Embolic Stroke of Undetermined Source and Detection of Atrial Fibrillation on Follow-Up: How Much Causality Is There?

George Ntaios, MD,* Vasileios Papavasileiou, MD,*† Gregory Y.H. Lip, MD,‡ Haralampos Milionis, MD,§ Konstantinos Makaritsis, MD,* Anastasia Vemmou, MD,‖ Eleni Koroboki, MD,‖ Efstathios Manios, MD,‖ Konstantinos Spengos, MD,¶ Patrik Michel, MD,# and Konstantinos Vemmos, MD‖

Background: There is increasing debate whether atrial fibrillation (AF) episodes during follow-up in patients with embolic stroke of undetermined source (ESUS) are causally associated with the event. AF-related strokes are more severe than strokes of other etiologies. In this context, we aimed to compare stroke severity between ESUS patients diagnosed with AF during follow-up and those who were not. We hypothesized that, if AF episodes detected during follow-up are indeed causally associated with the index event, stroke severity in the AF group should be higher than the non-AF group. *Methods:* Dataset was derived from the Athens Stroke Registry. ESUS was defined by the Cryptogenic Stroke/ESUS International-Working-Group criteria. Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS) score. Cumulative probabilities of recurrent stroke or peripheral embolism in the AF and non-AF ESUS groups were estimated by

From the *Department of Medicine, Larissa University Hospital, School of Medicine, University of Thessaly, Larissa, Greece; †Stroke Service, Department of Neurosciences, Leeds Teaching Hospitals NHS Trust and Medical School, University of Leeds, Leeds, UK; ‡University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, UK; §Department of Medicine, Ioannina University Hospital, School of Medicine, University of Ioannina, Ioannina, Greece; ‖Department of Clinical Therapeutics, Medical School of Athens, Alexandra Hospital, Athens, Greece; ¶Department of Neurology, Eginition Hospital, University of Athens Medical School, Athens, Greece; and #Neurology Service, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland.

Received March 22, 2016; revision received June 26, 2016; accepted August 7, 2016.

Disclosures: Dr. Ntaios: None related directly to this work. Dr. Papavasileiou: None related directly to this work. Dr. Lip: None related directly to this work. Consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. Dr. Milionis: None related directly to this work. Dr. Makaritsis: None related directly to this work. Dr. Vemmou: None related directly to this work. Dr. Koroboki: None related directly to this work. Dr. Manios: None related directly to this work. Dr. Spengos: None related directly to this work. Dr. Michel: None related directly to this work. Dr. Vemmos: None related directly to this work.

Author contribution: G. Ntaios: study concept, statistical analysis and interpretation, preparation of manuscript, study supervision. V. Papavasileiou: statistical analysis and interpretation, critical revision of the manuscript. G.Y. Lip: critical revision of the manuscript. H. Milionis: critical revision of the manuscript. K. Makaritsis: critical revision of the manuscript. A. Vemmou: acquisition of data and critical revision of the manuscript. E. Koroboki: acquisition of data and critical revision of the manuscript. E. Manios: critical revision of the manuscript. K. Spengos: critical revision of the manuscript. P. Michel: critical revision of the manuscript. K. Vemmos: acquisition of data, statistical analysis and interpretation, critical revision of manuscript, and study supervision.

Address correspondence to George Ntaios, MD, MSc (ESO Stroke Medicine), PhD, FESO, Department of Medicine, Larissa University Hospital, School of Medicine, University of Thessaly, Biopolis 41110, Larissa, Greece. E-mail: gntaios@med.uth.gr.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.08.015

Kaplan–Meier analyses. *Results:* Among 275 ESUS patients, AF was detected during follow-up in 80 (29.1%), either during repeated electrocardiogram monitoring (18.2%) or during hospitalization for stroke recurrence (10.9%). NIHSS score was similar between the two groups (5 [2-13] versus 5 [2-14], $P = .998$). More recurrent strokes or peripheral embolisms occurred in the AF group compared with the non-AF group (42.5% versus 13.3%, $P = .001$). *Conclusions:* Stroke severity is similar between ESUS patients who were diagnosed with AF during follow-up and those who were not. Given that AF-related strokes are more severe than strokes of other etiologies, this finding challenges the assumption that the association between ESUS and AF detected during follow-up is as frequently causal as regarded. **Key Words:** Stroke—atrial fibrillation—embolism—stroke severity.

Introduction

A new clinical entity termed *embolic stroke of undetermined source* (ESUS) was recently introduced by the Cryptogenic Stroke/ESUS International Working Group, which describes stroke patients for whom the source of embolism remains undetected despite standard investigation. Potential embolic sources include covert atrial fibrillation (AF), mitral and aortic valves, the left cardiac chambers, the proximal cerebral arteries of the aortic arch, the venous system via paradoxical embolism, artery-to-artery embolism (even without stenosis), in situ thrombosis, prothrombotic disorders, and others.[1]

In a recent analysis of the Athens Stroke Registry, episodes of AF were detected during follow-up in approximately one third of ESUS patients, either at repeated electrocardiogram (ECG) monitoring or during hospitalization for a recurrent stroke.[2] Although covert AF could potentially be the causative mechanism in these patients, there is increasing debate whether episodes of AF during follow-up of an ischemic stroke patient are causally associated with the event—especially for AF episodes detected remotely after the index event—or represent only a (still) innocent bystander.[3]

Numerous studies have shown that AF-related strokes have more severe clinical presentation compared with other etiologies.[4-6] In this context, we aimed to compare stroke severity between ESUS patients who were diagnosed with AF during follow-up and those who were not. We hypothesized that if AF episodes detected during follow-up are indeed causally associated with the index event, stroke severity in the AF group should be higher than in the non-AF group. Second, we compared the long-term risk of stroke recurrence and peripheral embolism between these two groups.

Methods

The study population was derived from the Athens Stroke Registry, which includes all consecutive patients with an acute first-ever ischemic stroke admitted in Alexandra University Hospital, Athens, Greece, between June 1992 and December 2011.[7] The methodology followed to register data in the Athens Stroke Registry was described elsewhere.[2] The scientific use of the data collected in the Athens Stroke Registry was approved by the local Ethics Committee.

Patients were classified as ESUS when the related diagnostic work-up (as described by the Cryptogenic Stroke/ESUS International-Working-Group criteria) was completed. In particular, ESUS was defined as a visualized nonlacunar brain infarct in the absence of the following: (1) extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia; (2) major-risk cardioembolic source; and (3) any other specific cause of stroke (e.g. arteritis, dissection, migraine/vasospasm, drug misuse).[1]

With regard to AF detection, all patients had a 12-lead ECG at admission. In patients on sinus rhythm, AF paroxysms were sought by (1) repeated ECGs during hospital stay; (2) continuous ECG monitoring for 1 week or until discharge for patients treated in the acute stroke unit (ECG was observed by a trained nurse personnel and intermittently analyzed by the treating physician); and (3) 24-hour Holter ambulatory ECG monitoring in cases that AF was strongly suspected from the clinical presentation and/or brain imaging findings (e.g. multiterritorial infarcts, strokes presenting with maximum severity at onset, largely dilated left atrium) and (1) and (2) were negative.

Stroke severity was evaluated with the National Institutes of Health Stroke Scale (NIHSS) score.[8] For the study period between 1992 and 1998, NIHSS was calculated from the Scandinavian Stroke Scale using the following formula: NIHSS score = 25.68 – (.43*Scandinavian Stroke Scale score).[9] Functional outcome was assessed by the modified Rankin scale score.

Patients were prospectively followed-up at 1, 3, and 6 months after discharge and yearly thereafter. Follow-up was routinely performed in the outpatient clinic. In case of patients with severe handicap, clinical follow-up was assessed at patient's residence or by telephone interview. Lost-to-follow-up was defined as inability to reach the patient or the patient's proxies at a scheduled time point.

Recurrent stroke was defined as a cerebrovascular event of sudden onset, lasting >24 hours, subsequent to the initial