# Cervical Artery Dissection in Young Adults in the Stroke in Young Fabry Patients (sifap1) Study 

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## Key Words

Dissection • Vertebral artery dissection • Carotid arteries • Cerebral infarcts in young adults . Cerebral ischaemia . Acute ischaemic stroke • Risk factors for stroke


#### Abstract

Background: Patients with carotid artery dissection (CAD) have been reported to have different vascular risk factor profiles and clinical outcomes to those with vertebral artery dissection (VAD). However, there are limited data from recent, large international studies comparing risk factors and clini-


cal features in patients with cervical artery dissection (CeAD) with other TIA or ischemic stroke (IS) patients of similar age and sex. Methods: We analysed demographic, clinical and risk factor profiles in TIA and IS patients $\leq 55$ years of age with and without CeAD in the large European, multi-centre, Stroke In young FAbry Patients 1 (sifap1) study. Patients were further categorised according to age (younger: 18-44
C.K. and M.G.H. contributed equally to this work. Clinical Trial Registration URL: http://www.clinicaltrials.gov; NCT00 414583.
years; middle-aged: 45-55 years), sex, and site of dissection. Results: Data on the presence of dissection were available in 4,208 TIA and IS patients of whom 439 (10.4\%) had CeAD: 196 (50.1\%) had CAD, 195 (49.9\%) had VAD, and 48 had multiple artery dissections or no information regarding the dissected artery. The prevalence of CAD was higher in women than in men ( 5.9 vs. $3.8 \%, \mathrm{p}<0.01$ ), whereas the prevalence of VAD was similar in women and men ( 4.6 vs. $4.7 \%$, n.s.). Patients with VAD were younger than patients with CAD (median $=41$ years (IQR $=35-47$ years) versus median $=45$ years (IQR $=39-49$ years); $p<0.01$ ). At stroke onset, about twice as many patients with either CAD ( $54.0 \mathrm{vs} .23 .1 \%, \mathrm{p}<0.001$ ) or VAD ( 63.4 vs. $36.6 \%, \mathrm{p}<0.001$ ) had headache than patients without CeAD and stroke in the anterior or posterior circulation, respectively. Compared to patients without CeAD, hypertension, concomitant cardiovascular diseases and a patent foramen ovale were significantly less prevalent in both CAD and VAD patients, whereas tobacco smoking, physical inactivity, obesity and a family history of cerebrovascular diseases were found less frequently in CAD patients, but not in VAD patients. A history of migraine was observed at a similar frequency in patients with CAD (31\%), VAD (27.8\%) and in those without CeAD (25.8\%). Conclusions: We identified clinical features and risk factor profiles that are specific to young patients with CeAD, and to subgroups with either CAD or VAD compared to patients without CeAD. Therefore, our data support the concept that certain vascular risk factors differentially affect the risk of CAD and VAD.
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## Introduction

The incidence of cervical artery dissection (CeAD) is estimated to be $3-5 / 100,000 /$ year [1, 2] and more often affects carotid than vertebral arteries (1.87-5.0 vs. 0.97$1.5 / 100,000 /$ year) $[1,3,4]$. CeAD is recognised as a very important cause of TIA and ischaemic stroke (IS) in the young and is the underlying pathomechanism in 11-18\% of patients under 55 years of age $[1,5,6]$.

The assumption that TIA and IS patients with CeAD tend to have fewer vascular risk factors than other stroke subtypes is supported by data from recent multicentre registries $[7,8]$. These registries also suggest different risk factor profiles, clinical presentations, and clinical outcomes in patients with carotid artery dissection (CAD) and those with vertebral artery dissection (VAD). Patients with CAD were found to be a few years older, more often male and less commonly smokers, while patients with VAD more often suffered from thunderclap headache, neck pain, and

IS instead of TIA [7-9]. However, data comparing risk factors and clinical features in TIA or IS patients with CeAD overall, and in CAD and VAD subgroups with other aetiological subtypes of similar age and sex are limited.

Therefore, we sought to compare the clinical characteristics and risk factor profiles in young TIA and IS patients with and without CeAD, and among subgroups of patients with CAD and VAD versus those without CeAD in a large population with newly diagnosed cerebrovascular disease in Europe.

## Methods

The Stroke In young Fabry Patients 1 (sifap1) study was a prospective, international multicentre study to establish the prevalence of Fabry's disease in young patients with cerebrovascular events (CVE) in Europe [10]. A total of 5,023 patients were recruited between April 2007 and January 2010 at 47 centres in 15 European countries. Patients were included if they had experienced a CVE within the preceding 3 months, were aged $18-55$ years, and had cerebral magnetic resonance imaging (MRI) within 1 month of inclusion. CVE included TIA (i.e., symptoms $<24 \mathrm{~h}$ without infarction or haemorrhage on MRI or CT) and IS (i.e., symptoms $>24 \mathrm{~h}$ without haemorrhage on MRI or CT at stroke onset). Diagnostic work up was performed in accordance with the European Stroke Organisation Guidelines [11]. The study was performed according to the Helsinki Declaration and approved by the Ethics Committees at the lead study centre (Rostock) and at each study site. All patients or their legal representatives gave written informed consent to participate.

In this sub-study of sifap1, we compared the distinctive features of TIA and IS patients with and without CeAD regarding the differential involvement of cervical arteries, presenting symptoms, and vascular risk factors. For analyses of clinical presentation, we compared CAD patients with anterior circulation stroke patients without CeAD and VAD patients with posterior circulation stroke patients without CeAD. Stroke territory was defined according to MRI.

Presenting symptoms were assessed using dichotomized questionnaires that were completed by experienced neurologists and stroke physicians at each centre. 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 [12] and as described previously by sifap1 investigators [13].

Patients with CeAD were identified from the TOAST subgroup attributed to 'acute CVE of other determined aetiology'. The diagnosis was confirmed by MRI, MR-angiography, ultrasonography or CT-angiography, based on the judgement of the treating neurologists, stroke physicians and neuroradiologists at each study centre. In addition, all MRI images transferred to the database were interpreted by the central imaging committee, which was blinded for the patients' diagnosis. Depending on the applied imaging modality, diagnostic characteristics of CeAD included the presence of intramural haematoma, long tapering stenosis, at times ending in an occlusion, intimal flap, or double lumen of the carotid or vertebral arteries [14].

All patients with other TIA or IS subtypes were classified as having had a TIA or IS without CeAD for the purpose of this substudy of sifapl.

> Statistical Analyses
> Patients with CeAD were categorised into age groups ('younger': $18-44$ years and 'middle-aged': $45-55$ years), according to their sex (male or female), and their dissected artery (ICA or VA). Frequencies, means and medians in different characteristics were compared between sexes, young and middle-aged patients with CAD or VAD versus those without CeAD. Logistic regression models with random intercepts were performed to account for centre heterogeneity. A two-sided p value <0.05 was considered statistically significant; no adjustment for multiple testing was applied in this observational study. Thus, significances may not be interpreted as strictly confirmatory. Statistical analyses were performed with SPSS 22.0 and SAS 9.3.

## Results

Among 5,023 patients enrolled in sifap1, 4,464 had TIA or IS. We had to exclude 256 patients from our analysis due to missing data regarding the presence or absence of CeAD. Subsequently, we analysed data of 4,208 patients ( 2,500 men, 1,708 women, 1,692 young, 2,516 mid-dle-aged) and identified 439 (10.4\%) patients with TIA $(\mathrm{n}=118)$ and IS $(\mathrm{n}=321)$ with CeAD and 3,769 patients without CeAD. Diagnosis of dissection was made by MRI/MR-angiography ( $\mathrm{n}=279,63.6 \%$ ), ultrasonography ( $\mathrm{n}=255,58.1 \%$ ), and CT-angiography ( $\mathrm{n}=15,3.4 \%$ ), (some patients had multiple imaging modalities used to confirm diagnosis). There was a nonsignificant trend for women ( $204,11.9 \%$ ) to be more frequently affected by dissection than men (235, 9.4\%, p $=0.058$ age-adjusted). The prevalence of CeAD was almost twice as high in young ( 246 of $1,692,14.5 \%$ ) than in middle-aged patients ( 193 of $2,516,7.7 \%, \mathrm{p}<0.0001$ ). Overall, the median score on the modified Rankin Scale (mRS), the Barthel Index (BI) and National Institute of Health Stroke Scale (NIHSS) scores obtained during the acute phase of stroke indicated quite a low degree of impairment in the entire sifap 1 cohort (tables 1,2 ). In patients with CAD, neurological deficits were slightly more impairing than in patients without CeAD according to mRS (median $=2$, interquartile range (IQR) $1-4$ vs. $2, \mathrm{IQR} 1-3, \mathrm{p}<0.001$ ) and BI (median $=90$, IQR $26-100$ vs. 100, IQR $70-100, \mathrm{p}<$ 0.001 ), while there was no relevant difference in patients with VAD.

There were 16 (3.6\%) patients with multiple artery dissections and 32 (7.3\%) with missing information on the affected cervical artery. Among the remaining 391 pa-
tients with CeAD in whom precise data were available and in whom either the carotid or the vertebral artery was involved, the proportion of CAD $(\mathrm{n}=196,50.1 \%)$ and VAD ( $\mathrm{n}=195,49.9 \%$ ) was similar.

CAD was more prevalent in women than in men (5.9 vs. $3.8 \%, \mathrm{p}<0.01$ ), whereas VAD was comparable prevalent in women and men ( 4.6 vs. $4.7 \%$, n.s.). VAD patients were younger than CAD patients (median $=41$ years ( $\mathrm{IQR}=35-47$ years) versus median $=45$ years $(\mathrm{IQR}=$ 39-49 years); p < 0.01). Furthermore, TIA and IS caused by VAD less frequently had a history of prior TIA than those caused by CAD ( 3.7 vs. $10.0 \%$, $\mathrm{p}<0.05$, data not shown) or those caused by a non-CeAD aetiology ( 3.7 vs. $9.5 \%, \mathrm{p}<0.05$ ). A direct comparison of well-documented modifiable and non-modifiable risk factors between CAD and VAD patients revealed only a significantly higher prevalence of LDL-cholesterol levels $\geq 3.37 \mathrm{mmol} / \mathrm{l}$ in VAD patients ( 39 vs. $20 \%, \mathrm{p}<0.01$, data not shown). Differences in the prevalence of well-documented modifiable and non-modifiable risk factors between patients without CeAD and those with CAD and VAD, respectively, are shown in figure 1 a and b . Compared to patients without CeAD, hypertension, concomitant cardiovascular diseases and a patent foramen ovale were observed less frequently in both CAD and VAD patients, whereas tobacco smoking, physical inactivity, obesity and a family history of cerebrovascular diseases were significantly less prevalent in patients with CAD, but not in patients with VAD (tables 1, 2; fig. 1a, b). A history of migraine was similar in patients with CAD (31\%), VAD (27.8\%) and in those without CeAD (25.8\%). High-risk alcohol consumption as defined as consuming $>5$ alcoholic drinks/ day at least once/month within the previous year was an important risk factor in young male stroke patients without CeAD (42.7\%), but was less frequently seen in male CAD (33\%) and VAD patients (32.1\%; p value for interaction between sex and high-risk alcohol consumption was $<0.05$ in VAD, but not significant in CAD; tables 1, 2).

For comparison of the presenting symptoms at stroke onset between patients with CAD or VAD and nonCeAD patients, we restricted our analysis to those nonCeAD stroke patients with an MRI-proven infarction of either the anterior ( $\mathrm{n}=1,493$ ) or the posterior circulation ( $\mathrm{n}=547$ ). Headache was about twice as common in patients with CAD (54.0 vs. $23.1 \%, \mathrm{p}<0.001$ ) and VAD ( 63.4 vs. $36.6 \%, \mathrm{p}<0.001$ ) compared to patients without CeAD and stroke in the anterior and posterior circulation, respectively (tables 3, 4). Furthermore, loss of consciousness, nausea/vomiting, and visual field symptoms were more frequent in patients with CAD than in patients
Table 1. Risk factors of TIA and IS patients with carotid artery dissection compared to those patients without cervical artery dissection

|  | Patients without CeAD, total ( $\mathrm{n}=3,769$ ) | Patients <br> with CAD, <br> total $(\mathrm{n}=192)$ | Patients without CeAD vs. patients with CAD total, $\mathrm{p}^{\mathrm{a}}$ | Patients without CeAD vs. patients with CAD |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  | men without <br> CeAD $(\mathrm{n}=2,265)$ | men with <br> CAD $(\mathrm{n}=94)$ | women <br> without <br> CeAD $(\mathrm{n}=1,504)$ | women <br> with <br> CAD <br> ( $\mathrm{n}=98$ ) | age 18-44 <br> years without <br> CeAD <br> ( $\mathrm{n}=1,446$ ) | age 18-44 <br> years with <br> CAD <br> ( $\mathrm{n}=93$ ) | age 45-55 <br> years without <br> CeAD $(\mathrm{n}=2,323)$ | age 45-55 <br> years with <br> CAD <br> ( $\mathrm{n}=99$ ) |
| Clinical scales |  |  |  |  |  |  |  |  |  |  |  |
| Modified Rankin scale | 2 [1-3] | 2 [1-4] | <0.001 | 2 [1-3] | 2 [1-4] | 2 [1-3] | 2 [1-4] | 2 [1-3] | 3 [1-4] | 2 [1-3] | 2 [1-4] |
| Barthel index | 100 [70-100] | 90 [26-100] | <0.001 | 100 [70-100] | 90 [25-100] | 100 [70-100] | 90 [29-100] | 100 [70-100] | 85 [23-100] | 100 [70-100] | 90 [45-100] |
| NIHSS | 3 [1-5] | 4 [1-11] | 0.088 | 3 [1-6] | 4 [2-13] | 2 [1-5] | 4 [1-9] | 2 [1-5] | 4 [1-13] | 3 [1-5] | 4 [1-10] |

Risk factors (valid $\mathbf{n}$ )
Non-modifiable risk factors
$\begin{array}{llllllll}\text { Age } \geq 45 \text { years }(\mathrm{n}=3,961) & 2,323(61.6) & 99(51.6) & 0.007^{*} & 1,493(65.9) & 55(58.5) & 830(55.2) & 44(44.9)\end{array}$
Male sex ( $\mathrm{n}=3,961$ )
History of any

| $(\mathrm{n}=3,931)$ | $746(19.9)$ | $24(12.6)$ | 0.025 | $449(20.0)$ | $10(10.6)$ | $297(19.9)$ | $14(14.6)$ | $256(17.8)$ | $10(10.8)$ | $490(21.3)$ | $14(14.4)$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |


| History of TIA $(\mathrm{n}=3,909)$ | $354(9.5)$ | $19(10.0)$ | 0.735 | $217(9.7)$ | $8(8.5)$ | $137(9.2)$ | $11(11.5)$ | $127(8.9)$ | $8(8.6)$ | $227(9.9)$ | $11(11.3)$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |


| cardiovascular disease $(\mathrm{n}=3,744)$ | 1,494 (42.0) | 62 (33.7) | 0.082 | 808 (37.9) | 33 (37.1) | 686 (48.0) | 29 (30.5) | 537 (39.1) | 31 (34.8) | 957 (43.8) | 31 (32.6) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Family history of cerebrovascular disease ( $\mathrm{n}=3,759$ ) | 1,366 (38.2) | 55 (30.1) | 0.042 | 776 (36.2) | 27 (30.3) | 590 (41.2) | 28 (29.8) | 476 (34.6) | 24 (27.0) | 890 (40.4) | 31 (33.0) |
| Tobacco smoking (current or quit within last 5 years) ( $\mathrm{n}=3,919$ ) | 2,086 (56.0) | 85 (44.5) | 0.005 | 1,335 (59.7) | 41 (44.1) | 751 (50.4) | 44 (44.9) | 796 (55.6) | 41 (44.6) | 1,290 (56.2) | 44 (44.4) |
| Physical inactivity ( $\mathrm{n}=3,841$ ) | 1,778 (48.6) | 68 (37.0) | 0.003 | 1,045 (47.5) | 28 (31.1) | 733 (50.3) | 40 (42.6) | 625 (44.5) | 37 (42.5) | 1,153 (51.2) | 31 (32.0) |
| Hypertension ( $\mathrm{n}=3,940$ ) | 1,801 (48.1) | 56 (29.2) | <0.001 | 1,183 (52.6) | 36 (38.3) | 618 (41.3) | 20 (20.4) | 430 (29.9) | 19 (20.4) | 1,371 (59.3) | 37 (37.4) |
| Dyslipidemia ( $\mathrm{n}=3,804$ ) | 1,312 (36.3) | 26 (14.0) | <0.001 | 868 (40.1) | 18 (19.4) | 44 (30.5) | 8 (8.6) | 336 (24.0) | 14 (15.2) | 976 (44.0) | 12 (12.8) |
| High LDL $\geq 3.37 \mathrm{mmol} / \mathrm{l}$ $(\mathrm{n}=2,725)$ | 1,110 (42.6) | 24 (20.3) | <0.001 | 700 (44.6) | 16 (27.1) | 410 (39.5) | 8 (13.6) | 342 (35.4) | 7 (13.5) | 768 (46.8) | 17 (25.8) |
| $\text { Low HDL } \leq 1 \mathrm{mmol} / \mathrm{l}$ $(\mathrm{n}=2,783)$ | 740 (27.8) | 36 (30.3) | 0.661 | 597 (37.3) | 26 (43.3) | 143 (13.5) | 10 (16.9) | 264 (26.9) | 11 (21.6) | 476 (28.3) | 25 (36.8) |
| Obesity (BMI $\geq 30$ ) $\mathrm{n}=3,958$ ) | 870 (23.1) | 20 (10.4) | <0.001 | 526 (23.2) | 13 (13.8) | 344 (22.9) | 7 (7.1) | 296 (20.5) | 8 (8.6) | 574 (24.7) | 12 (12.1) |
| Diabetes ( $\mathrm{n}=3,941$ ) | 399 (10.6) | 14 (7.3) | 0.262 | 286 (12.7) | 11 (11.7) | 113 (7.5) | 3 (3.1) | 92 (6.4) | 5 (5.4) | 307 (13.3) | 9 (9.1) |

Table 1. (continued)

|  | Patients without CeAD, total ( $\mathrm{n}=3,769$ ) | Patients with CAD, total$(\mathrm{n}=192)$ | Patients without CeAD vs. patients with CAD total, $\mathrm{p}^{\mathrm{a}}$ | Patients without CeAD vs. patients with CAD |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  | men without <br> CeAD $(\mathrm{n}=2,265)$ | men with CAD $(\mathrm{n}=94)$ | women <br> without <br> CeAD $(\mathrm{n}=1,504)$ | women <br> with <br> CAD $(\mathrm{n}=98)$ | age 18-44 <br> years without <br> CeAD $(\mathrm{n}=1,446)$ | age 18-44 <br> years with <br> CAD $(\mathrm{n}=93)$ | age 45-55 <br> years without <br> CeAD $(\mathrm{n}=2,323)$ | age 45-55 <br> years with <br> CAD $(\mathrm{n}=99)$ |
| Cardiovascular disease $(\mathrm{n}=3,851)$ | 353 (9.6) | 6 (3.2) | 0.008 | 252 (11.5) | 4 (4.3) | 101 (6.9) | 2 (2.1) | 86 (6.1) | 4 (4.4) | 267 (11.9) | 2 (2.1) |
| Coronary heart disease $(\mathrm{n}=3,907)$ | 166 (4.5) | 2 (1.1) | 0.052 | 130 (5.8) | 2 (2.2) | 36 (2.4) | - | 29 (2.0) | 2 (2.2) | 137 (6.0) | - |
| Congestive heart failure $(\mathrm{n}=3,926)$ | 41 (1.1) | 1 (0.5) | 0.469 | 32 (1.4) | - | 9 (0.6) | 1 (1.0) | 13 (0.9) | 1 (1.1) | 28 (1.2) | - |
| Myocardial infarction $(\mathrm{n}=3,942)$ | 124 (3.3) | 1 (0.5) | 0.078 | 101 (4.5) | 1 (1.1) | 23 (1.5) | - | 20 (1.4) | 1 (1.1) | 104 (4.5) | - |
| Peripheral artery disease $(\mathrm{n}=3,922)$ | 83 (2.2) | 2 (1.0) | 0.298 | 59 (2.6) | 2 (2.1) | 24 (1.6) | - | 12 (0.8) | 1 (1.1) | 71 (3.1) | 1 (1.0) |
| Valvular disease ( $\mathrm{n}=3,905$ ) | 90 (2.4) | 1 (0.5) | 0.127 | 50 (2.2) | - | 40 (2.7) | 1 (1.0) | 39 (2.7) | - | 51 (2.2) | 1 (1.0) |
| PFO ( $\mathrm{n}=3,147$ ) | 782 (25.8) | 12 (10.8) | <0.001 | 455 (24.9) | 9 (16.1) | 327 (27.1) | 3 (5.5) | 386 (32.7) | 3 (6.8) | 391 (21.1) | 9 (13.4) |
| Atrial fibrillation ( $\mathrm{n}=3,925$ ) | 91 (2.4) | - | 0.994 | 63 (2.8) | - | 28 (1.9) | - | 19 (1.3) | - | 72 (3.1) | - |
| Less well-documented or potentia High risk alcohol consumption $(\mathrm{n}=3,804)$ | ally modifiab $1,216$ | isk factors $49 \text { (26.6) }$ | 0.176 | 924 (42.7) | 29 (33.0) | 292 (20.0) | 20 (20.8) | 436 (31.2) | 26 (28.6) | 780 (35.1) | 23 (24.7) |
| Migraine ( $\mathrm{n}=3,868$ ) | 950 (25.8) | 58 (31.0) | 0.075 | 393 (17.8) | 19 (20.7) | 557 (37.8) | 39 (41.1) | 416 (29.6) | 27 (29.3) | 534 (23.5) | 31 (32.6) |
| Night-time sleep $\leq 6$ h/night $(\mathrm{n}=3,958)$ | 680 (18.1) | 27 (14.1) | 0.237 | 470 (20.8) | 15 (16.0) | 210 (14.0) | 12 (12.2) | 232 (16.1) | 15 (16.1) | 448 (19.3) | 12 (12.1) |
| Obstructive sleep apnea $(\mathrm{n}=3,850)$ | 120 (3.3) | 3 (1.6) | 0.300 | 98 (4.5) | 3 (3.2) | 22 (1.5) | - | 37 (2.6) | - | 83 (3.7) | 3 (3.1) |
| * Not age adjusted. <br> Results are expressed as num <br> CAD = Carotid artery dissec interquartile range; $\mathrm{LDL}=$ low- <br> ${ }^{\text {a }}$ Adjusted for age and centre | mbers with per tion; CeAD density lipop heterogene | ntage in par rvical artery in; NIHSS = | ntheses or m dissection; T National In | edians with IQ IA = transient titute of Health | in square chaemic att Stroke Scale | ckets. <br> k; IS = ischae core; $\mathrm{PFO}=$ | c stroke; B ent foram | I = body mass ovale. | dex; $\mathrm{HDL}=$ | high density lip | protein; IQ |

Table 2. Risk factors of TIA and IS patients with vertebral artery dissection compared to those patients without cervical artery dissection

|  | Patients without CeAD, total$(\mathrm{n}=3,769)$ | Patients <br> with VAD, <br> total $(\mathrm{n}=191)$ | Patients without CeAD vs. patients with VAD total, $\mathrm{p}^{\mathrm{a}}$ | Patients without CeAD vs. patients with VAD |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  | men without CeAD $(\mathrm{n}=2,265)$ | men with <br> VAD $(\mathrm{n}=115)$ | women <br> without <br> CeAD $(\mathrm{n}=1,504)$ | women <br> with <br> VAD $(\mathrm{n}=76)$ | age 18-44 <br> years without <br> CeAD $(\mathrm{n}=1,446)$ | age 18-44 <br> years with <br> VAD $(\mathrm{n}=126)$ | age 45-55 <br> years without <br> CeAD $(\mathrm{n}=2,323)$ | age 45-55 <br> years with <br> VAD <br> ( $\mathrm{n}=65$ ) |
| Clinical scales |  |  |  |  |  |  |  |  |  |  |  |
| Modified Rankin scale | 2 [1-3] | 2 [1-3] | 0.027 | 2 [1-3] | 2 [1-3] | 2 [1-3] | 2 [1-3] | 2 [1-3] | 2 [1-4] | 2 [1-3] | 2 [1-3] |
| Barthel index | 100 [70-100] | 90 [60-100] | 0.083 | 100 [70-100] | 90 [65-100] | 100 [70-100] | 85 [56-100] | 100 [70-100] | 85 [60-100] | 100 [70-100] | 90 [70-100] |
| NIHSS | 3 [1-5] | 2 [1-4] | 0.028 | 3 [1-6] | 2 [1-4] | 2 [1-5] | 3 [1-4] | 2 [1-5] | 2 [1-4] | 3 [1-5] | 2 [1-4] |

Risk factors (valid $\mathbf{n}$ )
Non-modifiable risk factors

| Male sex ( $\mathrm{n}=3,960$ ) | 2,265 (60.1) | 115 (60.2) | 0.269 |  |  |  |  | 772 (53.4) | 77 (61.1) | 1,493 (64.3) | 38 (58.5) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| History of any cerebrovascular event ( $\mathrm{n}=3,931$ ) | 746 (19.9) | 10 (5.3) | <0.001 | 449 (20.0) | 7 (6.1) | 297 (19.9) | 3 (3.9) | 256 (17.8) | 5 (4.0) | 490 (21.3) | 5 (7.7) |
| History of TIA ( $\mathrm{n}=3,909$ ) | 354 (9.5) | 7 (3.7) | 0.017 | 217 (9.7) | 5 (4.4) | 137 (9.2) | 2 (2.6) | 127 (8.9) | 3 (2.4) | 227 (9.9) | 4 (6.2) |
| Family history of cardiovascular disease ( $\mathrm{n}=3,745$ ) | 1,494 (42.0) | 65 (35.1) | 0.210 | 808 (37.9) | 34 (30.9) | 686 (48.0) | 31 (41.3) | 537 (39.1) | 39 (31.5) | 957 (43.8) | 26 (42.6) |
| Family history of cerebrovascular disease ( $\mathrm{n}=3,760$ ) | 1,366 (38.2) | 61 (33.2) | 0.380 | 776 (36.2) | 39 (35.1) | 590 (41.2) | 22 (30.1) | 476 (34.6) | 39 (32.2) | 890 (40.4) | 22 (34.9) |

Well-documented and modifiable risk factorn
Well-documented and modifiable risk factors
Tobacco smoking

| (current or quit within last 5 years) ( $\mathrm{n}=3,916$ ) | 2,086 (56.0) | 92 (48.9) | 0.100 | 1,335 (59.7) | 59 (52.2) | 751 (50.4) | 33 (44.0) | 796 (55.6) | 60 (48.4) | 1,290 (56.2) | 32 (50.0) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Physical inactivity ( $\mathrm{n}=3,843$ ) | 1,778 (48.6) | 85 (45.7) | 0.826 | 1,045 (47.5) | 43 (38.4) | 733 (50.3) | 42 (56.8) | 625 (44.5) | 57 (46.3) | 1,153 (51.2) | 28 (44.4) |
| Hypertension ( $\mathrm{n}=3,937$ ) | 1,801 (48.1) | 56 (29.6) | 0.007 | 1,183 (52.6) | 36 (31.9) | 618 (41.3) | 20 (26.3) | 430 (29.9) | 26 (20.8) | 1,371 (59.3) | 30 (46.9) |
| Dyslipidemia ( $\mathrm{n}=3,804$ ) | 1,312 (36.3) | 49 (26.3) | 0.281 | 868 (40.1) | 36 (32.4) | 444 (30.5) | 13 (17.3) | 336 (24.0) | 24 (19.7) | 976 (44.0) | 25 (39.1) |
| $\begin{aligned} & \text { High LDL } \geq 3.37 \mathrm{mmol} / \mathrm{l} \\ & (\mathrm{n}=2,730) \end{aligned}$ | 1,110 (42.6) | 48 (39.0) | 0.775 | 700 (44.6) | 37 (48.7) | 410 (39.5) | 11 (23.4) | 342 (35.4) | 22 (30.6) | 768 (46.8) | 26 (51.0) |
| Low HDL $\leq 1 \mathrm{mmol} / \mathrm{l}$ $(\mathrm{n}=2,793)$ | 740 (27.8) | 33 (25.6) | 0.655 | 597 (37.3) | 28 (35.0) | 143 (13.5) | 5 (10.2) | 264 (26.9) | 20 (26.0) | 476 (28.3) | 13 (25.0) |
| Obesity ( $\mathrm{BMI} \geq 30$ ) $(\mathrm{n}=3,957)$ | 870 (23.1) | 32 (16.8) | 0.170 | 526 (23.2) | 18 (15.7) | 344 (22.9) | 14 (18.4) | 296 (20.5) | 20 (15.9) | 574 (24.7) | 12 (18.5) |
| Diabetes ( $\mathrm{n}=3,941$ ) | 399 (10.6) | 8 (4.2) | 0.043 | 286 (12.7) | 4 (3.5) | 113 (7.5) | 4 (5.3) | 92 (6.4) | 2 (1.6) | 307 (13.3) | 6 (9.2) | Diabetes ( $n=3,91$ )

Table 2. (continued)

|  | Patients without CeAD, total ( $\mathrm{n}=3,769$ ) | Patients with VAD, total ( $\mathrm{n}=191$ ) | Patients without CeAD vs. patients with VAD total, $\mathrm{p}^{\mathrm{a}}$ | Patients without CeAD vs. patients with VAD |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  | men without <br> CeAD $(\mathrm{n}=2,265)$ | men with <br> VAD $(\mathrm{n}=115)$ | women <br> without <br> CeAD $(\mathrm{n}=1,504)$ | women <br> with <br> VAD $(\mathrm{n}=76)$ | age 18-44 <br> years without <br> CeAD $(\mathrm{n}=1,446)$ | $\begin{aligned} & \text { age } 18-44 \\ & \text { years with } \\ & \text { VAD } \\ & (\mathrm{n}=126) \end{aligned}$ | age 45-55 <br> years without <br> CeAD $(\mathrm{n}=2,323)$ | $\begin{aligned} & \text { age } 45-55 \\ & \text { years with } \\ & \text { VAD } \\ & (\mathrm{n}=65) \end{aligned}$ |
| Cardiovascular disease $(\mathrm{n}=3,853)$ | 353 (9.6) | 4 (2.1) | 0.004 | 252 (11.5) | 2 (1.7) | 101 (6.9) | 2 (2.7) | 86 (6.1) | 2 (1.6) | 267 (11.9) | 2 (3.1) |
| Coronary heart disease $(\mathrm{n}=3,908)$ | 166 (4.5) | 1 (0.5) | 0.062 | 130 (5.8) | 1 (0.9) | 36 (2.4) | - | 29 (2.0) | 1 (0.8) | 137 (6.0) | - |
| Congestive heart failure $(\mathrm{n}=3,926)$ | 41 (1.1) | - | 0.992 | 32 (1.4) | - | 9 (0.6) | - | 13 (0.9) | - | 28 (1.2) | - |
| Myocardial infarction $(\mathrm{n}=3,941)$ | 124 (3.3) | 2 (1.0) | 0.216 | 101 (4.5) | 2 (1.7) | 23 (1.5) | - | 20 (1.4) | 1 (0.8) | 104 (4.5) | 1 (1.5) |
| Peripheral artery disease $(\mathrm{n}=3,921)$ | 83 (2.2) | 2 (1.0) | 0.548 | 59 (2.6) | - | 24 (1.6) | 2 (2.6) | 12 (0.8) | 1 (0.8) | 71 (3.1) | 1 (1.5) |
| Valvular disease ( $\mathrm{n}=3,906$ ) | 90 (2.4) | - | 0.993 | 50 (2.2) | - | 40 (2.7) | - | 39 (2.7) | - | 51 (2.2) | - |
| PFO ( $\mathrm{n}=3,159$ ) | 782 (25.8) | 23 (18.7) | 0.013 | 455 (24.9) | 13 (17.3) | 327 (27.1) | 10 (20.8) | 386 (32.7) | 13 (16.5) | 391 (21.1) | 10 (22.7) |
| Atrial fibrillation ( $\mathrm{n}=3,926$ ) | 91 (2.4) | 4 (2.1) | 0.870 | 63 (2.8) | 2 (1.7) | 28 (1.9) | 2 (2.6) | 19 (1.3) | 3 (2.4) | 72 (3.1) | 1 (1.5) |
| Less well-documented or potentiall High risk alcohol consumption $(\mathrm{n}=3,802)$ | y modifiable $1,216$ | factors $54 \text { (29.7) }$ | 0.446 | 924 (42.7) | 35 (32.1) | 292 (20.0) | 19 (26.0) | 436 (31.2) | 39 (31.7) | 780 (35.1) | 15 (25.4) |
| Migraine ( $\mathrm{n}=3,868$ ) | 950 (25.8) | 52 (27.8) | 0.852 | 393 (17.8) | 23 (20.4) | 557 (37.8) | 29 (39.2) | 416 (29.6) | 35 (28.0) | 534 (23.5) | 17 (27.4) |
| Night-time sleep $\leq 6 \mathrm{~h} /$ night $(\mathrm{n}=3,957)$ | 680 (18.1) | 29 (15.2) | 0.722 | 1,793 (79.2) | 94 (81.7) | 210 (14.0) | 8 (10.5) | 232 (16.1) | 19 (15.1) | 448 (19.3) | 10 (15.4) |
| Obstructive sleep apnea $(\mathrm{n}=3,848)$ | 120 (3.3) | 6 (3.2) | 0.721 | 98 (4.5) | 6 (5.3) | 22 (1.5) | - | 37 (2.6) | 2 (1.6) | 83 (3.7) | 4 (6.3) |

* Not adjusted for age.
$\mathrm{VAD}=$ Vertebral artery dissection; $\mathrm{Ce} \mathrm{AD}=$ cervical artery dissection; TIA = transient ischaemic attack; $\mathrm{IS}=$ ischaemic stroke; $\mathrm{BMI}=$ body mass index; $\mathrm{HDL}=$ high density lipoprotein; IQR $=$ interquartile range; LDL = low-density lipoprotein; NIHSS = National Institute of Health Stroke Scale Score; PFO = patent foramen ovale.

[^0]

Fig. 1. a Non-modifiable risk factors, and $\mathbf{b}$ well-documented and modifiable risk factors in TIA and ischaemic stroke patients without cervical artery dissection (CeAD, black bars), with carotid artery dissection (CAD, grey bars) and with vertebral artery dissec-
tion (VAD, white bars). Significant differences to patients without CeAD are indicated by an asterisk $\left({ }^{*}\right)$ for CAD or hash key $\left({ }^{\#}\right)$ for VAD patients. CVD = Cardiovascular disease; CVE = cerebrovascular event; $\mathrm{PFO}=$ patent foramen ovale.
cerebrovascular events. The higher proportion of CAD patients with only local symptoms compared with VAD patients [7, 9] may in part explain the almost equal percentage of CAD (51\%) and VAD (49.9\%) in our study. A similar percentage of VAD and CAD like in our study was also reported from the Dijon Stroke Registry, which also included only patients with TIA and IS [1]. Another important reason for a higher prevalence of VAD than expected may be a greater awareness of dissection, especially in younger patients, and improvements in diagnostic tools and access to MRI during the last decade. This has also been observed in a population-based study from the Mayo Clinic, where the incidence of CAD exceeded that of VAD by a factor of 4 before 1994, whereas the frequency of CAD and VAD was similar after 1994 [3].

As reported in earlier studies $[8,17,18]$, most vascular risk factors were also less common in patients with CAD or VAD than in patients without CeAD in sifap1 (tables 3, 4). Prior studies comparing patients with CAD and VAD did not report significant differences regarding the prevalence of vascular risk factors between CAD and VAD except for a higher prevalence of current smoking in patients with VAD [7, 9, 15]. Comparing CAD and VAD patients with TIA and IS patients without CeAD of similar age and sex, we found that most of the well-documented and modifiable vascular risk factors were significantly
Table 3. Clinical presentation and risk factors of patients with and without cervical artery dissection and anterior circulation CVE stratified by sex and age group

| Clinical presentation (valid n) | Patients with anterior circulation stroke and without CeAD, total $(\mathrm{n}=1,493)$ | TIA and IS patients with CAD |  |  |  |  | CAD vs. anterior circulation stroke and no CAD, $\mathrm{p}^{\mathrm{a}}$ | Within patients with CAD |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | total $(\mathrm{n}=192)$ | $\begin{aligned} & \text { men } \\ & (\mathrm{n}=94) \end{aligned}$ | women $(\mathrm{n}=98)$ | $\begin{aligned} & \text { age } 18-44 \\ & \text { years } \\ & (\mathrm{n}=93) \end{aligned}$ | $\begin{aligned} & \text { age } 45-55 \\ & \text { years } \\ & (\mathrm{n}=99) \end{aligned}$ |  | sex, $\mathrm{p}^{\text {a }}$ | age, $\mathrm{p}^{\text {b }}$ |
| Presenting symptoms |  |  |  |  |  |  |  |  |  |
| Stupor or coma ( $\mathrm{n}=1,682$ ) | 29 (1.9) | 5 (2.6) | 3 (3.2) | 2 (2.0) | 2 (2.2) | 3 (3.0) | 0.609 | 0.663 | 0.785 |
| Loss of consciousness ( $\mathrm{n}=1,677$ ) | 54 (3.6) | 13 (6.8) | 10 (10.6) | 3 (3.1) | 4 (4.3) | 9 (9.1) | 0.038 | 0.089 | 0.169 |
| Headache ( $\mathrm{n}=1,671$ ) | 343 (23.1) | 102 (54.0) | 49 (52.7) | 53 (55.2) | 51 (56.0) | 51 (52.0) | <0.001 | 0.728 | 0.408 |
| Nausea/vomiting ( $\mathrm{n}=1,675$ ) | 129 (8.7) | 32 (16.9) | 17 (18.3) | 15 (15.6) | 19 (20.9) | 13 (13.3) | 0.002 | 0.367 | 0.011 |
| Aphasia ( $\mathrm{n}=1,680$ ) | 500 (33.6) | 74 (38.9) | 36 (38.7) | 38 (39.2) | 35 (38.0) | 39 (39.8) | 0.197 | 0.960 | 0.214 |
| Dysarthria ( $\mathrm{n}=1,678$ ) | 692 (46.5) | 65 (34.2) | 35 (37.2) | 30 (31.3) | 34 (36.6) | 31 (32.0) | 0.003 | 0.277 | 0.361 |
| Ataxia ( $\mathrm{n}=1,674$ ) | 211 (14.2) | 17 (9.0) | 7 (7.7) | 10 (10.2) | 9 (9.8) | 15 (15.5) | 0.054 | 0.544 | 0.934 |
| Diplopia ( $\mathrm{n}=1,674$ ) | 58 (3.9) | 4 (2.1) | 2 (2.2) | 2 (2.1) | 1 (1.1) | 3 (3.1) | 0.276 | 0.952 | 0.986 |
| Visual field symptoms ( $\mathrm{n}=1,674$ ) | 142 (9.6) | 49 (25.9) | 25 (27.2) | 24 (24.7) | 24 (26.1) | 25 (25.8) | <0.001 | 0.723 | 0.666 |
| Vertigo ( $\mathrm{n}=1,670$ ) | 237 (16.0) | 27 (14.4) | 16 (17.6) | 11 (11.5) | 11 (12.0) | 16 (16.8) | 0.499 | 0.270 | 0.979 |
| Paresis ( $\mathrm{n}=1,613$ ) | 1,092 (76.3) | 131 (72.4) | 67 (74.4) | 64 (70.3) | 58 (69.0) | 73 (75.3) | 0.281 | 0.575 | 0.558 |
| Somatosensory deficit ( $\mathrm{n}=1,544$ ) | 788 (57.5) | 98 (56.6) | 50 (57.5) | 48 (55.8) | 52 (65.0) | 46 (49.5) | 0.633 | 0.427 | 0.004 |

[^1]| Clinical presentation (valid n) | Patients with posterior circulation stroke without CeAD, total ( $\mathrm{n}=547$ ) | TIA and IS patients with VAD |  |  |  |  | VAD vs. posterior circulation stroke without VAD, $\mathrm{p}^{\mathrm{a}}$ | Within patients with VAD |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | $\begin{aligned} & \text { total } \\ & (\mathrm{n}=191) \end{aligned}$ | men $(\mathrm{n}=115)$ | women $(\mathrm{n}=76)$ | $\begin{aligned} & \text { age } 18-44 \\ & \text { years } \\ & (\mathrm{n}=126) \end{aligned}$ | $\begin{aligned} & \text { age } 45-55 \\ & \text { years } \\ & (\mathrm{n}=65) \end{aligned}$ |  | sex, $\mathrm{p}^{\text {a }}$ | age, $\mathrm{p}^{\text {b }}$ |
| Presenting symptoms |  |  |  |  |  |  |  |  |  |
| Stupor or coma ( $\mathrm{n}=737$ ) | 13 (2.4) | 6 (3.1) | 4 (3.5) | 2 (2.6) | 6 (4.8) | - | 0.954 | 0.640 | 0.240 |
| Loss of consciousness ( $\mathrm{n}=735$ ) | 29 (5.3) | 8 (4.2) | 5 (4.3) | 3 (4.0) | 6 (4.8) | 2 (3.1) | 0.505 | 0.887 | 0.799 |
| Headache ( $\mathrm{n}=732$ ) | 198 (36.6) | 121 (63.4) | 72 (62.6) | 49 (64.5) | 82 (65.1) | 39 (60.0) | <0.001 | 0.739 | 0.437 |
| Nausea/vomiting ( $\mathrm{n}=737$ ) | 235 (43.0) | 110 (57.6) | 65 (56.5) | 45 (59.2) | 76 (60.3) | 34 (52.3) | 0.002 | 0.751 | 0.480 |
| Aphasia ( $\mathrm{n}=733$ ) | 69 (12.7) | 12 (6.3) | 6 (5.2) | 6 (8.0) | 9 (7.1) | 3 (4.7) | 0.007 | 0.429 | 0.763 |

Table 4. (continued)

| Clinical presentation (valid n) | Patients with posterior circulation stroke without CeAD, total ( $\mathrm{n}=547$ ) | TIA and IS patients with VAD |  |  |  |  | VAD vs. posterior circulation stroke without VAD, $\mathrm{p}^{\mathrm{a}}$ | Within patients with VAD |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | $\begin{aligned} & \text { total } \\ & (\mathrm{n}=191) \end{aligned}$ | men $(\mathrm{n}=115)$ | women $(\mathrm{n}=76)$ | age 18-44 <br> years <br> ( $\mathrm{n}=126$ ) | $\begin{aligned} & \text { age } 45-55 \\ & \text { years } \\ & (\mathrm{n}=65) \end{aligned}$ |  | sex, $\mathrm{p}^{\text {a }}$ | age, $\mathrm{p}^{\text {b }}$ |
| Dysarthria ( $\mathrm{n}=731$ ) | 250 (46.0) | 66 (35.1) | 42 (36.8) | 24 (32.4) | 46 (36.5) | 20 (32.3) | 0.022 | 0.528 | 0.876 |
| Ataxia ( $\mathrm{n}=729$ ) | 257 (47.5) | 85 (45.2) | 57 (50.4) | 28 (37.3) | 55 (44.7) | 30 (46.2) | 0.666 | 0.113 | 0.325 |
| Diplopia ( $\mathrm{n}=729$ ) | 138 (25.7) | 50 (26.2) | 36 (31.3) | 14 (18.4) | 35 (27.8) | 15 (23.1) | 0.965 | 0.050 | 0.954 |
| Visual field symptoms ( $\mathrm{n}=726$ ) | 31 (5.8) | 17 (9.1) | 11 (9.7) | 6 (8.1) | 13 (10.7) | 4 (6.2) | 0.610 | 0.760 | 0.976 |
| Vertigo ( $\mathrm{n}=732$ ) | 312 (57.6) | 140 (73.7) | 87 (75.7) | 53 (70.7) | 95 (76.0) | 45 (69.2) | <0.001 | 0.390 | 0.017 |
| Paresis ( $\mathrm{n}=708$ ) | 235 (44.8) | 56 (30.4) | 30 (26.8) | 26 (36.1) | 38 (31.4) | 18 (28.6) | 0.001 | 0.169 | 0.665 |
| Somatosensory deficit ( $\mathrm{n}=678$ ) | 235 (46.6) | 79 (45.4) | 46 (43.8) | 33 (47.8) | 47 (41.2) | 32 (53.3) | 0.701 | 0.609 | 0.938 |

Figures in parentheses are percentages.
$V A D=$ vertebral artery dissection; TIA $=$ transient ischaemic attack; IS $=$ ischaemic stroke; CeAD $=$ cervical artery dissection. Multiple regressions adjusted for ${ }^{\text {a }}$ age and centre heterogeneity (if not indicated differently (c)) and ${ }^{\mathrm{b}}$ sex and centre heterogeneity (if not indicated differently (c)). (c) Not adjusted for centre heterogeneity because of very low numbers and unstable models.
less frequent in patients with CAD, while hypertension, diabetes and concomitant cardiovascular disease were also significantly less frequent in VAD patients compared to patients without CeAD. Although VAD patients were significantly younger than CAD patients, the percentage of patients with increased levels of most risk factors was higher in VAD than in CAD patients. Specifically, high LDL-cholesterol was twice as frequent in patients with VAD as in patients with CAD and even more frequently seen in male VAD patients than in patients without CeAD. Furthermore, patients with VAD less frequently had a history of prior TIA or other cerebrovascular events than patients with CAD or without CeAD.

Several prior case-control studies and registries identified migraine as an independent risk factor for CeAD [17, 19]. In sifap1, migraine was equally common in TIA and IS patients with CAD, VAD or without CeAD patients. Furthermore, the reported migraine prevalence of $29 \%$ in CeAD patients and distribution between the sexes was in line with previous case series of young stroke patients overall (17.2-26.1\%) [20,21] and specifically in those with CeAD (25-35.7\%) [17, 22]. Thus, we cannot confirm an association of migraine and the occurrence of CAD or VAD.

Consistent with previous reports [1, $7,9,22$ ], headache was the symptom that most commonly separates CeAD patients from patients without CeAD. In VAD patients, headache was frequently accompanied by nausea, vomiting and vertigo. This observation emphasises that the combination of focal symptoms with headache should prompt physicians to take CeAD into account. It is, however, also important to emphasise that 23.1 and $36.6 \%$ of patients without dissection and IS in the anterior and posterior circulation, respectively, also had headache [23], which is more frequent than what was reported in earlier stroke registries [24].

Patients with CAD had a higher mRS and a lower BI in the acute phase after stroke indicating that patients with CAD were more severely impaired than those without CeAD. As shown before in other CeAD registries [7, 9], the NIHSS is less valuable in assessing the severity of strokes affecting the brainstem and the cerebellum. This is the most likely reason for the lower NIHSS of VAD patients as compared to CeAD patients.

Our study has strengths and limitations. The strengths of sifapl are the prospective nature of the recruitment of patients in 47 multinational study centres, the standardisation of data assessment, and a blinded central analysis of MRI-images. The limitations are as follows: (1) The need for participants' informed consent or assent from a
legal representative might have led to exclusion of some more severely affected patients although severe stroke was not an exclusion criterion in sifap1. This might partly explain the overall low median NIHSS-scores in sifap1, but does not in any way invalidate the main finding of this study. (2) Similar to the majority of studies on CeAD, sifapl did not include a control group of age- and sexmatched healthy individuals from the same catchment area as the sifapl patients. Therefore, we cannot comment on associations between certain risk factors and the presence of CeAD in CeAD patients versus healthy controls. However, we did have the unique opportunity of comparing profiles in patients with CeAD with contemporaneously recruited young patients without CeAD. (3) Ultrasonography and CT-angiography did not undergo central reading. (4) We have limited information on trauma preceding CeAD to separate spontaneous dissection or dissection associated with minor trauma from those caused by relevant trauma. However, as patients were recruited from regular stroke units but not from neurosurgical or surgical intensive care units, the number of patients with CeAD caused by relevant trauma included into sifap 1 is considered being very low and not influencing our statistical analyses. (5) Our patients are predominantly European Caucasians and application of our data is only valid for this distinct ethnic group and geographic locations included in this large multicentre collaborative
study. Nevertheless, our findings provide invaluable insight into the clinical profiles of patients with CAD and VAD in Europe.

In summary, the present analysis of the sifap 1 study has expanded our knowledge base by facilitating identification of different clinical features and risk factor profiles that are specific to young patients with CeAD, and to subgroups with either CAD or VAD compared with patients without CeAD. Our findings support the concept that certain vascular risk factors differentially affect the risk of CAD and VAD, and support the design of future, prospective studies and trials that should analyse data from CAD and VAD patient subgroups separately.

## Acknowledgments

We thank all centres and patients who have contributed to the study.

## Disclosure Statement

Sifap1 (Stroke In young FAbry Patients, www.sifap.eu, NCT00414583) has been supported by an unrestricted scientific grant from Shire Human Genetic Therapies to the University of Rostock. The sponsor of the study had no role in the study design, data collection, data analysis, interpretation, writing of the manuscript, or the decision to submit the manuscript for publication.

## References

- Béjot Y, Daubail B, Debette S, Durier J, Giroud M: Incidence and outcome of cerebrovascular events related to cervical artery dissection: the Dijon Stroke Registry. Int J Stroke 2014;9:879-882.
-2 Schievink WI, Roiter V: Epidemiology of cervical artery dissection. Front Neurol Neurosci 2005;20:12-15.
-3 Lee VH, Brown RD, Mandrekar JN, Mokri B: Incidence and outcome of cervical artery dissection: a population-based study. Neurology 2006;67:1809-1812.
-4 Schievink WI: Spontaneous dissection of the carotid and vertebral arteries. N Engl J Med 2001;344:898-906.
-5 Yesilot Barlas N, Putaala J, Waje-Andreassen U, Vassilopoulou S, Nardi K, Odier C, Hofgart G, Engelter S, Burow A, Mihalka L, Kloss M, Ferrari J, Lemmens R, Coban O, Haapaniemi E, Maaijwee N, Rutten-Jacobs L, Bersano A, Cereda C, Baron P, Borellini L, Valcarenghi C, Thomassen L, Grau AJ, Palm F, Urbanek C, Tuncay R, Durukan Tolvanen A, van Dijk EJ, de Leeuw FE, Thijs V, Greisenegger S, Vemmos K, Lichy C, Bereczki D, Csiba L, Mi-
chel P, Leys D, Spengos K, Naess H, Tatlisumak T, Bahar SZ: Etiology of first-ever ischaemic stroke in European young adults: the 15 cities young stroke study. Eur J Neurol 2013; 20:1431-1439.
-6 Fromm A, Waje-Andreassen U, Thomassen L, Naess H: Comparison between ischemic stroke patients $<50$ years and $\geq 50$ years admitted to a single centre: the Bergen stroke study. Stroke Res Treat 2011;2011:183256.
$>_{7}$ von Babo M, De Marchis GM, Sarikaya H, Stapf C, Buffon F, Fischer U, Heldner MR, Gralla J, Jung S, Simonetti BG, Mattle HP, Baumgartner RW, Bousser MG, Arnold M: Differences and similarities between spontaneous dissections of the internal carotid artery and the vertebral artery. Stroke 2013;44: 1537-1542.
- 8 Debette S, Metso T, Pezzini A, Abboud S, Metso A, Leys D, Bersano A, Louillet F, Caso V, Lamy C, Medeiros E, Samson Y, GrondGinsbach C, Engelter ST, Thijs V, Beretta S, Béjot Y, Sessa M, Lorenza Muiesan M, Amouyel P, Castellano M, Arveiler D, Tatlisumak T, Dallongeville J: Association of vascu-
lar risk factors with cervical artery dissection and ischemic stroke in young adults. Circulation 2011;123:1537-1544.
>9 Debette S, Grond-Ginsbach C, Bodenant M, Kloss M, Engelter S, Metso T, Pezzini A, Brandt T, Caso V, Touzé E, Metso A, Canaple S, Abboud S, Giacalone G, Lyrer P, Del Zotto E, Giroud M, Samson Y, Dallongeville J, Tatlisumak T, Leys D, Martin JJ: Differential features of carotid and vertebral artery dissections: the CADISP study. Neurology 2011;77: 1174-1181.
10 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.
-11 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.
-12 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. Circulation 2006;113:e873-e923.
-13 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.
$>14$ Debette S, Metso TM, Pezzini A, Engelter ST, Leys D, Lyrer P, Metso AJ, Brandt T, Kloss M, Lichy C, Hausser I, Touzé E, Markus HS, Abboud S, Caso V, Bersano A, Grau A, Altintas A, Amouyel P, Tatlisumak T, Dallongeville J, Grond-Ginsbach C: CADISP-genetics: an International project searching for genetic risk factors of cervical artery dissections. Int J Stroke 2009;4:224-230.
-15 Dziewas R, Konrad C, Dräger B, Evers S, Besselmann M, Lüdemann P, Kuhlenbäumer G, Stögbauer F, Ringelstein EB: Cervical artery dissection - clinical features, risk factors, therapy and outcome in 126 patients. J Neurol 2003;250:1179-1184.
-16 Metso AJ, Metso TM, Debette S, Dallongeville J, Lyrer PA, Pezzini A, Lichy C, Kloss M, Brandt T, Touzé E, Southerland AM, Worrall BB, Abboud S, Del Zotto E, Leys D, Engelter S, Grond-Ginsbach C, Tatlisumak T: Gender and cervical artery dissection. Eur J Neurol 2012;19:594-602.
-17 Metso TM, Tatlisumak T, Debette S, Dallongeville J, Engelter ST, Lyrer PA, Thijs V, Bersano A, Abboud S, Leys D, Grond-Ginsbach C, Kloss M, Touzé E, Pezzini A, Metso AJ: Migraine in cervical artery dissection and ischemic stroke patients. Neurology 2012;78: 1221-1228.
-18 Pezzini A, Caso V, Zanferrari C, Del Zotto E, Paciaroni M, Bertolino C, Grassi M, Agnelli G, Padovani A: Arterial hypertension as risk factor for spontaneous cervical artery dissection. A case-control study. J Neurol Neurosurg Psychiatry 2006;77:95-97.

19 Tzourio C, Benslamia L, Guillon B, Aïdi S, Bertrand M, Berthet K, Bousser MG: Migraine and the risk of cervical artery dissection: a case-control study. Neurology 2002;59: 435-437.
20 Putaala J, Metso AJ, Metso TM, Konkola N, Kraemer Y, Haapaniemi E, Kaste M, Tatlisumak T: Analysis of 1,008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki young stroke registry. Stroke 2009;40:1195-1203.
21 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.
-22 Arnold M, Kappeler L, Georgiadis D, Berthet K, Keserue B, Bousser MG, Baumgartner RW: Gender differences in spontaneous cervical artery dissection. Neurology 2006;67:10501052.

23 Kropp P, Holzhausen M, Kolodny E, Becker U, Dichgans M, Diez-Tejedor E, Enzinger C, Fazekas F, Fuentes B, Karpinska A, Meyer W, Tanislav C, Böttcher T, Rolfs A: Headache as a symptom at stroke onset in 4,431 young ischaemic stroke patients. Results from the 'Stroke in Young Fabry Patients (SIFAP1) study'. J Neural Transm 2013;120:1433-1440.

- 24 Kumral E, Bogousslavsky J, van Melle G, Regli F, Pierre P: Headache at stroke onset: the Lausanne stroke registry. J Neurol Neurosurg Psychiatry 1995;58:490-492.


[^0]:    ${ }^{\text {a }}$ Adjusted for age and centre heterogeneity.

[^1]:    Figures in parentheses are percentages.
    CAD $=$ Carotid artery dissection; TIA $=$ transient ischaemic attack; IS = ischaemic stroke; CeAD $=$ cervical artery dissection; $\mathrm{CVE}=$ cerebrovascular event.
    Multiple regressions adjusted for ${ }^{\text {a }}$ age and centre heterogeneity (if not indicated differently (c)) and ${ }^{\text {b }}$ sex and centre heterogeneity (if not indicated differently (c)).
    (c) Not adjusted for centre heterogeneity because of very low numbers and unstable models.

