Atherosclerosis 242 (2015) 97–101

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Impact of cardiovascular risk factors on severity of peripheral artery disease

Thomas R. Wyss [a, b], Luise Adam [a], Alan G. Haynes [c], Nils Kucher [a], Guenther Silbernagel [a], Dai-Do Do [a], Juerg Schmidli [b], Iris Baumgartner [a, *]

[a] Clinic for Angiology, Swiss Cardiovascular Centre, University Hospital, Freiburgstrasse, 3010 Bern, Switzerland
[b] Department of Cardiovascular Surgery, Swiss Cardiovascular Centre, University Hospital, Freiburgstrasse, 3010 Bern, Switzerland
[c] Clinical Trials Unit, Department of Clinical Research, Institute of Social and Preventive Medicine, University of Bern, Finkenhubelweg 11, 3012 Bern, Switzerland

ARTICLE INFO

Article history:
Received 16 January 2015
Received in revised form
29 June 2015
Accepted 2 July 2015
Available online 4 July 2015

Keywords:
Peripheral artery disease
Diabetic vascular disease
Age
Diabetes mellitus
Renal insufficiency

ABSTRACT

Objective: The development of peripheral artery disease is affected by the presence of cardiovascular risk factors. It is unclear, whether particular risk factors are leading to different clinical stages of peripheral artery disease. The aim of this retrospective cross-sectional study was to assess the association of cardiovascular risk factors with the presence of critical limb ischaemia.

Methods: The study cohort was derived from a consecutive registry of patients undergoing endovascular therapy in a tertiary referral centre between January 2000 and April 2014. Patients undergoing first-time endovascular intervention for chronic peripheral artery disease of the lower extremities were included. Univariate and multivariate logistic regression models were used to assess the association of age, sex, diabetes mellitus, hypertension, dyslipidaemia, smoking, and renal insufficiency with critical limb ischaemia vs. intermittent claudication.

Results: A total of 3406 patients were included in the study (mean age 71.7 ± 11.8 years, 2075 [61%] male). There was a significant association of age (OR 1.67, 95%-CI 1.53–1.82, $p < 0.001$), male gender (OR 1.23, 95%-CI 1.04–1.47, $p = 0.016$), diabetes (OR 1.99, 95%-CI 1.68–2.36, $p < 0.001$) and renal insufficiency (OR 1.62, 95%-CI 1.35–1.96, $p < 0.001$) with the likelihood of critical limb ischaemia. Smoking was associated with intermittent claudication rather than critical limb ischaemia (OR 0.78, 95%-CI 0.65–0.94, $p = 0.010$), while hypertension and dyslipidaemia did not show an association with critical limb ischaemia.

Conclusions: In peripheral artery disease patients undergoing first-time endovascular treatment, age, male gender, diabetes, and renal insufficiency were the strongest predictors for the presence of critical limb ischaemia.

1. Introduction

Cardiovascular risk factors affect development, progression and anatomic distribution of peripheral artery disease (PAD) [1–5]. Its prevalence is associated with the number of risk factors [6]. It has also been shown that risk factor control is worse in patients with PAD compared to coronary artery disease and cerebrovascular disease [7]. Additionally, the extent of symptomatic PAD has a substantial influence on outcome: claudicants have a considerably better prognosis compared to patients with critical limb ischaemia [8,9]. The latter is a severe disease and the consequences can be dire – amputation, disability and death [10–12]. Repeated hospitalisations and interventions are causing a high economic burden [13]. Optimal control of arterial hypertension, diabetes mellitus, dyslipidaemia, and smoking is essential and current guidelines on management of PAD have addressed this issue. Unfortunately, sufficient risk factor control is often missing in patients presenting

* Corresponding author. Clinical and Interventional Angiology, Swiss Cardiovascular Centre, University Hospital and University of Bern, Freiburgstrasse, 3010 Bern, Switzerland.
E-mail addresses: thomas.wyss@insel.ch (T.R. Wyss), luise.adam@insel.ch (L. Adam), alan.haynes@ctu.unibe.ch (A.G. Haynes), nils.kucher@insel.ch (N. Kucher), guenther.silbernagel@insel.ch (G. Silbernagel), dai-do.do@insel.ch (D.-D. Do), juerg.schmidli@insel.ch (J. Schmidli), iris.baumgartner@insel.ch (I. Baumgartner).

http://dx.doi.org/10.1016/j.atherosclerosis.2015.07.002
0021-9150/

with critical limb ischaemia [11]. Cardiovascular risk factors may independently influence the degree of the clinical stage and therefore disease outcome. Risk tailored patient management depends on reliable risk stratification models [14]. It is unclear, however, whether different risk profiles lead to different stages of PAD. Better understanding of the association of risk factors and clinical presentation may support the clinician in sound decision-making regarding timing and indication of treatment or follow-up visits to improve outcome. High-risk patients may benefit from closer surveillance schemes and earlier revascularization to avoid disease progression.

The aim of this study was to assess the association of cardiovascular risk factors with the presence of critical limb ischaemia in patients undergoing endovascular treatment for the first time. Our hypothesis was that patients differ regarding their cardiovascular risk profile.

2. Methods

The local ethics committee approved this analysis and waived the need for individual patient consent (approval number 302/2014). This is a retrospective cross-sectional study originating from a consecutive registry of patients undergoing endovascular therapy in a tertiary referral centre between January 2000 and April 2014. We explored primary interventions in patients with chronic PAD of the lower extremities of atherosclerotic origin. In case of multiple interventions at the same time, only the intervention for the highest clinical severity was retained. Patients with non-atherosclerotic lesions, interventions in bypasses and dissections, hypogastric arteries, or prior to endovascular aneurysm repair (coiling/embolisation), erectile dysfunction, all secondary interventions, and acute limb ischaemia were excluded. Critical limb ischaemia (corresponding to Fontaine stages III–IV and Rutherford categories 4–6, respectively) was defined as a chronic condition presenting with ischaemic rest pain, with an ankle pressure of <50 mmHg or toe pressure <30 mmHg, or ischaemic lesions/gangrene, with an ankle pressure of <70 mmHg or toe pressure <50 mmHg, respectively [9]. Risk factors included in the analysis were age, gender, diabetes mellitus, arterial hypertension, dyslipidaemia, smoking, and renal insufficiency. Diabetes mellitus was defined as a fasting plasma glucose level ≥7.0 mmol/l or glycated haemoglobin >6.0%, or assumed if the patient was on hypoglycaemic drugs [3]. Arterial hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, or assumed if the patient was on antihypertensive drugs [3]. Dyslipidaemia was claimed in the presence of a total cholesterol level >5 mmol/L, or high-density lipoprotein cholesterol level <1 mmol/L, or triglyceride level >2 mmol/L, or assumed if the patient was on lipid-lowering drugs [3]. Patients were classified as smokers (current or former; ≥1 pack-year of tobacco use) or non-smokers based on patient interview or chart documentation [3]. Renal function was grouped according to estimated glomerular filtration rates using the Modification of Diet in Renal Disease method [15]. Moderate to severe renal insufficiency was defined as an estimated glomerular filtration rate <60 ml/min per 1.73 m^2, corresponding to chronic kidney disease stages ≥3 [16].

In univariate and multivariate logistic regression models using two sided Wald tests the association of age, sex, diabetes mellitus, hypertension, dyslipidaemia, smoking, and renal insufficiency with the clinical severity of PAD (critical limb ischaemia vs. intermittent claudication) was assessed. Crude estimates are from logistic regression models containing only the specified risk factor while adjusted values are from models including all risk factors. Odds ratios >1 represent that patients were more likely to suffer from critical limb ischaemia vs. intermittent claudication. The odds ratio for age represents increase in odds per decade increase of age. Missing data was accounted for using multiple imputation with age, sex, diabetes mellitus, hypertension, dyslipidaemia, creatinine, smoking, and the severity of PAD in the model to create 25 imputed datasets. A sensitivity analysis was carried out using only those patients with complete information on covariates. Additionally, we performed an analysis stratified for diabetes to assess whether associations of hypertension, dyslipidaemia, smoking, and renal insufficiency differed between diabetics and non-diabetics. A $p < 0.05$ was considered statistically significant. All analyses were performed using Stata version 13.1 (Stata Corporation, College Station, Texas).

Table 1
Demographic data and cardiovascular risk profile of 3406 patients included in the study.

	Missings	Claudicants	CLI	P value
	N (%)	N = 2346 (69%)	N = 1060 (31%)	
Age, years		69.5 ± 11.7	76.6 ± 10.4	<0.001
Male		1468 (63%)	607 (57%)	0.003
Diabetic	379 (11%)	647 (30%)	427 (48%)	<0.001
Hypertension	399 (12%)	1628 (76%)	703 (81%)	0.006
Dyslipidaemia	725 (21%)	1153 (59%)	374 (52%)	0.001
Smoking	517 (15%)	1144 (55%)	274 (34%)	<0.001
Renal insufficiency	988 (29%)	532 (32%)	397 (54%)	<0.001

Age is mean ± SD, categorical variables are n (%).

3. Results

Overall, there were 8875 procedures entered as primary interventions conducted on 4175 patients. The severity level was not recorded for 1899 interventions. Patients received up to 14 interventions, but only the first procedure for a given patient was retained in the analysis (excluding 787 interventions). In the case of multiple interventions at the same time, only the intervention for the highest severity was retained (excluding 2744 interventions). Furthermore, only interventions addressing Fontaine severity stages IIa, IIb, III and IV (corresponding to Rutherford categories 1–6) were retained (excluding a further 39 patients). This resulted in a final sample size of 3406 patients. Demographic data and pre-interventional characteristics (including missing values) of the patients at the time of the first intervention are shown in Table 1. Table 2 shows the association of each factor with the stage at which the patient received the first treatment.

Table 2
Associations of age, sex, diabetes, hypertension, dyslipidaemia, smoking, and renal failure with peripheral arterial disease severity stage in 3406 patients who were treated for the first time.

Risk factor	CLI relative to claudicant stage					
	Crude			Adjusted		
	OR	95%-CI	P value	OR	95%-CI	P value
Age, decades	1.80	1.68–1.94	<0.001	1.67	1.53–1.82	<0.001
Male	0.80	0.69–0.93	0.003	1.23	1.04–1.47	0.016
Diabetic	2.15	1.84–2.52	<0.001	1.99	1.68–2.36	<0.001
Hypertension	1.30	1.05–1.59	0.015	0.95	0.75–1.20	0.645
Dyslipidaemia	0.75	0.63–0.89	0.001	0.87	0.72–1.06	0.179
Smoking	0.43	0.37–0.50	<0.001	0.78	0.65–0.94	0.010
Renal insufficiency	2.43	2.05–2.89	<0.001	1.62	1.35–1.96	<0.001

Odds ratios (OR) >1 represent that patients with the risk factor are more likely to be treated at the critical limb ischaemia than at the claudicant stage. Crude estimates are from logistic regression models containing only the specified risk factor. Adjusted values are from logistic regression models including all risk factors.