and years of life lost (YLL) in patients with different manifestations of vascular disease.

Design: The design was a prospective cohort study.

Methods: A total of 5911 patients with stable coronary artery disease, cerebrovascular disease, peripheral artery disease (PAD), abdominal aortic aneurysm or polyvascular disease were followed-up for mortality. Cause-specific standardised mortality ratios (SMRs) and YLL, compared to the Dutch population, were estimated. Determinants for cause-specific mortality were evaluated using competing risks models.

Results: During a median follow-up of 6.0 years (interquartile range (IQR): 3.1–9.2), 958 (16.2%) patients died. All-cause mortality was increased compared to the general population (SMR: 1.26, 95% confidence interval (CI): 1.18–1.34). Patients with PAD and polyvascular disease were at highest risk, especially for ischaemic heart disease (SMR: 2.52, 95% CI: 1.70–3.60 and SMR: 3.97, 95% CI: 3.18–4.90, respectively). Patients with PAD were at increased risk of dying from cancer (SMR: 1.67, 95% CI: 1.25–2.17). On average, patients with vascular disease of ≥50 years died 7.8 years younger than the general population, with 80% of the excess YLL attributable to cardiovascular disease. In middle-aged patients the excess YLL were about 10 years, of which 24% were lost due to cancer. Important determinants for mortality were male gender, smoking, physical inactivity, renal insufficiency and polyvascular disease.

Conclusions: Patients with manifest vascular disease are at increased risk of both cardiovascular and cancer mortality, particularly patients with PAD or polyvascular disease. On average, patients with vascular disease of ≥50 years die 7.8 years younger than the general population.

Keywords

Cardiovascular disease, mortality, cause of death, years of life lost, competing risks

Received 18 July 2014; accepted 15 December 2014

[1]Department of Vascular Medicine, University Medical Centre Utrecht, the Netherlands
[2]Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, the Netherlands
[3]Department of Vascular Surgery, University Medical Centre Utrecht, the Netherlands
[4]Department of Cardiology, University Medical Centre Utrecht, the Netherlands
[5]Department of Neurology, University Medical Centre Utrecht, the Netherlands

Corresponding author:
Frank LJ Visseren, Department of Vascular Medicine, University Medical Centre Utrecht, F 02.126, P.O. Box 85500, 3508 GA Utrecht, the Netherlands.
Email: f.l.j.visseren@umcutrecht.nl

Introduction

Advances in the treatment and prevention of cardiovascular disease have led to a significant decrease in cardiovascular-related mortality in developed countries in the last decades.[1–3] The prevalence of patients in a chronic phase of cardiovascular disease, however, is still growing. Recent estimates of prevalent cardiovascular disease in more than one-third of American adults highlight the great burden of this chronic disease on

public health.[2] Although there is a lack of high quality and comparable incidence data across Europe, it is clear that cardiovascular disease also causes a very substantial burden of morbidity in Europe, with hospital discharge rates for cardiovascular disease of over 2500 per 100,000 population in 2010.[3] Atherosclerosis, the major cause of cardiovascular disease, is characterised by a progressive systemic nature and frequently manifests as coronary artery disease (CAD), cerebrovascular disease (CeVD), peripheral artery disease (PAD) or an abdominal aortic aneurysm (AAA), but often multiple vascular locations are affected.[4] Patients with atherosclerotic disease have a 18.3% (95% confidence interval (CI): 17.4%–19.1%) four-year risk of new cardiovascular events, including cardiovascular death, especially those patients with manifestations of atherosclerotic disease in different vascular territories (polyvascular disease vs risk factors only hazard ratio (HR):1.99, 95% CI: 1.78–2.24).[5] Furthermore, several observational studies indicate that the risk of non-vascular causes of death, such as cancer, may be increased as well.[6–10] Compared to the general population, patients with manifest vascular disease have a 19% higher five-year risk of developing cancer, including cancers of the lung, kidney and bladder,[10] possibly as a result of shared risk factors, such as smoking and obesity.[10,11] Detailed information on cause-specific mortality may guide preventive measures in the growing group of patients with chronic cardiovascular disease. Thus far, however, studies on mortality and risk factors for cause-specific mortality were generally confined to a particular cardiovascular patient group, such as CAD or stroke patients or did not consider non-vascular mortality.[5–7,9]

In the present prospective cohort study in patients with different manifestations of vascular disease (i.e. CAD, CeVD, PAD, AAA or polyvascular disease), cause-specific mortality and years of life lost (YLL) were assessed and compared to the general population. Furthermore, important determinants for specific causes of death were evaluated.

Methods

Study population

Patients originated from the Second Manifestations of ARTerial disease (SMART) study, an ongoing prospective cohort study at the University Medical Center Utrecht in the Netherlands. The central aims of the SMART study are to determine prevalence of concomitant atherosclerotic disease and of risk factors for atherosclerotic disease and to study the incidence of future cardiovascular events and its predictors. A detailed description of the study has been published previously.[12] In short, all newly referred out-patients, aged 18–80 years with a recent history of manifest atherosclerotic disease or traditional cardiovascular risk factors (hypertension, dyslipidaemia and diabetes mellitus) are asked to participate in the SMART study. The participation rate was approximately 80%.[12] CAD was defined as a recent diagnosis of angina pectoris with a confirmed stenosis on a coronary angiogram, myocardial infarction (MI) or coronary revascularisation (coronary artery bypass graft or percutaneous coronary intervention). Patients with CeVD include those with a recent diagnosis of ischaemic stroke, transient ischaemic attack or amaurosis fugax. PAD was defined as a clinical diagnosis of PAD (Fontaine stage 2–4), which was confirmed by either an ankle-brachial index (ABI) of $\leq$0.90 in rest or decrease in ABI of at least 20% after exercise, whereas AAA was defined as a distal aortic anteroposterior diameter of $\geq$3 cm, as measured with ultrasonography. Polyvascular disease was defined as having two or more of the aforementioned clinical manifestations of vascular disease, either as qualifying event or in the medical history. Exclusion criteria were a terminal malignancy, dependency in daily activities or not sufficiently fluent in the Dutch language. At inclusion, patients underwent a standardised cardiovascular screening program, including a questionnaire on cardiovascular history, assessment of risk factors, ABI, and ultrasonography of the carotid arteries and abdominal aorta to detect any additional (sub)clinical atherosclerosis. The local ethics committee approved the study and all patients gave their written informed consent.

For the present study, data of 5911 patients with a recent diagnosis of CAD, CeVD, PAD, AAA or polyvascular disease between September 1996–March 2012 were used.

Follow-up and death ascertainment

Patients were biannually asked to complete a questionnaire on hospitalisation and outpatient clinic visits for follow up. Deaths of patients were reported by relatives of the patient, the general practitioner or specialist. Further information on cause of death was collected by retrieving hospital discharge letters and/or contacting the patients' general practitioner. Physicians of an endpoint committee independently audited all events on the basis of the available clinical information. In case of disagreement, specific cases were discussed until consensus was reached. Primary causes of death, coded according to the *International classification of diseases*, tenth edition (ICD-10),[13] were grouped into ischaemic heart disease, cerebrovascular disease, cancer, infection and the combination of accidents

and suicides (Supplementary Material, Appendix 1). National cause-specific mortality rates and life-expectancy data of the general Dutch population were retrieved from Statistics Netherlands.[14] Of the present study population, 215 patients (4%) were lost to follow-up.

Data analyses

Cause-specific standardised mortality ratios (SMRs), adjusted for five-year age groups, sex and calendar year, were calculated using cause-specific national mortality rates. Corresponding 95% CIs were computed assuming a Poisson distribution. Cumulative cause-specific mortality, as a function of years since study inclusion, was estimated while taking deaths by causes other than the one under study into account as competing risks.[15] Expected all-cause cumulative mortality was estimated based on national mortality data. The distribution of causes of death for different strata of vascular disease at inclusion was evaluated using cumulative mortality estimates at five and 10 years. Average YLL[16] were calculated for the study population of $\geq$50 years and background population, which was matched on age, sex, calendar-year and being alive at the age of entry into the study. Average excess YLL due to cardiovascular, cancer and other deaths were then calculated as the difference between the observed and expected average YLL and were plotted against age after fitting a cubic smoothing spline. Age-standardised YLL rates for specific causes of death were calculated to facilitate comparison to other populations.

Potential determinants for cause-specific mortality, including gender, smoking status (never, former and current), alcohol consumption status (never, former and current), physical activity as measured by hours $\times$ metabolic equivalent of task (MET) per week, body mass index (BMI), metabolic syndrome (according to the revised National Cholesterol Education Program (NCEP) definition)[17], diabetes mellitus, estimated glomerular filtration rate (eGFR) as estimated by the Modification of Diet in Renal Diseases (MDRD)-formula, number of localisations of atherosclerotic disease (one, two or more) and years since first vascular event were evaluated with proportional subdistribution hazards regression models,[18] accounting for competing risk of death by causes other than the one under study. All models included adjustment for potential confounding by sex, age, smoking status, pack-years of smoking, alcohol consumption, BMI, physical activity, use of lipid-lowering medication, blood-pressure lowering medication, glucose-lowering medication and antithrombotics at baseline. Furthermore, multivariable-adjusted HRs of Fontaine stage II and stage III–IV vs CAD as well of Fontaine stage II vs stage III–IV were computed for all-cause mortality to differentiate between PAD patients. A detailed description of the models and model assumptions can be found in the Supplementary Material: Appendix 2.

Statistical analyses were performed in R, version 2.15.3 (www.r-project.org; packages: 'Hmisc', 'RiskRegression', 'cmprsk').

Results

Baseline characteristics

Baseline characteristics of the study population according to localisation of vascular disease at inclusion are shown in Table 1. Overall, the mean age was 60.3 years (standard deviation (SD): 10.2 years) and 75% of the patients were men. The most common localisation of vascular disease at inclusion was CAD (48%), whereas 21% of patients had CeVD, 12% of patients had PAD, 3% of patients had an AAA and 16% of patients had polyvascular disease. Patients with history of AAA were most likely to have polyvascular disease (61% of AAA patients), whereas 21% of CAD patients, 28% of CeVD patients and 40% of PAD also had other manifestations of vascular disease. Mean age and number of ever smokers, as well as several metabolic parameters, such as total cholesterol and C-reactive protein, tended to be higher among patients included with PAD or AAA. In most strata, the majority of patients were treated with blood pressure-lowering and lipid-lowering medication, as well as with antithrombotic therapy, particularly patients with CAD. Most patients had their first vascular event $<$1 year before enrolment, except for patients with polyvascular disease, of whom 80% had their first vascular event $\geq$2 years before enrolment.

Cause-specific mortality

During a median follow-up of 6.0 years (interquartile range (IQR): 3.1–9.2 years), 958 patients (13%) had died. All-cause mortality was higher in the total study population as 939 deaths were observed during the period from 1997–2011, whereas 748 deaths were expected based on mortality rates from the general Dutch population (SMR: 1.26, 95% CI: 1.18–1.34; Table 2). Particularly cardiovascular death was higher (SMR: 2.10, 95% CI: 1.92–2.29), including death due to ischaemic heart disease (SMR: 2.02, 95% CI: 1.75–2.32) and cerebrovascular disease (SMR: 1.37, 95% CI: 1.05–1.75). The highest mortality was observed in patients with polyvascular disease, particularly for mortality due to ischaemic heart disease (SMR: 3.97, 95% CI: 3.18–4.90). Total and cancer mortality was significantly lower in patients with CAD compared to the general population (SMR: 0.72, 95% CI: 0.63–0.82

Table 1. Baseline characteristics of study population according to localisation of vascular disease at inclusion.

	Coronary artery disease ($n = 2842$)	Cerebrovascular disease ($n = 1224$)	Peripheral artery disease ($n = 724$)	Abdominal aorta aneurysm ($n = 191$)	Polyvascular disease ($n = 930$)
Age (years)	60 (10)	59 (11)	58 (11)	67 (7)	64 (9)
Male gender %	81	59	63	93	82
Smoking, current %	24	35	64	41	35
Smoking, past %	52	42	27	49	54
Pack-years of smoking[a]	21 (9–34)	22 (10–35)	29 (17–42)	31 (16–45)	26 (13–41)
Current alcohol consumption %	15	19	30	32	24
Physical activity (hours × MET per week)	39 (19–69)	33 (14–57)	22 (5–48)	25 (7–48)	23 (6–48)
Body mass index (kg/m^2)	27 (4)	26 (4)	26 (4)	26 (3)	27 (4)
Waist circumference (cm)	97 (11)	92 (12)	93 (12)	97 (11)	97 (12)
Visceral adipose tissue (cm)	9 (3)	8 (2)	9 (2)	9 (2)	10 (3)
Systolic blood pressure (mm Hg)	137 (20)	142 (21)	146 (21)	144 (19)	144 (21)
Diastolic blood pressure (mm Hg)	80 (11)	82 (11)	82 (11)	85 (11)	80 (12)
Metabolic parameters					
eGFR (ml/min/1.73 m^2)	77 (16)	78 (17)	79 (19)	72 (19)	71 (18)
Total cholesterol (mmol/l)	4.6 (1.1)	5.0 (1.2)	5.6 (1.2)	5.4 (1.1)	5.0 (1.2)
Low density lipoprotein (mmol/l)	1.2 (0.3)	1.4 (0.4)	1.3 (0.4)	1.2 (0.3)	1.2 (0.4)
High density lipoprotein (mmol/l)	2.6 (0.9)	3.0 (1.1)	3.5 (1.1)	3.5 (1.0)	3.0 (1.0)
Serum triglycerides (mmol/l)	1.4 (1.0)	1.2 (0.9)	1.5 (1.1)	1.4 (1.1)	1.5 (1.1)
C-reactive protein (mg/l)	1.6 (0.8–3.4)	1.8 (0.8–4.1)	3.2 (1.5–6.4)	3.9 (1.8–8.0)	3.0 (1.4–6.0)
Fasting serum glucose (mmol/l)	5.8 (5.4–6.5)	5.6 (5.2–6.1)	5.7 (5.3–6.4)	5.7 (5.3–6.3)	5.9 (5.4–6.7)
Metabolic syndrome[b] %	56	41	49	52	59
Medical history					
Coronary artery disease %	100	0	0	0	80
Cerebrovascular disease %	0	100	0	0	51
Peripheral arterial disease %	0	0	100	0	51
Abdominal aortic aneurysm %	0	0	0	100	32
Years since first vascular event					
<1 year before enrolment %	67	80	90	64	11
1–2 years before enrolment %	9	12	3	15	8
≥ 2 years before enrolment %	24	9	7	20	80
Diabetes mellitus %	16	12	15	8	22
Cancer %	3	4	6	9	5
Medication					
Blood pressure-lowering medication %	92	49	37	48	78
Glucose-lowering medication %	13	9	10	5	16
Lipid-lowering medication %	81	51	34	28	67
Platelet inhibitor medication %	89	74	44	33	77
Oral anticoagulants %	11	7	8	7	19

eGFR: estimated glomerular filtration rate; MET: metabolic equivalent of task. All data are expressed as percentages, mean (standard deviation (SD)) or median (interquartile range). Percentages may not add up to 100% because of rounding; eGFR estimated by the Modification of Diet in Renal Diseases (MDRD) formula. [a]For ever smokers only; [b]according to the revised National Cholesterol Education Program definition.

and 0.73, 95% CI: 0.58–0.90, respectively), whereas no clear differences were seen with regard to cardiovascular mortality, including deaths due to ischaemic heart disease (SMR: 1.07, 95% CI: 0.77–1.46). In the total study population, mortality due to cancer, infectious disease and accidents and suicide were not higher compared to the general population. However, risk of cancer death was markedly higher in PAD patients

Table 2. Cause-specific standardised mortality ratios in patients with manifest vascular disease.

	Cause of death						
Localisation of vascular disease	Infection	Cancer	Cardiovascular disease (total)	Ischemic heart disease	Cerebrovascular disease	Accidents and suicide	All causes
Coronary artery disease							
Observed	11	84	91	40	12	3	209
Expected	14.3	115.8	85.0	37.3	16.0	8.4	290.5
SMR (95% CI)	0.77 (0.38–1.38)	0.73 (0.58–0.90)	1.07 (0.86–1.31)	1.07 (0.77–1.46)	0.75 (0.39–1.31)	0.36 (0.07–1.04)	0.72 (0.63–0.82)
Cerebrovascular disease							
Observed	7	58	80	32	22	3	174
Expected	8.9	57.3	50.6	21.2	10.4	4.2	160.1
SMR (95% CI)	0.79 (0.32–1.62)	1.01 (0.77–1.31)	1.58 (1.25–1.97)	1.51 (1.03–2.13)	2.12 (1.33–3.20)	0.71 (0.15–2.09)	1.09 (0.93–1.26)
Peripheral artery disease							
Observed	7	54	72	30	9	3	161
Expected	4.8	32.4	28.0	11.9	5.9	2.5	89.7
SMR (95% CI)	1.46 (0.59–3.00)	1.67 (1.25–2.17)	2.57 (2.01–3.24)	2.52 (1.70–3.60)	1.53 (0.70–2.90)	1.20 (0.25–3.51)	1.79 (1.53–2.09)
Abdominal aorta aneurysm							
Observed	6	17	42	12	4	2	76
Expected	3.0	17.0	17.0	7.2	3.5	1.1	50.8
SMR (95% CI)	2.00 (0.73–4.35)	1.00 (0.58–1.60)	2.47 (1.78–3.34)	1.67 (0.86–2.91)	1.14 (0.31–2.93)	1.82 (0.22–6.57)	1.50 (1.18–1.87)
Polyvascular disease							
Observed	13	66	200	87	16	2	319
Expected	8.6	55.9	50.6	21.9	10.2	3.7	156.5
SMR (95% CI)	1.51 (0.80–2.58)	1.18 (0.91–1.50)	3.95 (3.42–4.54)	3.97 (3.18–4.90)	1.57 (0.90–2.55)	0.54 (0.07–1.95)	2.04 (1.82–2.27)
Total							
Observed	44	279	485	201	63	13	939
Expected	39.6	278.5	231.1	99.6	46.0	20.0	747.6
SMR (95% CI)	1.11 (0.81–1.49)	1.00 (0.89–1.13)	2.10 (1.92–2.29)	2.02 (1.75–2.32)	1.37 (1.05–1.75)	0.65 (0.35–1.11)	1.26 (1.18–1.34)

CI: confidence interval; SMR: standardised mortality ratio. Presented standardised mortality ratios represent the quotient of observed and expected mortality and are adjusted for age (five-year age groups), sex and calendar year.

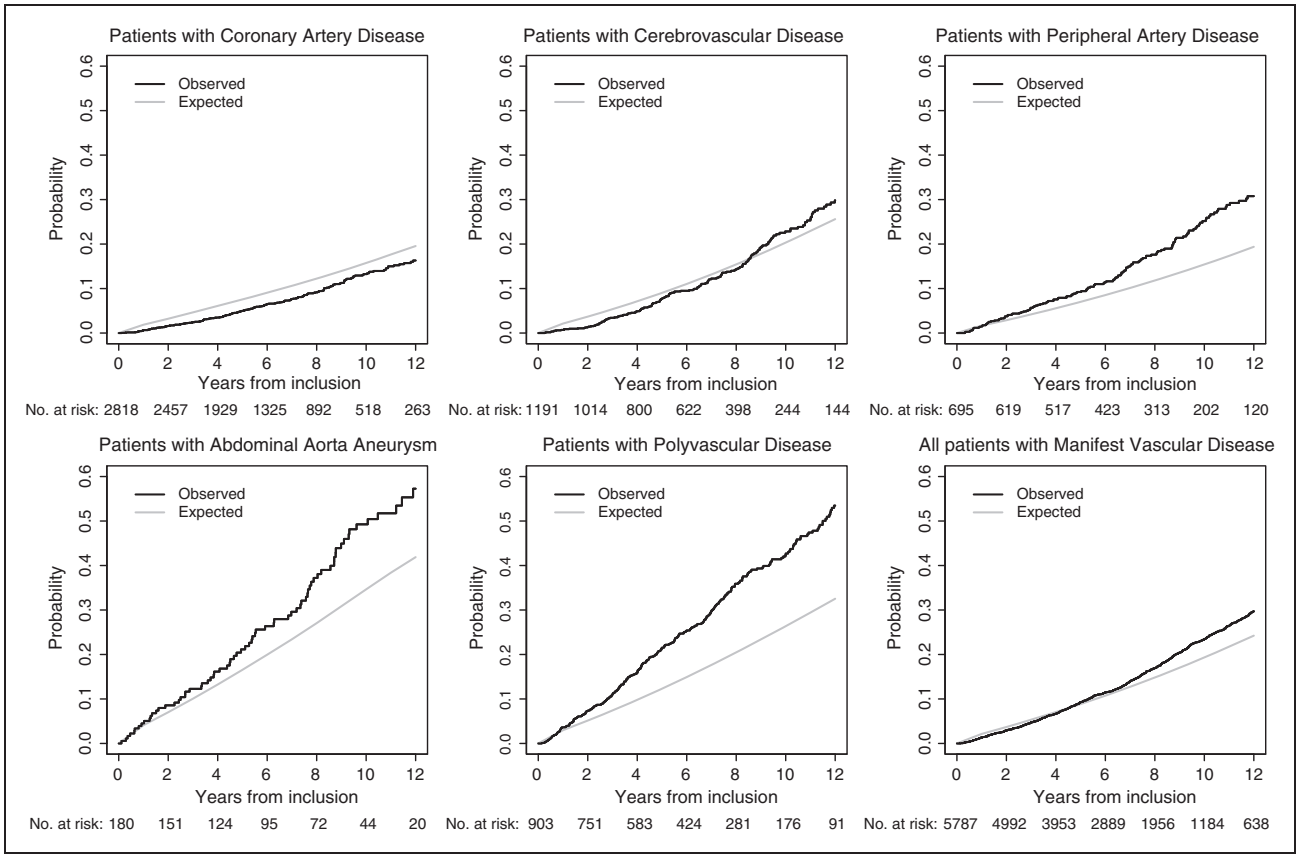

Figure 1. Observed and expected cumulative mortality of patients with different manifestations of vascular disease.

(SMR: 1.67, 95% CI: 1.25–2.17) compared to the general population.

Cumulative mortality

Observed and expected cumulative mortality for the different strata of vascular disease are shown in Figure 1. In accordance with the SMRs, observed all-cause mortality was lower than expected in patients with CAD over the entire follow-up. The most important causes of death in this group, cardiovascular disease (42.7% and 46.8% of total deaths at five and 10 years, respectively) and cancer (42.7% and 35.4% of total deaths at 5 and 10 years, respectively), occurred at a constant rate over follow-up (Supplementary Material, Appendix 3, 4 and 5). Patients with CeVD were more likely to die from cardiovascular disease, with a five and 10-year probability of 4.0% (95% CI: 2.9–5.4%) and 11.2% (8.7–14.%), respectively. A high mortality was observed in patients with PAD (five-year probability: 9%, 95% CI: 7–12%), AAA (five-year probability: 21%, 95% CI: 15–27%) and polyvascular disease (five-year probability: 21%, 95% CI: 18–24%). Although cardiovascular disease was the most frequent cause of death (49.7% of total deaths at five years), cancer was also responsible for an important share of mortality (36.4%) in patients with PAD. Of the patients with AAA or polyvascular disease who died during follow-up, more than half died of cardiovascular disease. Other causes of death, including infectious diseases and accidents or suicide were seen relatively often in patients with AAA (10.0% and 2.9% of deaths after 10 years, respectively).

Years of life lost

Average excess YLL compared to the general population are shown in Figure 2. On average, patients with vascular disease of $\geq$50 years died 7.8 years younger than individuals in the general population. The excess of YLL decreased with increasing age. Patients with vascular disease of age 50 years lost 10.6 potential life-years more than the general population of same age and sex in the same period. Seventy-two percent of the excess of YLL was caused by premature cardiovascular deaths. In patients between the ages of 50–60 years non-vascular causes were more important, with 20% of the total excess of YLL being attributable to death due to cancer. The age-standardised YLL rate of the study population was 18,762 per 100,000

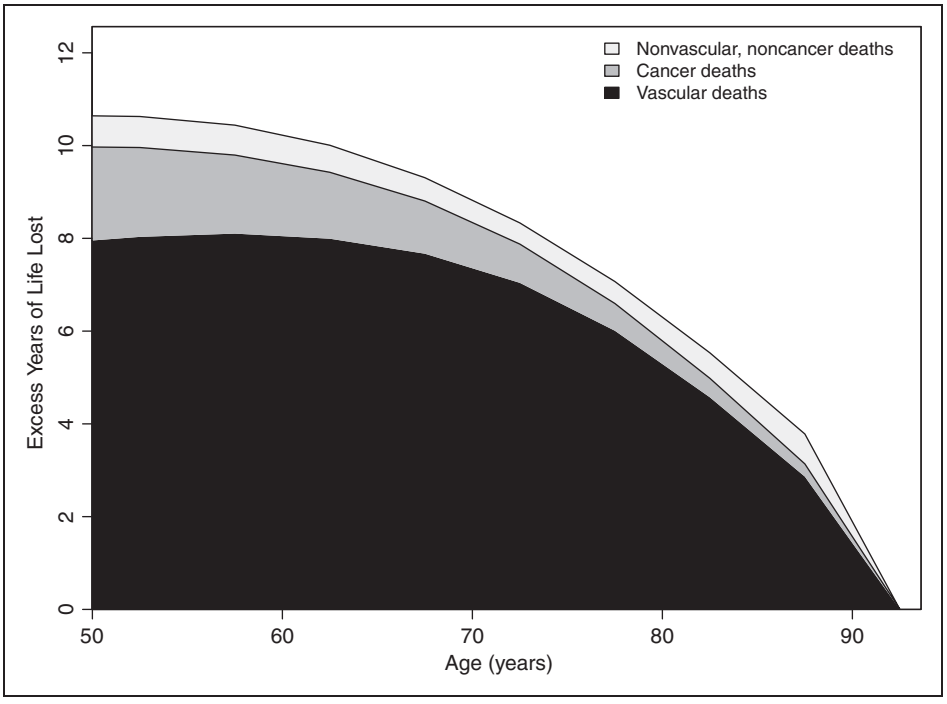

Figure 2. Average excess years of life lost due to vascular disease, cancer and other causes, adjusted for calendar year and sex in patients with manifest vascular disease of different ages.

person-years for cardiovascular causes, 4131 per 100,000 person-years for cancer and 3053 per 100,000 person-years for other causes of death. No distinct trends in the distribution of YLL over time were observed (Supplementary Material, Appendix 6).

Determinants for cause-specific mortality

Male gender, smoking, BMI $<20\,kg/m^2$ and eGFR $<30\,ml/min/1.73\,m^2$ were important determinants for all-cause mortality (Figure 3). Important risk factors for vascular death included male gender (HR: 1.49, 95% CI: 1.17–1.90), current smoking (HR: 2.40, 95% CI: 1.80–3.22), metabolic syndrome (HR: 1.24, 95% CI: 1.03–1.49), diabetes (HR: 1.51, 95% CI: 1.02–2.23), eGFR $<30\,ml/min/1.73\,m^2$ (HR: 4.77, 95% CI: 2.78–8.18), PAD (HR: 1.98, 95% CI: 1.39–2.82), AAA (HR: 2.41, 95% CI: 1.57–2.82), polyvascular disease (HR: 3.70, 95% CI: 2.86–4.80) and >2 years since first vascular event (HR: 1.87, 95% CI: 1.55–2.27). Higher physical activity was associated with a lower risk of vascular death (HR for 19–50 h × MET/week: 0.75, 95% CI: 0.60–0.93 and HR for >50 h × MET/week: 0.58, 95% CI: 0.45–0.76). Current smoking and a BMI $<20\,kg/m^2$ were related to higher risk of cancer mortality and other non-vascular causes of death. Furthermore, patients with PAD were at higher risk of cancer death compared to CAD patients (HR: 1.61, 95% CI: 1.09–2.38), particularly smoking-related cancers (HR: 2.21, 95% CI: 1.24–3.95; Supplementary Material, Appendix 7). Patients with PAD Fontaine stage III–IV ($n = 54$) were at increased risk of premature death compared to patients with Fontaine stage II ($n = 670$; HR: 1.85, 95% CI: 1.17–2.94). Compared to patients with CAD, the HR for PAD Fontaine stage II was 1.84 (95% CI: 1.47–2.30) whereas the HR for Fontaine stage III–IV was 3.44 (95% CI: 2.20–5.38).

Discussion

In this hospital-based cohort of patients with stable vascular disease, all-cause mortality was higher compared to the general population. On average, patients with vascular disease of ≥50 years die 7.8 years younger than the general population. Although cardiovascular disease is the most important cause of death in these patients, 28% of the excess of premature deaths was attributable to non-vascular causes, with cancer being the most important. Patients with CAD had a lower risk than the general population, whereas a twofold increased mortality was observed in patients with PAD or polyvascular disease. Most important determinants for vascular mortality were male gender, smoking, BMI $<20\,kg/m^2$, impaired renal function, polyvascular disease and time since first vascular event. Low physical activity and presence of PAD were related to a higher risk of vascular and non-vascular mortality.

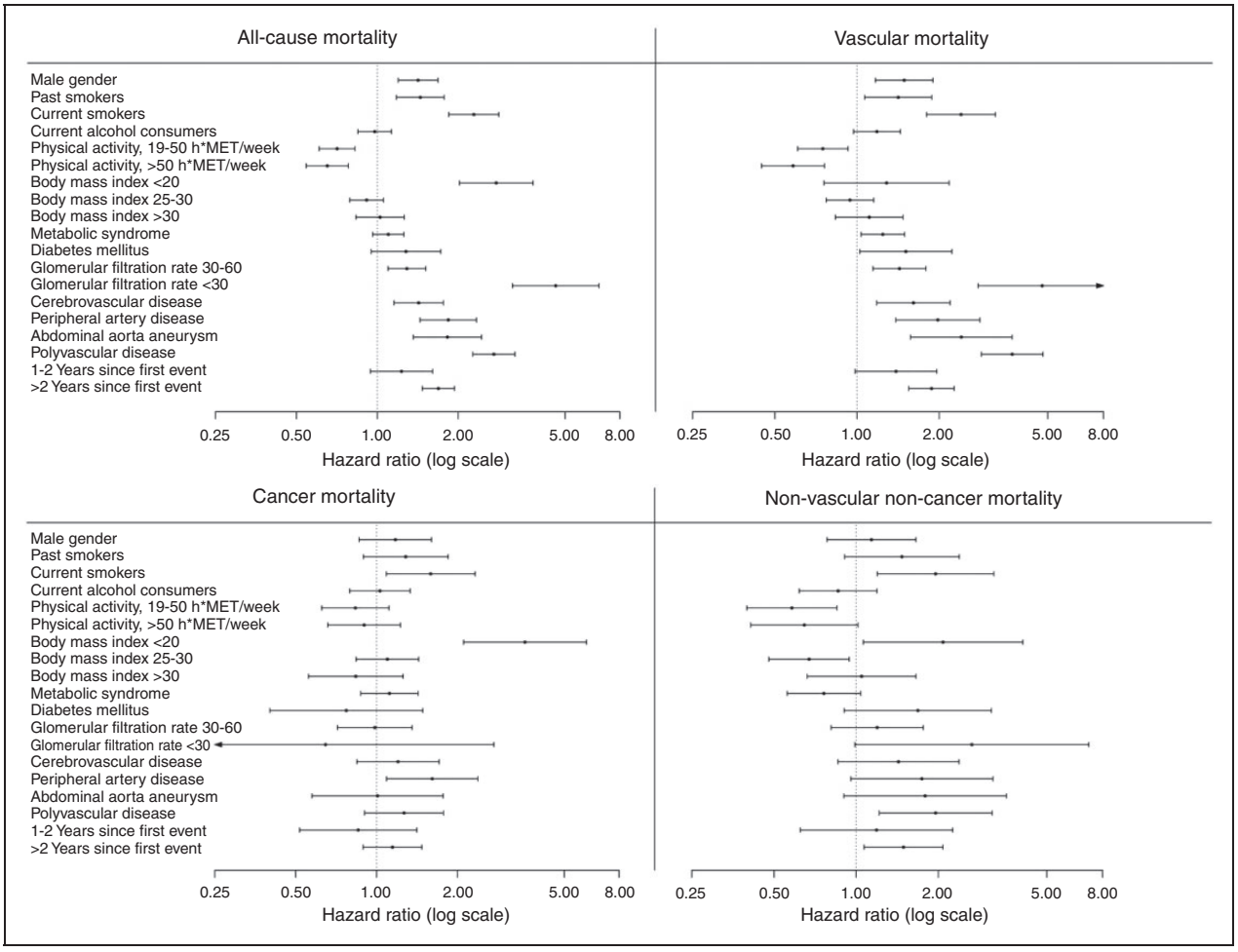

Figure 3. Multivariable-adjusted hazard ratios for determinants of cause-specific mortality. Reference categories: female gender for gender; never for smoking status; never for alcohol-drinking status; $\leq$19 hours $\times$ metabolic equivalent of task (MET) per week for physical activity; 20–25 kg/m^2 for body mass index; no diabetes for diabetes mellitus; $\geq$60 ml/min/1.73 m^2 for estimated glomerular filtration rate; coronary artery disease for localisation of vascular disease; one year for years since first vascular event.

In accordance with results from the Reduction of Atherothrombosis for Continued Health (REACH) study,[5,19] an international registry of outpatients either with vascular disease or at high risk for developing vascular disease, we observed that patients with PAD, in particular those with Fontaine III–IV, and polyvascular disease were at highest risk of premature death. Although, similar to the REACH study,[5] the majority of deaths in these patient groups were caused by cardiovascular disease, we showed that cancer mortality was higher as well compared to the general population, particularly in patients with PAD.

Remarkably, mortality in patients with CAD was lower than expected based on general population data. This finding may be explained by the fact that this group consists of patients who survived their initial ischaemic event, underwent coronary revascularisation and received optimal secondary prevention advice and treatment.[20] Furthermore, patients with a terminal malignancy were not included in the present cohort, while these patients were likely to be present in the reference group and thus contribute to a higher risk. Hence, caution should be exerted when extrapolating these results to CAD patients in general. The comparison among the strata of vascular disease, however, is not subject to the aforementioned limitations. Mortality was significantly higher in patients with CeVD, PAD, AAA, or polyvascular disease compared to CAD patients, adjusted for age, sex, smoking, pack-years, alcohol, BMI and physical activity. As expected, patients with CAD were most likely to die from ischaemic heart disease. Although patients with CeVD had a higher risk of dying from recurrent CeVD compared to the general population, ischaemic heart disease was the most common vascular cause of death in these patients as well. In contrast to death by ischaemic heart disease,

CeVD mortality was high during first years and decreased during follow-up. This finding corresponds with results from the Danish MONICA study in 4162 patients after a first stroke, which included the acute phase after a stroke in the follow-up.[6] In this study, CeVD accounted for 32.1% of deaths and ischaemic heart disease for 22.7% of deaths. In contrast to the present results, a significant 26% increase in risk of dying from cancer was observed in stroke patients in the MONICA population. PAD or AAA patients were also at high risk of dying from ischaemic heart disease, but in these groups other vascular causes of death, as well as non-vascular causes were also important. In line with results of the present study, several studies have showed a high cancer prevalence (ranging from 9–16%) and increased cancer mortality in patients with PAD.[9,21] Although the present analyses were adjusted for smoking status and pack-years, the difference in cancer mortality between PAD and CAD patients may be partly explained by a residual effect of smoking, as the risk increase was more prominent for smoking-related cancers than for non-smoking-related cancers.

The reduction in life-expectancy was particularly prominent in middle-aged patients with vascular disease, with an average of 10 excess life-years lost. Also considering that 20% of the excess of YLL was attributable to cancer deaths, these results underline the need for intensive risk factor treatment in these patients, not only for cardiovascular disease, but also for cancer. In line with findings from population-based studies,[22–24] we showed that a number of important modifiable risk factors, including smoking, low physical activity and diabetes increase both vascular and cancer mortality. Generally, only the effects on the occurrence of cardiovascular events are taken into account in studies that evaluate the benefits of risk factor treatment in patients with vascular disease. Given the results of the present study, however, targeting shared risk factors might be a sensible strategy to decrease premature mortality simultaneously from cardiovascular disease and cancer.

Notable strengths of this study include the large sample size and possibility of directly comparing patients with different manifestations of vascular disease. In addition, the data on cause of death was of high quality and over 96% complete. Furthermore, we used competing risk methods that allow direct interpretation of the effect estimates in terms of risk, because evaluation of time-to-event data of causes of death without accounting for competing risks could lead to bias.[15]

This study has some limitations. First, the relative mortality risk in patients with vascular disease might have been underestimated by using the general Dutch population, in which vascular disease is highly prevalent, as reference group to calculate SMRs. Also, the SMRs for cancer mortality should be interpreted considering that the presence of a terminal malignancy served as exclusion criterion for the SMART study, which could have led to an underestimation of the relative risk of cancer mortality. Furthermore, due to the limited number of patients for whom a risk factor assessment during follow-up was available, it was not possible to account for changes over time in the analyses. In addition, multiple pre-specified determinants were tested in the regression analyses, which could have led to some false-positive findings. However, as our effect estimates were robust and generally in line with results from previous studies,[5,22–24] this is not likely.

Conclusions

In this contemporary cohort of patients with vascular disease, mortality was higher compared to the general population of similar age and sex. Patients with vascular disease of $\geq$50 years die 7.8 years younger, not only from cardiovascular disease but also from cancer. Patients with PAD or polyvascular disease are particularly at increased risk of premature death. These results underline the necessity of targeting mutual and cause-specific risk factors to prevent early death in patients with stable vascular disease.

Acknowledgments

The authors gratefully acknowledge the contribution of the SMART research nurses, R van Petersen (data-manager), H Pijl (vascular manager) and the members of the SMART Study Group: A Algra, Julius Center for Health Sciences and Primary Care; PA Doevendans, Department of Cardiology; Y van der Graaf, Julius Center for Health Sciences and Primary Care; DE Grobbee, Julius Center for Health Sciences and Primary Care; LJ Kappelle, Department of Neurology; WPTM Mali, Department of Radiology; FL Moll, Department of Vascular Surgery; GEHM Rutten, Julius Center for Health Sciences and Primary Care; FLJ Visseren, Department of Vascular Medicine.

Funding

The SMART study was supported by a grant of the board of directors of the University Medical Center Utrecht. The funder had no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data, nor in preparation, review, and approval of the manuscript.

Conflict of interest

Dr. Kappelle has received speaker's fees from Boehringer Ingelheim and Bristol Meyer Squibb and has served as a consultant to Boehringer Ingelheim. Dr. Visseren's department receives grant support from the Netherlands Organisation for Health research and Development, and the

Catharijne foundation Utrecht; and speaker fees from Merck. The other authors have no disclosures.

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2095–2128.
2. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics–2012 update: A report from the American Heart Association. *Circulation* 2012; 125: e2–e220.
3. Nichols M, Townsend N, Scarborough P, et al. Cardiovascular disease in Europe: Epidemiological update. *Eur Heart J* 2013; 34: 3028–3034.
4. Viles-Gonzalez JF, Fuster V and Badimon JJ. Atherothrombosis: A widespread disease with unpredictable and life-threatening consequences. *Eur Heart J* 2004; 25: 1197–1207.
5. Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA* 2010; 304: 1350–1357.
6. Bronnum-Hansen H, Davidsen M and Thorvaldsen P. Long-term survival and causes of death after stroke. *Stroke* 2001; 32: 2131–2316.
7. Bronnum-Hansen H, Jorgensen T, Davidsen M, et al. Survival and cause of death after myocardial infarction: The Danish MONICA study. *J Clin Epidemiol* 2001; 54: 1244–1250.
8. Erdem G, Bakhai A, Taneja AK, et al. Rates and causes of death from non-ST elevation acute coronary syndromes: Ten year follow-up of the PRAIS-UK registry. *Int J Cardiol* 2012; 168: 490–494.
9. Vaartjes I, de Borst GJ, Reitsma JB, et al. Long-term survival after initial hospital admission for peripheral arterial disease in the lower extremities. *BMC Cardiovasc Disord* 2009; 9: 43.
10. van Kruijsdijk RC, van der Graaf Y, Peeters PH, et al. Cancer risk in patients with manifest vascular disease: Effects of smoking, obesity, and metabolic syndrome. *Cancer Epidemiol Biomarkers Prev* 2013; 22: 1267–1277.
11. van Kruijsdijk RC, van der Wall E and Visseren FL. Obesity and cancer: The role of dysfunctional adipose tissue. *Cancer Epidemiol Biomarkers Prev* 2009; 18: 2569–2578.
12. Simons PC, Algra A, van de Laak MF, et al. Second manifestations of ARTerial disease (SMART) study: Rationale and design. *Eur J Epidemiol* 1999; 15: 773–781.
13. World Health Organisation (WHO). *WHO international statistical classification of diseases and related health problems*. Tenth revision, vol. 2. Geneva, Switzerland: WHO, 1993.
14. Statistics Netherlands. Causes of death; main primary causes of death, age, sex. http://statline.cbs.nl/statweb/?LA=EN (accessed 30 June 2013).
15. Putter H, Fiocco M and Geskus RB. Tutorial in biostatistics: Competing risks and multi-state models. *Stat Med* 2007; 26: 2389–2430.
16. Aragon TJ, Lichtensztajn DY, Katcher BS, et al. Calculating expected years of life lost for assessing local ethnic disparities in causes of premature death. *BMC Public Health* 2008; 8: 116.
17. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; 112: 2735–2752.
18. Fine JP and Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; 94: 496–509.
19. Alberts MJ, Bhatt DL, Mas JL, et al. Three-year follow-up and event rates in the international Reduction of Atherothrombosis for Continued Health Registry. *Eur Heart J* 2009; 30: 2318–2326.
20. Lafeber M, Grobbee DE, Spiering W, et al. The combined use of aspirin, a statin, and blood pressure-lowering agents (polypill components) in clinical practice in patients with vascular diseases or type 2 diabetes mellitus. *Eur J Prev Cardiol* 2013; 20: 771–778.
21. El Sakka K, Gambhir RP, Halawa M, et al. Association of malignant disease with critical leg ischaemia. *Br J Surg* 2005; 92: 1498–1501.
22. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr, et al. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA* 1989; 262: 2395–2401.
23. Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* 1999; 341: 1097–1105.
24. Doll R, Peto R, Boreham J and Sutherland I. Mortality in relation to smoking: 50 Years' observations on male British doctors. *Br Med J* 2004; 328: 1519.