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ORIGINAL ARTICLE

Undiagnosed major risk factors in acute ischaemic stroke patients: frequency, profile, stroke mechanisms and outcome

André Rêgo[1,2] | Stefania Nannoni[3] | Ali Scherz[1] | Ashraf Eskandari[1] | Alexander Salerno[1] | Miguel Pereira[4] | Davide Strambo[1] | Patrik Michel[1]

[1]Stroke Center, Service of Neurology, Department of Clinical Neurosciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

[2]Hospital Prof. Doutor Fernando Fonseca, Serviço de Neurologia, Amadora, Portugal

[3]Stroke Research Group, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

[4]plaindata.ai, Cambridge, UK

Correspondence
André Rêgo, Stroke Center, Service of Neurology, Department of Clinical Neurosciences, Lausanne University Hospital and University of Lausanne, Switzerland.
Email: andre.fm.go@gmail.com

Abstract

Background and purpose: There is scarce clinical information about the clinical profile of patients with acute ischaemic stroke with previously undiagnosed major vascular risk factors (UMRFs).

Methods: This was a retrospective analysis of data from the Acute Stroke Registry and Analysis of Lausanne registry between 2003 and 2018 with univariate and multivariate logistic regression analyses comparing clinical profiles of patients with UMRFs to patients with at least one previously diagnosed MRF (DMRF).

Results: In all, 4354 patients (median age 70 years [interquartile range 15.2], 44.7% female) were included after excluding 763 (14.9%) for lack of consent and three for missing information. Amongst 1125 (25.8%) UMRF patients, 69.7% ($n = 784$) had at least one newly diagnosed MRF and the others none. The newly detected MRFs were dyslipidaemia (61.4%), hypertension (23.7%), atrial fibrillation (10.2%), diabetes mellitus (5.2%), ejection fraction <35% (2.0%) and coronary disease (1.0%). Comparing UMRF patients to DMRF patients, multivariate analysis showed a positive association with lower age, non-Caucasian ethnicity, contraceptive use (<55 years old), smoking (≥55 years old) and patent-foramen-ovale-related stroke mechanism. A negative association was found with pre-stroke antiplatelet use and higher body mass index. Functional outcome did not differ. Cerebrovascular recurrences were similar between groups.

Conclusions: In this large single-centre cohort, 69.7% of patients with acute ischaemic stroke and UMRF were newly diagnosed with at least one new MRF, the most common being dyslipidaemia, hypertension or atrial fibrillation. Patients of the UMRF group were younger, more often smokers and on contraceptives, and had more patent-foramen-ovale-related strokes.

KEYWORDS
cardiometabolic risk factors, ischaemic stroke, prognosis, treatment outcome

INTRODUCTION

The majority of studies evaluating newly diagnosed risk factors in patients with acute ischaemic stroke (AIS) focused on single or selected risk factors only, namely atrial fibrillation, dyslipidaemia, structural cardiac abnormalities and type 2 diabetes mellitus. Such studies indicated that atrial fibrillation was newly diagnosed in 10.5%–11.2% after stroke [1, 2]; dyslipidaemia in 20.4% [3]; type 2 diabetes mellitus in 9.4%–16.4% [2, 4]; and structural cardiac disease in about 3% [2].

Hypertension is the most important modifiable risk factor and the combination of metabolic risk factors including hypertension, diabetes mellitus and dyslipidaemia accounts for more than two-thirds of stroke-related disability-adjusted life-years [5]. Identifying, preventing and treating vascular risk factors in the general population before stroke could reduce AIS incidence by as much as 75% [6]. Screening programmes, several public health measures (including tobacco legislation, exercise promotion and salt reduction) and polypill strategies may add to stroke prevention [7, 8].

There is insufficient information about the frequency of previously undiagnosed (or unknown) major vascular risk factors (MRFs) in patients with AIS. One study confirmed the existence of an important share of patients with AIS and previously inadequate treatment of several vascular risk factors [9]. Recent work from our group on non-established vascular risk factors found that only 2% of patients with AIS had no MRFs at all [10]; this study did not, however, assess the frequency of undiagnosed MRFs (UMRFs), or patient profiles and outcomes in patients with no known MRFs before stroke onset.

AIMS

The main goal of our study was to assess the vascular risk factors, comorbidities, clinical characteristics, stroke aetiologies and long-term outcome of AIS patients with UMRFs compared to patients with previously diagnosed MRFs (DMRFs). Our main hypotheses were that a significant proportion of underdiagnosed vascular risk factors, a higher prevalence of less well-established vascular risk factors and a higher number of infrequent stroke mechanisms in patients with UMRFs would be found.

METHODS

Registry description and data collection

This was a retrospective study of data from included patients from the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) between January 2003 and December 2018. ASTRAL is a single-centre-based cohort of AIS patients admitted to the stroke unit and/or intensive care unit of Lausanne University Hospital within 24 h of last known well time [11]. The exclusion criteria were a patient's refusal to reuse their clinical data for retrospective research and missing data on one of the considered potential undiagnosed MRFs.

Data were collected in a pre-specified manner and included demographics (age, sex, ethnicity and insurance status) and clinical variables (National Institutes of Health Stroke Scale [NIHSS], vigilance impairment at admission, acute temperature, acute blood glucose and acute systolic blood pressure). Vascular risk factors were considered as 'major' according to the INTERSTROKE study [12]. Medical comorbidities were collected using the Elixhauser and Charlson indices [13, 14].

Acute imaging data consisted mostly of computed tomography (CT) and CT angiography of cervical and intracranial arteries. Alberta Stroke Program Early CT Score (ASPECTS) was determined for acute non-contrast CT. Pre-treatment data included pre-stroke use of antiplatelets and contraceptives.

Stroke aetiology was defined according to the TOAST classification system [15], but some categories were added: dissection; embolic stroke of undetermined source (ESUS); rare (other determined) causes; patent-foramen-ovale-(PFO)-related stroke (defined as ESUS with risk of paradoxical embolism score ≥7 and no other cause) and unknown cause non-ESUS stroke (cryptogenic stroke without an embolic pattern).

Functional outcome was assessed using the modified Rankin Scale (mRS) at 12 months during in-person follow-up in the stroke outpatient clinic, or by telephone interview, both by mRS-certified medical personnel.

Recurrences were considered present in survivors if at least one new episode of ischaemic stroke, transient ischaemic attack (TIA), retinal ischaemia (persistent or transient), intracerebral haemorrhage or subarachnoid haemorrhage was diagnosed, ascertained by a review of medical charts and neuroimaging at the 12-month follow-up.

Undiagnosed major vascular risk factors (UMRFs)

Major risk factors were defined according to the INTERSTROKE study, with the exception of diet and exercise habits, both not available in ASTRAL.

The MRFs that would by nature be known to patients or physicians before stroke were not included in the calculations of frequencies (i.e., active smoking, body mass index [BMI] >30 kg/m^2, mechanical valves, depression/psychosis [used according to the Elixhauser definitions as surrogates for 'stress' in INTERSTROKE], alcohol abuse and personal history of stroke/TIA/retinal ischaemia) [13]. These naturally known MRFs were distinguished from potential UMRFs, including hypertension, dyslipidaemia (low-density lipoprotein >100 mg/dL, used as a surrogate for apolipoprotein profile in INTERSTROKE), diabetes mellitus, atrial fibrillation/flutter and other structural cardiac disease (newly diagnosed and documented coronary artery disease, and/or dilated cardiomyopathy with ejection fraction <35%, low ejection fraction) [12].

Study design and statistics

Patients were excluded who refused consent (see below) or had missing dependent variables.

Each patient could have (1) already naturally known MRFs (from the four MRFs usually known before the current stroke) and (2) newly diagnosed MRFs at the time of stroke (from the five potentially undiagnosed MRFs), as depicted in Figures 1 and S1.

Two groups were then created, and patients were considered as belonging to the UMRF group if none of the five potentially diagnosed MRFs above were diagnosed before the stroke. The comparison group had at least one of the five MRFs diagnosed before the current stroke (DMRF group). The frequency of already known and newly diagnosed MRFs in the overall population and in each patient group was described first.

A univariate logistic regression analysis (UVA) was then carried out to compare the UMRF and DMRF groups concerning demographics, vascular risk factors, other comorbidities, pre-stroke treatments and clinical presentation. All variables with a p value <0.05 in the UVA were then included in a multivariate logistic regression analysis (MVA) to assess confounding factors and determine better the effects of each covariate. Additionally, both the UVA and MVA were done separately in subgroups of patients <55 years old and ≥55 years old.

A second MVA was performed with the aim of evaluating in detail the differences in stroke mechanisms between the two groups. This analysis included the stroke mechanisms as covariates and it was adjusted for age, sex and the already known MRFs (BMI, smoking, alcohol, mechanical valve and depression/psychosis).

To assess functional outcome, a Rankin shift analysis was performed with mRS as an ordinal outcome variable with six levels: levels 5 and 6 were merged into a single level and the remaining levels from 0 to 4 were retained as distinct. This model assumes that the differences in the 'in treatment' odds ratio (OR) between every two consecutive levels are constant and therefore a single OR is obtained for each variable, corresponding to the risk difference in cases and controls at the same level. Variables used for adjustment were age, sex, NIHSS at admission, acute level of consciousness, pre-stroke mRS, acute glucose, initial ASPECTS on non-contrast CT, peripheral artery disease, chronic kidney disease, active cancer, depression/psychosis, stroke mechanism and all significant variables from the first MVA.

Recurrence of cerebrovascular events at 12 months was investigated using a logistic regression model adjusted for age, sex, peripheral artery disease, cancer, depression, psychosis, aspirin intake before stroke, TOAST, admission ASPECTS, previous clinical stroke or TIA, pre-stroke mRS and all significant variables from the first MVA.

All statistical analyses were carried out with R statistical software version 4.1.1 and RStudio version 1.4.1717. A type I error rate of 0.05 was considered as the threshold for statistical significance.

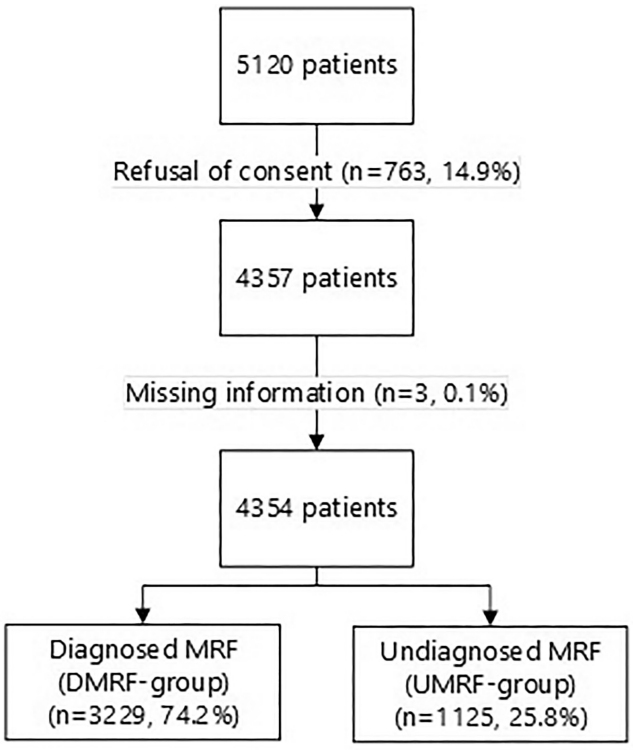

FIGURE 1 Patient inclusion flowchart. DMRF, diagnosed major risk factor; UMRF, undiagnosed major risk factor.

Ethical considerations

The ASTRAL database is approved by our institution as a clinical and research registry and follows institutional regulations. All data were anonymized before analysis following the principles of the Swiss Human Research Ordinance, excluding therefore the need for local ethics committee approval or active patient consent according to the Swiss Human Research Act and the applicable data protection legislation. Patient refusal of scientific use of their routinely collected data was honoured, and such patients were excluded from the study.

RESULTS

After excluding 766 (15.0%) of the 5120 eligible patients because of refusal of scientific use of their data (n=763) or missing information on the potentially UMRFs (n=3), 4354 were eligible for the analysis (see Figure 1). When comparing excluded with included patients, no statistically significant differences were found regarding sex or NIHSS, but the excluded patients were slightly older (see Table S1).

In the overall population (n=4354, median age 70 years [interquartile range, IQR, 15.2], 44.7% female), both known and newly diagnosed MRFs were common: hypertension was present in 68.6% followed by dyslipidaemia (51.4%), atrial fibrillation (21.6%), structural cardiac disease (20.3%) and diabetes mellitus (17.2%), as described in Tables 1 and S2. The median number of undiagnosed MRFs was 2 (IQR 1) in the UMRF group and 3 (IQR 2) in the DMRF group.

TABLE 1 Univariate comparison of main demographics, clinical variables, major risk factors and comorbidities.

Variable	Study cohort (*N* = 4354)	UMRF group (*N* = 1125)	DMRF group (*N* = 3229)	OR	95% CI lower	95% CI upper
Demographics						
Age	69.98 (15.21)	59.02 (17.32)	73.8 (12.29)	0.93	0.93	0.94
Sex (female)	1944 (44.66%)	495 (44%)	1449 (44.89%)	0.96	0.84	1.11
Ethnicity (Caucasian)	4193 (96.59%)	1065 (94.92%)	3128 (97.17%)	0.54	0.39	0.77
MRF always known before current stroke						
Body mass index	25.74 (4.66)	24.56 (4)	26.17 (4.8)	0.92	0.90	0.94
Smoking	1023 (23.74%)	380 (34.02%)	643 (20.14%)	2.04	1.76	2.38
Alcohol abuse	459 (10.61%)	117 (10.47%)	342 (10.65%)	0.98	0.78	1.22
Mechanical heart valve	93 (2.14%)	7 (0.62%)	86 (2.67%)	0.23	0.10	0.46
Psychosis	392 (9.07%)	101 (9.07%)	291 (9.07%)	1.00	0.79	1.26
Depression	208 (4.79%)	53 (4.73%)	155 (4.82%)	0.98	0.71	1.34
Potentially UMRF before current stroke						
Hypertension	2985 (68.56%)	267 (23.73%)	2718 (84.17%)	—	—	—
Dyslipidaemia	2238 (51.40%)	691 (61.42%)	1547 (47.91%)	—	—	—
Diabetes mellitus	750 (17.23%)	58 (5.16%)	692 (21.43%)	—	—	—
Atrial fibrillation	941 (21.61%)	115 (10.22%)	826 (25.58%)	—	—	—
Structural cardiac disease	885 (20.33%)	34 (3.02%)	851 (26.35%)	—	—	—

Abbreviations: CI, confidence interval; DMRF, diagnosed major risk factor; MRF, major risk factor; OR, odds ratio; UMRF, undiagnosed major risk factor.

TABLE 2 Multivariate comparison of demographics, clinical variables, vascular risk factors and comorbidities in subgroups of patients with age <55 years and ≥55 years.

Variable	OR	95% CI lower	95% CI upper	*p* value
≥55 years				
Body mass index	0.89	0.84	0.93	0.000
Smoking	1.71	1.10	2.68	0.018
PFO (± ASA)	1.29†	0.84	2.00	0.243
Congestive heart failure	0.51†	0.21	1.10	0.102
Aspirin intake (before stroke)	0.14	0.07	0.27	0.000
Contraceptive use in females (before stroke)	2.07†	0.59	7.24	0.247
<55 years				
Body mass index	0.86	0.80	0.91	0.000
Smoking	0.79	0.58	1.08	0.141
PFO (± ASA)	2.62	1.53	4.57	0.001
Congestive heart failure	0.42†	0.16	1.09	0.075
Aspirin intake (before stroke)	0.17	0.05	0.55	0.005
Contraceptive use in females (before stroke)	3.54†	1.08	15.02	0.054

Note: Non-significant differences in the univariate analysis are marked with †.

Abbreviations: ASA, atrial septal aneurysm; CI, confidence interval; OR, odds ratio; PFO, patent foramen ovale.

The DMRF group made up 74.2% of the population (3329/4354; see Tables 1 and S2). In this group, the combined frequency of known and newly diagnosed hypertension was 84.2%, followed by dyslipidaemia (47.9%), structural cardiac disease (26.3%), atrial fibrillation (25.6%) and diabetes mellitus (21.4%). When only considering new diagnoses, the incidence of hypertension was 8.6%, of dyslipidaemia 37.9%, of diabetes mellitus 4.1%, of atrial fibrillation 11.2%, of low ejection fraction 2.4% and of coronary artery disease 1.7%.

When comparing the UMRF and DMRF groups by MVA, UMRF patients showed a positive association with lower age, non-Caucasian

ethnicity, PFO, contraceptive use (in patients <55 years old) and smoking, as described in Table 2 (see Table S5). Negative associations were also found with antiplatelet use before the event and higher BMI.

Regarding stroke mechanisms, the MVA showed a higher frequency of PFO-related strokes and a lower frequency of large vessel, lacunar, cardiac or multiple coexisting causes in the UMRF group (see Tables 3, S4 and S6).

Functional outcome at 12 months in the unadjusted analysis was better in the UMRF group, but not different in the adjusted analysis (OR_{adj} for Rankin shift 1.13, IQR 0.93–1.38), as shown in Tables 4 and S7. Cerebrovascular recurrences at 12 months were similar between groups (OR_{adj} 1.09, IQR 0.77–1.54).

TABLE 3 Multivariate comparison of stroke mechanism in subgroups of patients with age <55 years and ≥55 years.

Variable	OR‡	95% CI lower	95% CI upper	*p* value
≥55 years				
Atherosclerosis	0.67	0.47	0.97	0.031
Cardiac	0.26	0.18	0.37	0.000
Lacunar	0.79†	0.54	1.15	0.222
Multiple/coexisting causes	0.15	0.07	0.29	0.000
PFO (± ASA)	4.28	1.64	11.69	0.003
<55 years				
Atherosclerosis	0.37	0.14	0.92	0.036
Cardiac	0.12	0.04	0.31	0.000
Lacunar	0.16	0.06	0.41	0.000
Multiple/coexisting causes	0.05	0.00	0.49	0.019
PFO (± ASA)	2.63	1.02	6.79	0.043

Note: Non-significant differences in the univariate analysis are marked with †.

Abbreviations: ASA, atrial septal aneurysm; BMI, body mass index; CI, confidence interval; OR, odds ratio; PFO, patent foramen ovale.

‡Multivariate adjustment for age, sex, BMI, smoking, alcohol, mechanical valve, depression, psychosis.

DISCUSSION

In this single-centre cohort of patients with AIS, a large proportion (69.7%) of UMRF patients were found to have at least one MRF. This population of patients is younger, of non-Caucasian ethnicity, taking more oral contraceptives and less previous antiplatelet treatment. They less often have 'classic' stroke mechanisms and more often have PFO-related strokes. Long-term functional outcome and recurrences were similar between the two groups.

The most frequent undiagnosed MRFs in these apparently 'healthy' UMRF group patients were dyslipidaemia (61.4%), hypertension (23.7%) and atrial fibrillation (10.2%), respectively. When comparing our results with the literature a higher prevalence of dyslipidaemia was found, perhaps related to the diagnostic criteria that were used [3]. Regarding new atrial fibrillation and cardiac structural disease, similar incidences were reported for the acute phase of stroke [1, 2]. Interestingly, a lower frequency of newly diagnosed diabetes was found, possibly because other studies concentrated particularly on this topic, had older cohorts and used multiple and more sensitive tests, including for pre-diabetes [2, 4].

The positive association of UMRF with younger age, non-Caucasian ethnicity and smoking (in elderly patients) could be due to such patients being less inclined to visit medical doctors, either because of self-perception, neglect or difficulties in accessing healthcare, issues that could merit further investigation to improve stroke prevention. The association of UMRF with PFO and contraceptive pills may be because these stroke risk factors can stand independently of MRF [16]. It was expected that less antiplatelet use would be found in the UMRF group, as this is a surrogate marker for vascular patients whose risk factor profile is already well explored. A plausible explanation could not be found for a lesser association with overweight in this population, which may represent another 'obesity paradox'. The lower number of risk factors in the UMRF population

TABLE 4 Functional outcome and cerebrovascular recurrences at 12 months (univariate analysis).

Variable	Study cohort (*N* = 4354)	UMRF group (*N* = 1125)	DMRF group (*N* = 3229)	OR	95% CI lower	95% CI upper
Adjusted analysis						
Functional independence	—	—	—	1.13†,‡	0.93	1.38
Recurrent cerebrovascular events	—	—	—	1.09†,‖	0.77	1.54

Note: Non-significant differences in the univariate analysis are marked with †.

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; DMRF, diagnosed major risk factor; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; UMRF, undiagnosed major risk factor; OR, odds ratio; TIA, transient ischaemic attack; TOAST, trial of ORG 10172 in acute stroke treatment.

‡Functional outcome adjusted for age, sex, peripheral artery disease, chronic kidney disease, depression, psychosis, cancer, depression, psychosis, aspirin intake before stroke, TOAST, ASPECTS, NIHSS on admission, vigilance impairment, glucose at admission and pre-stroke mRS.

‖Recurrences adjusted for age, sex, peripheral artery disease, cancer, depression, psychosis, aspirin intake before stroke, TOAST, ASPECTS, previous clinical stroke or TIA and pre-stroke mRS.

may explain the lower frequency of traditional stroke mechanisms in the UMRF group.

The finding of similar functional outcome and recurrent cerebrovascular events in both groups could be explained by similar acute stroke treatments and rehabilitation protocols.

This analysis is different from our previous work on patients without any MRFs after a standardized stroke work-up [10]. There, the frequency of patients without any MRF was found to be 2%. Here, the incidence of at least one newly diagnosed MRF in the UMRF group was calculated and was found to be 69.7%.

The strengths of this study include the large population sample and its practical value on informing stroke-treating physicians when facing a patient with presumed absence of MRFs to avoid the use of clinical scores to stratify patients on vascular risk that rely on this knowledge (or the lack of it), but also public health professionals to further promote their screening especially amongst contraceptive users, smokers and people with difficulties in accessing healthcare.

The limitations are its retrospective and single-centre design; the analysed Western European population with easy access to preventive medicine may underestimate the incidence of UMRF in other healthcare settings as Switzerland has over 99% of the population fully covered or insured for primary care costs [17]. The exclusion of 15% of our patients from the analysis due to consent issues may limit the generalizability of results, despite the similar demographic profile of excluded patients. Furthermore, our register does not collect data as continuous variables for the majority of risk factors, nor is there information on diet and physical activity which are considered as MRFs in INTERSTROKE [12]. Finally, and for the same reasons, the MRF 'psychosocial factors' was replaced with 'history of depression and/or psychosis'.

CONCLUSION

In this large single-centre AIS cohort, 69.7% of patients with undiagnosed MRFs were newly diagnosed with at least one MRF, the most common being dyslipidaemia, hypertension and atrial fibrillation. Patients with UMRF were younger, non-Caucasian, smokers, contraceptive users (in patients <55 years old) and had more PFO-related strokes, but similar functional outcomes and recurrences as the group with at least one diagnosed MRF before stroke. These observations show the need for a systematic search of major and minor vascular risk factors in apparently 'healthy' stroke patients, for timely diagnosis and therapy to prevent further strokes, and should also alert public health measures in order to improve vascular risk factor awareness and their importance on general health and their importance on avoiding AIS.

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CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

André Rêgo https://orcid.org/0000-0002-3342-3515
Stefania Nannoni https://orcid.org/0000-0002-1825-1874

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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