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Acute ischemic stroke in the absence of established vascular risk factors: patient characteristics, stroke mechanism, and long-term outcome

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THESE

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Acute ischemic stroke in the absence of established vascular risk factors: patient characteristics, stroke mechanism, and long-term outcome

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Accidents vasculaires cérébrales ischémiques aigus sans facteurs de risque vasculaires établies : Caractéristiques des patients, mécanismes des AVC, et évolution à long terme

(Titre original: « Acute ischemic stroke in the absence of established vascular risk factors: patient characteristics, stroke mechanism, and long-term outcome")

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Résumé

Contexte

Chez certains patients victimes d'un accident vasculaire cérébral ischémique aigu (AIA), on n'identifie aucun facteur de risque vasculaire établi (FRVE). Nous avons cherché à évaluer les caractéristiques cliniques, les mécanismes des accidents vasculaire cérébraux (AVC) et l'évolution à long terme de ces patients.

Méthodes

Nous avons analysé rétrospectivement et successivement les patients victimes d'un AIA dans le Registre des AVC de Lausanne (2003-2018) qui ont eu une évaluation complète des FRVE (hypertension, diabète, sources cardioemboliques majeures, dyslipidémie, tabagisme, obésité, abus d'alcool, antécédents d'AVC/accidents transitoires et dépression/psychose). Nous avons comparé des patients sans FRVE à des patients avec ≥1 FRVE en utilisant des modèles statistiques appropriés.

Résultats

Sur les 4'889 patients consécutifs, 103 (2,1 %) n'avaient aucun FRVE. Dans l'analyse de régression multiple, les patients sans FRVE étaient significativement plus jeunes (OR=0,13 ; 95%CI=0,08-0,20) et avaient plus d'AVC multiterritoriaux (OR=3,38 ; 95%CI=1,26-9,05). Les AVC étaient plus souvent liés à un foramen ovale perméable (FOP) (OR=3,02 ; 95 % IC=1,44-6,32) et moins à l'athérosclérose, à une cause cardio-embolique ou à un mécanisme lacunaire.

Chez les patients de moins de 55 ans, le FOP (RC = 2,76 ; 95 % IC = 1,50-5,08) et l'utilisation de contraceptifs chez les femmes (HR = 2,75 ; 95 % IC = 1,40-5,41) étaient plus fréquents, et le syndrome d'apnée du sommeil (HR = 0,09 ; 95 % IC = 0,01-0,63) était moins fréquent. Chez les patients de plus de 55 ans, le sexe féminin (HR=2,84 ; 95%CI=1,43-5,65) et un cancer actif (HR=3,27 ; 95%CI=1,34-7,94) étaient plus fréquents.

À 12 mois, les patients sans FRVE avaient une évolution fonctionnelle moins favorable (Rankin-shift-OR_{adj}=0,63; 95%CI=0,42-0,95) ainsi qu'un taux de récidive et de décès plus élevé (HR_{adj}=2,11; 95%CI=1,19-3,74).

Conclusions

Dans une large cohorte consécutive d'AIA, seuls 2% n'avaient aucun FRVE. Parmi ces patients, nous avons identifié chez les jeunes une augmentation des FOP et une augmentation de l'utilisation de contraceptifs (chez les femmes). Chez les patients âgés nous avons identifié une augmentation des cancers actifs. Ces résultats pourraient influencer le bilan des accidents vasculaires cérébraux et la prévention secondaire.

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ORIGINAL ARTICLE

Acute ischaemic stroke in the absence of established vascular risk factors: Patient characteristics, stroke mechanism and long-term outcome

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Abstract

Background and purpose: Some acute ischaemic stroke (AIS) patients do not display established vascular risk factors (EVRFs). The aim was to assess their clinical characteristics, stroke subtype etiological classification and long-term outcome.

Methods: All consecutive AIS patients from the Acute Stroke Registry of Lausanne (2003–2018) were retrospectively analyzed with complete assessment of the following EVRFs: hypertension, diabetes, major cardioembolic sources, dyslipidemia, smoking, obesity, alcohol abuse, previous stroke/transient ischaemic attack and depression/psychosis. Patients without EVRFs were compared to patients with one or more EVRFs using appropriate statistical models.

Results: Of 4889 included patients, 103 (2.1%) had no EVRFs. In multiple regression analysis, patients without EVRFs were significantly younger (odds ratio [OR] 0.13; 95% confidence interval [CI] 0.08–0.20) and had more multiterritorial strokes (OR 3.38; 95% CI 1.26–9.05). Strokes were more often related to patent foramen ovale (PFO) (OR 3.02; 95% CI 1.44–6.32) and less to atherosclerosis, cardioembolism or small vessel disease. In patients <55 years old, PFO (OR 2.76; 95% CI 1.50–5.08) and contraceptive use in females (OR 2.75; 95% CI 1.40–5.41) were more frequent, whereas sleep apnea syndrome (OR 0.09; 95% CI 0.01–0.63) was less. In patients ≥55 years, female sex (OR 2.84; 95% CI 1.43–5.65) and active cancer (OR 3.27; 95% CI 1.34–7.94) were more prevalent. At 12 months, patients without EVRFs had worse adjusted functional outcome (Rankin shift OR_{adj} 0.63; 95% CI 0.42–0.95) and higher rate of recurrence and death (adjusted hazard ratio 2.11; 95% CI 1.19–3.74).

Conclusions: In a consecutive cohort of AIS patients, only 2% showed no EVRFs. PFO and contraceptive use exhibited a strong association with the absence of EVRFs in younger patients and female sex and active cancer in elderly patients. Our findings highlight the importance of searching for previously unknown risk factors and/or unusual stroke mechanisms in patients without EVRFs.

KEYWORDS
acute ischaemic stroke, stroke etiology, stroke in the young, vascular risk factor

Nannoni and Scherz-Moussa Youma contributed equally.

BACKGROUND

Knowledge and identification of risk factors for acute ischaemic stroke (AIS) are important for planning and implementation of primordial, primary and secondary prevention. It is known currently that modifiable risk factors are associated with approximately 90% of the population attributable risk of stroke in each major region of the world [1]. Similarly, more than 90% of the stroke burden (i.e., disability-adjusted life years) is attributable to modifiable risk factors [2]. Established vascular risk factors (EVRFs) include hypertension, diabetes mellitus, atrial fibrillation/flutter, other cardiac diseases (mechanical heart valves, very low ejection fraction, myocardial infarction), dyslipidemia, unhealthy diet, obesity, waist-to-hip ratio, psychosocial factors, current smoking, physical inactivity and heavy alcohol consumption [1].

Although most ischaemic stroke patients have at least one of these EVRFs, a minority of patients do not display any, even after a thorough work-up. Such patients may exhibit specific characteristics and comorbidities leading to stroke through various stroke mechanisms.

Candidate conditions predisposing to stroke in these patients may be non-EVRFs. These may include, for example, migraine [3] (especially migraine with aura [4]), oncological diseases (active or in remission) [5], diseases of other organs than heart and vessels, dementia [6], hematological abnormalities (anemia, procoagulant states), medicines and illicit drug use, and sleep apnea [7,8]. Also, racial disparities, which encompass socioeconomic factors, clustering of certain vascular risk factors, as well as genetic predisposition, may contribute to stroke risk [9]. Finally, other mechanisms may lead to stroke in these patients, such as cervical artery dissection, rare cardiac causes of stroke (endocarditis, benign cardiac tumors, patent foramen ovale [PFO]), vasculitis, monogenic conditions (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL, or Fabry's disease) [10] or diagnostic and therapeutic interventions.

The main goal of our study was to assess the clinical characteristics, stroke subtype etiological classification and long-term outcome of AIS patients without an EVRF. Specifically, a large cohort of consecutive AIS patients admitted to a single stroke center was analyzed, a subgroup of patients without an EVRF was identified and they were compared to AIS patients who had at least one EVRF. Several variables, including (i) clinical characteristics (demographics, non-EVRFs and comorbidities, stroke severity); (ii) radiological and metabolic characteristics; (iii) etiological classification of stroke; and (iv) 12-month recurrence rate and 12-month functional outcome were compared between the two subgroups.

METHODS

Data source and study design

All consecutive patients from the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) between January 2003 and December 2018 were retrospectively studied. ASTRAL is a single-center-based cohort study of AIS patients admitted to the stroke unit and/or intensive care unit of Lausanne University Hospital within 24 h of last well time, as published previously [11]. For this study, all AIS patients with a complete assessment of EVRFs (see below) were included. For the 12-month outcome analysis, patients admitted up to December 2017 were considered.

For each patient, a large range of prespecified parameters in ASTRAL were prospectively collected, including demographics (age, sex, ethnicity and health insurance status), vascular risk factors and comorbidities as defined below, National Institutes of Health Stroke Scale [NIHSS] and clinical stroke symptoms. Information about prestroke handicap (estimated by the modified Rankin Scale [mRS]) and medical treatment was noted. Also, multiple physiological and laboratory acute parameters were registered, including temperature, systolic and diastolic blood pressure, glucose, creatinine, total cholesterol, C-reactive protein, hemoglobin and hematocrit. For acute neuroimaging, acute brain imaging on admission (computed tomography [CT] scan or magnetic resonance imaging [MRI]) was assessed for early ischaemic changes, chronic stroke lesions and the presence of leukoaraiosis. Information about the vascular territory of acute stroke and the affected site was collected. Vascular imaging (CT OR MRI based) was reviewed to judge the presence and site of occlusion and the status of collateral circulation. In addition, the following time metrics were determined: interval from last proof of good health (LPGH) to awakening or found, interval from LPGH to hospital arrival (i.e., onset-to-door time) and interval from LPGH to acute treatment (i.e., onset-to-needle time). The acute treatment type (including intravenous thrombolysis and/or endovascular treatment) was recorded. Regarding the stroke mechanism, the classical TOAST classification system [12] was adopted and the following etiological categories were added: "embolic strokes of undetermined source" (ESUS), including patients with cryptogenic stroke, an embolic pattern and risk of paradoxical embolism score <7); "PFO-related stroke" (defined as ESUS with risk of paradoxical embolism score [RoPE] ≥7 and no other cause); "unknown cause, non-ESUS" (i.e., cryptogenic stroke without an embolic pattern); dissection; other determined/rare causes; and multiple/coexisting causes.

Functional outcome at 12 months was assessed with the mRS [13] in the stroke outpatient clinic or by phone interview [14] by mRS-certified medical personnel. Stroke recurrences (including transient ischaemic attacks) and death within the first 12 months were assessed in the same way and analyzed together.

Established vascular risk factors (EVRFs) and other comorbidities

Vascular risk factors were considered as "established" if their odds ratio (OR) or hazard ratio (HR) was significantly elevated, as in two recent major population-based studies, INTERSTROKE [1] and the Global Burden of Disease stroke risk factor assessment [2]. The definition of each EVRF in ASTRAL followed internationally recognized criteria, as described in the baseline publication [11] and in Table S1. A specific

EVRF was considered to be present if it had been diagnosed before the index stroke, or if it was newly discovered during the hospital stay.

Using this approach, the following EVRFs were considered for the current study: hypertension, diabetes mellitus, major cardiac causes, active smoking status, dyslipidemia, obesity, depression or psychosis, alcohol abuse, personal history of stroke or transient ischaemic attack or retinal ischaemia (for detailed definitions of these risk factors see Table S1).

Age is a clearly recognized risk factor for stroke. However, given that no clear cut-off of when age becomes an important risk factor emerged, it was decided to perform the analysis in two separate populations using the conventional cut-off of 55 years, that is to analyze the data in a "younger" (<55 years) and "older" (≥55 years) population.

Some EVRFs according to INTERSTROKE [1] and the Global Burden of Disease stroke risk factor assessment [2] were not available in our registry and therefore were not analyzed in this analysis. These included waist-to-hip ratio, information on diet and physical activity, ratio of apolipoprotein B to A1, psychosocial stress, history of head trauma, family history of stroke and cardiovascular disease, and air pollution.

Given their controversial role across previous studies, the following were considered as "non-established" risk factors: sex (whose effect may depend on age [15]), migraine [3], PFO [16,17] oral contraceptive use/hormone replacement therapy [18], suspected or documented sleep apnea syndrome [19], symptomatic peripheral arterial disease, oncological disease [20] and other comorbidities as listed below.

In addition, the following comorbidities were analyzed according to the Elixhauser [21] and Charlson indexes [22]: congestive heart failure, pulmonary circulation disorders, chronic paralysis and hemiplegia, dementia, other neurological disorders, chronic pulmonary disease, hypothyroidism, renal failure, liver disease, peptic ulcer disease, acquired immunodeficiency syndrome, rheumatoid arthritis, coagulopathy, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemia and drug abuse. These were considered as non-EVRFs too.

Statistics and ethical considerations

First, demographics, clinical stroke characteristics and comorbidities were compared between patients without an EVRF and patients with one or more EVRFs in the younger (<55 years) and the older (≥55 years) populations, in univariate analyses. Then, logistic regression analysis (LRA) was performed to identify independent associations of non-established risk factors and comorbidities with absence of EVRFs, in the overall study cohort and in the younger and older subgroups. This was done via a stepwise elimination method, starting with a model including all candidate covariates and then applying a software-based backwards elimination of non-significant variables.

A second series of univariate analyses was performed comparing radiological and metabolic characteristics of patients without EVRFs and patients with one or more EVRFs in the younger and older populations.

The third analysis focused on stroke mechanisms, using other demographic and clinical variables for adjustment. Again, this analysis was carried out in the overall study cohort and in younger and older subgroups.

For all LRAs, if no non-EVRF patients were observed in one of the groups (separation problem), Firth's method was used to estimate the OR [23].

Finally, functional outcome at 12 months was assessed with an mRS shift analysis, adjusted for age, stroke severity, Alberta Stroke Program Early Computed Tomography Score [ASPECTS], stroke etiology and significant variables from the first LRA (sex, private health insurance, vascular territory, presence of PFO, sleep apnea syndrome and renal failure). For the comparison of further events in the first 12 months after the index stroke between EVRF and non-EVRF groups, stroke recurrence and mortality were combined due to the relatively small number of each event in the non-EVRF group. Patients at the time of lost to follow-up were censored, and a Cox proportional hazards model was applied.

Missing data were imputed using multivariate imputation by chained equations. Statistical analyses were conducted using R statistical software version 3.4.2 (R Core Team 2017, R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria).

The cantonal commission on ethics in human research (CER-Vaud) approved the scientific use of anonymized data from ASTRAL according to local legislation. The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Baseline characteristics

During the study period, 4889 AIS patients were included. Of these, 103 (2.1%) patients showed no EVRF. The median age of the patients was 73.8 (interquartile range, IQR, 20.3) years and 44.4% were female (Table 1); the most frequent stroke mechanism was cardioembolism (31.5%), followed by large artery atherosclerosis (14.9%) and small vessel disease (10.8%) (Table 1).

In the population aged <55 years (N = 746), patients without an EVRF (N = 64, 8.5%) were younger and more frequently female compared to patients with at least one EVRF. In the population aged ≥55 years (N = 4143), patients without an EVRF (N = 39, 1.0%) were more frequently female. For further characterization of these two populations see Tables S2, S3, S4, S5, S6 and S7 in Appendix S1.

Clinical variables independently associated with the absence of EVRFs

In the LRA of the whole population, patients without an EVRF were significantly younger, more frequently female and had private health insurance. They had stroke that more frequently involved both

TABLE 1 Patient characteristics of the overall cohort, including stroke mechanisms

Variable	Study cohort (*N* = 4889)	No EVRF (*n* = 103)	Any EVRF (*n* = 4786)	OR	95% CI
Demographics					
Age	73.8 (20.3)	46.7 (38.3)	74.0 (19.7)	0.93*	0.92–0.94
Sex, female	2170 (44.4%)	62 (60.2%)	2108 (44.1%)	1.92*	1.29–2.86
Ethnicity, non-Caucasian	175 (3.59%)	7 (6.8%)	168 (3.5%)	2.00	0.91–4.37
Private health insurance	874 (18.1%)	23 (22.6%)	851 (18.0%)	1.33	0.83–2.13
Comorbidities					
Migraine (±aura)	243 (5.0%)	15 (14.6%)	228 (4.8%)	3.39*	1.93–5.95
PFO or atrial septal defect	440 (33.3%)	37 (68.5%)	403 (31.8%)	4.68	2.6–8.41
Active cancer	273 (5.6%)	7 (6.8%)	266 (5.6%)	1.23	0.57–2.69
Sleep apnea syndrome	1070 (22.6%)	3 (2.9%)	1067 (23.0%)	0.10	0.03–0.32
Drug abuse	101 (2.1%)	0 (0%)	101 (2.1%)	0.22	0.01–3.66
Treatment before stroke					
Aspirin	1574 (32.3%)	6 (5.8%)	1568 (32.8%)	0.13*	0.06–0.29
Contraceptive use in females	104 (2.2%)	15 (14.6%)	89 (1.9%)	8.89*	4.95–15.98
Clinical stroke characteristics					
NIHSS on admission	6 (10)	7 (14)	6 (10)	1.03*	1.01–1.06
Vigilance impairment	576 (12.0%)	19 (18.5%)	557 (11.8%)	1.69*	1.02–2.79
Stroke etiologies					
Atherosclerosis	709 (14.9%)	3 (2.9%)	706 (15.2%)	0.17*	0.05–0.53
Cardioembolism	1497 (31.5%)	6 (5.8%)	1491 (32.0%)	0.13*	0.06–0.30
Lacunar	514 (10.8%)	4 (3.9%)	510 (11.0%)	0.33*	0.12–0.90
Dissection	190 (4.0%)	21 (20.4%)	169 (3.6%)	6.80*	4.11–11.25
ESUS	654 (13.7%)	14 (13.6%)	640 (13.7%)	0.99	0.56–1.75
Undetermined, and/or incomplete work-up	511 (10.7%)	16 (15.5%)	495 (10.6%)	1.55	0.90–2.66
Other determined, rare causes	237 (5.0%)	12 (11.7%)	225 (4.8%)	2.60*	1.40–4.81
Multiple/coexisting causes	295 (6.2%)	0 (0%)	295 (6.3%)	0.07	0.00–1.16
PFO	153 (3.2%)	27 (26.2%)	126 (2.7%)	12.78*	7.96–20.51

Note: Continuous variables are reported as median (and interquartile range), whereas categorical variables are reported as numbers (and percentages). Results from the univariate analysis in the "No EVRF" and "Any EVRF" groups are reported as odds ratio (OR) and 95% confidence interval (CI).

Abbreviations: ESUS, embolic stroke of undetermined source; EVRF, established vascular risk factor; NIHSS, National Institutes of Health Stroke Scale; PFO, patent foramen ovale.

*Asterisks denote significant differences in the univariate comparison.

anterior and posterior circulation. Contraceptive use in females and PFO were more common, and sleep apnea syndrome and renal failure less prevalent (Table 2).

LRA of the population aged <55 years showed that the absence of an EVRF was significantly associated with a higher prevalence of PFO and contraceptive use in females, and a lower prevalence of sleep apnea syndrome (Table 2). In patients aged ≥55 years, the LRA demonstrated that patients without an EVRF were significantly more often female, privately insured and affected by active cancer (Table 2).

Stroke etiology in patients without an EVRF

The LRA exploring the stroke mechanism in patients with and without EVRFs showed that ischaemic stroke in patients without an EVRF was more often PFO-related and less often due to the usual stroke mechanisms, that is, atherosclerosis, cardioembolism and small vessel disease (Table 3).

In the population aged <55 years, PFO emerged as the most important stroke etiology, whereas in patients >55 years stroke was less frequently due to atherosclerosis and cardioembolism (Table 3). Arterial dissections were more frequent in patients without an EVRF in the univariate analysis (Table 1) but not in the LRA.

Long-term outcome in patients without an EVRF

In the unadjusted analyses, the proportions of functional independence (mRS = 0–2) at 12 months were similar in patients with and without EVRFs, both in younger and older populations. Similarly, the

TABLE 2 Results from the logistic regression analysis (LRA) exploring the clinical characteristics of the subgroup of patients without an EVRF compared to the subgroup of patients with at least one EVRF in the study cohort

Variable	OR	95% CI	*p* value
Total study cohort (*N* = 4889)			
Age >55 years	0.13	0.08–0.20	<0.001
Sex, female	1.82	1.16–2.84	0.009
Private health insurance	2.02	1.21–3.35	0.007
Anterior and posterior circulation involvement	3.38	1.26–9.05	0.015
PFO or septal atrial defect	2.28	1.25–4.17	0.007
Sleep apnea syndrome	0.15	0.05–0.48	0.001
Renal failure	0.10	0.01–0.75	0.025
Contraceptive use	2.01	0.01–4.00	0.047
Study population aged <55 years (*N* = 746)			
Patent foramen ovale	2.76	1.50–5.08	0.001
Sleep apnea syndrome	0.09	0.01–0.63	0.016
Contraceptive use	2.75	1.40–5.41	0.003
Study population ≥55 years (*N* = 4143)			
Sex, female	2.84	1.43–5.65	0.003
Private health insurance	2.36	1.22–4.57	0.011
Active cancer	3.27	1.34–7.94	0.009

Note: Results of the LRAs restricted to patients <55 years and ≥55 years are given at the end of the table. Only significant results are shown and are reported as odds ratio (OR) and 95% confidence interval (CI).

Results in all three analyses were adjusted for all independent variables that were significantly different in the univariate analysis, and for admission National Institutes of Health Stroke Scale and pre-stroke modified Rankin Scale.

Abbreviations: EVRF, established vascular risk factor; PFO, patent foramen ovale.

TABLE 3 Results from the logistic regression analysis (LRA) exploring stroke etiologies in the subgroup of patients without an EVRF compared to the subgroup of patients with at least one EVRF in the total study cohort

Stroke etiology	OR	95% CI	*p* value
Total study cohort[a] (*N* = 4889)			
Atherosclerosis	0.18	0.06–0.57	0.004
Cardioembolism	0.14	0.05–0.34	<0.001
Small vessel disease	0.33	0.11–0.93	0.037
PFO-related stroke	3.02	1.44–6.32	0.003
Study population aged <55 years[b] (*N* = 746)			
PFO-related stroke	3.07	1.74–5.42	<0.001
Study population aged ≥55 years[b] (*N* = 4143)			
Atherosclerosis	0.20	0.06–0.73	0.014
Cardioembolism	0.07	0.02–0.26	<0.001

Note: Results of the LRAs restricted to patients <55 years and ≥55 years are given at the end of the table. Only significant results are shown and reported as odds ratio (OR) and 95% confidence interval (CI).

Abbreviations: EVRF, established vascular risk factor; PFO, patent foramen ovale.

[a]Results adjusted for age ≥55 years, sex, National Institutes of Health Stroke Scale on admission and contraception in women.

[b]Results adjusted for sex, National Institutes of Health Stroke Scale on admission and oral contraceptive use in women.

frequencies of recurrent cerebrovascular events or death did not show significant differences across the two groups of patients (Table 4).

After adjusting for potential confounders and stroke mechanisms, patients without an EVRF presented worse clinical outcome at 12 months (Rankin shift OR_{adj} 0.64; 95% confidence interval 0.43–0.96).

The unadjusted Kaplan–Meier curve of stroke recurrence and mortality is shown in Figure S1 (Appendix S1). The adjusted Cox model showed a significantly higher risk of stroke recurrence and death over 12 months in patients without an EVRF (HR_{adj} 2.11; 95% confidence interval 1.19–3.74). This result could be attributed mainly to the higher mortality rate in patients without an EVRF (Table 4).

TABLE 4 Unadjusted long-term outcome measures at 12 months in the cohorts aged <55 years and ≥55 years, with subgroups of patients with no EVRF and with one or more EVRFs

Population <55 years	Study cohort (*N* = 746)	No EVRF (*N* = 64)	Any EVRF (*N* = 682)	OR	95% CI
Functional independence (mRS = 0–2), *n* (%)	514 (79.7%)	48 (80%)	466 (79.7%)	1.02	0.53–1.98
mRS, median (IQR)	1 (2)	1 (2)	1 (1)	1.01	0.85–1.19
Recurrent cerebrovascular events or death, *n* (%)	107 (16.3%)	9 (14.7%)	98 (16.4%)	0.88	0.42–1.84
Time to first recurrent event, days	10 (59.8)	8 (10)	10 (61.9)	0.98	0.94–1.02
Deaths, *n* (%)	43 (6.67%)	6 (10%)	37 (6.32%)	1.65	0.66–4.08
Population ≥55 years	**Study cohort (*N* = 4143)**	**No EVRF (*N* = 39)**	**Any EVRF (*N* = 4104)**	**OR**	**95% CI**
Functional independence (mRS = 0–2), *n* (%)	1850 (53.7%)	18 (47.4%)	1832 (53.8%)	0.77	0.41–1.47
mRS, median (IQR)	2 (4)	3.5 (5)	2 (4)	1.15	1.00–1.33
Recurrent cerebrovascular events or death, *n* (%)	902 (3%)	11 (29.7%)	891 (3%)	1.21	0.59–2.45
Time to first recurrent even, days	52 (137.7)	4 (0)	52 (138.7)	0.88	0.59–1.33
Deaths, *n* (%)	854 (24.8%)	15 (39.5%)	839 (24.6%)	1.99*	1.04–3.84

Note: For the adjusted functional outcome (Rankin shift), see the Results section in the text.

Abbreviations: CI, confidence interval; EVRF, established vascular risk factor; IQR, interquartile range; mRS, modified Rankin Scale; OR, odds ratio.

*Asterisk denotes significant difference in the univariate comparison.

The evolution of the HR with time is in concordance with the Kaplan–Meier survival curves: in patients without an EVRF, there are proportionally more events in the days following the index event, but no events are observed after about 70 days (Figure S2, Appendix S1).

DISCUSSION

In a consecutive cohort of 4889 AIS patients assessed for multiple vascular risk factors, we demonstrated that only 2.1% showed no EVRFs. Such patients were more often younger, female, contraceptive users and privately insured. They had less sleep apnea and renal failure. Classical stroke mechanisms like atherosclerosis, small vessel disease and cardioembolism were less frequent in patients without an EVRF, but PFO-related stroke was more frequent. Despite a more favorable risk factor profile, these patients had a worse 12-month functional outcome.

Although previous epidemiological studies have shown that EVRFs account for more than 90% of the population attributable risk for ischaemic stroke [1,2], it was surprising to find only 2.1% of our AIS population to be free of EVRFs. Our proportion may even be an overestimation, as the risk related to several other EVRFs such as diet, physical activity, ratio of apolipoprotein B to A1, waist-to-hip ratio, head trauma, family history of stroke and cardiovascular disease, and air pollution was not evaluated. As expected, the proportion of non-EVRF patients was higher in patients below age 55 years (8.6%), whereas it was even lower in patients >55 years (1.0%).

Data on stroke populations without major risks factors are scant and mostly focus on stroke in young adults below age 55 [24–26]. There is growing evidence of an increasing trend of early-onset stroke incidence [27]. In our cohort of consecutive AIS, we demonstrated that approximately 15% of all AIS occurred in patients below the age of 55 years, calling for a better knowledge of stroke risk factors and causes in this population.

Amongst the younger subgroup of patients, we found that more than 90% had at least one traditional vascular risk factor. Amongst the young patients without an EVRF, a major association with the presence of a PFO was found [28], both as a comorbidity and a stroke mechanism. This adds further weight to the recommendation for PFO closure in patients without other significant risk factors [29,30]. Similarly, oral contraceptive use in women was strongly associated with absence of EVRFs in our cohort. This correlation in young patients without EVRFs seems even more important than in epidemiological data of unselected women [18]. Interestingly, the association with hormone therapy was independent of the PFO-related stroke risk in our population, suggesting that paradoxical embolization through a PFO is insufficient to explain these strokes and that a prothrombotic mechanism may exist in these patients in the arterial circulation . Our data indicate that oral contraceptive use in young female stroke patients is higher than previously reported [31], and that this treatment has a direct impact on patients. These results suggest avoiding estrogen-containing oral contraception whenever possible after a previous ischaemic stroke, in line with current recommendations [32,33].

In the older stroke population, the proportion of patients with no EVRF (1%) was lower than in the younger patients. The reason for female sex being an independent predictor in this population is speculative. It may stem from the fact that atrial fibrillation (overt and occult) increases steeply with age and women generally live longer than men [34,35].

A higher prevalence of active cancer in the group of older patients with no EVRF is described and, consistently, a higher frequency of multiterritorial cerebral infarctions and of stroke related to other/rare causes. This suggests that malignancy could play a relevant role in stroke occurring in patients with no traditional risk factors and that, in cancer-related stroke, several pathophysiological mechanisms (different from cardioembolism and atherosclerotic mechanisms) could contribute to stroke occurrence. These could include coagulation disorders and infections, or complications related to therapeutic interventions [36].

It was surprising that the prognosis of non-EVRF patients at 1 year was worse than the comparison group, with a shift towards higher disability in the adjusted analysis. Given the higher risk factor load and (in general) higher comorbidity load in patients with EVRFs, rather the contrary was expected. This difference was present despite adjustment for the initially higher stroke severity in non-EVRF patients and was associated with a higher risk of stroke recurrence or death in the Cox regression analysis. One possible explanation may be the higher prevalence of active oncological disease in elderly non-EVRF patients, leading to death within 12 months after the index stroke.

The clinical implications of our analysis are severalfold. First, the extremely high proportion of ischaemic stroke patients with EVRFs underlines the importance of primary prevention, that is, the detection and treatment of risk factors before a first cerebrovascular event. Secondly, oral contraceptive use and a PFO emerged as decisive risk factors in otherwise healthy young stroke patients. Translating this finding into clinical practice, our study highlights the importance of an extensive diagnostic work-up after a cryptogenic stroke in the young, which might include the screening for a hypercoagulation state and for structural cardiac disease; also, the likelihood of a causal relationship between PFO and stroke should be properly assessed in patients with cryptogenic stroke and PFO, to ensure the best management in terms of stroke recurrence prevention. Thirdly, active cancer should be considered as a cause (known or unknown) of ischaemic stroke in elderly stroke patients without EVRFs. In this population of stroke patients, screening for hidden malignancy (by serological or radiological tests) should be performed, especially in those showing characteristics suggesting a cancer-related stroke mechanism, such as elevated D-dimer and a multiterritorial cerebral involvement. Finally, stroke patients without EVRFs cannot be assured that their long-term functional outcome is better than for other patients harboring one or more EVRFs; in fact, the opposite seems true.

Interesting research questions for future research may be derived from our results. Further research could increase our knowledge on unusual mechanisms causing stroke in patients without established risk factors. This may include the study of inherited or acquired thrombophilic disorders that could predispose to cerebral embolism (such as the study of gene–gene and gene–environment interactions and their impact on the resultant clinical manifestations); the study of mechanisms by which migraine with aura increases stroke risk (encompassing cortical spreading depression, or higher prevalence of other cardiovascular risk factors amongst migraineurs); and the understanding of the interactions between multiple less well documented vascular risk factors (such as the biological link between PFO and migraine).

The limitations of our study include its retrospective and single-center nature, investigating a typical Western Caucasian population. Secondly, some risk factors were not available in our stroke registry, including some well-known vascular risk factors (such as diet, physical inactivity or family cerebrovascular history) as well as some emerging risk factors (such as air pollution), potentially leading to overestimation of patients without EVRFs. Thirdly, the presence of a vascular risk factor was defined as both “known” or “newly diagnosed”; it was therefore not possible to investigate the proportion and impact of previously present, but undetected, EVRFs.

In conclusion, we demonstrated that absence of EVRFs in ischaemic stroke patients is rare and that several “minor” risk factors gain particular relevance in such patients. In particular, PFO and contraceptive use emerged as major predictors of stroke in patients below the age of 55 years, and female sex and cancer in older patients. Further studies should address these issues in other ethnic and geographical populations, and investigate the impact of existing but undiagnosed vascular risk factors in ischaemic stroke patients.

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CONFLICT OF INTEREST

Stefania Nannoni reports no disclosure. Ali Scherz-Moussa Youma reports no disclosure. Michael Amiguet reports no disclosure. Ashraf Eskandari reports no disclosure. Davide Strambo reports no disclosure. Patrik Michel in the last 3 years has received research grants from the ERISTA program (BMS/Pfizer) and consulting and speaker fees from Amgen and Medtronic. All support goes to his institution for stroke education and research.

AUTHOR CONTRIBUTIONS

Stefania Nannoni: conceptualization (equal); data curation (equal); writing original draft (lead). Ali Scherz-Moussa Youma: conceptualization (equal); data curation (equal); writing original draft (equal). Michael Amiguet: formal analysis (lead); methodology (equal); writing review editing (equal). Ashraf Eskandari: data curation (equal); methodology (equal); resources (equal). Davide Strambo: conceptualization (equal); data curation (equal); methodology

(equal); writing review editing (equal). Patrik Michel: conceptualization (equal); methodology (lead); supervision (lead); writing review editing (lead).

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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