

AI SYF: FIRST NATIONAL, PROSPECTIVE, MULTICENTER STUDY OF YOUNG PATIENTS WITH STROKE IN ARGENTINA

PABLO BONARDO¹, LUCIANA LEÓN CEJAS¹, JULIETA MAZZIOTTI¹, ALBERTO ZINNERMAN², MANUEL FERNÁNDEZ PARDAL¹, ALEJANDRA MARTÍNEZ², PATRICIA RICCIO³, SEBASTIÁN AMERISO⁴, EDUARDO BENDERSKY⁵, PEDRO NOFAL⁶, PATRICIA CAIROLA⁷, LORENA JURE⁸, ANDREA SOTELO⁹, IGNACIO CASAS PARERA¹⁰, ANALÍA SÁNCHEZ LUCEROS¹¹, LUCIANO SPOSATO³, RICARDO C. REISIN¹,
ON BEHALF OF AISYF INVESTIGATORS

¹Hospital Británico de Buenos Aires, ²Hospital Posadas, Buenos Aires, ³Fundación Favaloro, Buenos Aires, ⁴FLENI, Buenos Aires, ⁵INAREPS Mar del Plata, Buenos Aires, ⁶Sanatorio Parque Tucumán, Tucumán, ⁷Hospital Durand, Buenos Aires, ⁸Sanatorio Parque Rosario, Rosario, Santa Fe, ⁹Sanatorio Adventista del Plata, Libertador San Martín, Entre Ríos, ¹⁰Instituto de Oncología Ángel H. Roffo, Buenos Aires, ¹¹Academia Nacional de Medicina, Buenos Aires, Argentina

Abstract Up to 15% of all strokes affect young patients and the incidence of ischemic stroke in this population is rising. Nevertheless, there is limited information of cerebrovascular events in this population both in our country and in Latin America. The aim of our study was to evaluate the clinical characteristics and risk factors of young adults with stroke in Argentina. This is a prospective, multicenter study of stroke in young adults (18 - 55 years) in Argentina. Patients presenting with a cerebrovascular event within 180 days were included. Stroke subtypes were classified according to TOAST criteria. A total number of 311 patients were enrolled (men 53.9%, mean age: 43.3 years). Ischemic strokes occurred in 91.8% (brain infarcts 82.6%, transient ischemic attack 9.2%) and hemorrhagic strokes in 8.2%. The most frequent vascular risk factors (including ischemic and hemorrhagic strokes) were: hypertension 120 (41%), smoking 92 (31.4%), dyslipidemia 81 (27.6%) and, overweight/obesity: 74 (25.3%). Stroke subtypes were: large artery disease 12.3%, cardioembolism 7.5%, small artery occlusion 11.5%, other defined etiology 27.1%, and undetermined etiology 41.6%. Our study demonstrates that vascular risk factors are very frequent in young adults with stroke. Our findings underline that urgent strategies are required for primary and secondary stroke prevention in this group of patients.

Key words: cerebral hemorrhage, developing countries, young patients, ischemic stroke, stroke, Latin America

Resumen *AI SYF: primer estudio nacional, prospectivo y multicéntrico de pacientes jóvenes con ataque cerebral en Argentina.* Aproximadamente un 15% de todos los ataques cerebrovasculares afectan a pacientes jóvenes y su incidencia estaría en aumento. Existe escasa información sobre el ataque cerebral en esta población tanto en nuestro país como en Latinoamérica. El objetivo de nuestro estudio fue evaluar las características clínicas y los factores de riesgo de los adultos jóvenes con ictus en Argentina. Realizamos un estudio prospectivo y multicéntrico en adultos jóvenes (18-55 años) en Argentina, que presentaron un evento cerebrovascular dentro de los 180 días previos. Los subtipos de ictus se clasificaron según los criterios de TOAST. Se incluyeron un total de 311 pacientes (hombres 53.9%, edad media: 43,3 años). Los ataques cerebrovasculares isquémicos ocurrieron en el 91.8% (infartos cerebrales 82.6%, ataque isquémico transitorio 9.2%) y los eventos hemorrágicos correspondieron al 8.2%. Los factores de riesgo vascular más frecuentes (incluyendo los eventos isquémicos y hemorrágicos) fueron: hipertensión 120 (41%), tabaquismo 92 (31.4%), dislipidemia 81 (27.6%) y sobrepeso/obesidad: 74 (25.3%). Los subtipos de ictus isquémicos fueron: arteriopatía de gran vaso 12.3%, cardioembolismo 7.5%, oclusión de pequeña arteria 11.5%, otra etiología definida 27.1% y etiología indeterminada 41.6%. Los factores de riesgo vascular son muy frecuentes en los adultos jóvenes con ictus. Nuestros hallazgos subrayan que se requieren estrategias urgentes para la prevención primaria y secundaria del ictus en este grupo particular de pacientes en nuestro país.

Palabras clave: hemorragia cerebral, países en desarrollo, pacientes jóvenes, ataque cerebrovascular isquémico, ataque cerebral, América Latina

KEY POINTS

- Approximately 15% of all strokes affect young patients, in the most productive period of life. Recent evidence suggests an increasing incidence with variable mortality.
- Stroke is an important health problem in Latin America, but there are only few well designed population based stroke incidence studies.
- The 3 most frequent vascular risk factors in our population were hypertension, sedentarism, and smoking. At least 1 of them was present in nearly 75% of patients with ischemic disease.
- The recognition of etiologies and vascular risk factors among young patients with stroke is of outmost importance to develop public health policies with the aim of primary and secondary prevention

Approximately 15% of all strokes affect young patients, with substantial consequences because affects people in their most productive period of their lives. Currently we lack specific management guidelines for this group of patients. Moreover the list of stroke etiologies is more diverse compared to older people; and almost one-third remains cryptogenic despite extensive work¹⁻³.

Recent evidence suggests an increasing incidence⁴ with variable mortality (between 2-6%). There is worldwide variation attributed to better control of vascular risk factors (VRF) in richer countries^{2,3,5}.

Stroke is an important health problem in Latin America (LA)⁶, but there are only few well designed population based stroke incidence studies in LA⁷⁻¹³. The reported prevalence of stroke in an Argentine town with 75 000 inhabitants, was of 868 per 100 000 population, and less than 25% were patients under 60 years of age¹⁴. Two national hospital registries identified hypertension as the most prevalent VRF in our country^{12,13}.

We organized the AISYF study (Argentinean Initiative to study Stroke in the Young and Fabry disease) first national, multicenter, and prospective study of stroke in young patients in Argentina, in order to identify their etiologies, clinical characteristics and VRF.

Materials and methods

We performed a prospective, multicenter, nationwide study of ischemic and hemorrhagic stroke in young adults in Argentina. The study was conducted at 22 public and private centers across the country, coordinated by the Department of Neurology at Hospital Británico de Buenos Aires between January 2011 and December 2015. The protocol was approved by our institutional review board. All patients gave their informed consent. Results regarding the identification of patients with Fabry disease in young patients with stroke were already published¹⁵.

Inclusion criteria: we enrolled patients between the ages of 18 and 55 years with either a TIA (defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction), an brain infarct (defined as a focal neurological deficit due to infarction of central nervous system tissue)¹⁶ or an intracerebral

hemorrhage (defined as a focal neurological deficit associated with focal collection of blood within the brain parenchyma)¹⁷ within 180 days of their stroke.

Exclusion criteria: patients with ischemic stroke following subarachnoid hemorrhage, cancer or trauma and patients with a hemorrhagic stroke due to a vascular malformation (e.g., aneurysm, arteriovenous malformation or cavernous hemangioma) or suspected to be related to cancer, trauma or anticoagulation. We also excluded those with either an epidural or subdural hemorrhage.

Stroke Subtype Classification and Etiological Workup: demographic data, cardiovascular risk factors, clinical and neuroimaging data were collected. VRF computed tomography and/or magnetic resonance images were performed in all patients. They all underwent comprehensive etiological investigations, including brain and vascular imaging, electrocardiography, echocardiography, extensive laboratory testing. Information on comorbidities and VRFs were collected using a standardized case report form. All variables analyzed were checked for completeness, range, and outliers. TOAST criteria were used to define the clinical subtypes of ischemic stroke¹⁸. Intracerebral hemorrhage was categorized by location^{17, 19}.

Analysis of the demographic characteristics: the following VRFs were evaluated: -Hypertension (systolic blood pressure > 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg in 2 recordings outside the acute event or treatment with antihypertensive medication at least during the previous 2 weeks).

-Diabetes (randomized blood glucose > 200 mg/dl or fasting blood glucose ≥ 126 mg/dl in 2 determinations). - Smoking (one or more cigarettes per day in the last 2 months). - Alcohol abuse (intake > 100 g/day = one liter of wine or two liters of beer per day in the last 2 months, or acute intoxication during the 24 hours prior to stroke). - Overweight (body mass index between 25 and 29.9 kg/m²) and obesity (body mass index > 30 kg/m²). -Sedentarism (walking <1 km/day). -Hyperlipidemia (total fasting cholesterol ≥ 200 mg/dl and/or fasting LDL cholesterol ≥ 130 mg/dl and/or fasting triglycerides ≥ 200 mg / dl).

In addition, personal and family history of previous cerebrovascular events, history of migraine, use of contraceptives, sympathicomimetic vasoconstrictors, anti-migraine drugs and use of illicit drugs were recorded.

All data was presented as percentage for categorical variables or as mean and standard error for numerical variables. The t Test was used for numerical variables, and for categorical variables the χ^2 test was performed. A two-tailed value of $p < 0.05$ was considered statistically significant.

Results

A total of 311 patients were enrolled, we excluded 18 for incomplete information (Fig. 1). The remaining 293 had a mean age of 43.3 years (range 20-55 years); 158 were men (53.9%), 242 suffered cerebral infarctions (82.6%), 24 (8.2%) cerebral hemorrhages and 27 (9.2%) presented TIA. The frequency of stroke increased with age in both genders, with a higher prevalence in females among younger patients, and males among older patients (Fig. 2). VRFs were: hypertension 120 (41%), smoking 92 (31.4%), dyslipidemia 81 (27.6%), overweight/obesity: 74 (25.3%), diabetes 36 (12.3%), previous stroke/TIA 37 (12.6%), alcohol abuse 18 (6.1%), previous TIA 17 (5.8%) and previous hemorrhagic stroke 6 (2%).

Fig. 1.– Study flow chart

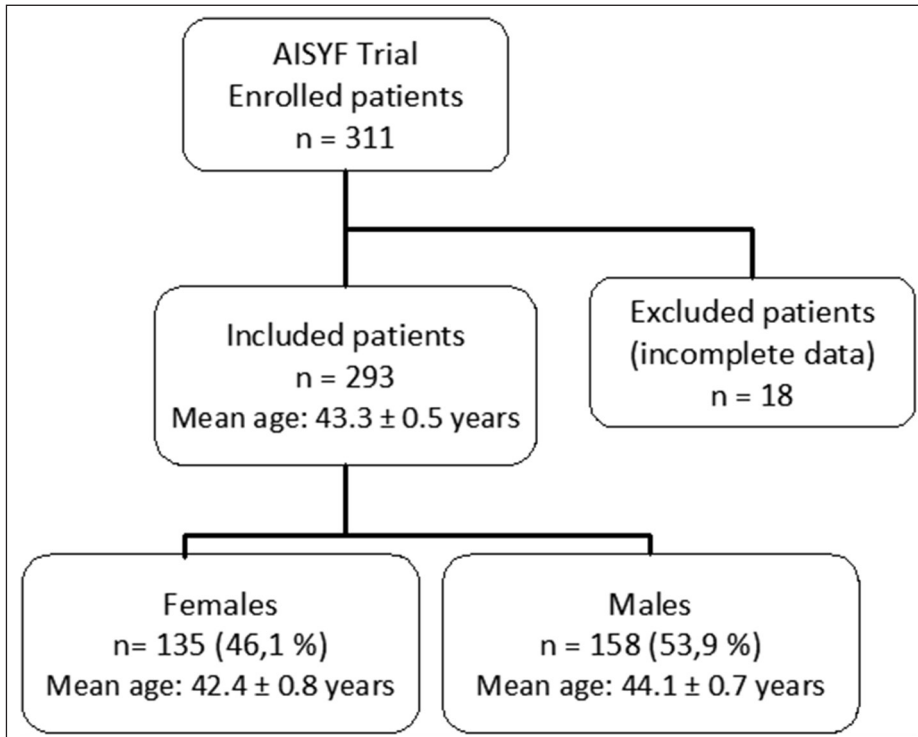
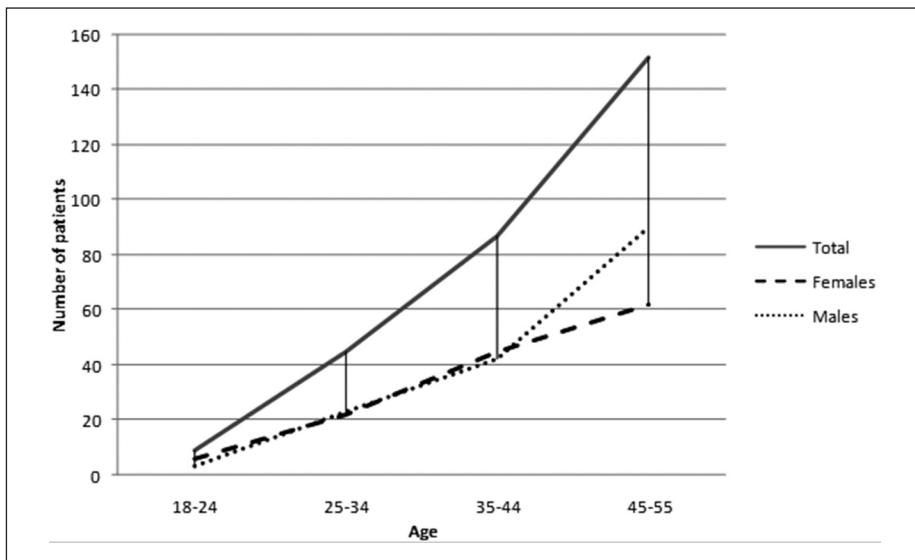


Fig. 2.– Stroke frequency according to age and sex



In patients with ischemic stroke: 69 (25.7%) had no VRF, 71 (26.3%) had 1 VRF, and 129 (48%) had 2 or more VRFs. The most frequent were sedentarism, hypertension and smoking. Men had significantly higher frequency of sedentarism, arterial hypertension, obesity, alcohol consumption and diabetes compared with females (Table 1). Etiologies according to the TOAST classification were: large vessel atheromatosis: n = 33 (12.3%), cardioembo-

lism: n = 20 (7.5%), small artery disease: n = 31 (11.5%), other causes: non atherosclerotic vasculopathy n = 73 (27.1%) and undetermined etiology: n = 112 (41.6%). Undetermined etiologies included 16 patients (5.9%) who presented 2 or more causes, 55 (20.4%) with a negative evaluation (cryptogenic), and 41 (15.2%) with an incomplete evaluation. Older patients presented a lower prevalence of undetermined causes and a higher frequency of

TABLE 1.— Vascular risk factors and stroke history on patients with ischemic stroke

	Total n = 269 (%)	Males n = 144(%)	Females n = 125(%)	p
Hypertension	104 (38.7)	66 (45.8)	38 (30.4)	0.003
Diabetes	32 (11.9)	25 (17.4)	7 (5.6)	0.002
Smoking	85 (31.6)	52 (36.1)	33 (26.4)	0.099
Alcohol	12 (4.5)	10 (6.9)	2 (1.6)	0.002
Overweight/obesity	69 (25.6)	48 (33.3)	21 (16.8)	0.002
Sedentarism	112 (41.6)	69 (47.9)	43 (34.4)	0.043
Hyperlipidemia	70 (26.0)	44 (30.6)	26 (20.4)	0.258
Previous ischemic stroke	20 (7.4)	13 (9.0%)	7 (5.6)	0.297
Previous transient ischemic attack	17 (6.3)	10 (6.9)	7 (5.6)	0.667
Previous hemorrhagic stroke	6 (2.2%)	3 (2.1)	3 (2.4)	0.852

Values are expressed in number and percentages. Significance ($p < 0.05$)

large and small vessel disease (Fig. 3). Among the less common causes of stroke (including non-atherosclerotic vasculopathies and patients with more than one probable cause) we found: 31 with arterial dissections, 12 with cerebral venous thrombosis, 3 had migraine infarcts, 24 had thrombophilia including 2 with simultaneous alteration of 2 coagulation factors (antiphospholipid syndrome in 11 patients, factor V Leiden in 8, prothrombin 20210 in 4, protein C deficiency in 1 and protein S deficiency in 2), 5 patients with vasculitis, 12 with strokes associated with vasoconstrictors or contraceptives and 1 patient each with CADASIL, extrinsic carotid artery compression, Klippel-Trenaunay-Weber syndrome and Fabry disease¹⁵.

We divided our patients into 2 groups according to their ages (< 45 years and \geq 45 years). Those older than 45 years had significantly higher frequency of hypertension, diabetes, sedentarism, overweight/obesity, hypercholesterolemia, atherosclerotic disease and small vessel disease. Oral contraceptive use, presence of patent foramen ovale and non-atherosclerotic etiologies were significantly higher in younger patients (Table 2).

Clinical characteristics of patients with cerebral hemorrhage are summarized in Table 3. Compared with ischemic stroke patients the prevalence of arterial hypertension ($p = 0.009$) and alcohol consumption ($p = 0.002$) were significantly higher in those with brain hemorrhages.

Discussion

The recognition of etiologies and VRF among young patients with stroke is of utmost importance to develop public health policies with the aim of primary and secondary prevention. The 3 most frequent VRFs in our population including ischemic and hemorrhagic stroke were: hypertension, sedentarism, and smoking. One of

the most relevant findings was the presence of at least 1 VRF in nearly 75% of patients with ischemic disease, and the frequency increased with age²⁰⁻²². Other factors previously reported in association with stroke, such as diabetes and alcoholism²³ were rare in our cohort, except in those with hemorrhagic strokes in whom alcohol consumption was significantly higher than in ischemic stroke²⁴. Recent population studies have identified smoking as one of the most prevalent VRFs²⁵. In our population smoking affected almost one-third, and it was the most frequent VRF among those under 45 years^{25, 26}. A similar finding was recently reported by European studies of stroke in young patients^{20, 22}.

The slight predominance of women among our younger patients; was probably related to specific risk factors at this age, such as the use of oral contraceptives, pregnancy, puerperium and migraine^{9, 20, 21, 27}. In a study of young Mexican women, migraine, smoking and use of oral contraceptives were the main risk factors for brain infarcts⁹. Moreover, the risk of stroke in youngers than 45 years suffering from migraine with aura is twice than that of those without aura^{28, 29} and smoking associated with contraceptive use increases the risk of stroke^{20, 30}.

There is limited information of stroke in young patients in LA⁹⁻¹¹. In a report of 106 Brazilian patients, (15 to 40 years old), 86% had ischemic strokes of which 16% were undetermined¹¹. In a large Mexican cohort with infarcts, 300 were younger than 40 years and 32% were cryptogenic¹⁰.

In our study 25% of patients with cerebral ischemia, and especially the younger ones, presented non-atherosclerotic vascular etiologies, including cervicocephalic arterial dissections, cerebral venous thrombosis and thrombophilia^{1, 26}. These pathologies require a high index of suspicion because they are frequently misdiagnosed³¹.

Fig. 3.- TOAST classification according to age and sex

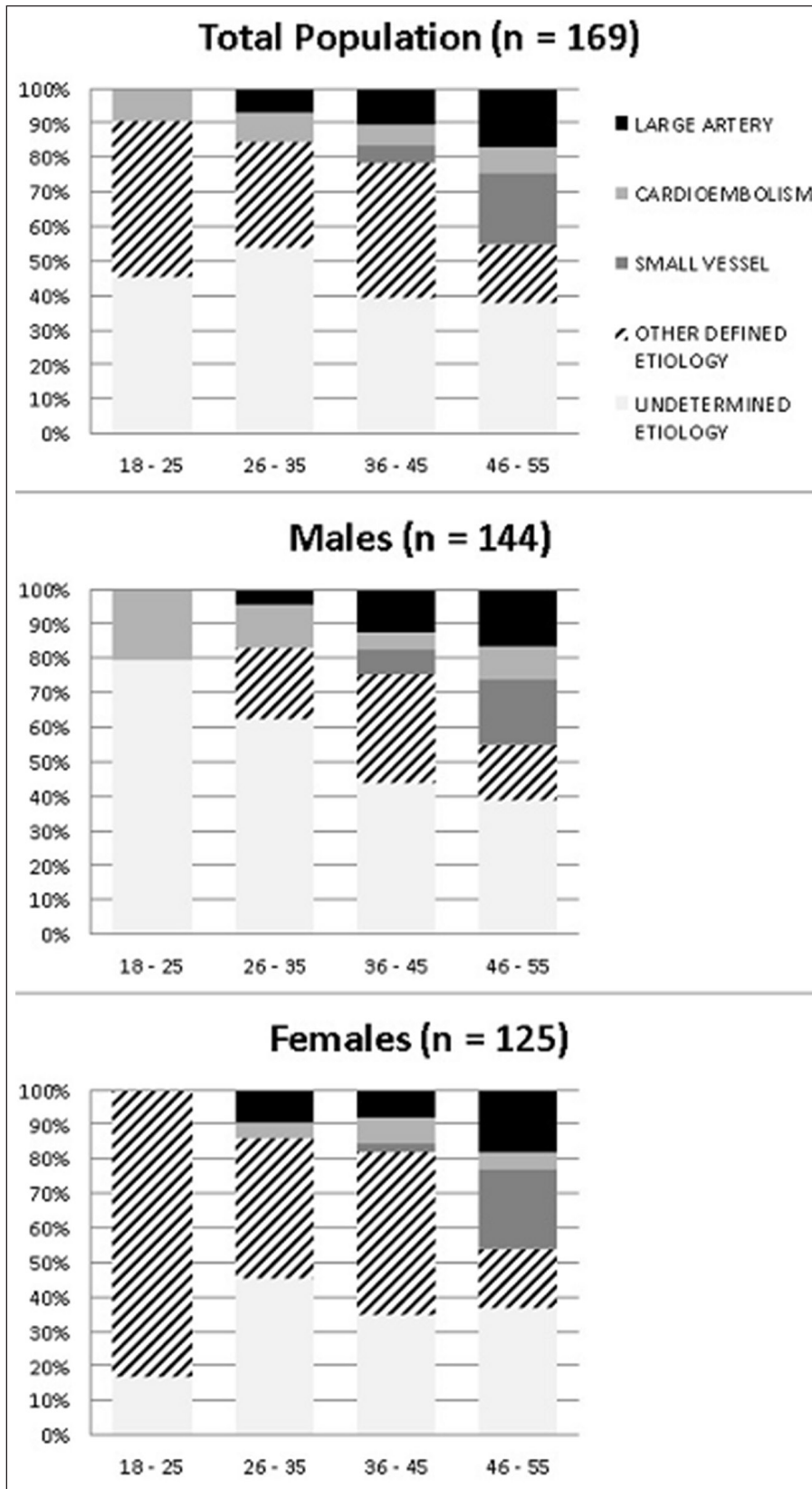


TABLE 2.— Clinical characteristics of ischemic stroke (n = 269) according to age

	Patients < 45 years n = 132 (49%)	Patients ≥ 45 years n = 137 (51%)	p
Sex (males)	65 (49.2)	79 (57.6)	0.18
TIA	11 (8.3)	16 (11.6)	0.42
Brain infarct	121 (91.7)	121 (88.6)	0.42
Motor symptoms	85 (64.3)	97 (70.8)	0.32
Sensory symptoms	35 (26.5)	40 (29.1)	0.68
Cranial nerves	15 (11.3)	16 (11.6)	1
Hemianopsia	21 (15.9)	16 (11.6)	0.37
Neglect	5 (3.7)	8 (5.8)	0.57
Amaurosis fugax	4 (3)	3 (2.1)	0.71
Ataxia	15 (11.3)	18 (13.1)	0.71
Aphasia	26 (16.6)	27 (19.7)	1
Dysarthria	38 (28.7)	51 (37.2)	0.19
Vertigo	17 (12.8)	12 (8.7)	0.32
Loss of consciousness	14 (10.6)	11 (8)	0.53
Hypertension	26 (19.6)	78 (56.9)	< 0.001
Diabetes	3 (2.2)	29 (21.1)	< 0.001
Smoking	36 (27.2)	49 (35.7)	0.15
Alcohol	6 (4.5)	6 (4.3)	1
Overweight/Obesity	22 (16.7)	47 (34.3)	0.001
Sedentarism	41 (31)	71 (51.8)	0.001
Hypercholesterolemia	18 (13.6)	44 (32.1)	< 0.001
High LDL	12 (9)	15 (10.9)	0.68
Previous ischemic stroke	6 (4.5)	13 (9.4)	0.15
Previous TIA	7 (5.3)	10 (7.2)	0.61
Previous hemorrhagic stroke	1 (0.7)	3 (2.1)	0.62
Oral contraceptives	27 (20.4)	8 (5.8)	< 0.001
Illicit drugs	7 (5.3)	2 (1.4)	0.09
Migraine	24 (18.1)	15 (10.9)	0.11
Migraine with aura	19 (14.3)	12 (8.7)	0.18
Atrial fibrillation	1 (0.7)	3 (2.1)	0.62
Dilated miocardiopathy	0	5 (3.6)	0.06
Patent foramen ovale	5 (3.7)	0	0.027
Family history of Ischemic stroke	17 (12.8)	19 (13.8)	0.85
Large artery atherosclerosis	10 (7.5)	23 (16.7)	0.025
Cardioembolism	10 (7.5)	10 (7.2)	1
Small vessel occlusion	4 (3.03)	27 (19.7)	< 0.001
Stroke of other determined etiology	49 (37.1)	24 (17.5)	< 0.001
Stroke of other undetermined etiology	59 (44.6)	53 (38.6)	0.32
Two or more etiologies	7 (5.3)	9 (6.5)	0.79
Cryptogenic	29 (21.9)	26 (18.9)	0.55
Incomplete evaluation	23 (17.4)	18 (13.1)	0.39

TIA: transient ischemic attack

Values are expressed in number and percentages. Significance: p < 0.05

The majority of stroke studies in young people used the etiologic classification of TOAST^{21, 32-35}. Our series, as in other similar studies, has a high proportion of patients included within indeterminate causes, probably due to 2

fundamental reasons: the operational classification criteria used in each study and the depth of the complementary examinations performed²⁶. In some studies migraine infarcts, or those occurring during pregnancy or the puer-

TABLE 3.– *Clinical characteristics of brain hemorrhages (n = 24)*

Characteristics	n (%)
Sex:	
Males	14 (58.3)
Symptoms:	
Motor deficits	21 (87.5)
Sensitive deficits	8 (33.3)
Cranial nerves	2 (8.3)
Hemianopia	4 (16.7)
Neglect	1 (4.2)
Aphasia	3 (12.5)
Ataxia	2 (8.3)
Dysarthria	6 (25)
Vertigo	2 (8.3)
Loss of consciousness	5 (20.8)
Vascular risk factors:	
Hypertension	16 (66.7)
Diabetes	4 (16.7)
Smoking	7 (29.2)
Alcoholism	6 (25)
Overweight/obesity	5 (20.8)
Sedentarism	8 (33.3)
Dyslipidemia	11 (45.83)
Previous stroke	
Ischemic	1 (4.2)
Hemorrhagic	2 (8.3)
Location:	
Lobar	7 (29.2)
Deep	14 (58.3)
Cerebellum	2 (8.42)
Brainstem	0
Intraventricular hemorrhage	4 (16.7)

perium are included as other identifiable causes³⁵, while in other publications these etiologies are considered as indeterminate. Likewise, there is a greater frequency of indeterminate causes in the younger due not only to the existence of less recognized etiologies in this age group but also to the greater presence of VRFs in the elderly which may explain different pathophysiological mechanisms of the cerebrovascular attack.

The strength of our study is that this is, in our knowledge, the first large, multicentric, national and prospective analysis of stroke in young patients in Argentina. Limitations include that not every center had access to all diagnostic tests and this may explain the high frequency of patients in the undetermined category. In addition, the majority of our patients were evaluated in urban medical centers and therefore it is possible that those in rural areas may present different clinical char-

acteristics. These limitations are frequent problems in developing countries^{7, 36}.

In conclusion, our results have multiple implications for the daily clinical practice and the development of public health policies. It demonstrated that VRFs are very frequent even in young adults and therefore it is mandatory to develop strategies for stroke prevention in the younger population.

Sources of funding: The study was sponsored by a research Grant from Shire HGT/Takeda

Conflict of interest: Ricardo Reisin has received speaker and scientific consulting fees from Novartis, Gador, Shire/Takeda, Amicus and Genzyme.

Luciana León Cejas has received speaker's fees from Shire/Takeda and Pfizer.

Pablo Bonardo has received speaker's fees from Shire/Takeda.

References

1. Singhal AB, Biller J, Elkind MS, et al. Recognition and management of stroke in young adults and adolescents. *Neurology* 2013; 81: 1089-97.
2. Kittner SJ, Stern BJ, Wozniak M, et al. Cerebral infarction in young adults: the Baltimore-Washington cooperative young stroke study. *Neurology* 1998; 50: 890-4.
3. Kristensen B, Malm J, Carlberg B, et al. Epidemiology and etiology of ischemic stroke in young adults aged 18 to 44 years in northern Sweden. *Stroke* 1997; 28: 1702-9.
4. Ekker MS, Verhoeven JI, Vaartjes I, van Nieuwenhuizen KM, Klijn CJM, de Leeuw FE. Stroke incidence in young adults according to age, subtype, sex, and time trends. *Neurology* 2019; 92: 2444-54.
5. Sarti C, Rastenyte D, Cepaitis Z, Tuomilehto J. International trends in mortality from stroke, 1968 to 1994. *Stroke*. 2000; 31: 1588-601.
6. Avezum A, Costa-Filho FF, Pieri A, Martins SO, Marin-Neto JA. Stroke in Latin America: burden of disease and opportunities for prevention. *Glob Heart* 2015; 10: 323-31.
7. Camargo ECS, Bacheschi LA, Massaro AR. Stroke in Latin America. *Neuroimaging Clin N Am* 2005; 15: 283-96.
8. Saposnik G, Del Brutto OH. Stroke in South America: a systematic review of incidence, prevalence, and stroke subtypes. *Stroke* 2003; 34: 2103-7.
9. Barinagarrementeria F, Gonzalez-Duarte A, Miranda L, Cantú C. Cerebral infarction in young women: analysis of 130 cases. *Eur Neurol* 1998; 40: 228-33.
10. Barinagarrementeria F, Figureoa T, Huebe J, Cantú C. Cerebral infarction in people under 40 years. *Cerebrovasc Dis* 1996; 6: 75-9.
11. Siqueira Neto JI, Santos AC, Fabio SR, Sakamoto AC. Cerebral infarction in patients aged 15 to 40 years. *Stroke* 1996; 27: 2016-9.
12. Atallah AM, Fustinoni O, Beigelman R, Cirio JJ. High prevalence of hemorrhagic stroke and untreated hypertension, frequent blood pressure lowering and inappropriate use of aspirin in the first Argentina National Stroke Registry (ARENAS). *V World Stroke Congr Vancouver* 2004; Abstract.
13. Sposato LA, Esnaola MM, Zamora R, et al. Quality of ischemic stroke care in emerging countries: The argentinian national stroke registry (ReNACer). *Stroke* 2008; 39: 3036-41.
14. Melcon CM, Melcon MO. Prevalence of stroke in an Argentine community. *Neuroepidemiology* 2006; 27: 81-8.
15. Reisin RC, Mazziotti J, Cejas LL, et al. Prevalence of Fabry disease in young patients with stroke in Argentina. *J Stroke Cerebrovasc Dis* 2018; 27: 575-82.
16. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 2011; 42: 227-76.
17. Woo D, Sauerbeck LR, Kissela BM, et al. Genetic and environmental risk factors for intracerebral hemorrhage: preliminary results of a population-based study. *Stroke* 2002; 33: 1190-5.
18. Adams HPJ, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. *Stroke* 1993; 24: 35-41.
19. Flaherty ML, Woo D, Haverbusch M, et al. Racial variations in location and risk of intracerebral hemorrhage. *Stroke* 2005; 36: 934-7.
20. Rolfs A, Fazekas F, Grittner U, et al. Acute cerebrovascular disease in the young: the stroke in young Fabry patients study. *Stroke* 2013; 44: 340-9.
21. Putaala J, Metso AJ, Metso TM, et al. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki young stroke registry. *Stroke* 2009; 40: 1195-203.
22. Putaala J, Yesilot N, Waje-Andreassen U, et al. Demographic and geographic vascular risk factor differences in European young adults with ischemic stroke: the 15 cities young stroke study. *Stroke* 2012; 43: 2624-30.
23. Sundell L, Salomaa V, Vartiainen E, Poikolainen K, Laatikainen T. Increased stroke risk is related to a binge-drinking habit. *Stroke* 2008; 39: 3179-84.
24. An SJ, Kim TJ, Yoon B-W. Epidemiology, risk factors, and clinical features of intracerebral hemorrhage: an update. *J Stroke* 2017; 19: 3-10.
25. Love BB, Biller J, Jones MP, Adams Jr HP, Bruno A. Cigarette smoking. A risk factor for cerebral infarction in young adults. *Arch Neurol* 1990; 47: 693-8.
26. Ferro JM, Massaro AR, Mas J-L. Aetiological diagnosis of ischaemic stroke in young adults. *Lancet Neurol* 2010; 9: 1085-96.
27. Rasura M, Spalloni A, Ferrari M, et al. A case series of young stroke in Rome. *Eur J Neurol* 2006; 13: 146-52.
28. Schürks M, Rist PM, Bigal ME, Buring E, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2009; 339: b3914.
29. Wolf ME, Szabo K, Griebbe M, et al. Clinical and MRI characteristics of acute migrainous infarction. *Neurology* 2011; 76: 1911-7.
30. Gill SK. Cardiovascular risk factors and disease in women. *Med Clin North Am* 2015; 99: 535-52.
31. Cejas LL, Mazziotti J, Zimmerman A, et al. Misdiagnosis of acute ischemic stroke in young patients. *Medicina (B Aires)* 2019; 79: 90-4.
32. Arnold M, Halpern M, Meier N, et al. Age-dependent differences in demographics, risk factors, co-morbidity, etiology, management, and clinical outcome of acute ischemic stroke. *J Neurol* 2008; 255:1503-7.
33. Musolino R, La Spina P, Granata A, et al. Ischaemic stroke in young people: a prospective and long-term follow-up study. *Cerebrovasc Dis* 2003; 15: 121-8.
34. Leys D, Bandu L, Henon H, et al. Clinical outcome in 287 consecutive young adults (15 to 45 years) with ischemic stroke. *Neurology* 2002; 59: 26-33.
35. Varona JF, Bermejo F, Guerra JM, Molina JA. Long-term prognosis of ischemic stroke in young adults. Study of 272 cases. *J Neurol* 2004; 251: 1507-14.
36. Estol CJ, Esnaola y Rojas MM. Stroke in Argentina. *Int J Stroke* 2010; 5: 35-9.

SUPPLEMENTARY MATERIAL**Participating centers and investigators of AISYF trial****Hospital Británico:**

Reisin Ricardo
 Mazziotti Julieta
 León Cejas Luciana
 Bonardo Pablo
 Miñarro Diego
 Fernández Pardal Manuel
 Belén Tillard

Hospital de Clínicas

De Francesco Laura
 Tkachukt Verónica

Hospital Presidente Peron

Humanchio Janina

Fundación Favaloro

Riccio Patricia
 Sposatto Luciano
 Klein Francisco
 Muñoz Francisco
 Gonzalez Toledo Eugenia

FLENI

Ameriso Sebastián
 Pujol Virginia
 Povedano Guillermo

Hospital Posadas

Zinnerman Alberto
 Martínez Alejandra
 Conti Eugenia
 Messina Juan

Instituto de Oncología Ángel H. Roffo

Casas Parera Ignacio
 Tafur José

Sanatorio Mitre

Gatto Emilia
 Persi Gabriel

INAREPS Mar del Plata

Bendersky Eduardo
 Montero Lorena
 Ateca Alicia

Hospital Zubizarreta

Allegri Ricardo
 Bartoloni Leonardo

Hospital Tornú

Di Egidio Mariana
 Ciardi Celina
 Alleva Alejandro

CEMIC

Rivero Alberto
 Romano Marina

Hospital Durand

Cairola Patricia

Academia Nacional de Medicina

Sanchez Luceros Analía
 Meschengesier Susana

Hospital de Vicente López

Halfon Javier
 Schubaroff Pablo

Hospital Español

Calandra Cristian

Hospital San Martín

Pedersoli Luis Martín
 Zuccolo Laura

Hospital Municipal de Campana

Reynoso Félix

Sanatorio Parque Tucumán

Nofal Pedro
 Leri Mónica

CENAC Rosario

Bruera Guadalupe

Sanatorio Parque Rosario

Lorena Jure

Sanatorio Adventista del Plata

Sotelo Andrea