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Prevalence of extracranial carotid artery disease in symptomatic peripheral artery disease and implications for long-term outcome

Bernhard Zierfuss[a], Ladislaja Witt-Dörring[a], Anna Ceschi a Santa Croce[a,b], Antonia Hannes[a,c], Moritz Staudacher[a], Gerfried Pesau[a], Oliver Schlager[a], Michael Gschwandtner[a], Gerit-Holger Schernthaner[a] and Clemens Höbaus[a]

[a]Division of Angiology, Department of Medicine 2, Medical University of Vienna, Austria; [b]Kepler University Hospital, Linz, Austria; [c]Göttlicher Heiland Hospital, Vienna, Austria

ABSTRACT

Background: Patients with peripheral artery disease (PAD) still experience excessive rates of fatal cardiovascular events. In this context, the relevance of co-existing extracranial carotid artery disease (ECAD) on outcome in patients with PAD is unclear. Thus, this study elucidates long-term outcome effects of the presence of both atherosclerotic entities for further risk stratification.

Materials and methods: A total of 669 patients from the Lip-LEAD study with symptomatic PAD (Fontaine stage 2–4) were evaluated for ECAD (internal carotid artery stenosis >50%) with ultrasonography within 6 months after endovascular repair for PAD. Outcome was assessed with a long-term follow-up period with a maximum of 10 years.

Results: Patients presenting with ECAD ($n=245$, 36.7%) exhibited worse hemodynamic parameters of PAD than those without (ankle-brachial index (ABI). (0.53 (0.37–0.68) vs. 0.57 (0.47–0.68), $p=0.009$; toe-brachial index (TBI) (0.50 (0.36–0.63) vs. 0.55 (0.42–0.70), $p=0.005$). Significant correlations between grade of carotid stenosis and ABI as well as TBI were present (r=-0.190, $p<0.001$; r=-0.219, $p<0.001$). Cox-regression analyses revealed worse outcome in patients with ECAD for both all-cause and cardiovascular (CV)-mortality after multivariable adjustment for traditional CV risk-factors [1.48 (2.02–2.17); 2.10 (1.19–3.69)].

Conclusion: Patients with additional ECAD to symptomatic PAD exhibited an unfavourable long-term outcome in comparison to those without. The results suggest that the additional presence of ECAD highlights a highly vulnerable cohort of patients with symptomatic PAD at risk for further fatal CV events and thus should be considered for further diagnostic evaluation and stronger risk modification initiatives.

KEY MESSAGES

- This study shows that the combination of ECAD and PAD is worse for long-term outcome in a cohort of patients with well-treated traditional CV risk factors.
- Grade of carotid artery stenosis was highly associated with worse hemodynamic parameters of PAD.
- In addition, patients with both ECAD and PAD were generally better treated for traditional CV risk factors. Thus, a further underyling mechanism might be causal for this polyvascular disease.
- Work-up for ECAD is not generally established in PAD. Yet, the results highlight that patients with PAD and ECAD are a subpopulation that needs intensified work-up and monitoring. Screening of such comorbidity might be benefitial to further improve patient care of this vulnerable patient collective.

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PAD; carotid artery stenosis; mortality; polyvascular disease

Introduction

Peripheral artery disease (PAD) poses a high risk for further cardiovascular (CV) events [1,2]. These high event-rates [3] are similar between symptomatic or asymptomatic patients. Despite recent advances in therapy for atherosclerotic disease, these numbers are still higher than those of coronary artery disease (CAD) [4,5]. While underlying mechanisms for different atherosclerotic entities share common modifiable risk factors, such as hypertension, hypercholesterolemia, smoking, and diabetes mellitus (DM) differences in nuances of these and further novel risk factors are

CONTACT Clemens Höbaus clemens.hoebaus@meduniwien.ac.at Division of Angiology, Department of Internal Medicine 2, Medical University of Vienna, Waehringer Guertel 18-20, 1090, Vienna, Austria.

present in various affected vascular beds [6]. These aforementioned risk factors exert even different impact between iliac, femoral or below the knee (BTK) lesions in PAD [7]. Exemplarily, smoking is the most relevant risk factor for iliac lesions, while DM is most prevalent for BTK lesions [7]. Differences of the modifying potential of CV risk factor vary between ECAD and PAD to an even bigger extent. While ECAD is mainly driven by hypertension, most relevant modifiable risk factors for PAD are smoking and diabetes. These differences extend to histopathologic differences between PAD and ECAD lesions. While latter are generally lipid rich with a necrotic core and strong infiltration of inflammatory cells, PAD plaques are generally formed by a thick fibrous cap [8]. However, PAD in general, as an atherosclerotic affection of limb arteries, is accepted as an expression of systemic vascular disease. This can best be seen by the high co-prevalences of 24.8% with CAD and of 40.2% with cerebrovascular disease in the REACH registry [9]. However, it is unclear if these high co-prevalences of atherosclerosis in other vascular beds lead to worse outcome in patients with PAD. Furthermore, no screening algorithm for extracranial carotid artery disease (ECAD) in PAD is established or any evidence is available that this strategy improves patient care. Evaluation of ECAD, as stenosis of the internal carotid artery (ICA) of more than 50% [10], primarily focuses on the major and important goal of stroke prevention [11,12]. The incidence rate for cerebral thrombosis due to embolization rises as ECAD stenosis progresses [8]. Data for this field are more robust for symptomatic ECAD [11,12]. Treatment and follow-up data for asymptomatic disease in ECAD are not as abundantly available. However, it is likely that aforementioned medical therapy improvements further enhanced outcome, especially in cases of conservative management of ECAD. A recent study showed that the event-rate of a stroke within 5-years for patients with severe asymptomatic ECAD lies at 4.7% [13]. Data for all-cause mortality or CV-mortality on the other hand are scarce, especially in a cohort of patients with PAD. We thus sought to evaluate implications of outcome for concomitant ECAD in patients with symptomatic PAD over a long-term follow-up of up to ten years.

Materials and methods

Patients and study design

The patients from this study originate from the Vienna Lip-LEAD study, which has previously been described [14]. In brief, these patients were retrospectively included to further evaluate traditional risk factor goals in a single-centre study. Prior to initiation, this study was approved by the institutional review board (Ethikkommission der Medizinischen Universität Wien, approval number EK1806/2019) and follows institutional Good Clinical Practice guidelines as well as the Declaration of Helsinki [15]. All patients that were admitted from 1/January/2013 to 31/December/2018 for endovascular repair of symptomatic PAD to the inpatient ward of the Division of Angiology, Medical University of Vienna, were included. Inclusion was performed retrospectively. Informed consent was waived by the IRB due to the retrospective design of the study. No minors were included into the study. Assessment of relevant concomitant diseases, including history of previous PAD operations/endovascular repair, history of stroke, coronary artery disease, history of myocardial infarction, heart failure, smoking habits, arterial hypertension, hyperlipidaemia, diabetes mellitus, and previous operations/procedures on extracranial carotid arteries were assessed by available medical charts and/or due to patient's declaration at admission to the inpatient ward. Measurement of routine laboratory parameters including a lipid panel, kidney and liver function parameters as well as inflammatory markers and a complete blood count were performed at the day of admission to our inpatient ward. The CKD-EPI formula of 2012 was used for the estimated glomerular filtration rate (eGFR) calculation [16].

PAD assessment

Indication for revascularization due to symptomatic PAD was assessed by experienced vascular consultants at our department prior to admission. The Fontaine stage grading system was used for the definition of clinical PAD severity. Fontaine stage II was defined as intermittent claudication (IC). Fontaine stages III and IV were defined as critical limb ischemia (CLI). Acute limb ischemia (ALI) due to thromboembolic events were excluded from this study due to the different pathophysiologic origin. Indication for revascularization was symptomatic PAD and shared decision making for IC and acuity in terms of CLI. Furthermore, patients were initially not included in LIP-LEAD, if selected for surgical treatment at the outpatient ward. Specially trained vascular medical personnel performed oscillometry and ankle-brachial index (ABI) measurements with a Doppler sonographic probe (ELCAT, Wolfratshausen, Germany). ABI was defined as the ratio of the ankle divided by the brachial systolic blood pressure according to the TASC II criteria [17]. Toe pressures were measured using a photopletysmograph infrared sensor

and a small blood pressure cuff around the toe (ELCAT, Wolfratshausen, Germany). Toe-brachial index (TBI) was defined as the ratio of the toe divided by the brachial systolic blood pressure. Accordingly, a resting TBI < 0.7 or an ABI < 0.9 were defined as pathologic findings. In the case of incompressible arteries or an ABI > 1.4 mediasclerosis was diagnosed. PAD stenosis location and relevance prior to endovascular repair were evaluated by ultrasonography or contrast-enhanced CT/MR-scans at the physicians' discretion. All PAD procedures followed the correspondent guidelines from ESC [18] and AHA/ACC [19].

ECAD assessment

All available carotid ultrasound reports that were performed for any reason at our department were assessed within a time frame of six months prior or after the index event of peripheral revascularization. An internal carotid artery (ICA) stenosis of more than 50% on any site was defined as ECAD. Duplex sonographic criteria for ECAD diagnosis were validated according to angiographic features at our department [20]. The percentage of stenosis was defined with the carotid ratio (CR), which is defined as the peak systolic velocity (PSV) ratio between the common carotid artery (CCA) and the ICA. A CR below 2 was equal to a stenosis of < 50%, a CR between 2 and 4 to a stenosis of 50-70% and a CR above 4 to a stenosis of > 70% [20]. Analysis of carotid stenosis was performed in this study regardless of the clinical situation of a symptomatic or asymptomatic status. 50 patients had a known history of carotid endarterectomy (CEA) or stenting (CAS). Those patients were subjected to the group of known ECAD for outcome analyses, but were excluded from CR analyses, since stenoses were already treated. In terms of ICA stenosis on both sides, the grade of the more severe stenosis was used for statistical analysis.

Outcome analysis

Survival data was acquired from the central death database of the federal republic of Austria. The cut-off date for information on mortality was set at the 31/August/2021. ICD codes from the I category were deemed as CV death and further adjudicated to available medical records.

Statistical analysis

The entire statistical analysis was performed with SPSS 28.0 (SPSS Inc. Chicago, IL, USA). Figures were drawn with GraphPad Prism 9.0 (GraphPad Software Inc., San Diego, CA, USA). Data are presented as mean ± standard deviation (SD) or median and percentiles (25^{th}, 75^{th}), as appropriate. A two-sided p-value <0.05 was defined as statistically significant. Student's t-tests or nonparametric equivalents and chi-square tests were applied, as appropriate. Carotid stenoses were assessed in groups below and above 50% ICA stenosis and in a further group comparison of 0-50%, 50-70% and above 70% stenosis of any ICA for graphical comparison and evaluated by Kaplan-Meier analyses. A log-rank test was used for statistical comparison. Cox regression analyses were performed with group comparison below and above 50% ICA stenosis. For this cause a multivariable-adjusted model was performed with traditional CV risk factors (age, sex, active smoking, HbA1c, low density lipoprotein-cholesterol (LDL-C), presence of arterial hypertension, eGFR, Fontaine stage, lipoprotein (a), and C-reactive protein). A ROC analysis for ECAD diagnosis with multivariable adjustement (age, sex, active smoking, LDL-C, history of hypertension, HbA1c) for with or without ABI was performed.

Results

Baseline characteristics

Out of the entire population of 669 patients a total of 245 (36.7%) patients with PAD had concomitant ECAD fulfilling sonographic diagnostic criteria. 50 patients (7.5%) already underwent CAS or CEA, 100 patients (14.9%) had ECAD between 50–70% and 95 patients (14.2%) had ECAD >70%. Patients with ECAD stenosis were significantly older (69 ± 10 vs. 68 ± 11 years $p = 0.029$), had higher systolic blood pressure (153 ± 28 vs. 142 ± 22 mmHg $p = 0.027$) and a higher BMI (27.8 ± 5.0 vs. 26.8 ± 4.7 kg/m^2, $p = 0.016$). Accordingly, the traditional CV risk factors diabetes mellitus (50.6%, vs. 39.9%, $p = 0.007$) and arterial hypertension (94.3% vs. 89.2%, $p = 0.003$) were significantly more prevalent in the ECAD group. Measurements of PAD were significantly worse in the ECAD group (ABI 0.53 (0.37–0.68) vs. 0.57 (0.47–0.68), $p = 0.009$; TBI 0.50 (0.36–0.63) vs. 0.55 (0.42–0.70), $p = 0.005$). Renal excretory function parameters were lower in the ECAD group (serum creatinine 1.03 (0.82–1.33) vs. 0.97 (0.79–1.20) mg/dL, $p = 0.046$; eGFR 79.8 ± 28.5 vs. 85.8 ± 28.5 ml/min/1.72m^2, $p = 0.009$). Contrarily, LDL-C levels were significantly lower in the ECAD group (83.3 ± 34.2 vs. 90.4 ± 39.0 mg/dL, $p = 0.025$), which might be explained by higher statin and ezetimibe prescription rates. However, those did not reach statistically significant results (statin 90.2% vs. 86.6%, $p = 0.164$; ezetimibe 10.2% vs. 7.8%, $p = 0.284$). Similarly, but statistically significant, rates of any antihypertensive

medication intake were significantly higher in the ECAD group (88.2% vs. 81.1%, $p=0.018$). A detailed overview can be seen on Table 1.

Associations between PAD measurements and ECAD

While no significant difference between severity of PAD and categories of ECAD was seen (intermittend claudication (IC) vs. critical limb ischemia (CLI); ICA <50%: 343 vs. 107, ICA 50-70%: 78 vs. 22, ICA >70%: 69 vs. 26; overall $p=0.590$) significant correlations were seen between CR and ABI as well as TBI (r=-0.190, $p<0.001$; r=-0.219, $p<0.001$). Those findings prompted us to further perform a ROC analysis with a binary logistic multivariable regression model (age, sex, active smoking, LDL-C, history of hypertension, HbA1c) for ECAD with or without the addition of ABI. The area under the curve (AUC) improved from 0.60 (95% CI 0.52-0.64) to 0.66 (0.59-0.72).

Table 1. Baseline characteristics. Patients are divided for ECAD status. Data are shown as mean ± standard deviation or median and interquartile range, as applicable. A p-value < 0.05 (two-sided) was considered statistically significant. Bold values in the p-value column depict significant results.

	no ECAD	ECAD	*p-value*
n	424	245	
Demographics			
age	68 ± 11	69 ± 10	***0.029***
sex n(%)	157 (37%)	84 (34.3%)	*0.477*
systolic BP (mmHg)	142 ± 22	153 ± 28	***0.027***
diastolic BP (mmHg)	77 ± 11	78 ± 12	*0.895*
BMI (kg/m²)	26.8 ± 4.7	27.8 ± 5.0	***0.016***
Medical history			
intermittent claudication n(%)	322 (75.9%)	182 (74.3%)	*0.632*
Critical limb ischemia n(%)	102 (24.1%)	63 (25.7%)	
CAD n(%)	144 (34.0%)	96 (39.2%)	*0.175*
History of stroke n(%)	31 (7.3%)	29 (11.8%)	*0.048*
MCI n(%)	64 (15.1%)	39 (15.9%)	*0.776*
Atrial fibrillation n(%)	54 (12.7%)	30 (12.2%)	*0.854*
History of HF n(%)	49 (11.6%)	39 (15.9%)	*0.108*
Cardiovascular risk factors			
Diabetes mellitus n(%)	169 (39.9%)	124 (50.6%)	***0.007***
arterial hypertension n(%)	378 (89.2%)	231 (94.3%)	***0.025***
hyperlipidemia n(%)	365 (86.1%)	218 (89.0%)	*0.281*
active smoking n(%)	135 (38.8%)	89 (43.6%)	*0.264*
Measurements			
ABI	0.57 (0.47-0.68)	0.53 (0.37-0.68)	***0.009***
TBI	0.55 (0.42-0.70)	0.50 (0.36-0.63)	***0.005***
Laboratory parameters			
Serum creatinine (mg/dl)	0.97 (0.79-1.20)	1.03 (0.82-1.33)	***0.046***
eGFR (CKD-EPI) (mg/min)	85.8 ± 28.5	79.8 ± 28.5	***0.009***
LDL-C (mg/dl)	90.4 ± 39.0	83.3 ± 34.2	***0.025***
HDL-C (mg/dl)	47 (37-59)	31 (7-57)	*0.386*
Lipoprotein (a) (nmol/L)	22 (8-108)	31 (7-119)	*0.778*
triglycerides (mg/dl)	128 (94-180)	134 (95-185)	*0.328*
HbA1c (rel.%)	6.3 ± 1.2	6.4 ± 1.2	*0.337*
C-reactive protein (mg/dl)	0.30 (0.13-0.80)	0.35 (0.14-0.77)	*0.594*
Medication			
antihypertensive therapy n(%)	344 (81.1%)	216 (88.2%)	***0.018***
RAAS blockade n(%)	266 (74.9%)	167 (77.0%)	*0.583*
statin usage n(%)	367 (86.6%)	221 (90.2%)	*0.164*
ezetimibe n(%)	33 (7.8%)	25 (10.2%)	*0.284*

BP blood pressure, BMI body mass index, CAD coronary artery disease, MCI myocardial infarction, HF heart failure, ABI ankle-brachial index, TBI toe-brachial index, LDL-C low density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, eGFR estimated glomerular filtration rate, RAAS renin-angiotensin-aldosteron.

Outcome analyses

After a median observation period of 4.7 years (25th percentile 3.3 years, 75th percentile 6.4 years) 201 patients died (absolute event-rate 30.0%, calculated annually event-rate 6.4%). A total of 86 events were adjudicated as fatal CV-events (absolute event-rate 13.0%, calculated annually event-rate 2.8%). Kaplan-Meier curves revealed a clear-cut association between overall-mortality (log-rank $p<0.001$) and CV-mortality (log-rank $p<0.001$) between patients with ECAD and those without. When ECAD was divided into categories <50%, 50-70% and >70% KM-curves showed a trend for all-cause mortality (log-rank $p=0.073$), while KM-curves for CV-mortality showed a strong clear-cut association with worse outcome with higher stenosis grade of ECAD (log-rank $p<0.001$). A detailed overview can be seen on Figure 1.

These findings were further subjected to Cox-regression analyses for presence of additional ECAD vs. those without. Models showed significant associations both for all-cause mortality [hazard ratio (HR) 1.73 (95% CI 1.20-2.49)] and CV-mortality in crude fashion [HR = 2.25 (95% CI 1.31-3.87)]. These associations sustained multivariable adjustment for traditional CV risk factors (age, sex, arterial hypertension, LDL-C, HbA1c, eGFR, lipoprotein(a), c-reactive protein) and stage of PAD [1.48 (2.02-2.17); 2.10 (1.19-3.69)]. A detailed overview can be seen in Table 2.

Discussion

The findings of this study highlight the major relevance of additional manifest ECAD for patients with PAD. ECAD, as defined as ICA stenosis above 50% was associated both with worse all-cause mortality and CV-mortality over a long-term follow-up period of patients with symptomatic PAD. These findings withstood adjustment for traditional CV risk factors and stage of PAD (IC vs. CLI) in Cox-regression analyses.

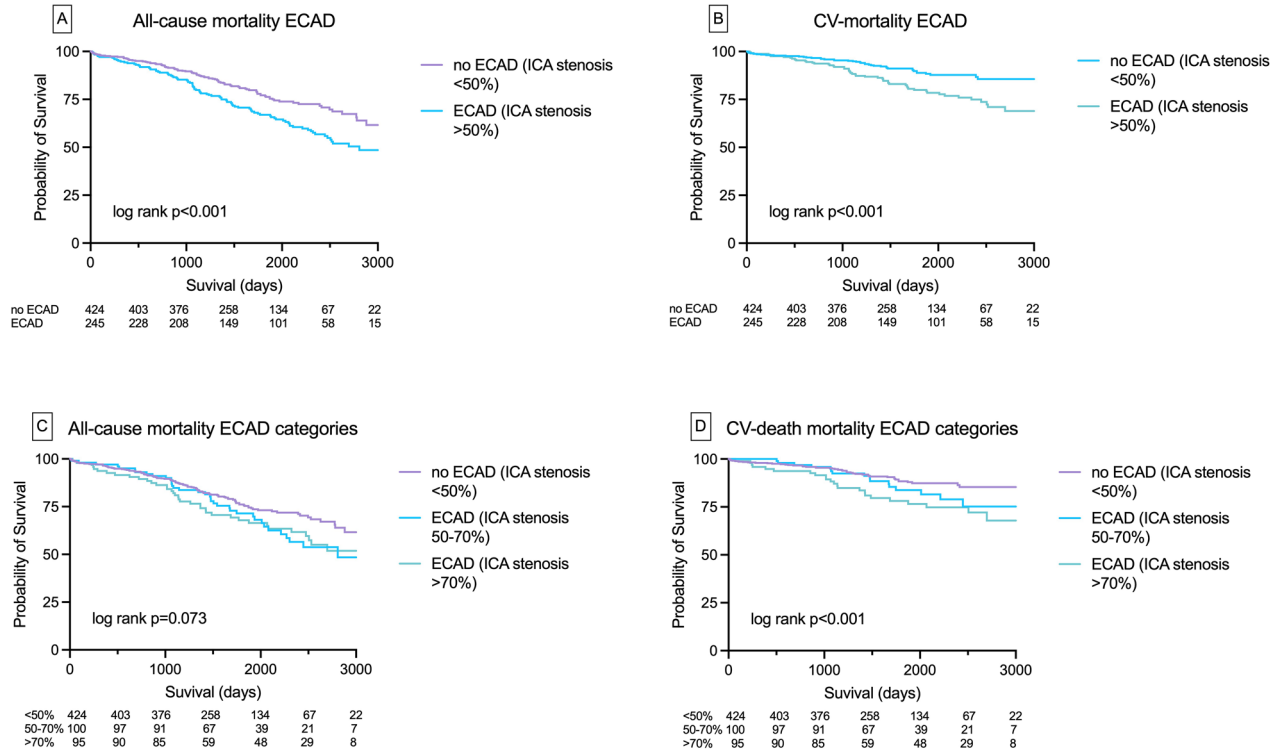

Figure 1. Panel of Kaplan-Meier curves for presence of ECAD. (A) Analysis for all-cause mortality and ECAD ($p < 0.001$); (B) Analysis for CV-mortality and ECAD ($p < 0.001$); (C) Analysis for all-cause mortality and ECAD with categories <50%, 50-70%, >70% ($p = 0.008$); (D) Analysis for CV-mortality and ECAD with categories <50%, 50-70%, >70% ($p < 0.001$).

Table 2. Cox-regression analyses for presence of ECAD. Models are presented for crude and multivariable adjusted analyses. Bold values in the p-value column depict significant results.

	Cox Regression Analyses		
		Multivariable Adjusted	
	Crude	Model 1	Model 2
All-cause mortality	**1.73 (1.20–2.49)**	**1.54 (1.06–2.22)**	**1.48 (2.02–2.17)**
CV-mortality	**2.25 (1.31–3.87)**	**1.94 (1.13–3.34)**	**2.10 (1.19–3.69)**

Model 1: + age, sex, Model 2: +active smoking, history of hypertension, LDL-C, HbA1c, C-reactive protein, Fontaine stage (intermittent claudication, critical limb ischemia), lipoprotein (a), eGFR.

Furthermore, a relevant association of hemodynamic parameters of PAD and ECAD was found. In line with this, an exploratory ROC analysis for diagnostic accuracy of ECAD with traditional CV risk factors further improved with the addition of ABI to the model.

Our results are consistent to previous reports of increased cardiovascular risk in patients with manifest carotid artery disease in comparison to minor carotid artery lesions [21]. Similarly, a study found that patients with ECAD exhibited a higher incidence of MACE compared to those without [22]. Data from the Framingham Offspring Study showed that the addition of an increased intima media thickness or plaques in the internal carotid artery significantly improved the risk classification for cardiovascular disease in the general population [23]. Furthermore, meta-analyses have reported a dose-response relationship between the severity of ICA stenosis and the risk of cardiovascular events [24]. While a subanalysis [25] from the VOYAGER PAD [26] trial found that polyvascular disease in terms of PAD with our without CAD increases both MALE and MACE, no outcome data is available for the combination of PAD and ECAD. The bottom line of the data from VOYAGER showcases the importance of aggressive secondary prevention in PAD patients needing revascularisation. Abundant data shows that PAD patients not only have the worst mortality rates of all atherosclerotic manifestations, but also suffer from the before mentioned high rates of MACE, as shown in the EUCLID trial [27]. The risk for latter is even more increased in combination with CAD [27]. Likewise MALE are also exorbitantly elevated in PAD [28]. Yet, no data underlines similar results for the combination of ECAD and PAD. It remains unclear if both MACE and MALE are likewise increased for this combination of CV diseases over a long-term period. The findings of our study add information about the combined risk for mortality of PAD and ECAD, which was also not yet known from published studies. Our data thus suggests that it would be reasonable to evaluate the combination of ECAD and PAD and the relation of MACE and MALE over a long-term period.

Despite the fact, that patients of the ECAD group in this study had worse rates of traditional CV-risk factors with higher rates of DM and arterial hypertension, those patients were more stringently treated and/or showed increased adherence to prescribed medication. This can be seen with significantly lower LDL-C levels and almost identical HbA1c levels despite higher rates of DM in the ECAD group. Thus, it is likely that the worse outcome in terms of all-cause and CV-mortality might be rooted from an additional, yet unspecified effect.

While a single traditional cardiovascular risk factor alone might not be responsible for the difference in outcome, ECAD might be an effect of a series of unfavorable changes, beginning with (carotid) wall sheer stress. Alterations of vascular dynamics leading to the progression of atherosclerosis have previously been suggested in ECAD [29]. It seems reasonable that ECAD began to develop under sustained or prolonged conditions of arterial hypertension. This notion is supported by the higher rate of arterial hypertension in ECAD in our cohort. This might have led to a rate of 36.7% of PAD patients with concomitant ECAD. Data from comparable cohorts report only a prevalence of 14-19% of ECAD in PAD [6,10]. However, since both atherosclerotic entities share common risk factors [30,31] and histopathologic studies found even higher rates of atherosclerotic plaques in different vascular beds at the same time, these low numbers of latter mentioned studies seem rather unlikely [32]. This hypothesis is even more supported by similar rates in the REACH registry [9]. Previous dedicated screening studies for prevalence of ECAD in PAD patients found similarly high rates of co-presence of both entities to our results [22,33].

Thus, this mentioned discrepancy can likely be explained by high numbers of undetected ECAD in PAD. Current guidelines by the European Society of Cardiology (ESC)/European Society for Vascular Surgery (ESVS) [10] and the European Society for Vascular Medicine (ESVM) [6] do not specifically recommend routine screening for ECAD in PAD. However, the principle of individualized risk stratification is central to contemporary cardiovascular guidelines, including those mentioned for PAD. While this study cannot show the utility for routine screening of ECAD in PAD, it gives further insight to those patients at excess risk for CV-mortality. Identifying those patients at excess risk despite optimized traditional CV risk factor might further lead to CV risk reduction. Our data presents evidence that checking for co-existing ECAD might select a vulnerable group within the PAD collective. In comparison to laboratory measurements or computed tomographic imaging options for risk stratification, diagnosis of ECAD with ultrasonography is both feasible and cost-effective. While screening for asymptomatic abdominal aortic aneurysm is recommended in selected situations, screening for asymptomatic ECAD is not, due to lack of evidence [34]. Our data on the other hand shows that screening for ECAD in symptomatic PAD might be a viable tool to further improve patient care of these patients and should be further tested.

This study has several limitations to consider. Firstly, ECAD was only diagnosed with present sonographic reports in a six-month timeframe to the index event of endovascular revascularization for symptomatic PAD. Secondly, only fatal outcome events were analyzed due to the study design. Especially of interest in a group of patients with CLI would be major adverse limb events (MALE). However, due to the study design no further information can be given on that issue. Thirdly, due to this circumstance no information on progression of ECAD is available. However, several strengths have to be taken into account too. Firstly, all patients were treated at a tertiary care center with specialized faculty. Secondly, sonographic features are standardized to a published and highly practiced protocol [20] at the department with case numbers up to several thousand annually. Thirdly, all patients were treated with best medical treatment according to current CV guideline recommendations.

The results of this analysis prompt further insight into the complex association between ECAD and PAD. A combination of both CV disease entitites depicts patients at excess risk for fatal events. This has to be seen in the context of still unsatisfactorily high event-rates of patients with PAD. Yet, examination of ECAD in symptomatic PAD seems reasonable, since sonographic evaluation of ECAD is both feasible and cost-effective. Identifying those vulnerable patients with the combination of ECAD and PAD and further optimizing CV risk factors in this highly vulnerable group might foster patient care and outcome.

Author contributions

BZ lead the project, supervised data collection, analyzed the data and wrote the initial draft of the manuscript. LWD helped with data collection and data analysis. ACSC helped with data collection and data analysis. AH helped with data collection and data analysis. MS, helped with data interpretation and manuscript preparation. GP helped with data interpretation and manuscript preparation. OS helped with data interpretation and manuscript preparation. MG helped with data interpretation and manuscript preparation. GHS supervised the project, helped with data interpretation and manuscript preparation. CH supervised the project, helped with manuscript preparation and drafted the final manuscript. All authors have read and approved the final work.

Disclosure statement

No potential conflicts of interest was reported by the author(s).

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ORCID

Clemens Höbaus http://orcid.org/0000-0002-9704-1452

Data availability statement

Data of this study is available from the corresponding upon reasonable request.

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