

Clinical Research

Circadian and Seasonal Distribution of Cardioembolic Strokes Due to Atrial Fibrillation

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Introduction: A seasonal and circadian distribution of the incidence of stroke has been described in many countries, with peaks during the winter period and the morning hours. In Greece, a cardioembolic aetiology accounts for the most important stroke subgroup, while atrial fibrillation (AF) is the commonest cause.

Methods: In 2 groups of 335 and 360 patients with cardioembolic stroke (CES) due to AF we studied the time distribution of the onset of symptoms over 24 hours and one year, respectively. The χ^2 test ("goodness of fit" model) was then used to compare the incidence of CES per two-hour interval over 24 hours, per month and per season over the course of the year, with the expected values in each case.

Results: There was a statistically significant difference ($p < 0.001$) between the actual findings and a uniform 24-hour distribution. The daily distribution was unusual, with 2 peaks between 08:00-10:00 and 16:00-18:00. There was a similar difference ($p < 0.001$) in the comparison over the year, with an increased incidence being apparent during the winter months. The differences between the seasons were also significant, with the largest number of CES during the winter and the smallest during the summer.

Conclusions: The well-established increase in stroke in the morning, just a few hours after awakening, is probably related to corresponding changes in various biological parameters. The appearance of a second peak late in the afternoon may similarly be related to awakening from siesta. Further population studies are needed to confirm the increased incidence of CES during the winter months.

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The incidence of stroke in a number of hospital and population studies from various countries of the world has been shown to have a circadian¹⁻⁶ and a seasonal^{4,7-9} distribution, characterised by an increase in the morning hours¹⁰ and a variation over the year with a clear peak during the winter. However, other investigators reported an opposite seasonal distribution for various types of stroke.¹¹

Recently published data showed a correlation between the type of stroke and its time of appearance.¹²⁻¹⁴ According to these findings, it does not appear that any single one of the common vascular risk factors is directly related with the in-

creased incidence of CE during the morning hours.¹⁵ Other recent publications have described a similar yearly distribution, with a significant increase during the winter months for various factors that are causally related with the incidence of stroke.¹⁶⁻¹⁹ A similar periodicity has also been reported for the onset of episodes of paroxysmal atrial fibrillation (AF).²⁰ The relation between stroke and cardiac arrhythmias, and AF in particular, has been the object of some study.¹⁴

Ischaemic infarcts of cardioembolic origin are the most frequent type of stroke in Greece, while AF appears to be the most significant risk factor for CES in

this country.^{21,22} Accordingly, we studied the circadian and seasonal variation in the incidence of stroke in patients with CES due to AF. The main aim of the study was to examine whether the double-peaked circadian distribution that generally characterises stroke incidence in Greece²³ would also be seen among CES patients of this particular subgroup.

Material and Methods

The data used came from the prospective recording and study of all patients with acute stroke who were

admitted to our hospital (The Athens Stroke Registry) with onset of stroke less than 1 week before. The detailed diagnostic and clinical criteria used in this study have already been published.²¹ For the study of the daily circadian rhythm we used 1,630 consecutive patients (June 1992-December 2002, Figure 1), while for the study of seasonal distribution we took an exact 10-year period, during which 1,485 cases were recorded (1/1/1993 to 31/12/2002). All patients were examined by a general physician and a neurologist during the first 48 hours following the onset of symptoms and underwent a computerised

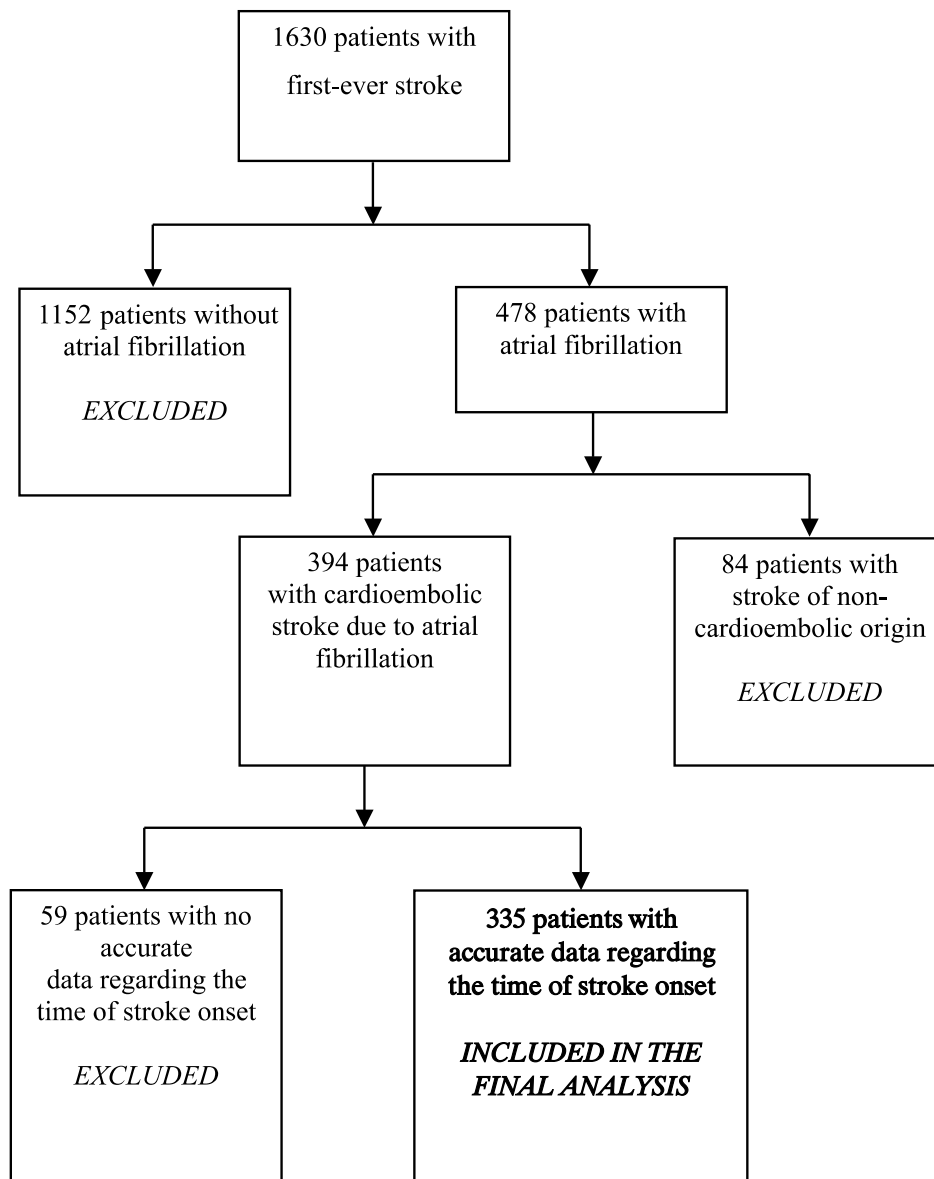


Figure 1. Flow chart illustrating the selection process for patients with cardioembolic stroke due to atrial fibrillation who were included in the study of the circadian distribution of the onset of symptoms.

tomography scan (CT) of the brain. A second CT or magnetic resonance imaging (MRI) examination was carried out between the 4th and the 14th day. Most patients also underwent a vascular examination (ultrasound or angiogram), while selected patients had an echocardiographic (transthoracic or transoesophageal) examination and 24-hour Holter electrocardiographic recording. Patients with subarachnoid haemorrhage, transient ischaemic attacks (TIAs), or recurrent stroke were excluded from the study. The diagnosis of CES was based on:

a. the presence of one or more foci with high risk for cardiac emboli: AF, atrial flutter, sick sinus syndrome with or without valvular disease, prosthetic valves, history of recent myocardial infarction, existence of left ventricular aneurysm or hypokinesia with or without mural thrombus, endocarditis, dilated cardiomyopathy, and

b. one or more of the following criteria: obstruction with significant stenosis (>50%) and/or ulceration of the extracranial arteries ipsilateral to the ischaemic region visualised on imaging; detection of a single infarct by CT or MRI in the region of a single cerebral artery, or of infarctions in multiple branches of other divisions of the major cerebral arteries, or, finally, detection of a haemorrhagic infarct; the existence of typical clinical signs, such as sudden and maximal neurological deficit at onset, absence of previous TIAs and initially decreased level of consciousness.²¹

From the patients who were diagnosed as having CES (478) we selected those in whom AF was considered to be the cause of stroke (394). This group made up the population of this study (Figure 1). Following the guidelines of the American College of Cardiology / American Heart Association Task Force, we made a distinction between paroxysmal and permanent AF.²⁴

The time of stroke onset is one of the parameters recorded for each patient included in the Athens Stroke Registry. All patients without disturbances of level of awareness were thoroughly questioned as to the exact time of onset of symptoms and their replies were cross-checked by asking their relatives the same questions. In the case of patients with aphasic disorders or compromised level of awareness the time of onset was determined on the basis of the relatives' answers. For the patients who noticed their symptoms after waking, stroke was considered to have started during sleep. Fifty-nine patients with an unclear time of stroke onset were excluded from the study (Figure 1).

Table 1. Characteristics of patients with cardioembolic stroke due to atrial fibrillation (n=394, age [mean \pm standard deviation] 75.1 \pm 9.4 years).

	N	%
Age		
<65 years	47	11.9
65-74 years	117	29.7
>75 years	230	58.4
Men		
Arterial hypertension	258	65.5
Diabetes mellitus	85	21.6
Smoking	61	15.5
Hypercholesterolaemia	58	14.7
Coronary artery disease	67	17.0
Heart failure	44	11.2
Atrial fibrillation		
Permanent	247	62.7
Paroxysmal	147	37.3
First diagnosed	83	21.1
Treatment with coumarin	48	12.2
Treatment with aspirin	79	20.1

Statistical analysis

If the stroke onset is independent of the time of day, the start of symptoms should be uniformly distributed over a 24-hour period. After dividing the day into 12 2-hour intervals we compared the incidence of stroke in these 12 intervals with that expected from the uniform distribution, using the χ^2 goodness-of-fit test. The confidence level was set at 95%. Strokes that occurred while the patients were awake were analysed directly, while strokes during sleep were distributed uniformly over the three 2-hour intervals prior to awakening before being included in the analysis. For the monthly and seasonal analysis the same goodness-of-fit χ^2 tests were applied to the 12 months and the four seasons of the year.

Results

Basic characteristics of the study population

In the period from June 1992 to December 2002, 1,630 patients with first-ever acute stroke were admitted to our hospital. Around one third of the cases had a cardioembolic aetiology (n=517, 31.7%). From the total population 478 (29.3%) patients had AF, while CES due to that arrhythmia occurred in 394 (82.4%) patients. The main demographic and clinical data from these patients are given in table 1.

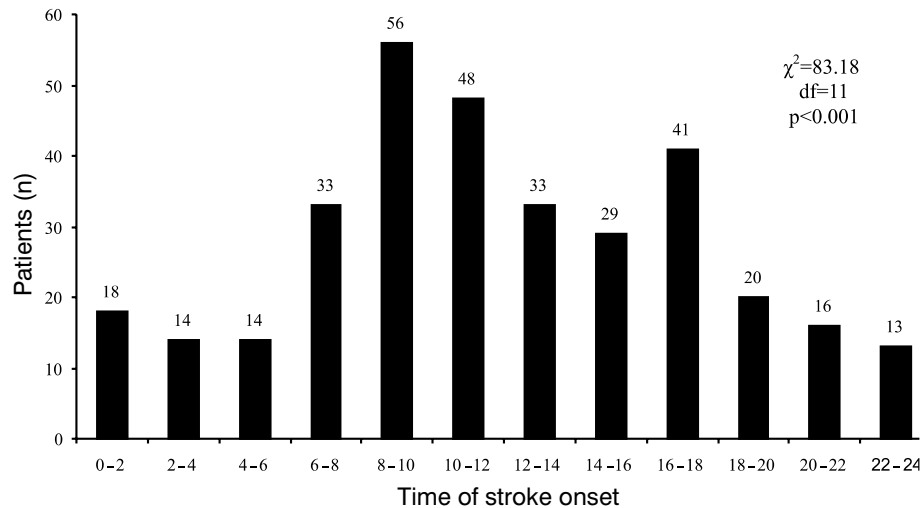


Figure 2. Daily circadian distribution of the onset of symptoms in patients with cardioembolic stroke due to atrial fibrillation (n=335).

The AF was permanent in 247 (62.7%) and paroxysmal in the remaining 147 (37.3%). AF was hence the most common cause of stroke in the whole patient population (394/1630=24.2%). Of the AF patients aged <65 years only 8 (17%) had no known risk factor for cardiac embolism (lone). Only one third of the patients (127, 32.2%) were under preventive treatment, either with antiplatelet agents (aspirin: 79 patients, 20.1%) or with anticoagulants (coumarin: 48 patients, 12.2%). Correct anticoagulant treatment on admission (INR=2.0-3.0) was recorded in only 8 (17%) of those 48 cases. The percentage of patients taking coumarin during 1992 and 2002 was 5.7% and 22%, respectively.

Daily circadian distribution of occurrence of CES due to AF

Precise data regarding the time of stroke onset were recorded in 335 of the above patients (149 men, 186 women, age range 35-95 years), and these were included in the detailed analysis (Figure 1). Reliable information about the time of onset could not be obtained in the remaining cases (59 patients), who were therefore excluded from the study. Only 10 patients (3%) noticed stroke symptoms on awakening from nocturnal sleep. Using the χ^2 test we compared the observed incidence of CES in twelve 2-hour intervals with the expected rate if the stroke distribution over the 24-hour period were uniform. There were statistically significant differences, with a characteristic double-peaked distribution of stroke incidence ($\chi^2=95.97$, $df=11$, $p<0.001$). Even when strokes noticed on awakening were distributed as described

above the statistical significance and the double-peaked distribution of symptom onset remained unchanged ($\chi^2=83.18$, $df=11$, $p<0.001$, Figure 2). The first peak corresponded to the morning hours, a little after waking (08:00-10:00) and the second peak occurred late in the afternoon (16:00-18:00).

Similar findings emerged when a separate analysis of the circadian distribution was carried out for each sex and for patients with permanent versus paroxysmal AF ($p<0.001$ in each case).

Seasonal distribution of CES due to AF

Of the 1,485 patients with first-ever acute stroke who were admitted to our hospital during the ten-year period 1/1/1993-31/12/2002 we studied 360 who were diagnosed as having CES due to AF (360/1485=24.24%). Comparing the actual monthly stroke incidence with the expected rate if the stroke distribution over the year were uniform, we found a statistically significant difference ($\chi^2=28.87$, $df=11$, $p<0.01$) with a lower stroke incidence during the period from May to September (Figure 3). Using the same methodology for the four seasons of the year we found similar statistically significant differences, with a clearly higher stroke incidence during the winter and a significant drop in the summer ($\chi^2=23.62$, $df=3$, $p<0.001$, Figure 4).

Discussion

CES are the most common type of stroke in our patients.²⁵ A trend has also been described for CES to be even more common than those due to large vessel

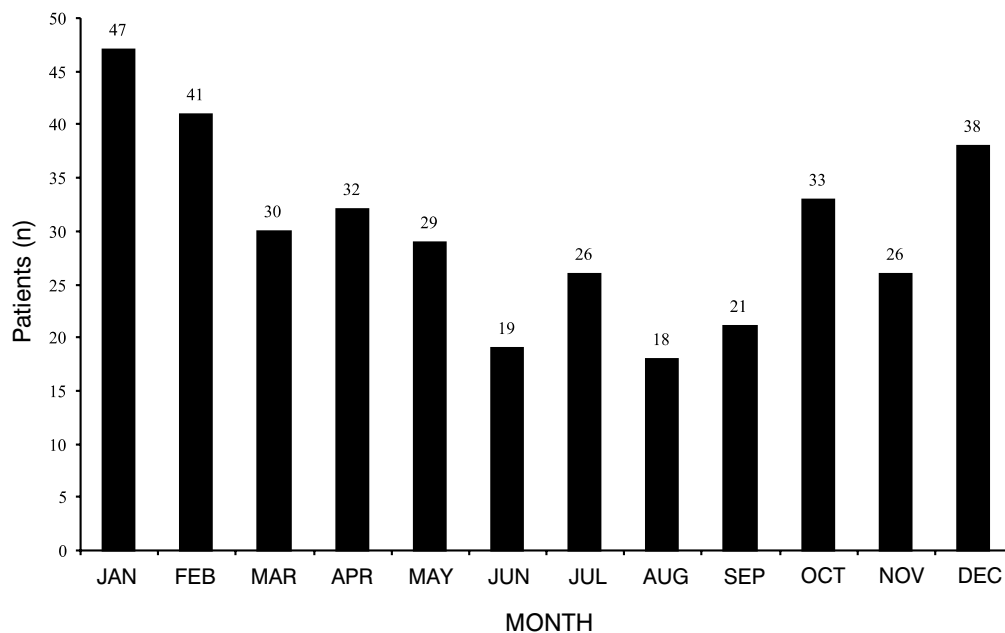


Figure 3. Monthly distribution of incidence of cardioembolic stroke due to atrial fibrillation (n=360).

atherothrombotic disease.^{21,26} This could be related with the higher incidence of AF in older people^{27,28} and might explain the steadily increasing number of diagnosed cases in recent years.²⁹ The disproportionately high percentage of cases of CES due to AF in our study could be partly attributed either to an increased incidence of AF in the Greek population or to the reluctance of doctors in this country^{21,22} to prescribe anticoagulants for primary stroke prevention in elderly patients with AF.^{30,31} There is no epidemiological evidence regarding the prevalence or incidence of AF in the Greek population. It is most

probable that many Greek patients with AF are not under correct preventive treatment. It is, however, difficult to draw conclusions from our data concerning the rate of preventive use of anticoagulants in the general population of AF patients. The fact that at the start of the study period (1992) the patients with CES due to AF who were taking coumarins represented 5.7%, whereas by the end (2002) this percentage had risen to 22%, is perhaps an indication that Greek doctors have become more sensitised in recent years to the correct preventive use of mainly coumarin compounds. Our findings show in

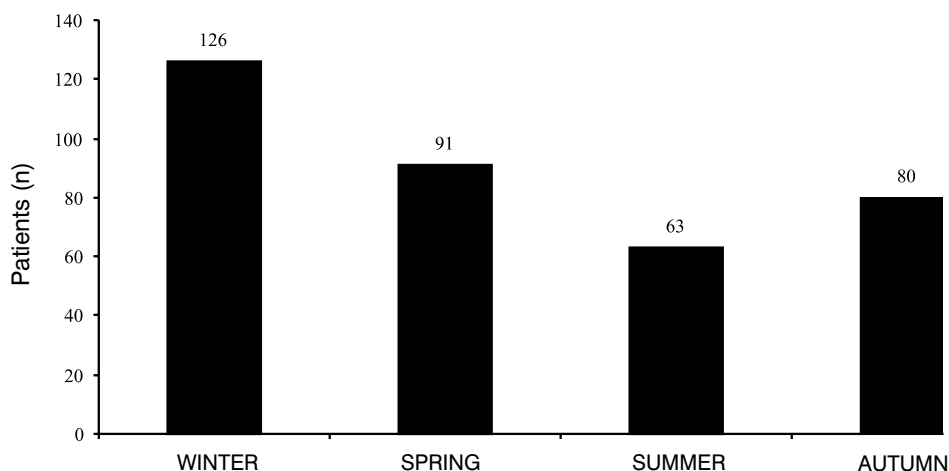


Figure 4. Seasonal distribution of incidence of cardioembolic stroke due to atrial fibrillation (n=360).

how many patients preventive anticoagulant treatment failed, mainly because of incorrect use, since only 17% of those taking anticoagulants had a correct prothrombin time (INR=2.0-3.0). It is disappointing to note that, in spite of the guidelines that have been published repeatedly during recent years, the majority of our patients were still not taking any antiplatelet treatment at all.²⁴

Circadian distribution of CES due to AF

A series of hospital and population studies have reported that the incidence of both ischaemic and haemorrhagic stroke shows a circadian distribution.^{1-6,12} An increase in the stroke incidence during the second half of the morning is generally accepted. A recent meta-analysis found that the risk of stroke occurring during the period 06:00-12:00 is 49% higher than would be expected if stroke occurred randomly with a uniform distribution over the day.¹⁰ Our own findings refer only to hospitalised patients with first-ever cardioembolic stroke due to AF and are in concordance with those reported by other similar studies as regards the higher stroke incidence during the morning hours. In agreement with previous findings for the overall stroke incidence in Greek patients,²³ we also found in this particular subgroup the same characteristic double-peaked time distribution for the occurrence of CES due to AF. The first and clearly higher peak is seen between 08:00-10:00, while a second, lower peak appears between 16:00-18:00.

The morning peak agrees with similar findings from a number of previous studies.¹⁻⁷ None of the common vascular risk factors appears to be correlated with this morning peak in stroke incidence.¹⁵ In contrast, the circadian variation seen in blood pressure,^{32,33} cardiac output, heart rate,³⁴⁻³⁶ vascular tone,³⁷ and physical activity³⁸ could be related with the occurrence of stroke. Fluctuations throughout the day, with a peak during the morning hours, have been described for haematocrit levels and blood viscosity.³⁹ Platelet aggregation and the activity of plasminogen activator inhibitor also show peak values during the period following awakening.⁴⁰ Conversely, intrinsic plasminogen activity is at its lowest level at the time of awakening.⁴¹ These changes in the physiological balance between thrombolysis and thrombosis might affect the time distribution of occurrences of stroke and therefore might be related with the proven morning surge in stroke incidence.

The second peak in stroke incidence during the afternoon is not easy to explain. A logical interpretation of this phenomenon could be that it is in some way related to siesta. This is a typical Greek custom that is not widely observed in other countries. We could hypothesise that in the Greek population, accustomed to take a nap in the middle of the afternoon, we could expect to find a different time distribution with two peaks for all or some of the above biological parameters. This hypothesis could find a basis in the above mentioned critical changes in physical activity, blood pressure, heart rate, cardiac output, vascular tone, platelet aggregation, the activity of plasminogen activator inhibitor and intrinsic plasminogen activity, which have been observed during the period following waking from nocturnal sleep,³²⁻⁴¹ and the higher risk of stroke during that time. Given that cardiovascular and vascular cerebral events appear clustered around the time after waking from nocturnal sleep, when the variations of the various parameters from their nocturnal mean are greatest, we could hypothesise that there would be a second increase in the occurrence of such events right after an additional sleep period in the course of the day. The recently published findings of Stergiou et al⁴² strongly support this view. There are indications that physical activity or intense exercise may also be of significance, causing an increase in plasma fibrinogen levels and thus influencing the hypercoagulant situation seen in chronic AF.⁴³ Furthermore, it has recently been suggested that there is a correlation between siesta and an increase in the risk of myocardial infarction, as well as a higher mortality from cardiovascular events.^{44,45} A double-peaked time distribution has also been described for the appearance of paroxysmal AF and ventricular tachyarrhythmias, with a first, morning peak and a second, lower peak in the evening hours.^{20,46-48}

There are no data in the international literature regarding a possible relation between AF and sleep during the day. Another parameter that is likely to contribute to the observed daily variation is the intensity and, by extension, the efficacy of oral anticoagulant medication in patients with AF.⁴⁹ Such variations might lead to the occurrence of stroke that could be prevented. In view of the small percentage of our CES patients who were taking anticoagulant or antiplatelet medication as a primary prevention regimen, it is clear that there is a long road ahead before we can improve the prevention of this particular type of stroke.

Seasonal distribution of CES due to AF

In parallel with the seasonal distribution in the incidence of stroke that has been previously described and is characterised by a significant increase in the winter and a reduction in the summer,⁵⁻⁹ other studies have shown a seasonal variation in a number of physiological parameters that might be causally related with the occurrence of stroke. In the summer months, for example, positive titres of antiphospholipid antibodies are more rarely seen,¹⁶ while plasma levels of the vasoconstrictor endothelin show variations with increased values during the winter, especially during January and February. During the same period the variation in the vasorelaxant nitric oxide (NO) reaches its nadir. The combination of these findings could explain in part the increased stroke incidence and coronary vessel disease that we see mainly during the winter.¹⁷ It has also been reported that plasma levels of fibrinogen and factor VII are significantly higher in winter. This seasonal change could provide a possible explanation for the seasonal variation seen in deaths from stroke and ischaemic heart disease in the elderly,^{18,19} as well as for our own findings.

Study limitations

The fact that the above findings are from a hospital study is the main factor that limits their significance. In hospital studies it is impossible to avoid certain systematic errors, mainly regarding the admission and selection of the patients who participate in the study. Thus, especially in the case of the seasonal distribution of stroke we cannot rule out the possibility that a part of the increase during the winter months was due to the general increase in the population of Athens –and especially in elderly people– that occurs every winter. Similar results from a future population study in Greece could support and reinforce our findings.

However, our observations could be useful, firstly by helping the establishment of primary stroke prevention with anticoagulants in patient with AF, and secondly by contributing to the better organisation of facilities for the treatment of acute stroke.

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