ORIGINAL ARTICLE

The prevalence of polyvascular disease in patients with carotid artery disease and peripheral artery disease

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ABSTRACT

BACKGROUND Cardiovascular disease remains the major cause of mortality in the Western World.

AIMS We aimed to assess the prevalence of polyvascular disease in patients with carotid artery disease and peripheral artery disease (PAD), and to determine the risk profile of patients with polyvascular disease.

METHODS The study included 1045 consecutive patients presenting to our department with carotid disease or PAD. Demographic characteristics, anthropometric parameters, and data on cardiovascular risk factors were collected in all patients. On the basis of medical history, patients were classified into those who had only symptomatic carotid disease or symptomatic PAD and those who had symptomatic polyvascular disease.

RESULTS Carotid disease alone was reported in 366 participants (35%), PAD alone, in 199 (19%), and polyvascular disease, in 480 (46%). Compared with carotid disease, PAD was more often a component of polyvascular disease (P = 0.002) and was combined with a higher number of other atherosclerotic diseases (P = 0.02). Compared with patients with symptomatic atherosclerotic disease in only 1 territory, patients with various types of polyvascular disease more often had hypertension (P from 0.03 to <0.001), dyslipidemia (P <0.001), high-sensitivity C-reactive protein levels of 3 mg/l or higher (P = 0.005), and more often were current smokers (P <0.001) or former smokers (P from 0.03 to 0.001).

CONCLUSIONS We showed a high prevalence of symptomatic polyvascular disease in patients with carotid disease or PAD. The risk profile was worse in patients with polyvascular disease than in those with a disease in a single vascular territory.

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INTRODUCTION Cardiovascular disease remains the major cause of death in the Western World. In Europe, despite recent reductions in mortality rates in numerous countries, cardiovascular disease still accounts for about half of all deaths (46%).[1] It is also the leading cause of death in Serbia, and, in 2013, it was responsible for 54% of all-cause deaths.[2]

Atherosclerosis is a chronic and progressive disease, which can affect any vascular territory (coronary, cerebrovascular, peripheral arterial) as a single disease or can occur in more than 1 territory as polyvascular disease.[3] The presence of atherosclerotic disease in a single vascular territory frequently indicates an increased risk of its presence in another territory.[3] The prevalence of polyvascular disease ranges from 6%[4] to 71%,[5] depending on the population studied and study design. Patients with polyvascular disease have a worse risk profile and prognosis than patients with the disease in a single arterial territory. Therefore, studies are needed to improve the detection and subsequent treatment of these patients.[6]

WHAT'S NEW?

In the present study, atherosclerotic risk factors were more frequent in patients with polyvascular disease than in those with a single vascular disease. The frequency of risk factors depended on which arteries were involved in the polyvascular disease and which single atherosclerotic disease was used for comparison—carotid disease or peripheral artery disease. Hypertension and dyslipidemia were found to be the risk factors for any type of polyvascular disease, while smoking and increased levels of high-sensitivity C-reactive protein were risk factors for peripheral artery disease both as a single vascular or polyvascular disease.

The aims of the present study were to assess the prevalence of polyvascular disease in patients with carotid disease or peripheral artery disease (PAD) and to determine the risk profile of patients with polyvascular disease.

METHODS This cross-sectional study included 1045 consecutive patients referred to the Department of Vascular Surgery at Dedinje Cardiovascular Institute in Belgrade, Serbia, because of carotid disease or PAD. The study was conducted between April 2006 and November 2007. We enrolled individuals with symptoms of cerebral ischemia (amaurosis fugax, transient ischemic attack, or stroke) and carotid stenosis of 50% or greater according to the North American Symptomatic Carotid Endarterectomy Trial criteria,[7] as well as patients with symptomatic PAD (claudication, rest pain, or gangrene). Carotid disease was assessed by ultrasound examinations with an Alfa10 color duplex system (Aloka Co., Ltd., Tokyo, Japan). Peak systolic velocities (PSVs), end-diastolic velocities (EDVs), and the ratio of the internal carotid artery to the common carotid artery were used to assess the degree of carotid stenosis. The characteristics and structure of the carotid plaque were also analyzed by ultrasonography. For ultrasound assessment of the degree of carotid stenosis, we used the following criteria: <50%, PSV <125 cm/s and EDV <40 cm/s; 50%–69%, PSV = 125–230 cm/s and EDV = 40–100 cm/s; 70%–90%, PSV = 230–500 cm/s and EDV = 100–300 cm/s; 90%–99%, unpredictable PSV and EDV, from very high to very low values; occlusion, undetectable flow in the internal carotid artery. The diagnosis of PAD was defined by Doppler sonography as an ankle–brachial index of less than 0.9. The ankle–brachial index has a sensitivity of 90% and a specificity of 95% for diagnosing PAD.[8] Doppler sonography of both lower limbs was performed, and the lowest value was recorded as the ankle–brachial index. The exclusion criteria were age under 18 years, malignant disease, previous endarterectomy, and rheumatoid arthritis.

Demographic characteristics, anthropometric parameters, as well as data on cardiovascular risk factors and personal medical histories were collected for all participants. Information regarding demographics, smoking and alcohol consumption, physical activity, use of antihypertensive and lipid-lowering medications, and history of other atherosclerotic diseases or diabetes mellitus was collected using a questionnaire. Patients were classified into 2 groups depending on educational status: participants with 12 years or less of schooling and those with more than 12 years of schooling. Each subject was classified as a nonsmoker, former smoker, or current smoker. Current smokers were defined as individuals who smoked at least 1 cigarette per day or stopped smoking within the past year. Former smokers were defined as those who quit smoking more than a year earlier. For the purpose of this study, alcohol consumption was defined as ever alcohol consumption (former and current). A participant who consumed less than 12 standard drinks a year was considered a nondrinker. Physical activity was defined as any type of nonoccupational physical exercise lasting more than 30 minutes per day during the previous month. Those who exercised more than once per week were considered physically active. The remaining participants were classified as physically inactive. The use of antihypertensive and lipid-lowering drugs was considered as an indicator of hypertension and dyslipidemia. On the basis of data from personal medical histories, all patients were classified as those who had symptomatic carotid disease alone or symptomatic PAD alone and those who had symptomatic polyvascular disease. Polyvascular disease was defined as the presence of symptomatic atherosclerotic disease in at least 2 major vascular territories.

Body weight and height, measured by standard procedures, were used to calculate body mass index (BMI). A BMI of less than 25 kg/m^2 was considered as normal weight; 25 to 29.9 kg/m^2, as overweight; and of 30 kg/m^2 or higher, as obesity.[9] Blood pressure was measured based on the recommendations by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[10] For estimation of metabolic parameters, fasting blood glucose, and lipoproteins (using commercial kits: Abbot, Libertyville Township, Illinois, United States, on an automated analyzer, AEROSET™, Abbot), blood samples were obtained after an overnight fast. Patients were instructed to abstain from drinking with the exception of water. The levels of high-sensitivity C-reactive protein (hs-CRP) and fibrinogen were measured using a fixed-time immunoturbidimetric assay (Olympus Diagnostics, O'Callaghan's Mills, Co. Clare, Ireland). The high level of hs-CRP was defined as 3 mg/l or higher, according to the Centers for Disease Control and Prevention recommendations.[11] Metabolic syndrome was defined according to National Cholesterol

Education Program III criteria.[12] The cutoff values for waist circumference of 102 cm for men and of 88 cm for women were used, as recommended for the European populations.[13]

Ethical approval The study was approved by the Ethics Committee at the Faculty of Medicine in Belgrade. All patients gave their written informed consent to participate in the study.

Statistical analysis Data were presented as counts and percentages. For data analysis, univariate and multivariate logistic regression analyses were used. Univariate analyses were adjusted for age and sex. All variables that differed significantly ($P \leq 0.1$) between the compared groups (patients with a single vascular disease vs those with polyvascular disease) in the univariate analysis were included in the multivariate analysis. An α level of 0.05 was used to indicate statistical significance. Data were analyzed using the SPSS software, version 20 (SPSS Inc., Chicago, Illinois, United States).

RESULTS Of the 1045 consecutive patients referred to the Department of Vascular Surgery at Dedinje Cardiovascular Institute due to carotid disease or PAD, 366 (35%) had carotid disease only, 199 (19%) had PAD only, and 480 (46%) had polyvascular disease. Carotid disease and PAD were observed in 94 patients (9%); carotid disease and coronary heart disease (CHD), in 183 (18%); PAD and CHD, in 99 (9%); and carotid disease, PAD, and CHD, in 65 (6%). In 39 patients (4%), abdominal aortic aneurysm was combined with other vascular diseases (with carotid disease in 8 patients; PAD in 9 patients; carotid disease and PAD in 7 patients; carotid and CHD in 2 patients; PAD and CHD in 11 patients; and carotid disease, PAD, and CHD in 2 patients).

Demographic characteristics and distribution of cardiovascular risk factors in patients with carotid disease alone and those with various combinations of carotid and other vascular diseases are presented in TABLES 1 and 2. Of the 727 patients with carotid disease, 23% also had PAD, 35% also had CHD, and 3% also had abdominal

TABLE 1 Comparison of demographic, anthropometric, and lifestyle characteristics between patients with polyvascular disease and carotid disease alone

Variable		Carotid disease (n = 366)	Carotid disease + PAD (n = 94)	Carotid disease + CHD (n = 183)	Carotid disease + PAD + CHD (n = 65)	All polyvascular diseases[a] (n = 361)
Age, years	<55	41 (11.2)	18 (19.1)	19 (10.4)	11 (16.9)	50 (13.9)
	55–64	123 (33.6)	31 (33.0)	50 (27.3)	23 (35.4)	106 (29.4)
	≥65	202 (55.2)	445 (47.9)[c]	114 (62.3)	31 (47.7)	205 (56.8)
Male sex		227 (62.0)	67 (71.3)[d]	102 (55.7)	46 (70.8)	232 (64.3)
<12 years of education		134 (36.6)	24 (25.5)[d]	73 (39.9)	23 (35.4)	125 (34.6)
Body mass index, kg/m^2	<25	118 (32.2)	40 (42.6)[c]	44 (24.0)[c]	22 (33.8)	115 (31.9)
	25–29.9	162 (44.3)	42 (44.7)	101 (55.2)[c]	31 (47.7)	182 (50.4)
	≥30	86 (23.5)	12 (12.8)[c]	38 (20.8)	12 (18.5)	64 (17.7)
Abdominal obesity[b]		176 (48.1)	34 (36.2)	103 (56.3)	30 (46.2)	174 (48.2)
Former smoking		117 (32.0)	36 (38.3)[e]	71 (38.8)	24 (36.9)[f]	139 (38.5)[e]
Current smoking		107 (29.2)	50 (53.2)[e]	44 (24.0)	33 (50.8)[e]	135 (37.4)[e]
Alcohol consumption (ever: former and current)		127 (34.7)	39 (41.4)	61 (33.3)	33 (50.8)[c]	142 (39.3)
Physical inactivity		332 (90.7)	84 (89.4)	173 (94.5)	60 (92.3)	335 (92.7)

Data are presented as number (%) of patients. *P* values were calculated according to univariate multinomial and binary logistic regressions where appropriate (all variables adjusted for age and sex).

a Any combination of carotid disease with PAD, CHD, and AAA

b Waist circumference ≥88 cm in women and ≥102 cm in men

c $P < 0.05$ (vs carotid disease)

d $P \leq 0.1$ (vs carotid disease)

e $P < 0.001$ (vs carotid disease)

f $P < 0.01$ (vs carotid disease)

Abbreviations: AAA, abdominal aortic aneurysm; CHD, coronary heart disease; PAD, peripheral artery disease

TABLE 2 Distribution of metabolic syndrome, blood pressure, and biochemical characteristics in patients with polyvascular disease versus carotid disease alone

Variable	Carotid disease (n = 366)	Carotid disease + PAD (n = 94)	Carotid disease + CHD (n = 183)	Carotid disease + PAD + CHD (n = 65)	All polyvascular diseases[a] (n = 361)
Metabolic syndrome	187 (51.1)	48 (51.1)	121 (66.1)[b]	40 (61.5)[c]	215 (59.6)[b]
SBP ≥140 mm Hg and/or DBP ≥90 mm Hg	234 (63.9)	64 (68.1)	131 (71.6)	45 (69.2)	249 (69.0)
Antihypertensive therapy	310 (84.7)	87 (92.6)[b]	176 (96.2)[e]	63 (96.9)[b]	341 (94.5)[e]
Total cholesterol ≥5.20 mmol/l	180 (49.2)	49 (52.1)	90 (49.2)	30 (46.2)	176 (48.8)
HDL-C ≤1.59 mmol/l	353 (96.4)	89 (94.7)	179 (97.8)	61 (93.8)	348 (96.4)
HDL-C ≤1.00 mmol/l	165 (45.1)	42 (44.7)	92 (50.3)	37 (56.9)	181 (50.1)
LDL-C ≥4.10 mmol/l	89 (24.3)	25 (26.6)	44 (24.0)	21 (32.3)	95 (26.3)
Triglycerides ≥1.70 mmol/l	154 (42.1)	51 (54.3)[c]	95 (51.9)[b]	36 (55.4)[c]	189 (52.4)[d]
Triglycerides ≥2.30 mmol/l	85 (23.2)	25 (26.6)	51 (27.9)	19 (29.2)	99 (27.4)
Use of lipid-lowering drugs	134 (36.6)	41 (43.6)	117 (63.9)[e]	35 (53.8)[d]	198 (54.8)[e]
Self-reported diabetes	116 (31.7)	41 (43.6)[b]	75 (41.0)[b]	25 (38.5)	144 (39.9)[b]
Fasting glucose ≥6.11 mmol/l	82 (22.4)	29 (30.9)	50 (27.5)[c]	19 (29.2)	100 (27.8)
Median SUA >341 µmol/l	168 (45.9)	49 (52.1)	91 (49.7)	38 (58.5)[c]	192 (53.2)[c]
hs-CRP ≥3 mg/l	123 (33.6)	45 (47.9)[b]	69 (37.7)	32 (49.2)[b]	157 (43.5)[d]
Fibrinogen ≥4 g/l	91 (25.1)	26 (28.0)	42 (23.1)	19 (29.2)	1 (25.3)

Data are presented as number (%) of patients. *P* values were calculated according to univariate multinomial and binary logistic regressions where appropriate (all variables adjusted for age and sex).

a Any combination of carotid disease with PAD, CHD, and AAA

b $P < 0.05$ (vs carotid disease)

c $P \leq 0.1$ (vs carotid disease)

d $P < 0.01$ (vs carotid disease)

e $P < 0.001$ (vs carotid disease)

Abbreviations: DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SUA, serum uric acid; others, see TABLE 1

aortic aneurysm. Among patients with polyvascular disease, 285 (79%) had atherosclerotic disease at 2 sites and 76 (21%), at 3 or 4 sites.

All variables that were significantly associated with polyvascular diseases in the univariate multinomial and binary logistic regression analyses ($P \leq 0.1$) were included in the multivariate logistic regression models (TABLE 3). Compared with patients with carotid disease alone, those with all polyvascular diseases taken together more often used antihypertensive drugs ($P = 0.001$) and lipid-lowering drugs ($P < 0.001$), more often had hs-CRP levels of 3 mg/l or higher ($P = 0.005$), and more often were former and current smokers ($P = 0.005$ and $P = 0.001$, respectively). Similar results were shown when we compared patients with carotid disease alone and those with carotid disease and PAD. For the latter group, the risk factors were as follows: use of antihypertensive drugs ($P = 0.009$), elevated hs-CRP levels ($P = 0.005$), former smoking ($P = 0.001$), current smoking ($P < 0.001$), and triglyceride levels of 1.7 mmol/l or higher ($P = 0.04$). Patients with carotid disease, PAD, and CHD more frequently used antihypertensive drugs ($P = 0.02$) and they were more often former and current smokers ($P = 0.03$ and $P < 0.001$, respectively). On the other hand, patients with carotid disease and CHD differed from those with a single carotid disease only in terms of a more frequent use of antihypertensive and lipid-lowering therapy ($P = 0.02$ and $P < 0.001$, respectively).

The distribution of demographic characteristics and risk factors in patients with PAD alone and those with various combinations of PAD and other vascular diseases is presented in TABLES 4 and 5. Of the 486 patients with PAD, 35% also had carotid disease, 23% also had CHD, and 6% also had abdominal aortic aneurysm. Among patients with polyvascular disease, 202 (70%) had atherosclerotic disease at 2 sites and 85 (30%) had atherosclerotic disease at 3 or 4 sites.

TABLE 3 Risk factors for polyvascular disease in comparison with carotid disease: results of multivariate logistic regression analysis

Variable	Carotid + PAD vs carotid disease		Carotid + CHD vs carotid disease		Carotid + PAD + CHD vs carotid disease		Carotid + PAD + CHD + AAA vs carotid disease	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Antihypertensive therapy	3.33 (1.35–8.20)	0.009	2.73 (1.18–6.29)	0.02	6.20 (1.39–27.67)	0.02	2.55 (1.44–4.52)	0.001
Triglycerides ≥1.70 mmol/l	1.73 (1.02–2.91)	0.04	–	–	–	–	–	–
Use of lipid-lowering drugs	–	–	2.66 (1.80–3.93)	<0.001	–	–	1.95 (1.41–2.70)	<0.001
hs-CRP ≥3 mg/l	2.13 (1.26–3.59)	0.005	–	–	–	–	1.59 (1.15–2.20)	0.005
Former smoking	4.40 (1.90–10.18)	0.001	–	–	2.73 (1.13–6.58)	0.03	1.76 (1.18–2.61)	0.005
Current smoking	7.32 (3.19–16.82)	<0.001	–	–	4.96 (2.06–11.95)	<0.001	2.37 (1.57–3.57)	0.001

Abbreviations: CI, confidence interval; OR, odds ratio; others, see TABLES 1 and 2

TABLE 4 Comparison of demographic, anthropometric, and lifestyle characteristics between patients with polyvascular disease and peripheral artery disease alone

Variable		Only PAD (n = 199)	PAD + carotid disease (n = 94)	PAD + CHD (n = 99)	PAD + carotid disease + CHD (n = 65)	All polyvascular diseases[a] (n = 287)
Age, years	<55	41 (20.6)	18 (19.1)	18 (18.2)	11 (16.9)	51 (17.8)
	55–64	86 (43.2)	31 (33.0)	38 (38.4)	23 (35.4)	100 (34.8)
	≥65	72 (36.2)	445 (47.9)	43 (43.4)	31 (47.7)	136 (47.4)
Male sex		160 (80.4)	67 (71.3)[c]	79 (79.8)	46 (70.8)	218 (76.0)
<12 years of education		49 (24.6)	24 (25.5)	31 (31.3)	23 (35.4)	80 (27.9)
Body mass index, kg/m^2	<25	83 (41.7)	40 (42.6)	36 (36.4)	22 (33.8)	111 (38.7)
	25–29.9	84 (42.2)	42 (44.7)	51 (51.5)	31 (47.7)	137 (47.7)
	≥30	32 (16.1)	12 (12.8)	12 (12.1)	12 (18.5)	39 (13.6)
Abdominal obesity[b]		88 (44.2)	34 (36.2)	36 (36.4)	30 (46.2)	112 (39.0)
Former smoking		52 (26.1)	36 (38.3)	40 (40.4)	24 (36.9)	111 (38.7)[d]
Current smoking		125 (62.8)	50 (53.2)	49 (49.5)	33 (50.8)	148 (51.6)
Alcohol consumption (ever: former and current)		101 (50.7)	39 (41.4)	56 (56.6)	33 (50.8)	140 (48.8)
Physical inactivity		175 (87.9)	84 (89.4)	93 (93.9)	60 (92.3)	262 (91.3)

Data are presented as number (%) of patients. *P* values were calculated according to univariate multinomial and binary logistic regressions where appropriate (all variables adjusted for age and sex).

a Any combination of PAD with carotid disease, CHD, and AAA

b Waist circumference ≥88 cm in women and ≥102 cm in men

c $P \leq 0.1$ (vs PAD)

d $P < 0.05$ (vs PAD)

Abbreviations: see TABLE 1

The risk factors for polyvascular disease in comparison with PAD alone, as revealed by the multivariate regression analysis, are presented in TABLE 6. Lipid-lowering therapy (*P* from 0.001 to <0.001) and antihypertensive therapy (*P* from <0.001 to 0.03) were independently associated with each polyvascular disease group (PAD and carotid disease; PAD and CHD; PAD, carotid disease, and CHD; and all polyvascular diseases taken together). The risk factors associated with all polyvascular diseases taken together included also female sex ($P = 0.04$) and former smoking ($P = 0.03$).

In comparison with patients who had carotid disease alone, those with PAD alone were more often male ($P = 0.02$), had lower educational status ($P = 0.02$), more often were former and current smokers ($P = 0.03$ and $P < 0.001$, respectively),

TABLE 5 Distribution of metabolic syndrome, blood pressure, and biochemical characteristics in patients with polyvascular disease versus peripheral artery disease alone

Variable	Only PAD (n = 199)	PAD + carotid disease (n = 94)	PAD + CHD (n = 99)	PAD + carotid disease + CHD (n = 65)	All polyvascular diseases[a] (n = 287)
Metabolic syndrome	124 (62.3)	48 (51.1)[b]	60 (60.6)	40 (61.5)	163 (56.8)
SBP ≥140 mm Hg and/or DBP ≥90 mm Hg	130 (65.3)	64 (68.1)	63 (63.6)	45 (69.2)	185 (64.5)
Antihypertensive therapy	155 (77.9)	87 (92.6)[c]	92 (92.9)[d]	63 (96.9)[d]	269 (93.7)[e]
Total cholesterol ≥5.20 mmol/l	105 (52.8)	49 (52.1)	47 (47.5)	30 (46.2)	142 (49.5)
HDL-C ≤1.59 mmol/l	192 (96.5)	89 (94.7)	98 (99.0)	61 (93.8)	276 (96.2)
HDL-C ≤1.00 mmol/l	117 (58.8)	42 (44.7)[b]	66 (66.7)	37 (56.9)	162 (56.4)
LDL-C ≥4.10 mmol/l	48 (24.1)	25 (26.6)	19 (19.2)	21 (32.3)	73 (25.4)
Triglycerides ≥1.70 mmol/l	110 (55.3)	51 (54.3)	52 (52.5)	36 (55.4)	155 (54.0)
Triglycerides ≥2.30 mmol/l	62 (31.2)	25 (26.6)	25 (25.3)	19 (29.2)	81 (28.2)
Use of lipid-lowering drugs	45 (22.6)	41 (43.6)[e]	52 (52.5)[e]	35 (53.8)[e]	137 (47.7)[e]
Self-reported diabetes	74 (37.2)	41 (43.6)	45 (45.5)	25 (38.5)	119 (41.5)
Fasting glucose ≥6.11 mmol/l	60 (30.2)	29 (30.9)	34 (34.3)	19 (29.2)	85 (29.6)
Median SUA >341 µmol/l	94 (47.2)	49 (52.1)	53 (53.5)	38 (58.5)[b]	159 (55.4)[b]
hs-CRP ≥3 mg/l	104 (52.3)	45 (47.9)	50 (50.5)	32 (49.2)	140 (48.8)
Fibrinogen ≥4 g/l	70 (35.5)	26 (28.0)	27 (28.4)	19 (29.2)	76 (27.0)[c]

Data are presented as number (%) of patients. *P* values were calculated according to univariate multinomial and binary logistic regressions where appropriate (all variables adjusted for age and sex).

a Any combination of carotid disease with PAD, CHD, and AAA

b $P \leq 0.1$ (vs PAD)

c $P < 0.05$ (vs PAD)

d $P < 0.01$ (vs PAD)

e $P < 0.001$ (vs PAD)

Abbreviations: see TABLES 1 and 2

TABLE 6 Risk factors for polyvascular disease in comparison with peripheral artery disease: results of multivariate logistic regression analysis

Variable	PAD + carotid disease vs PAD		PAD + CHD vs PAD		PAD + carotid disease + CHD vs PAD		PAD + carotid disease + CHD + AAA vs PAD	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Female sex	–	–	–	–	–	–	1.69 (1.02–2.78)	0.04
Use of lipid-lowering drugs	2.58 (1.47–4.52)	0.001	3.47 (2.04–5.9)	<0.001	3.33 (1.80–6.17)	<0.001	2.66 (1.72–4.11)	<0.001
Antihypertensive therapy	2.87 (1.18–6.97)	0.02	2.65 (1.11–6.31)	0.03	6.66 (1.51–29.27)	0.01	3.24 (1.73–6.09)	<0.001
Former smoking	–	–	–	–	–	–	2.27 (1.10–4.69)	0.03

Abbreviations: see TABLES 1, 2, and 3

as well as more often had metabolic syndrome ($P = 0.02$) and hs-CRP levels of 3 mg/l or higher ($P = 0.004$). On the other hand, patients with carotid disease alone were more often overweight ($P = 0.02$) or obese ($P = 0.01$) and more often used lipid-lowering drugs ($P = 0.01$).

DISCUSSION In the present study, 46% of patients who were referred to our center with carotid disease or PAD had clinical polyvascular disease. In comparison with patients who had symptomatic atherosclerotic disease in only 1 vascular territory, patients with polyvascular disease

significantly more often had hypertension, dyslipidemia, hs-CRP levels of 3 mg/l or higher, and significantly more often were smokers.

The prevalence of polyvascular disease varies between studies depending on the population studied, diagnostic methods used, as well as the frequency of atherosclerotic risk factors (including primary and secondary prevention) in various populations. In a study assessing the prevalence of polyvascular disease in patients with PAD, Vidakovic et al[5] reported that 1 vascular territory was affected in 29% of the patients, while 71% of the patients had polyvascular disease. The high prevalence of polyvascular disease in their study could be explained by the fact that atherosclerosis was assessed by ultrasonography, which might have revealed a number of asymptomatic cases. In the AGATA study (A Global Atherothrombosis Assessment) conducted in 24 countries, patients with atherosclerosis in 1 arterial territory had a 35% higher risk of the disease in 1 or more other arterial territories.[3] A lower prevalence of polyvascular disease in this study could be due to the fact that it included not only patients with prior evidence of atherosclerotic disease or current cardiovascular symptoms but also those at risk of vascular disease (age >55 years and presence of 2 or more risk factors). In a European study by Suárez et al,[6] which enrolled patients aged 45 years or older with documented CAD, cerebrovascular disease, or PAD or at least 3 predefined atherosclerotic risk factors, a single vascular disease was reported in 77% of the patients, and polyvascular disease, in 23%.

A similar frequency of polyvascular disease, ranging from 21.2% to 27.9%, has also been reported in more recent studies.[14-17] Colette et al[18] revealed the asymptomatic multisite artery disease in 21.7% of high-risk coronary patients. In 3 large clinical studies, the Global Registry of Acute Coronary Events,[19] MASCARA (Managing Acute Coronary Syndrome: current registry),[20] and the Alliance project,[21] the prevalence of polyvascular disease was 16%, 17%, and 13%, respectively. In the Gulf-Race-2 study (2nd Gulf Registry of Acute Coronary Events),[4] the prevalence was 6%, but it was assessed only in patients with acute coronary syndrome. According to the recent joint guidelines of the European Society of Cardiology and European Society for Vascular Surgery, endorsed by the European Stroke Organization,[22] multisite artery disease (polyvascular disease) is common in patients with atherosclerotic involvement in 1 vascular bed, and it ranges from 10% to 15% in patients with coronary artery disease to 60% to 70% in those with severe carotid stenosis or PAD. Despite these differences in the prevalence of polyvascular disease, it is generally accepted that atherosclerosis in any vascular territory increases the risk of any cardiovascular event.[22-24]

The relatively high prevalence of polyvascular disease in our study could be probably explained by the fact that polyvascular disease was assessed only in patients with carotid disease and PAD, in whom this frequency is higher compared with CHD patients.[22] In addition, the Department of Vascular Surgery at Dedinje Cardiovascular Institute specializes in all the diseases reported in this paper (but not as the only hospital to which such patients could be referred), and, consequently, more serious cases had been hospitalized in this institution.

In the present study, patients with polyvascular disease more often had PAD than carotid disease, which is in line with previous findings.[25] Moreover, compared with carotid disease, PAD was associated with a higher number of other atherosclerotic diseases.

Patients with polyvascular disease were found to have worse risk profiles than those with single atherosclerotic disease. In the study by Vidakovic et al,[5] polyvascular disease was strongly associated with older age, male sex, BMI of 25 kg/m^2 or higher, and elevated hs-CRP levels. Suárez et al[6] found that patients with polyvascular disease were older, more often were former or current smokers, and more often had hypertension, diabetes, and diabetic nephropathy. In the present study, the risk profile of patients with polyvascular disease depended on the type of vascular diseases involved and the type of single vascular disease to which they were compared (CAD or PAD). Our results point to the differences in risk factors between atherosclerotic disease of various sites. We had no data on risk factors in patients who had only CHD, but it seems that the risk factors were similar for patients with carotid disease and CHD and that they differed from those for PAD.

In a review article, Jashari et al[26] concluded that there is evidence for a clear relationship between coronary and carotid artery disease and that these entities have the same risk factors. However, due to conflicting data reported in available studies, further research is needed to elucidate the similarities and differences between these 2 diseases. While in our study hypertension and dyslipidemia were more frequent in any type of polyvascular disease (irrespective of whether we made comparisons with carotid alone or PAD alone), patients with PAD were more often former or current smokers and they more often had higher hs-CRP levels compared with patients with carotid disease either as a single disease or polyvascular disease. Compared with carotid disease, patients with PAD were also more often male and more often had metabolic syndrome, while patients with carotid disease more often had increased BMI and dyslipidemia.

It was previously reported that smoking selectively increased the raised abdominal aortic

lesions without affecting the coronary artery atherosclerotic burden.[27] This could explain our finding that, in comparison with patients with PAD, former smoking was significantly more common only in patients with polyvascular disease involving abdominal aorta aneurysm. In a Korean study,[28] the risk factors for PAD and CAD were the same. Hoshino et al[29] found that the majority of risk factors (sex, hypertension, dyslipidemia, and alcohol consumption) did not differ between stroke patients with and without asymptomatic PAD, but patients with stroke and asymptomatic PAD had a higher prevalence of diabetes mellitus. Liang et al[30] reported slightly different cardiovascular risk factor profiles for PAD and carotid artery stenosis (CAS). Hypertension and an increased ratio of low-density to high-density lipoprotein cholesterol were associated both with PAD and CAS, but diabetes was independently associated only with PAD and smoking was associated only with CAS. According to Criqui and Aboyans,[24] the major risk factors for PAD are similar to those for CAS and coronary artery disease, although there are some differences in their relative importance.

Other studies also suggested that the classic cardiovascular risk factors have a different impact in diverse arterial systems.[31,32] These differences in the risk profile of various atherosclerotic diseases could be explained by the regional discrepancies in the specific responses of vascular cells to the risk factors and modulators of atherosclerosis. It was postulated that there was a disparity in hemodynamic features, namely, in the extent of oscillation, turbulence, or level of shear in flow fields at the various high-susceptibility sites which "may prime the local vascular wall and its gene-expression profile to differentially interact with systemic risk factors, thereby resulting in the potential for variations in atherosclerotic outcomes at these local sites."[33] The artery-specific effect of atherosclerotic risk factors could explain why they were more common in patients with polyvascular disease and why the frequency of these factors depended on which arteries were involved in polyvascular disease and which single atherosclerotic disease was used for comparison.

Our study has several limitations. First, it was a cross-sectional study, which makes it difficult to assess causal relationships. Second, we included only patients with symptomatic atherosclerotic disease. Third, data on polyvascular disease were based on personal medical histories. Finally, we did not include patients with CHD alone.

In summary, the prevalence of symptomatic polyvascular disease in patients referred to our institution with carotid disease and PAD was high. Patients with polyvascular disease more often had some cardiovascular risk factors as compared with patients who had a disease in a single vascular territory. Hypertension and dyslipidemia were found to be risk factors for any type of polyvascular disease, while smoking and increased hs-CRP levels were risk factors for PAD as a single vascular or polyvascular disease. The high prevalence of polyvascular disease and its worse risk profile in comparison with patients with a single vascular disease indicate the need for improvement of primary and secondary prevention.

ARTICLE INFORMATION

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