Journal of Neurology (2018) 265:2379–2387
https://doi.org/10.1007/s00415-018-9005-6

ORIGINAL COMMUNICATION

Stroke recurrence and mortality in northeastern Greece: the Evros Stroke Registry

Georgios Tsivgoulis[1,2] · Aristeidis H. Katsanos[2,3] · Athanasia Patousi[1] · Maria Pikilidou[4] · Theodosis Birbilis[5] · Michael Mantatzis[6] · Maria Yavropoulou[7] · Christina Zompola[2] · Sokratis Triantafyllou[2] · Nikolaos Papanas[8] · Panagiotis Skendros[9] · Aikaterini Terzoudi[1] · George S. Georgiadis[10] · Pantelis Zebekakis[4] · Efstratios Maltezos[8] · Charitomeni Piperidou[1] · Ioannis Heliopoulos[1] · Konstantinos Vadikolias[1]

Received: 5 June 2018 / Revised: 7 August 2018 / Accepted: 10 August 2018 / Published online: 20 August 2018

Abstract

Up to date there is no population-based study from Greece providing long-term data on incidence of both all-cause mortality and stroke recurrence for patients with first ever stroke (FES). Adult patients with FES were registered during a 24-month period (2010–2012) and followed-up for 12 months. We calculated cumulative incidences of stroke mortality and recurrence. Univariable and multivariable Cox proportional hazards regression analyses were used to identify independent determinants of 1-year mortality and 1-year stroke recurrence. We prospectively documented 703 first ever stroke cases (mean age 75 ± 12 years; 52.8% males; ischemic stroke 80.8%, intracerebral hemorrhage 11.8%, subarachnoid hemorrhage 4.4%, undefined 3.0%) with a total follow-up time of 119,805 person-years. The cumulative incidence rates of mortality of all FES patients at 28 days, 3 months and 1 year were 21.3% (95% CI 18.5–24.5%), 26% (95% CI 22.9–29.4%) and 34.7% (95% CI 31.3–38.3%), respectively. The risk of 1-year mortality was independently ($p < 0.05$) associated with advancing age, history of hypertension, increased stroke severity on admission, and hemorrhagic FES type. Cumulative 1-year stroke mortality differed according to both index FES type (ischemic vs. hemorrhage; $p < 0.001$), but also across different ischemic stroke subtypes ($p = 0.025$). The cumulative incidence rates of recurrent stroke at 28 days, 3 months and 1 year were 2.0% (95% CI 1.2–3.6%), 4.2% (2.8–6.2%) and 6.7% (5.1–8.8%), respectively. Comparable to other population-based surveys, our study reports 1-year mortality and stroke recurrence rates in patients with FES. These findings highlight the need for effective secondary prevention strategies in a border region of southeastern Europe, which exhibits very high FES incidence rates.

Keywords Mortality · Recurrence · Ischemic stroke · Intracerebral hemorrhage · Subarachnoid hemorrhage · Epidemiology · Population-based · Greece

Introduction

Stroke survivors are known to have high-risk for stroke recurrence, cardiovascular events and death during follow-up compared to the general population [1, 2]. Both stroke recurrence and mortality rates are known to vary widely between different geographical areas and time-points, reflecting the existing temporal and spatial disparities in stroke epidemiology [3–6].

There is only a population-based study in Greece reporting long-term mortality incidence in an area of Southern Greece approximately 20 years ago [7]. Moreover, there is no population-based data on the short- and long-term incidence of stroke recurrence among patients with first ever stroke (FES). In view of the former considerations, we sought to determine long-term all-cause mortality and stroke recurrence incidence rates of patients with FES that have been recruited to the largest and most current prospective, population-based registry evaluating the incidence of FES in northeastern Greece [8].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-018-9005-6) contains supplementary material, which is available to authorized users.

✉ Georgios Tsivgoulis
tsivgoulisgiorg@yahoo.gr

Extended author information available on the last page of the article

Methods

Study population and definitions

The Evros stroke registry was a population-based study evaluating the incidence of FES among adult patients (≥ 18 years of age at index event) who were permanent residents of the Evros prefecture during a 2-year period (1/2/2010–31/1/2012). Evros prefecture represents a geographical region of 147,947 permanent inhabitants more than 20 years of age located in the far northeastern part of Greece [8]. Stroke classification in the Evros registry was performed according to the corresponding American Heart Association/American Stroke Association (AHA/ASA) updated definitions for ischemic stroke (IS), intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) [9]. Stroke events based solely on clinical findings without available neuroimaging (CT or MRI) within 14 days from the onset of symptoms or with no autopsy evidence to distinguish between infarct and hemorrhage were classified as undetermined strokes. Patients with IS were further classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [10].

Stroke severity and level of consciousness were assessed by certified neurologists using the National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS), respectively. For all patients we also prospectively recorded demographics (age, sex, ethnicity), history of vascular risk factors, admission systolic and diastolic blood pressure, available neuroimaging with CT and/or MRI, and additional examinations that were performed during hospitalization (duplex cervical vessel examination, transthoracic echocardiography, Holter-EKG). Excessive alcohol consumption was defined as > 4 drinks for women and > 5 drinks for men on 5 or more days in the past month [8].

Follow-up and outcome measures

All included patients were prospectively followed for 1 year following the index event at the outpatient clinics of our institutions, or with a structured telephone interview either of the patient or the first-degree relatives, in case of patient's inability to communicate (e.g., low state of consciousness or severe aphasia). Functional status at 1, 3 and 12 months after FES onset was assessed with the use of the modified Rankin Scale (mRS) score performed by the study neurologists [8]. All patients were evaluated at 28 days, 3 months and 12 months from the index event, independently of the area of residence after the index event. Patients who moved out of the study area after the index event were evaluated with a structured telephone interview, if they were unable to proceed to the outpatient clinics. Further information on the scheduled follow-up evaluations, neurological examination, structured telephone interviews and reasons for missing follow-up evaluations are available in the Online Supplement.

Mortality was defined as death from any cause within the 12 months after FES onset. In all deceased patients the cause of death was searched in hospital, primary care medical records or autopsy reports provided by the Forensic Department of Evros Province [8]. We also prospectively recorded all stroke events following the index event during the follow-up period. The definition of recurrent stroke was the same as for the index FES event and according to the World Health Organization (WHO) criteria, as "rapidly developing clinical symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 h or leading to death, with no apparent cause other than that of vascular origin" [8, 11]. Recurrent stroke symptoms had to occur at least 24 h after the index event, and should have not been attributable to edema, mass effect, brain shift syndrome, or hemorrhagic transformation [12]. Patients with transient episodes lasting less than 24 h and those with asymptomatic lesions detected by brain imaging ("silent infarcts") were not considered as recurrent strokes. All patients with a suspected stroke recurrence were examined by study neurologists as soon as possible after the event and the diagnosis was discussed at regular consensus meetings of the study team [8]. Further details regarding the definition and classification of recurrent strokes have previously been published [13].

Comparison with previously published studies

We compared the 1-year mortality rates of our population with that reported in a previously published follow-up study of a FES population-based registry in southern Greece (Arcadia Stroke Study) [7]. Since up to date no other population-based study from Greece provided data on stroke recurrence of patients with FES, we compared the stroke recurrence rates in our population with available population-based studies providing data on 1-year stroke recurrence rates of patients with FES.

Ethics and study approval

The complete study protocol was submitted before study initiation and was approved by the ethics committee of the University Hospital of Alexandroupolis. Written informed consent was obtained from all patients (or their first-degree relatives) prior to study enrollment [8].

Statistical analysis

Binary variables are presented as percentages, while continuous variables are expressed with their median values and corresponding interquartile ranges (IQRs). Assuming binomial distribution, in all outcome measures of interest the 95% confidence intervals (95% CI) for corresponding proportions were calculated with the adjusted Wald method [14]. Statistical comparisons between the different groups of patients, according to index FES type, were performed with the Pearson's χ^2 test and Kruskal–Wallis test, where appropriate.

Crude incidences of both 1-year mortality and 1-year stroke recurrence were estimated by the cumulative incidence function. Kaplan–Meier curves were generated for both the aforementioned outcomes of interest, while potential differences according to sex or FES type or first ever IS subtype were assessed with the log-rank test. To determine further potential independent predictors of 1-year mortality and 1-year stroke recurrence we used multivariable Cox proportional hazards regression analyses. As candidate variables for inclusion in the multivariable models we used all those baseline characteristics, including FES type (hemorrhagic vs. ischemic) that were found to yield a threshold of $p < 0.1$ in the initial univariable analyses. Final multivariate regression models were tested under a two-sided statistical significance hypothesis using the likelihood ratio test with an alpha value of 0.05. In multivariable models we excluded patients with missing data from the analysis, while we did not impute missing data.

We pooled the incidence rates of 1-year stroke recurrence reported in our study and in available studies using the metaprop command [15]. Given the effect of temporal changes in secondary stroke prevention strategies on stroke recurrence risk [4] we dichotomized available studies according to the year they were performed (before the year 1990 and after the year 1990). A random effects model (DerSimonian and Laird) [16] was then used to calculate both the pooled point estimate in each subgroup and the overall estimate. In both the overall analysis and between subgroups the presence of heterogeneity was assessed with the Cochran Q statistical test [17].

Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Results

During the 2-year study period, FES was documented in a total of 703 individuals (mean age 75 ± 12 years; 52.8% men; IS 80.8%, ICH 11.8%, SAH 4.4%, undefined 3.0%) with a total follow-up time of 119,805 person-years. The following baseline characteristics differed between different FES stroke subtypes (Table 1): age ($p < 0.001$), baseline NIHSS-scores ($p < 0.001$), baseline GCS scores ($p < 0.001$), SBP on admission ($p < 0.001$), DBP on admission ($p < 0.001$), baseline mRS-scores ($p < 0.001$), diabetes mellitus ($p = 0.011$), dyslipidemia ($p = 0.003$), atrial fibrillation ($p = 0.001$) and current smoking ($p = 0.002$).

Patients first assessed or hospitalized in neurological departments ($n = 188$) were significantly younger ($p < 0.001$) with higher male predominance ($p < 0.001$), higher smoking prevalence ($p < 0.001$), less frequent history of atrial fibrillation ($p = 0.003$) and more frequent family history of cardiovascular disease ($p < 0.001$) compared to patients first assessed or hospitalized in internal medicine departments ($n = 441$). Patients first assessed or hospitalized in neurological departments had more frequently hemorrhagic stroke (23.9 vs. 7.9%), presented with milder neurological deficits ($p < 0.001$) and higher DBP on admission ($p = 0.003$). Notably, patients first assessed or hospitalized in neurological departments had lower rates of both unknown stroke (0 vs. 4.1%) and cryptogenic ischemic stroke (21.8 vs. 46.9%; Supplemental Table I).

During the 1-year period follow-up period 40 patients (5.7%) were lost to follow-up. Reasons for the lost to follow-up are reported in the Online Supplement. The distributions of mRS-scores and losses-to-follow-up at 28-days, 3-months and 1-year after the FES index event are available in Fig. 1. We documented significant differences in the 24-h NIHSS-scores ($p < 0.001$), the mRS-scores distributions at 28 days ($p < 0.001$), 3 months ($p < 0.001$) and 1 year ($p = 0.002$) following the index event between the different stroke subtypes (Table 1). The cumulative incidence rates of mortality for all FES patients at 28 days, 3 months and 1 year were 21.3% (95% CI 18.5–24.5%), 26% (95% CI 22.9–29.4%) and 34.7% (95% CI 31.3–38.3%), respectively. The most common cause of death was cerebral edema (45.9%), followed by infections (13.6%). Both cumulative mortality rates and causes of death during the 1-year follow-up period differed significantly ($p < 0.001$) in different FES subgroups (IS, ICH, SAH & undefined) according to index FES type (Table 1; Fig. 2a), while no difference was found across sexes ($p = 0.194$; Supplemental Figure I). Further stratification of FES patients also revealed significant differences ($p = 0.025$) in 1-year all-cause mortality rates between IS subtypes (Fig. 2b). Multivariable regression analysis detected age (HR per 10-year increase 1.44, 95% CI 1.24–1.66, $p < 0.001$), hypertension (HR 0.68, 95% CI 0.48–0.96, $p = 0.028$), admission NIHSS-scores (HR per 1-point increase 1.13, 95% CI 1.11–1.16, $p < 0.001$) and hemorrhagic (vs. ischemic) FES type (HR 1.21, 95% CI 1.13–1.30, $p < 0.001$; Fig. 3) as independent predictors of 1-year mortality (Supplemental Table II). Graphical representation of 1-year mortality rates according

Table 1 Baseline characteristics and outcomes of interest during follow-up stratified by first ever stroke type

Variable	Total ($n=703$)	IS ($n=568$)	ICH ($n=83$)	SAH ($n=31$)	Undefined ($n=21$)	p value*
Baseline characteristics						
Age (median, IQR)	77 (71–83)	77 (71–82)	77 (67–83)	53 (42–74)	84 (80–91)	<0.001
Females (%)	47.2	47.7	43.4	35.5	66.7	0.142
Baseline NIHSS-score (median, IQR)	8 (4–16)	8 (4–15)	14 (8–20)	4 (2–24)	20 (6–28)	<0.001
GCS-score(median, IQR)	15 (14–15)	15 (15–15)	14.5 (13–15)	14 (12–15)	15 (11–15)	<0.001
Hypertension (%)	81.1	82.7	76.8	69.0	85.7	0.170
Diabetes (%)	26.3	29.1	17.1	10.3	14.3	0.011
Dyslipidemia (%)	67.0	70.7	53.7	55.2	52.4	0.003
Atrial fibrillation (%)	34.3	37.6	25.6	6.9	23.8	0.001
Smoking (%)	22.5	22.4	18.5	51.7	15.0	0.002
Coronary artery disease (%)	16.9	17.6	14.6	10.3	19.1	0.692
Alcohol (%)	9.2	8.4	13.9	20.7	5.0	0.071
Family history (%)	26.0	35.3	23.8	28.6	25.0	0.267
Greek ethnicity (%)	95.6	95.9	95.2	87.1	100.0	0.090
SBP on admission (median, IQR)	150 (130–175)	150 (130–170)	173 (140–190)	170 (140–190)	155 (130–170)	<0.001
DBP on admission (median, IQR)	80 (80–90)	80 (75–90)	90 (80–100)	90 (80–100)	80 (70–80)	<0.001
Baseline mRS score (median, IQR)	4 (3–5)	4 (3–5)	5 (4–5)	5 (2–5)	5 (3–5)	<0.001
Follow-up						
NIHSS-score at 24-h (median, IQR)	8 (4–18)	7 (3–16)	13 (6–30)	10 (1–30)	30 (4–30)	<0.001
mRS score at 28-days (median, IQR)	4 (2–6)	4 (2–5)	5 (3–6)	5 (3–6)	6 (4–6)	<0.001
mRS score at 3-months (median, IQR)	4 (2–6)	3 (2–6)	5 (3–6)	6 (2–6)	6 (4–6)	<0.001
mRS score at 1-year (median, IQR)	4 (2–6)	4 (1–6)	6 (2–6)	6 (2–6)	6 (6–6)	0.002
Stroke recurrence during follow-up (%, 95% CI)	6.7 (5.1–8.8)	7.2 (5.3–9.7)	1.2 (0–7.2)	12.9 (4.5–29.4)	4.8 (0–24.4)	0.098
Mortality during follow-up (%, 95% CI)	34.7 (31.3–38.3)	30.8 (27.1–34.7)	47.0 (36.6–57.6)	48.4 (32–65.2)	71.4 (49.8–86.4)	<0.001
Cause of death during follow-up (%)						<0.001
CE	45.9	40.9	75	80	0	
Infection	13.6	14.8	13.8	13.3	0	
Other cause	22.3	28.4	5.6	0	13.3	
Unknown cause	18.2	15.9	5.6	6.7	86.7	

IS ischemic stroke, *ICH* intracerebral hemorrhage, *SAH* subarachnoid hemorrhage, *NIHSS* National Institutes of Health Stroke Scale, *GCS* Glasgow Coma Scale, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *IQR* interquartile range, *CE* cerebral edema

*Comparisons are between groups of different first ever stroke types

to patient age per decade uncovered a J-shaped relationship, with patients 40–50 years of age presenting the lowest mortality rates (Fig. 4).

Patients first assessed or hospitalized in neurological departments had significantly lower 24-h NIHSS ($p<0.001$), 1-year mRS-scores ($p<0.001$) and 1-year mortality rate [18.6% (95% CI 13.6–24.8%) vs. 38.5% (95% CI 34.1–43.2%), $p<0.001$] compared to patients first assessed or hospitalized in internal medicine departments. No patient hospitalized in internal medicine department received intravenous thrombolysis. The rate of patients lost during the 1-year follow-up was lower among those first assessed or hospitalized in neurological departments compared to those first assessed or hospitalized in internal medicine departments (1.1 vs. 7.2%, $p=0.002$). Also, the cause of death was more likely to be unknown within deceased patients that were hospitalized in internal medicine departments compared to deceased patients hospitalized in neurological departments (21.6 vs. 3.1%; Supplemental Table I).

The cumulative incidence rates of recurrent stroke at 28-days, 3-months and 1-year were 2.0% (95% CI 1.2–3.6%), 4.2% (95% CI 2.8–6.2%) and 6.7% (95% CI 5.1–8.8%), respectively. The percentages of recurrent stroke subtypes are presented in Supplemental Figure II. No difference on the stroke recurrence rates was found between sexes (Supplemental Figure III). Stratification by index event type revealed a higher, but marginally non-significant ($p=0.057$), recurrence rate for SAH patients compared to other FES types (Table 1; Fig. 5a), while no significant differences ($p=0.325$) were detected on the risk of stroke recurrence

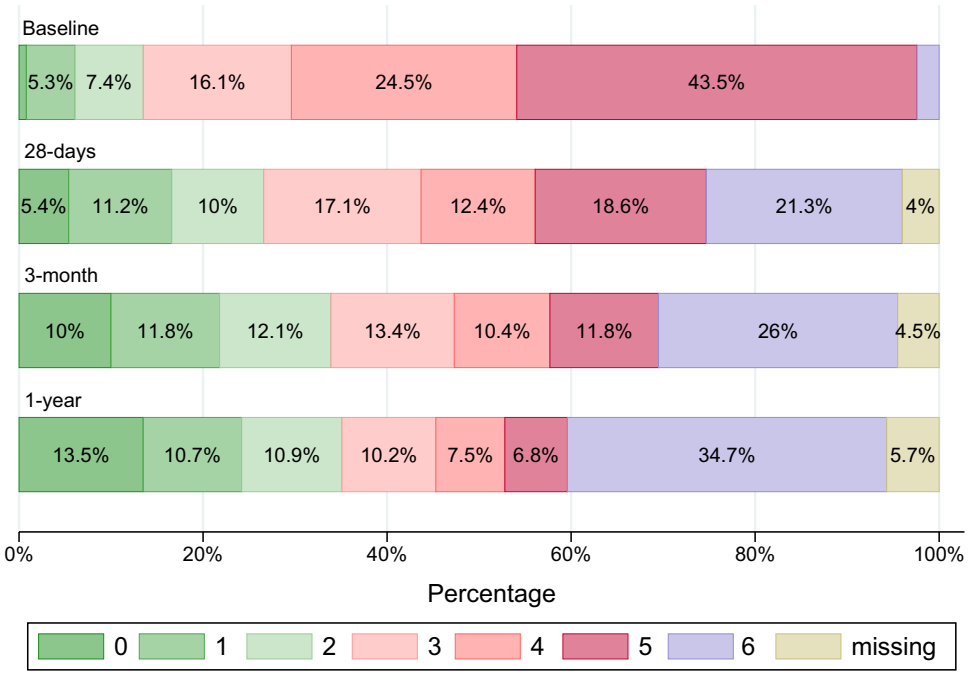

Fig. 1 Distribution of modified Rankin Scale scores at baseline assessment, 28 days, 3 months and 12 months following the index event

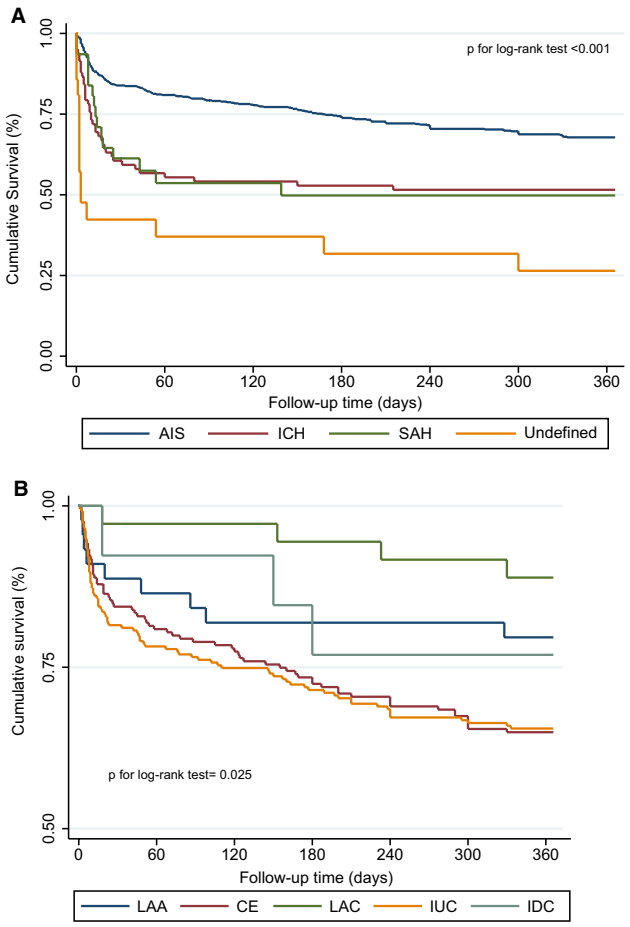

Fig. 2 Kaplan–Meier curves depicting all-cause mortality during the 1-year follow-up period stratified by **a** first ever stroke type and **b** first ever ischemic stroke subtype

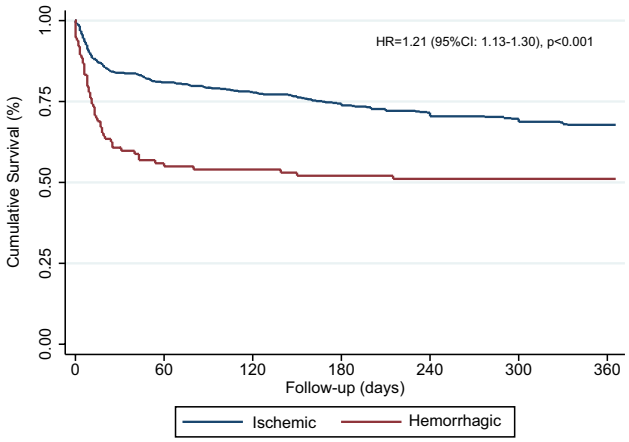

Fig. 3 Kaplan–Meier curves depicting all-cause mortality during the 1-year follow-up period in patients with ischemic or hemorrhagic stroke

among FES patients with different IS subtypes (Fig. 5b). Even though we found evidence of potential associations between the risk of stroke recurrence with both increasing age (HR per 10-year increase 1.27, 95% CI 0.96–1.67, $p=0.092$) and current smoking (HR 0.47, 95% CI 0.20–1.11, $p=0.087$) in univariable analyses, no independent associations of the these two variables with the risk of 1-year stroke recurrence were documented in multivariable analyses (Supplemental Table III). No difference was also detected on the stroke recurrence risk between patients with hemorrhagic or ischemic FES type (HR 1.03, 95% CI 0.80–1.33, $p=0.827$; Supplemental Figure IV). The risk of 1-month

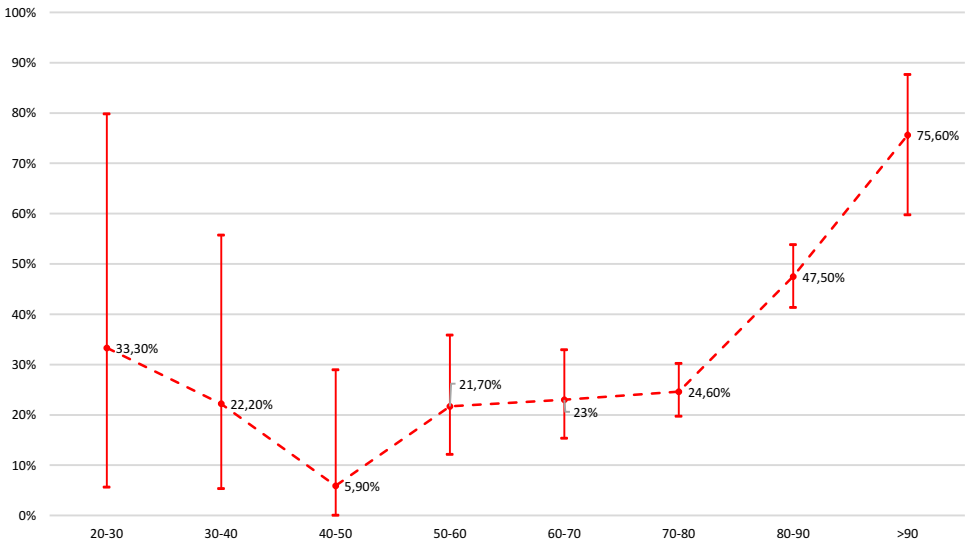

Fig. 4 Graphical representation of mortality rates according to patient age at first ever stroke event

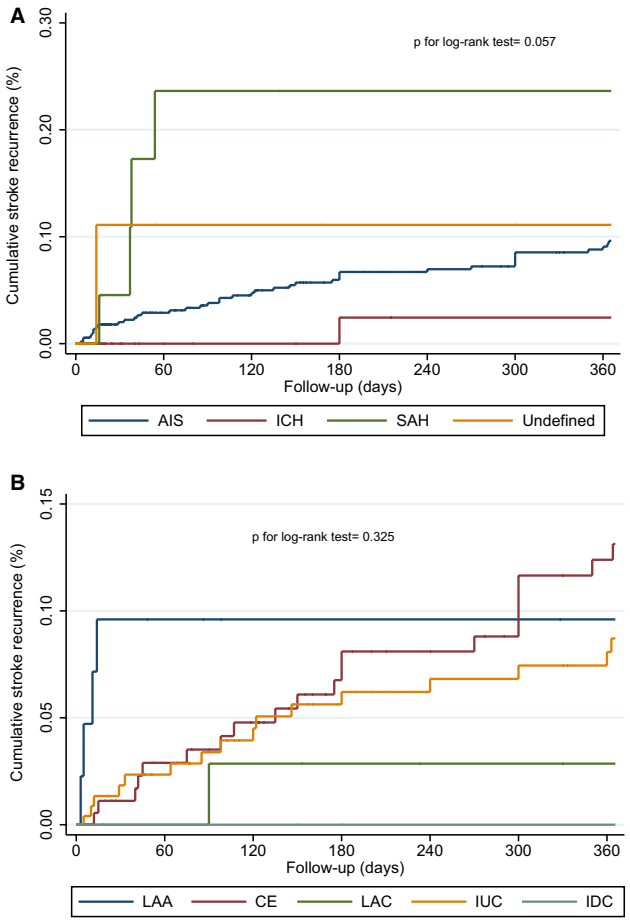

Fig. 5 Kaplan–Meier curves depicting stroke recurrence during the 1-year follow-up stratified by **a** first ever stroke type and **b** first ever acute ischemic stroke subtype

stroke recurrence was higher in patients with FES due to large-artery atherosclerosis (8.9%) compared to the rest of IS subtypes (p for log-rank test < 0.001).

Discussion

This is the first ever population-based study providing cumulative incidence rates of recurrent stroke events in Greek patients with FES. The reported recurrent stroke incidence in our population (6.7%, 95% CI 5.1–8.8%) is comparable to those previously reported by similar population-based studies of FES patients (9%, 95% CI 8–11%) [18–27], and especially with those studies performed after the year 1990 (7%, 95% CI 6–9%; Supplemental Figure V) [18–24]. Our study is the second to provide all-cause mortality rate in Greek FES patients during 1-year follow-up, which is consistent with the previously reported all-cause mortality rate of a population-based study performed approximately two decades ago in southern Greece (36.8%, 95% CI 32.8–40.8%; Supplemental Figure VI) [7]. Moreover, we found significant disparities in both baseline characteristics and outcomes of patients first assessed or hospitalized in neurological departments compared to patients first assessed or hospitalized in internal medicine departments. The number of patients first assessed or hospitalized in internal medicine departments ($n = 4$) was higher (441 vs. 188) than the number of patients first assessed or Hospitalized in neurological departments ($n = 2$) due to imbalances in bed availability between internal medicine ($n = 94$) and neurology ($n = 20$) departments in Evros perfecture.

In our population we found a higher, although not statistically significant, recurrence stroke risk for SAH patients compared to other FES types. This finding is consistent with previously published population-based studies of FES

patients, highlighting the increased risk of SAH recurrence compared to IS [27], especially in the first 6 months after the index event [21]. We also reported a significantly higher risk of all-cause mortality during the 1-year follow-up in patients with intracranial hemorrhage at index event compared to patients with cerebral ischemia, while among IS subtypes lacunar stroke patients had significantly lower 1-year mortality rates compared to patients with cardioembolic or cryptogenic strokes. These findings are consistent with previously published population-based studies of FES patients suggesting higher risk for all-cause mortality in hemorrhagic stroke compared to IS [19, 22], increased survival rates in patients with lacunar strokes, and higher mortality risk in IS due to cardioembolism [28, 29]. In our manuscript we also highlight the independent association of admission NIHSS-score with 1-year mortality, while the initial univariable relationship of GCS-score with mortality did not retain its significance in the final multivariable model. This is in contrast to the observations of the previously published Greek population-based study from Arcadia highlighting admission GCS as the most powerful predictor of mortality and functional outcome 1-year after the index event [7]. However, it should be noted that NIHSS-scores were unavailable in the Arcadia study [7] and this may have accounted for the potential discrepancy in findings between the two studies.

Even though the present population-based study is the first to our knowledge to present robust data on the 1-year outcomes of FES in southeastern Europe, an area presenting one of the highest incidences of FES worldwide, several limitations should also be acknowledged. First, since the present report presents results from a population-based registry the presence of ecological fallacy and residual confounding cannot be excluded. Moreover, it should be noted that we were not able to assess the effects of medical or other (e.g., surgical, rehabilitation) treatments during follow-up on both outcomes of mortality and stroke recurrence. However, as discussed extensively above, it should be highlighted that our results are consistent with those previously reported by similar study protocols in different populations and time-periods. Second, it should be noted that the lack of independent associations between baseline characteristics and risk of stroke recurrence on multivariable analyses could potentially be attributed to the low statistical power due to the limited number of recurrent strokes that occurred during the 1-year follow-up period. Moreover, due to the low number of recurrent strokes during 1-year follow-up we consider that additional analyses according to recurrent stroke subtype would be underpowered and thus were not performed. However, it should be noted that even though no statistically significant differences were documented in the recurrent stroke rates of different IS subtypes, patients with large-artery atherosclerosis in our population had a higher risk of 1-month stroke recurrence compared to other IS subtypes, but experience no other recurrent events beyond the first 30 days following the index event. In contrast, patients with cardioembolic or cryptogenic stroke experienced a constantly increasing stroke recurrence risk over time during the 1-year follow-up (Fig. 5b). Finally, it should be highlighted that approximately 6% of our study population had unavailable follow-up evaluations. Notably, the majority of patients with missing follow-up information were octagenarians who were assessed or hospitalized in internal medicine departments (Supplemental Table I). Contact information was unavailable or incorrect both for these patients and their family members. Moreover, it should be noted that the rates of patients lost to follow-up were similar in different stroke subtypes (IS, ICH, SAH, undefined stroke; Table 1). This observation indicates that the missing follow-up evaluations may not have affected the reported outcome event rates across different FES subtypes.

In conclusion, our study reports comparable to similar population-based studies all-cause mortality and stroke recurrence rates in patients with FES, highlighting that stroke survivors represent a continuing high-risk population. Given the high incidence rates and rapid population aging in southeastern Europe, dedicated rehabilitation programs and effective secondary prevention strategies are urgently needed for stroke survivors.

Author contributions Dr. GT: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. AHK: analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. AP: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. MP: analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. TB: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. MM: critical revision of the manuscript for important intellectual content. Dr. MY: critical revision of the manuscript for important intellectual content. Dr. CZ: critical revision of the manuscript for important intellectual content. Dr. ST: critical revision of the manuscript for important intellectual content. Dr. NP: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. PS: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. AT: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. GSG: critical revision of the manuscript for important intellectual content. Dr. PZ: critical revision of the manuscript for important intellectual content. Dr. EM: critical revision of the manuscript for important intellectual content. Dr. CP: critical revision of the manuscript for important intellectual content. Dr. IH: critical revision of the manuscript for important intellectual content. Dr. KV: critical revision of the manuscript for important intellectual content, study supervision.

Funding None.

Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. von Arbin M, Britton M, de Faire U (1992) Mortality and recurrences during eight years following stroke. J Intern Med 231:43–48
2. Schrader J, Lüders S, Kulschewski A et al (2005) Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (MOSES). Stroke 36:1218–1226
3. Zhang Y, Chapman AM, Plested M, Jackson D, Purroy F (2012) The incidence, prevalence, and mortality of stroke in France, Germany, Italy, Spain, the UK, and the US: a literature review. Stroke Res Treat 2012:436125
4. Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP (2011) Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. Stroke 42:1489–1494
5. Pickle LW, Mungiole M, Gillum RF (1997) Geographic variation in stroke mortality in blacks and whites in the United States. Stroke 28:1639–1647
6. Gillum RF, Kwagyan J, Obisesan TO (2011) Ethnic and geographic variation in stroke mortality trends. Stroke 42:3294–3296
7. Vemmos KN, Bots ML, Tsibouris PK et al (2000) Prognosis of stroke in the south of Greece: 1 year mortality, functional outcome and its determinants: the Arcadia Stroke Registry. J Neurol Neurosurg Psychiatry 69:595–600
8. Tsivgoulis G, Patousi A, Pikilidou M et al (2018) Stroke incidence and outcomes in northeastern Greece: the Evros Stroke Registry. Stroke 49:288–295
9. Sacco R, Kasner SE, Broderick JP et al (2013) An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 44:2064–2089
10. Adams HP Jr, Bendixen BH, Kappelle LJ et al (1993) 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 24:35–41
11. Hatano S (1976) Experience from a multicentre stroke register: a preliminary report. Bull WHO 54:541–553
12. Coull AJ, Rothwell PM (2004) Underestimation of the early risk of recurrent stroke: evidence of the need for a standard definition. Stroke 35:1925–1929
13. Tsivgoulis G, Bogiatzi C, Heliopoulos I et al (2012) Low ankle-brachial index predicts early risk of recurrent stroke in patients with acute cerebral ischemia. Atherosclerosis 2012 220:407–412
14. Lewis JR, Sauro J (2006) When 100% really isn't 100%: improving the accuracy of small-sample estimates of completion rates. J Usabil Stud 1:136–150
15. Nyaga VN, Arbyn M, Aerts M. Metaprop: a stata command to perform meta-analysis of binomial data (2014) Arch Public Health 72:39
16. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188
17. Cochran WG (1954) The combination of estimates from different experiments. Biometrics 10:101–129
18. Appelros P, Nydevik I, Viitanen M (2003) Poor outcome after first-ever stroke: predictors for death, dependency, and recurrent stroke within the first year. Stroke 34:122–126
19. Minelli C, Fen LF, Minelli DP (2007) Stroke incidence, prognosis, 30-day, and 1-year case fatality rates in Matão, Brazil: a population-based prospective study. Stroke 38:2906–2911
20. Modrego PJ, Mainar R, Turull L (2004) Recurrence and survival after first-ever stroke in the area of Bajo Aragon, Spain a prospective cohort study. J Neurol Sci 224:49–55
21. Mohan KM, Crichton SL, Grieve AP, Rudd AG, Wolfe CD, Heuschmann PU (2009) Frequency and predictors for the risk of stroke recurrence up to 10 years after stroke: the South London Stroke Register. J Neurol Neurosurg Psychiatry 80:1012–1018
22. Olindo S, Saint-Vil M, Jeannin S et al (2017) One-year disability, death and recurrence after first-ever stroke in a Black Afro-Caribbean population. Int J Stroke 12:844–850
23. Pennlert J, Asplund K, Glader EL, Norrving B, Eriksson M (2017) Socioeconomic status and the risk of stroke recurrence: persisting gaps observed in a Nationwide Swedish Study 2001 to 2012. Stroke 48:1518–1523
24. Salehi M, Amiri A, Thrift AG et al (2018) Five-year recurrence rate and the predictors following stroke in the Mashhad Stroke Incidence Study: a population-based cohort study of stroke in the middle east. Neuroepidemiology 50:18–22
25. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C (1994) Long-term risk of recurrent stroke after a first-ever stroke. Oxf Commun Stroke Project Stroke 25:333–337
26. Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson C (2004) Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. Stroke 35:731–735
27. Hata J, Tanizaki Y, Kiyohara Y et al (2005) Ten year recurrence after first ever stroke in a Japanese community: the Hisayama study. J Neurol Neurosurg Psychiatry 76:368–372
28. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO (2000) Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. Stroke 31:1062–1068
29. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU (2001) Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke 32:2735–2740

Affiliations

Georgios Tsivgoulis[1,2] · Aristeidis H. Katsanos[2,3] · Athanasia Patousi[1] · Maria Pikilidou[4] · Theodosis Birbilis[5] · Michael Mantatzis[6] · Maria Yavropoulou[7] · Christina Zompola[2] · Sokratis Triantafyllou[2] · Nikolaos Papanas[8] · Panagiotis Skendros[9] · Aikaterini Terzoudi[1] · George S. Georgiadis[10] · Pantelis Zebekakis[4] · Efstratios Maltezos[8] · Charitomeni Piperidou[1] · Ioannis Heliopoulos[1] · Konstantinos Vadikolias[1]

[1] Department of Neurology, University Hospital of Alexandroupolis, School of Medicine, Democritus University of Thrace, Alexandroupolis, Greece

[2] Second Department of Neurology, "Attikon" University Hospital, School of Medicine, National and Kapodistrian University of Athens, Iras 39, Gerakas Attikis, 15344 Athens, Greece

[3] Department of Neurology, School of Medicine, University of Ioannina, Ioannina, Greece

[4] First Department of Internal Medicine, AHEPA University Hospital, Hypertension Excellence Center, Aristotle University of Thessaloniki, Thessaloniki, Greece

[5] Department of Neurosurgery, University Hospital of Alexandroupolis, School of Medicine, Democritus University of Thrace, Alexandroupolis, Greece

[6] Department of Radiology, University Hospital of Alexandroupolis, School of Medicine, Democritus University of Thrace, Alexandroupolis, Greece

[7] Division of Endocrinology and Metabolism, AHEPA University Hospital, Thessaloniki, Greece

[8] Second Department of Internal Medicine, University Hospital of Alexandroupolis, School of Medicine, Democritus University of Thrace, Alexandroupolis, Greece

[9] First Department of Internal Medicine, University Hospital of Alexandroupolis, School of Medicine, Democritus University of Thrace, Alexandroupolis, Greece

[10] Department of Vascular Surgery, School of Medicine, Democritus University of Thrace, Alexandroupolis, Greece