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Posterior versus Anterior Circulation Stroke in Young Adults: A Comparative Study of Stroke Aetiologies and Risk Factors in Stroke among Young Fabry Patients (sifap1)

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Key Words
Posterior circulation · Ischaemic stroke · Young · Arterial dissection · Patent foramen ovale

Abstract
Background: Although 20–30% of all strokes occur in the posterior circulation, few studies have explored the characteristics of patients with strokes in the posterior compared to the anterior circulation so far. Especially data on young patients is missing. ***Methods:*** In this secondary analysis of data of the prospective multi-centre European sifap1 study that investigated stroke and transient ischemic attack (TIA) patients aged 18–55 years, we compared vascular risk factors, stroke aetiology, presence of white matter hyperintensities (WMH) and cerebral microbleeds (CMB) between patients with ischaemic posterior circulation stroke (PCS) and those having suffered from anterior circulation stroke (ACS) based on cerebral MRI. ***Results:*** We diagnosed PCS in 612 patients (29.1%, 407 men, 205 women) and ACS in 1,489 patients (70.9%). Their age (median 46 vs. 47 years, $p = 0.205$) and stroke severity (modified Rankin Scale: both 2, $p = 0.375$, Barthel Index 90 vs. 85, $p = 0.412$) were similar. PCS was found to be more frequent among the male gender (66.5 vs. 60.1% with ACS, $p = 0.003$). Vertebral artery (VA) dissection

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was more often the cause of PCS (16.8%) than was carotid artery dissection of ACS (7.9%, $p < 0.001$). Likewise, small vessel disease (Trial of Org 10172 in Acute Stroke Treatment [TOAST] = 3, PCS: 14.7%, ACS: 11.8%) and stroke of other determined aetiology (TOAST = 4, PCS: 24.5%, ACS: 16.0%) were more frequent in those with PCS. Furthermore, patent foramen ovale (PFO; PCS: 31.1%, ACS: 25.4%, $p = 0.029$) was more often detected in patients with PCS. In contrast, large-artery atherosclerosis (TOAST = 1, PCS: 15.4%, ACS: 22.2%) and cardio-embolic stroke (TOAST = 2, PCS: 15.6%, ACS: 18.0%) were less frequent in those with PCS ($p < 0.001$) as were preceding cerebrovascular events (10.1 vs. 14.1%, $p = 0.014$), TIA (4.8 vs. 7.7%, $p = 0.016$) and smoking (53.2 vs. 61.0%, $p = 0.001$). The presence, extent, and location of WMH and CMB did not differ between the 2 groups. ***Conclusions:*** Our data suggested a different pattern of aetiology and risk factors in young patients with PCS compared to those with ACS. These findings especially call for a higher awareness of VA dissection and potentially for more weight of a PFO as a risk factor in young patients with PCS. Clinical trial registration-URL: http://www.clinicaltrials.gov; NCT00414583.

Introduction

In Caucasian populations, up to 30% of all strokes occur in the posterior circulation [1–6]. Several population- and hospital-based registries in Caucasian and Asian populations consistently showed that compared to anterior circulation strokes (ACS), patients with posterior circulation stroke (PCS) were younger and more commonly male. These patients more frequently had small penetrating artery disease, smoked tobacco and had diabetes mellitus, while they less frequently had cardio-embolic stroke aetiologies, atrial fibrillation, valvular heart disease and hypertension [1, 3, 6–13]. Large artery disease was more frequent in patients with PCS according to some studies [12–14] and less frequent in patients with PCS according to some others [3, 11]. All of these registries included predominantly older patients (between 61 and 72 years) [1–12, 15].

From the few larger hospital-based registries, which included only young (<50 years) stroke patients, only 2 compared ACS and PCS patients and reported a higher proportion of PCS (36.2 and 42.3%) [16, 17] than expected from earlier studies with older patients. Young PCS patients more frequently had a cryptogenic aetiology, and less frequently had large artery disease, small vessel disease, cardio-embolism, and also cervical artery dissections than young ACS patients [16]. However, little is known regarding differences in risk factors and other clinical characteristics between young PCS and ACS patients. We therefore sought to compare the clinical characteristics and risk factor profiles of younger (18–55 years) ischaemic stroke (IS) patients with PCS and ACS in a large European population with a recently diagnosed cerebrovascular event (CVE).

Methods

Sifap1 is a prospective multi-centre European study, which primarily aimed to establish the prevalence of Fabry's disease in 5,023 young patients with CVE. The study was performed according to the Helsinki Declaration and approved by the Ethics Committees at the leading study centre (Rostock) and at each study site [18]. All patients or their legal representatives gave written informed consent. Patients were recruited between April 2007 and January 2010 at 47 centres in 15 European countries. Inclusion criteria were CVE <3 months prior, age of 18–55 years and a cerebral MRI ≤1 month of inclusion at least at a 1.5 Tesla unit. Diagnostic procedures were in accordance with the European Stroke Organisation Guidelines [19].

In this secondary analysis, we explored patients with IS in the posterior circulation as opposed to patients with ACS. We analysed vascular risk factors, stroke location and aetiology according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, and presence of white matter hyperintensities (WMH) and cerebral microbleeds (CMB). We defined PCS as neurologic symptoms >24 h with MRI evidence of acute or subacute IS in one of the following territories of the brainstem, the cerebellum, or the cerebrum: territories of (1) the vertebral arteries (VA), (2) the basilar artery and (3) the posterior cerebral artery (PCA) including all their arterial branches. Patients with ACS had respective lesions in the territories of the carotid arteries and in the anterior and middle cerebral arteries. To obtain the best possible homogenous group, patients with transient ischemic attack (TIA) and stroke patients with combined PCS and ACS were excluded. MRI criteria for IS, WMH and CMB have been described earlier [20]. National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), and Barthel Index (BI) were determined. All patients underwent extensive investigations to explore the aetiology of stroke including vascular imaging of the brain-supplying arteries by ultrasound, CT-angiography, and/or MR-angiography, ultrasound examination of the heart, screening for hypercoagulability, vasculitis and vascular risk factors (laboratory parameters and medical history). Risk factors were classified according to their strength of evidence and potential for modification as described in the current guidelines of the American Stroke Association [21] and as established in an earlier publication of the sifap1 investigators [22]. We studied the accumulation (0, 1, 2, 3, and 4 or more) of the following eight vascular risk factors: (1) cardiovascular disease (i.e., coronary artery and peripheral artery disease, myocardial infarction, congestive heart failure and valvular disease), (2) atrial fibrillation, (3) arterial hypertension, (4) diabetes mellitus, (5) dyslipidaemia, (6) current (including those who quit within the previous 5 years) tobacco smoking, (7) obesity (body mass index ≥30 kg/m^2), or (8)

physical inactivity in 4 age groups (18–24, 25–34, 35–44, and 45–55 years) of all patients with ACS and PCS, and men and women with PCS.

Statistical Analyses

Patients were categorised according to the location of the IS (PCS and ACS) and based on their gender (male or female). We report percentages or median and interquartile ranges (IQR) where appropriate. For testing differences between patients with PCS and ACS, we used binary logistic regression with random effects (random intercept models) to account for centre heterogeneity and adjusted for age. Insufficiently normally distributed data was log-transformed before analysis (Table 1). We further tested differences in the prevalence of stenoses or occlusions and of dissections of the extracranial brain supplying arteries and differences in stroke aetiologies according to TOAST classification between PCS and ACS patients with logistic regression with random effects (without adjustment for age; Table 2). MRI characteristics were tested in the context of gender and age differences, using logistic regression with random effects and adjustment for age and gender (Table 3). The number of risk factors was tested between PCS and ACS patients or between patient subgroups, using ordinal regression models with random effects (adjustment as indicated in results section). A 2-sided significance level of $\alpha = 0.05$ was considered. No adjustment for multiple testing was applied for this secondary data analysis. Statistical analyses used SPSS 22.0 and STATA 13 IC.

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The sponsors of the study had no role in the following processes: study design, data collection, analysis, interpretation, writing of the manuscript, or in decision-making to submit the manuscript for publication.

Results

Among 2,101 IS patients with brain infarcts with distinct allocation to either the anterior or the posterior circulation territory on MRI, we diagnosed PCS in 612 patients (29.1%; 407 men, 205 women, 265 in the 18–44 years range, 347 in the 45–55 years range) and ACS in 1,489 patients (70.9%; Table 1; Fig. 1). Both patient groups were of similar age (median 46 vs. 47 years, $p = 0.205$). In the group of patients with PCS, there were more men (66.5 vs. 60.1% with ACS, $p = 0.003$). While the impairment in activities of daily living as evaluated by mRS (both: 2) and BI (ACS: 90, PCS: 85) was similar in patients with ACS and patients with PCS, the NIHSS score was significantly higher in patients with ACS (median 4, IQR 2–4) than in those with PCS (median 3, IQR 1–5, $p < 0.001$; Table 1).

None of these functional scores showed any significant differences in terms of gender or age groups (data not shown). PCS were most often unilateral (527, 86.1%, bilateral: 83, 13.6%). About half of the patients with PCS had cerebellar infarctions (305, 49.8%), followed by infarctions of the brainstem (259, 42.3%), the PCA territory (134, 21.9%), and the thalamus (131, 21.4%). Numbers do not add up to 100% because of infarction in multiple locations.

Stroke aetiology was significantly different in patients with PCS compared to patients with ACS. In 16.8% of patients with PCS, stroke was related to arterial dissection of a VA, while only 7.9% of patients with ACS had a stroke due to dissection of a carotid artery ($p < 0.001$; Table 2). Patients with PCS also more frequently had MRI evidence of small vessel disease (TOAST = 3, PCS: 14.7%, ACS: 11.8%) and a stroke of other determined aetiology (TOAST = 4, PCS: 24.5%, ACS: 16.0%), whereas large-artery atherosclerosis (TOAST = 1, PCS: 15.4%, ACS: 22.2%) and cardio-embolic stroke (TOAST = 2, PCS: 15.6%, ACS: 18.0%) were documented less often in patients with PCS (p value for differences in TOAST between PCS and ACS: <0.001).

Regarding stroke risk factors, patients with PCS more often had a patent foramen ovale (PFO; PCS: 31.1%, ACS: 25.4%, $p = 0.029$; Table 1). The prevalence of PFO was higher in women than in men in both PCS (women: 34.4%, men: 29.4%) and ACS (women: 27.7%, men: 23.9%) patients. The presence of traditional risk factors, distribution of stroke aetiologies (according to TOAST classification), concomitant atrial fibrillation and coincident atrial septal aneurysms did not differ between patients with PFO and PCS compared to those with PFO and ACS (online suppl. Table 1, see www.karger.com/doi/10.1159/000454840).

Furthermore, patients with PCS less often had a history of CVE (not including TIA, 10.1 vs. 14.1%, $p = 0.014$) and of a TIA (4.8 vs. 7.7%, $p = 0.016$) and less often smoked tobacco (53.2 vs. 61.0%, $p = 0.001$) compared to patients with ACS. The remaining vascular risk factors were equally frequent in both groups. Manifestations of atherosclerosis such as myocardial infarction, coronary heart disease and peripheral artery disease were observed in 39% of patients classified as TOAST 1 but did not differ significantly between ACS and PCS (7.6 vs. 5.3%, $p = 0.128$).

The distribution of patients with 0, 1, 2, 3, or 4 or more risk factors between PCS and ACS patients was similar (ordinal regression adjusted for age-strata, $p = 0.245$; Fig. 2a, b). Notwithstanding their stroke location, the higher the age stratum, the more the accumulation of vascular risk factors in patients ($p < 0.001$ for all comparisons; Fig. 2a–d).

Table 1. Clinical scales, arterial pathology, and risk factors of patients with PCS compared to those patients with ACS

	Patients with ACS, total (n = 1,489)	Patients with PCS, total (n = 612)	Patients with PCS vs. patients with ACS, total, p value[a]
Clinical scales			
mRS (n = 2,101)	2 (1–4)	2 (1–4)	0.375
BI (n = 2,101)	90 (50–100)	85 (60–100)	0.412
NIHSS (n = 2,101)	4 (2–8)	3 (1–5)	<0.001
Arterial pathology			
Arterial dissection (of VA for patients with PCS, of ICA for patients with ACS)	117 (7.9)	103 (16.8)	<0.001
Stenosis[b] (of VA or BA for patients with PCS, of ICA for patients with ACS)	73/1,037 (7.1)	20/287 (7.0)	0.746
Stenosis or occlusion[b] (of VA or BA for patients with PCS, of ICA for patients with ACS)	144/861 (16.7)	52/287 (18.1)	0.565
Risk factors (valid n)			
Non-modifiable risk-factors			
Age, years (n = 2,101)	47 (41–51)	46 (40–51)	0.205
Age ≥45 years (n = 2,101)	922 (61.9)	347 (56.7)	0.055
Male gender (n = 2,101)	895 (60.1)	407 (66.5)	0.003
History of any CVE not including TIA (n = 2,101)	210 (14.1)	62 (10.1)	0.014
History of TIA (n = 2,079)	113 (7.7)	29 (4.8)	0.016
Family history of cardiovascular disease (n = 1,979)	545 (38.8)	234 (40.6)	0.398
Family history of cerebrovascular disease (n = 1,994)	538 (38.2)	212 (36.2)	0.448
Well-documented and modifiable risk-factors, %			
Tobacco smoking (current or quit within last 5 years) (n = 2,083)	900 (61.0)	323 (53.2)	0.001
Physical inactivity (n = 2,022)	758 (53.2)	288 (48.3)	0.072
Hypertension (n = 2,091)	732 (49.3)	289 (47.6)	0.990
Dyslipidemia (n = 2,019)	494 (34.4)	201 (34.4)	0.758
High LDL (≥3.37 mmol/L) (n = 1,454)	427 (41.5)	187 (44.0)	0.296
Low HDL (≤1 mmol/L) (n = 1,491)	334 (31.9)	134 (30.1)	0.539
Obesity (BMI ≥30) (n = 2,100)	317 (21.3)	144 (23.6)	0.160
Diabetes (n = 2,089)	149 (10.1)	76 (12.5)	0.054
Cardiovascular disease (n = 2,034)	145 (10.0)	42 (7.1)	0.077
Coronary heart disease (n = 2,071)	68 (4.6)	23 (3.8)	0.575
Congestive heart failure (n = 2,080)	15 (1.0)	5 (0.8)	0.664
Myocardial infarction (n = 2,088)	57 (3.5)	16 (2.6)	0.220
Peripheral artery disease (n = 2,079)	36 (2.4)	7 (1.2)	0.098
Valvular disease (n = 2,064)	30 (2.0)	10 (1.7)	0.610
PFO (n = 1,692)	306 (25.4)	152 (31.1)	0.029
Atrial fibrillation (n = 2,083)	37 (2.5)	16 (2.6)	0.733
Less well-documented or potentially modifiable risk-factors			
High risk alcohol consumption (n = 1,998)	463 (32.7)	176 (30.2)	0.316
Migraine (n = 2,048)	361 (24.9)	145 (24.2)	0.606
Night-time sleep ≤6 h/night (n = 2,099)	262 (17.6)	106 (17.3)	0.989
Obstructive sleep apnea (n = 2,036)	44 (3.1)	20 (3.4)	0.652

Values are n (%) or median (IQR).

ACS, anterior circulation stroke; BA, basilar artery; BMI, body mass index; HDL, high density lipoprotein; IS, ischaemic stroke; IQR, interquartile range; LDL, low-density lipoprotein; NIHSS, National Institute of Health Stroke Scale Score; PCA, posterior cerebral artery; PCS, posterior circulation stroke; PFO, patent foramen ovale; VA, vertebral artery.

[a] Adjusted for age and centre heterogeneity except for p values regarding the arterial pathology, which were adjusted for centre heterogeneity but not for age.

[b] Patients with dissections or vasculitis were excluded.

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Table 2. Overview about stroke aetiology in ACS and PCS

Valid *n*	Patients with PCS (*n* = 612)	Patients with ACS (*n* = 1,489)	*p* value
Stroke due to large-artery atherosclerosis (TOAST = 1) (*n* = 2,028)	91 (15.4)	319 (22.2)	<0.001
Cardioembolic stroke (TOAST = 2) (*n* = 2,028)	92 (15.6)	259 (18.0)	
Stroke due to small vessel occlusion (TOAST = 3) (*n* = 2,028)	87 (14.7)	169 (11.8)	
Stroke of other determined etiology (TOAST = 4) (*n* = 2,028)	145 (24.5)	230 (16.0)	
Stroke of undetermined etiology (TOAST = 5) (*n* = 2,028)	176 (29.8)	460 (32.0)	

Values are *n* (%).

ACS, anterior circulation stroke; PCS, posterior circulation stroke; TOAST classification: classifies stroke aetiology according to Trial of Org. 10172. *p* values are adjusted for centre heterogeneity.

We found WMH in about half of our patients without significant differences between PCS and ACS patients (PCS: 51.9%, ACS: 54.2%, $p < 0.05$). WMH occurred almost double as frequent in middle-aged than in young PCS patients (63.5 vs. 36.5%), while no gender differences were seen (Table 3). In contrast, CMB were seen less frequently (5% in PCS, 6% in ACS).

Discussion

Our study revealed significant differences between young PCS and ACS patients in terms of their risk factors and their underlying stroke aetiology. We found cervical artery dissections more frequently in patients with PCS, while large artery atherosclerosis and cardio-embolic strokes occurred more frequently in those with ACS. Furthermore, PCS patients less often smoked tobacco and less often had a history of CVE or prior TIA but more frequently had a PFO than ACS patients.

The overall prevalence of PCS was almost 30%, which is slightly lower than that observed in studies on young stroke patients [16, 17], but well within the range reported in studies across all ages. Compared with those studies, sifap1 confirms a higher frequency of small penetrating artery disease and a lower frequency of cardio-embolic stroke aetiology, large vessel disease, and tobacco smoking in young PCS patients than in young ACS patients, which has previously been reported in patients of older ages [1, 3, 6–13]. We could also confirm a trend towards a higher prevalence of diabetes mellitus in young PCS patients, which has formerly been reported in older patients [6, 9–12]. Beyond these already described differences, sifap1 further reveals a higher occurrence rate of cervical artery dissections and PFO in young PCS patients than in young ACS patients, which has not been reported before in studies including patients of all ages. These findings indicate that causes that are unrelated to atherosclerosis may play a greater role in PCS than in ACS, where large artery disease and cardio-embolic strokes are seen more frequently. The higher number of small subcortical infarcts and branch territory infarcts (TOAST = 3) is expected because the posterior circulation consists of relatively more brain tissue in brainstem and thalamus supplied by small penetrating arteries than the anterior circulation [8].

Cervical artery dissections represent the most frequent cause of the TOAST category of "other determined aetiology" in young stroke patients with a prevalence ranging from 7 to 15% [16, 17, 23–25]. In our sample, cervical artery dissections were detected in 16.8% of PCS and 7.9% of ACS patients, which is well within the range reported in these studies. However, the higher frequency of dissections in young PCS patients is in strong contrast to an earlier report [16], in which vertebral artery (VA) dissections were only reported in 3.6% of PCS patients. This difference may be explained by a higher detection rate of VA dissections in sifap1 due to an intensified and standardised diagnostic work-up in the sifap1-protocol and a better awareness for VA dissections in this recent investigation compared to older studies [26].

The prevalence of PFO (PCS 31.1%, ACS 25.4%) in our sample was comparable with the recent large multi-centre SISIFO study on older patients [27], but higher than in former large risk factor studies in young patients (8.3–14.3%) [17, 23, 25]. The higher prevalence in our study may be due to a higher rate of performing echocardiography in sifap1 (74.8% of the total cohort [28]). A clear association between PFO and cryptogenic stroke is well established in case–control studies [29, 30] but not in co-

Table 3. MRI data

Valid *n*	Patients with ACS, total (*n* = 1,489)	Patients with PCS					PCS vs. ACS, *p* value[a, b]	Within patients with PCS	
		total (*n* = 612)	men (*n* = 407)	women (*n* = 205)	Age 18–44 years (*n* = 265)	Age 45–55 years (*n* = 347)		sex, *p* value[a]	age, *p* value[b]
White matter hyperintensities prevalent (*n* = 1,995)	768 (54.2)	300 (51.9)	197 (51.0)	103 (53.6)	91 (36.5)	209 (63.5)	0.831	0.501	<0.001
Deep WMH (*n* = 1,999)	697 (49.1)	265 (45.7)	172 (44.4)	93 (48.2)	77 (30.9)	188 (56.8)	0.459	0.353	<0.001
Periventricular WMH (*n* = 1,997)	445 (31.4)	185 (32.0)	131 (33.9)	54 (28.1)	44 (17.7)	141 (42.9)	0.361	0.160	<0.001
WMH in the pons (*n* = 1,997)	80 (5.6)	30 (5.2)	21 (5.4)	9 (4.7)	6 (2.4)	24 (7.3)	0.948	0.725	0.013
Microbleeds prevalent (*n* = 876)	41 (6.4)	12 (5.1)	9 (6.0)	3 (3.6)	4 (4.0)	8 (5.9)	0.415	0.465	0.554
Cortico-subcortical (*n* = 869)	26 (4.1)	6 (2.6)					0.242		
Basal ganglia/thalamus (*n* = 867)	15 (2.4)	5 (2.2)					0.841		
Brainstem/cerebellum (*n* = 868)	14 (2.2)	9 (3.9)					0.175		

Values are *n* (%).
ACS, anterior circulation stroke; PCS, posterior circulation stroke; WMH, white matter hyperintensity.
[a] Adjusted for age.
[b] Adjusted for gender.

hort studies on asymptomatic individuals with PFO [30, 31]. Hence, some individuals with PFO are obviously at high risk for paradoxical embolism or embolism of in situ atrial thrombi, but their effect on the overall stroke risk in the general population is negligible [27, 31]. In their cases, the development of stroke in patients with PFO may be multifactorial with contributions from other factors like PFO size, degree of shunting, atrial septal aneurysm or hypercoagulability [31, 33]. Furthermore, the Risk of Paradoxical Embolism study identified young age, the absence of traditional risk factors and partial anterior or posterior territory embolic type of infarction as predictors for a PFO-attributable stroke [32]. In our study, we found a higher prevalence of PFO in patients with PCS compared to those with ACS, while the presence of traditional risk factors, proportion of cardio-embolic aetiology (category TOAST 2), concomitant atrial fibrillation and coincident atrial septum aneurysms did not differ between young stroke patients with PFO and PCS compared to those with PFO and ACS. Together with the findings from SISIFO [27] and other case–control studies, which reported a higher proportion of PCS in patients with PFO than in those without PFO [34–39], our results may indicate a higher proportion of stroke attributable to PFO in PCS than in ACS.

The impairment in activities of daily living (mRS and BI) did not differ between ACS and PCS patients, while the NIHSS suggested less severe stroke syndromes in PCS patients. However, as the NIHSS includes more symptoms of the anterior than of the posterior circulation, it is a well-established fact that patients with PCS score lower despite similar stroke severity.

There were limitations to our study. The absence of more severely affected patients may have impacted our study in a biased manner with regard to all measures. The presence of atrial septal aneurysm and the size of a right-to-left shunt were not consistently reported throughout the entire sample. Lastly, most sifap1 patients were European Caucasians. Thus, translation of data to other ethnic groups and geographic locations is not valid. Nevertheless, our outcomes are an invaluable step towards the understanding of risk factors and aetiology of PCS in young European stroke populations. Our study provides profound insight into the aetiology and risk factors of PCS as opposed to ACS. Cervical artery dissections and the presence of PFO were frequently seen in young stroke patients and even more frequently in those with PCS. Specifically, the high prevalence of VA dissection in PCS calls for even more accurate exploration of the posterior vasculature in young patients with PCS.

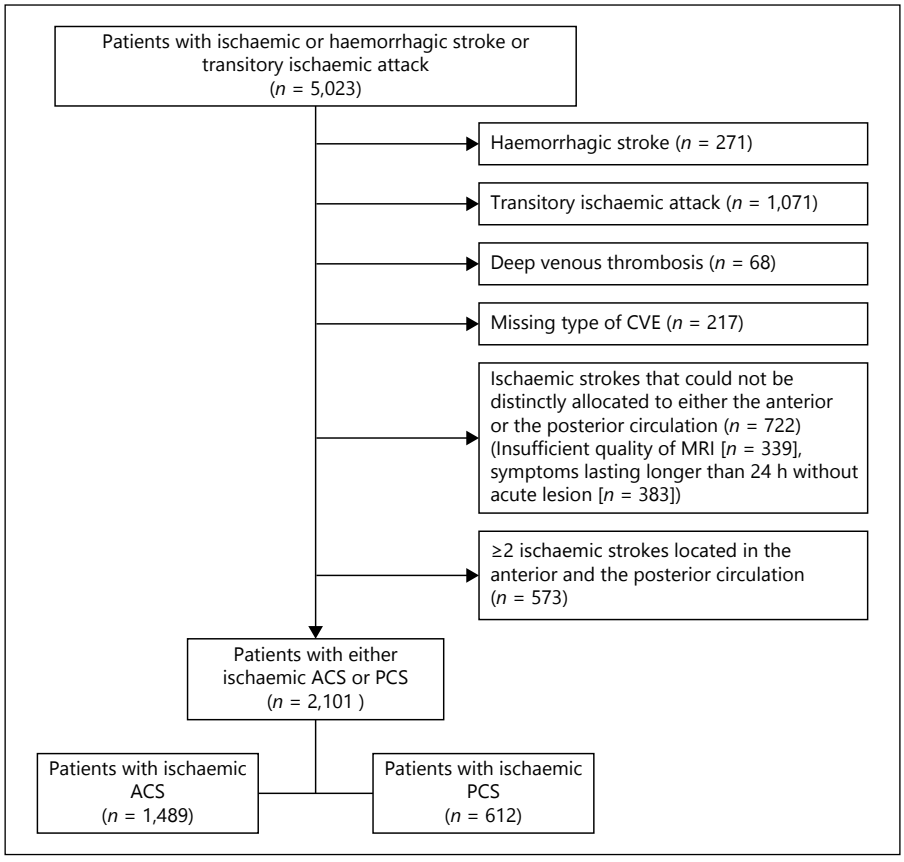

Fig. 1. Selection of patients with ischaemic ACS and PCS from the whole sifap1 cohort.

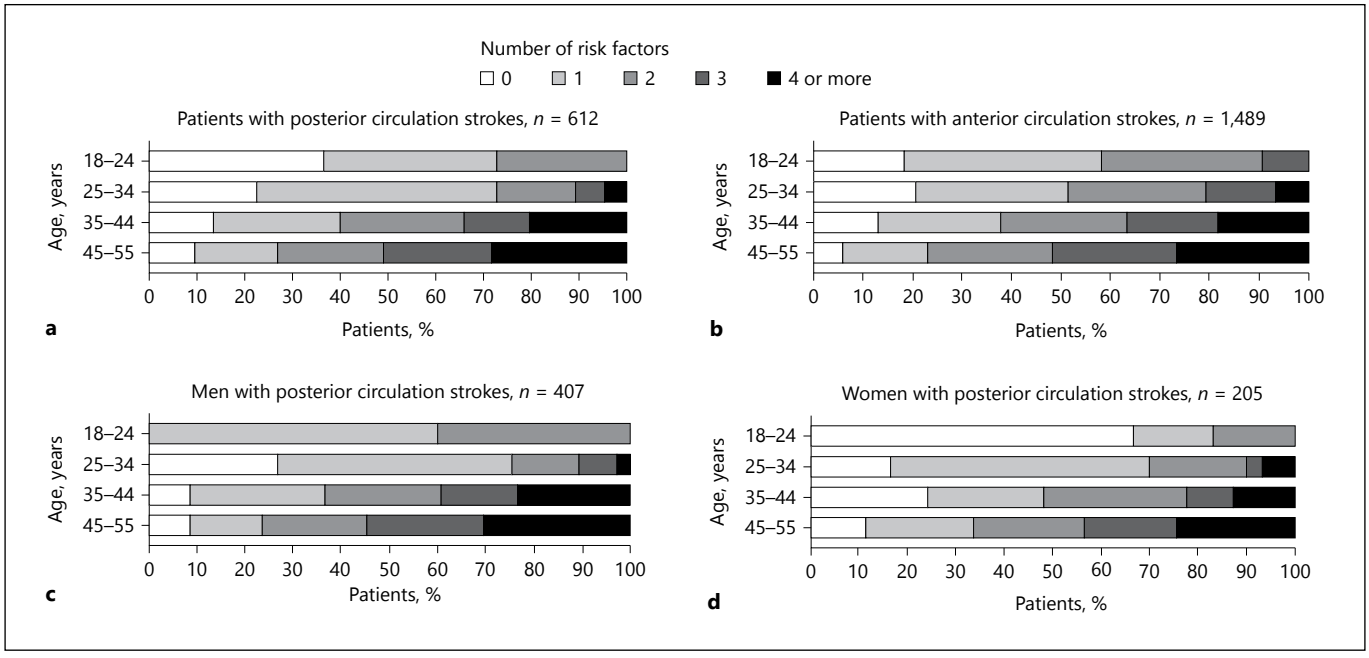

Fig. 2. Proportions of patients with none to 4 or more well-documented modifiable risk factors according to age group in the entire cohort of patients with PCS (**a**), the entire cohort of patients with ACS (**b**), men (**c**), and women (**d**). Accumulation of risk factors was similar in PCS and ACS patients ($p = 0.245$; **a**, **b**). Regarding PCS, women accumulated less risk factors than men ($p = 0.002$; **c**, **d**).

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References

1 Cates MJ, Paton JF, Smeeton NC, Wolfe CD: Hypertension before and after posterior circulation infarction: analysis of data from the South London stroke register. J Stroke Cerebrovasc Dis 2012;21:612–618.

2 De Marchis GM, Kohler A, Renz N, Arnold M, Mono ML, Jung S, Fischer U, Karameshev AI, Brekenfeld C, Gralla J, Schroth G, Mattle HP, Nedeltchev K: Posterior versus anterior circulation strokes: comparison of clinical, radiological and outcome characteristics. J Neurol Neurosurg Psychiatry 2011; 82:33–77.

3 Bogousslavsky J, van Melle G, Regli F: The Lausanne stroke registry: analysis of 1,000 consecutive patients with first stroke. Stroke 1988;19:1083–1092.

4 Olindo S, Khaddam S, Bocquet J, Chausson N, Aveillan M, Cabre P, Smadja D: Association between basilar artery hypoplasia and undetermined or lacunar posterior circulation ischemic stroke. Stroke 2010;41:2371–2374.

5 Moulin T, Tatu L, Vuillier F, Berger E, Chavot D, Rumbach L: Role of a stroke data bank in evaluating cerebral infarction subtypes: patterns and outcome of 1,776 consecutive patients from the Besançon stroke registry. Cerebrovasc Dis 2000;10:261–271.

6 Subramanian G, Silva J, Silver FL, Fang J, Kapral MK, Oczkowski W, Gould L, O'Donnell MJ: Risk factors for posterior compared to anterior ischemic stroke: an observational study of the registry of the Canadian stroke network. Neuroepidemiology 2009;33: 12–16.

7 Di Carlo A, Lamassa M, Baldereschi M, Pracucci G, Consoli D, Wolfe CD, Giroud M, Rudd A, Burger I, Ghetti A, Inzitari D: Risk factors and outcome of subtypes of ischemic stroke. Data from a multicenter multinational hospital-based registry. The European community stroke project. J Neurol Sci 2006;244: 143–150.

8 Caplan LR, Wityk RJ, Glass TA, Tapia J, Pazdera L, Chang HM, Teal P, Dashe JF, Chaves CJ, Breen JC, Vemmos K, Amarenco P, Tettenborn B, Leary M, Estol C, Dewitt LD, Pessin MS: New England medical center posterior circulation registry. Ann Neurol 2004; 56:389–398.

9 Tao WD, Liu M, Fisher M, Wang DR, Li J, Furie KL, Hao ZL, Lin S, Zhang CF, Zeng QT, Wu B: Posterior versus anterior circulation infarction: how different are the neurological deficits? Stroke 2012;43:2060–2065.

10 Zeng Q, Tao W, Lei C, Dong W, Liu M: Etiology and risk factors of posterior circulation infarction compared with anterior circulation infarction. J Stroke Cerebrovasc Dis 2015;24: 1614–1620.

11 Förster A, Gass A, Kern R, Griebe M, Hennerici MG, Szabo K: Thrombolysis in posterior circulation stroke: stroke subtypes and patterns, complications and outcome. Cerebrovasc Dis 2011;32:349–353.

12 Miyamoto N, Tanaka Y, Ueno Y, Tanaka R, Hattori N, Urabe T: Comparison of clinical backgrounds with anterior versus posterior circulation infarcts. J Stroke Cerebrovasc Dis 2010;19:393–397.

13 Caplan L, Chung CS, Wityk R, Glass T, Tapia J, Pazdera L, Chang HM, Dashe J, Chaves C, Vemmos K, Leary M, Dewitt L, Pessin M: New England medical center posterior circulation stroke registry: I. Methods, data base, distribution of brain lesions, stroke mechanisms, and outcomes. J Clin Neurol 2005;1: 14–30.

14 Vemmos KN, Takis CE, Georgilis K, Zakopoulos NA, Lekakis JP, Papamichael CM, Zis VP, Stamatelopoulos S: The Athens stroke registry: results of a five-year hospital-based study. Cerebrovasc Dis 2000;10:133–141.

15 Lee JH, Han SJ, Yun YH, Choi HC, Jung S, Cho SJ, Yu KH, Lee SM, Hwang SH, Song HK, Kwon KH, Lee BC: Posterior circulation ischemic stroke in Korean population. Eur J Neurol 2006;13:742–748.

16 Naess H, Nyland HI, Thomassen L, Aarseth J, Myhr KM: Etiology of and risk factors for cerebral infarction in young adults in western Norway: a population-based case-control study. Eur J Neurol 2004;11:25–30.

17 Putaala J, Metso AJ, Metso TM, Konkola N, Kraemer Y, Haapaniemi E, Kaste M, Tatlisumak T: Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki young stroke registry. Stroke 2009;40:1195–1203.

18 Rolfs A, Martus P, Heuschmann PU, Grittner U, Holzhausen M, Tatlisumak T, Böttcher T, Fazekas F, Enzinger C, Ropele S, Schmidt R, Riess O, Norrving B: Protocol and methodology of the stroke in young fabry patients (sifap1) study: a prospective multicenter European study of 5,024 young stroke patients aged 18–55 years. Cerebrovasc Dis 2011;31:253–262.

19 European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee: Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25:457–507.

20 Fazekas F, Enzinger C, Schmidt R, Dichgans M, Gaertner B, Jungehulsing GJ, Hennerici MG, Heuschmann P, Holzhausen M, Kaps M, Kessler C, Martus P, Putaala J, Ropele S, Tanislav C, Tatlisumak T, Norrving B, Rolfs A: MRI in acute cerebral ischemia of the young: the stroke in young fabry patients (sifap1) study. Neurology 2013;81:1914-1921.

21 Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, Culebras A, DeGraba TJ, Gorelick PB, Guyton JR, Hart RG, Howard G, Kelly-Hayes M, Nixon JV, Sacco RL: Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American academy of neurology affirms the value of this guideline. Circulation 2006;113:e873–e923.

22 von Sarnowski B, Putaala J, Grittner U, Gaertner B, Schminke U, Curtze S, Huber R, Tanislav C, Lichy C, Demarin V, Basic-Kes V, Ringelstein EB, Neumann-Haefelin T, Enzinger C, Fazekas F, Rothwell PM, Dichgans M, Jungehulsing GJ, Heuschmann PU, Kaps M, Norrving B, Rolfs A, Kessler C, Tatlisumak T: Lifestyle risk factors for ischemic stroke and transient ischemic attack in young adults in the stroke in young fabry patients study. Stroke 2013;44:119–125.
23 Rasura M, Spalloni A, Ferrari M, De Castro S, Patella R, Lisi F, Beccia M: A case series of young stroke in Rome. Eur J Neurol 2006;13:146–152.
24 von Sarnowski B, Schminke U, Grittner U, Fazekas F, Tanislav C, Kaps M, Tatlisumak T, Putaala J, Haeusler KG, Borges do Amaral E Silva AD, Kinsella JA, McCabe DJ, Tobin WO, Huber R, Willeit J, Furtner M, Bodechtel U, Rolfs A, Kessler C, Hennerici MG: Cervical artery dissection in young adults in the stroke in young fabry patients (sifap1) study. Cerebrovasc Dis 2015;39:110–121.
25 Spengos K, Vemmos K: Risk factors, etiology, and outcome of first-ever ischemic stroke in young adults aged 15 to 45 – the Athens young stroke registry. Eur J Neurol 2010;17:1358–1364.
26 Lee VH, Brown RD Jr, Mandrekar JN, Mokri B: Incidence and outcome of cervical artery dissection: a population-based study. Neurology 2006;67:1809–1812.
27 Consoli D, Paciaroni M, Galati F, Aguggia M, Melis M, Malferrari G, Consoli A, Vidale S, Bosco D, Cerrato P, Sacco S, Gandolfo C, Bovi P, Serrati C, Del Sette M, Cavallini A, Diomedi M, Postorino P, Reboldi P, Ricci S: Prevalence of patent foramen ovale in ischaemic stroke in Italy: results of SISIFO study. Cerebrovasc Dis 2015;39:162–169.
28 Rolfs A, Fazekas F, Grittner U, Dichgans M, Martus P, Holzhausen M, Bottcher T, Heuschmann PU, Tatlisumak T, Tanislav C, Jungehulsing GJ, Giese AK, Putaala J, Huber R, Bodechtel U, Lichy C, Enzinger C, Schmidt R, Hennerici MG, Kaps M, Kessler C, Lackner K, Paschke E, Meyer W, Mascher H, Riess O, Kolodny E, Norrving B: Acute cerebrovascular disease in the young: the stroke in young fabry patients study. Stroke 2013;44:340–349.
29 Overell JR, Bone I, Lees KR: Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. Neurology 2000;55:1172–1179.
30 Davis D, Gregson J, Willeit P, Stephan B, Al-Shahi Salman R, Brayne C: Patent foramen ovale, ischemic stroke and migraine: systematic review and stratified meta-analysis of association studies. Neuroepidemiology 2013;40:56–67.
31 Di Tullio MR, Jin Z, Russo C, Elkind MS, Rundek T, Yoshita M, DeCarli C, Wright CB, Homma S, Sacco RL: Patent foramen ovale, subclinical cerebrovascular disease, and ischemic stroke in a population-based cohort. J Am Coll Cardiol 2013;62:35–41.
32 Kent DM, Ruthazer R, Weimar C, Mas JL, Serena J, Homma S, Di Angelantonio E, Di Tullio MR, Lutz JS, Elkind MS, Griffith J, Jaigobin C, Mattle HP, Michel P, Mono ML, Nedeltchev K, Papetti F, Thaler DE: An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. Neurology 2013;81:619–625.
33 Sun YP, Homma S: Patent foramen ovale and stroke. Circ J 2016;80:1665–1673.
34 Heckmann JG, et al: Increased frequency of cardioembolism and patent foramen ovale in patients with stroke and a positive travel history suggesting economy class stroke syndrome. Heart 2006;92:1265–1268.
35 Hayashida K, Fukuchi K, Inubushi M, Fukushima K, Imakita S, Kimura K: Embolic distribution through patent foramen ovale demonstrated by (99m)Tc-MAA brain SPECT after Valsalva radionuclide venography. J Nucl Med 2001;42:859–863.
36 Jauss M, Wessels T, Trittmacher S, Allendorfer J, Kaps M: Embolic lesion pattern in stroke patients with patent foramen ovale compared with patients lacking an embolic source. Stroke 2006;37:2159–2161.
37 Kim BJ, Kim NY, Kang DW, Kim JS, Kwon SU: Provoked right-to-left shunt in patent foramen ovale associates with ischemic stroke in posterior circulation. Stroke 2014;45:3707–3710.
38 Nedeltchev K, Wiedmer S, Schwerzmann M, Windecker S, Haefeli T, Meier B, Mattle HP, Arnold M: Sex differences in cryptogenic stroke with patent foramen ovale. Am Heart J 2008;156:461–465.
39 Yasaka M, Otsubo R, Oe H, Minematsu K: Is stroke a paradoxical embolism in patients with patent foramen ovale? Intern Med 2005;44:434–438.