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Prevalence of patent foramen ovale in the Greek population is high and impacts on the interpretation of the risk of paradoxical embolism (RoPE) score

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Abstract

Background: The risk of paradoxical embolism (RoPE) score calculates the probability that patent foramen ovale (PFO) is causally related to stroke (PFO attributable fraction, PFOAF), based on PFO prevalence in patients with cryptogenic stroke (CS) compared with that in the general population. The latter has been estimated at 25%; however, PFO prevalence in nonselected populations varies widely.

Methods: Since PFO prevalence in Greece remains unknown, we evaluated it and we calculated PFOAF stratified by RoPE score in a cohort of patients with CS ⩽55 years old. PFO was detected according to the international consensus transcranial Doppler (TCD) criteria in 124 healthy subjects (H), in 102 patients with CS, and in 56 patients with stroke of known cause (nonCS). Each subject underwent unilateral middle cerebral artery recording after infusion of agitated saline, at rest, and after a controlled Valsalva maneuver. We characterized PFO as large (>20 microbubbles or curtain), moderate (11–20), and small (⩽10).

Results: PFO was detected in 42.7% of H, 49% of CS, and 25% of nonCS ($p = 0.013$). Large PFOs were numerically higher in CS [28.4% (29/102)] compared with H [19.3% (24/124); $p = 0.1$] and to nonCS [7.1% (4/56), $p = 0.04$]. The median RoPE score in patients with CS and PFO was seven. Even patients with very high RoPE score (9–10) had moderate PFOAF (57%). For any individual stratum up to RopE score 8, PFOAF was <33%.

Conclusions: PFO prevalence in the Greek population is much higher than the widely accepted 25%. PFO may be the cause of stroke in one out of nine Greek patients with CS. Among Greek CS patients who harbor a PFO, the latter is causal in one out of five. The established RoPE score cutoff of ⩾7 for having a probable PFO-associated stroke may overestimate the probability in patients deriving from populations with high PFO prevalence.

Keywords: cryptogenic stroke, patent foramen ovale, PFO-associated stroke, right-to-left cardiac shunt, RopE score, transcranial Doppler

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Introduction

Despite thorough investigation, the etiology of ischemic stroke remains undetermined in 10–40% of cases.[1] The etiologic significance of patent foramen ovale (PFO) in patients with cryptogenic stroke (CS) has been puzzling stroke physicians for decades. Patency of the foramen ovale is normal during fetal life, allowing blood from the inferior vena cava to pass from the right to the left atrium, bypassing the lungs. At birth, left atrial pressure is increased resulting in functional closure of the foramen ovale. Anatomic closure occurs later in infancy, but often the closure is incomplete and remains as PFO.[2] In most cases, the association of PFO with CS is

hypothetical, as paradoxical embolism or *in situ* thrombus formation can seldom be documented. Several randomized controlled trials and meta-analyses showed superiority of percutaneous PFO closure compared with antiplatelet agents in appropriately selected patients using specific devices.[3–5] However, the optimal candidates for PFO closure are still to be determined.

The risk of paradoxical embolism (RoPE) score is a clinical tool to facilitate the identification of patients with PFO-associated stroke, who might benefit from PFO closure, with higher RoPE scores implying greater possibility of causality (PFO-attributable fraction - PFOAF) between PFO and CS.[6] A high RoPE score (⩾7) implies that in 8 out of 10 patients with CS and a documented PFO, the latter may indeed be the cause of stroke. PFOAF is calculated by applying Bayes' theorem and by using PFO prevalence in patients with CS compared with that in healthy subjects. The latter is "fixed" at approximately 25%, based mainly on results from autopsy and transesophageal echocardiography (TEE) studies.[6] However, both autopsy and TEE are diagnostic modalities with inherent limitations that may underestimate the detection of small-to-medium right-to-left PFO-associated shunt (RLS).[7] Furthermore, potential heterogeneity in PFO prevalence in different healthy racial/ethnic populations may overrate or underrate PFOAF depending on numbers.

Transcranial doppler (TCD) with contrast medium infusion has excellent diagnostic accuracy and sensitivity that may even outclass TEE,[8] and is proposed as a first-choice screening tool for PFO in patients with CS.[9,10] Hitherto, PFO prevalence in the general population has been investigated by TCD in a single study.[11] In addition, small TCD studies were conducted in healthy nonmigraineurs compared with migraineurs.[12–14] Since optimal calculation of the PFOAF corresponding to RoPE score strata relies on the accurate estimation of PFO prevalence in the general population, (a) we estimated by TCD PFO prevalence in the Greek population, in a cohort of patients with CS and in patients with stroke of determined etiology (non-CS), and (b) we evaluated the fraction attributable to PFO in Greek patients with CS and PFO. Our study represents an attempt to investigate whether the RoPE stratification scheme can be applied universally without taking into consideration potential population-specific PFO prevalence discrepancies.

Methods

Subjects/inclusion criteria

The study protocol was approved by the Aristotle University of Thessaloniki Ethics Committee (No 228/11.04.2016), and written informed consent was obtained from all subjects. The study was conducted in two comprehensive stroke centers, in northern and in southern Greece, from March 2016 until November 2019. It included: (1) patients who were hospitalized with CS or with nonCS, and (2) healthy subjects from the general Greek population. All subjects were >17 and <56 years old.

Stroke patients. Ischemic stroke was defined as an acute focal neurological deficit, regardless of the duration of symptoms, which was associated with a recent relevant infarction on brain magnetic resonance imaging (MRI). The type of stroke was classified according the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria as follows.[15] (1) Stroke due to large-artery atherosclerosis: an infarction that was not due to small vessel occlusion (lacunar) and the imaging modalities (extracranial ultrasound, TCD, CT angiography, or MR angiography) were supportive of a luminal stenosis greater than 50% on an extracranial or intracranial artery, that supplies the ischemic region. (2) Stroke due to cardioembolism: an infarction with arterial occlusion due to an embolus arising presumably in the heart. Potential cardiac sources are atrial fibrillation permanent or paroxysmal, persistent atrial flutter, intracardiac thrombus, prosthetic metallic cardiac valves particularly with labile INR, mitral valve stenosis, recent (<4 weeks) myocardial infarction especially with subsequent severe hypokinesis of the cardiac wall, severe heart failure with left ventricular ejection fraction <30%, cardiac tumor such as myxoma, endocarditis and cardiomyopathies such as dilated myocardiopathy. (3) Stroke due to small-vessel occlusion (lacunar infarction): a subcortical infarction <1.5 cm on CT or <2 cm on MRI, that corresponds to a penetrating artery. Potential cardiac sources for embolism and a stenosis >50% in the relevant artery were ruled out. (4) Stroke of other determined etiology: an infarction attributed to other established causes (e.g. artery dissection, arteritis, Fabry disease, antiphospholipid syndrome and hypercoagulative states) or an infarction attributed to multiple co-existing causes. (5) Stroke of undetermined etiology or CS: an infarction for which an etiology was not determined despite extensive evaluation.

All patients with ischemic stroke were monitored (blood pressure, pulse oxymetry, ECG) for at least 3 days, and they were submitted to the following investigations: personal and family medical history for potential vascular risk factors and the use of medication, clinical examination (NIHSS, modified Rankin scale-mRS), 12-lead ECG, chest X-Ray, noncontrast brain CT scan, brain MRI and angiography (MRA), Doppler ultrasound of the extracranial arteries, transcranial Doppler (TCD) with bubble test, transthoracic echocardiography (TTE) and/or transesophageal echocardiography (TEE), blood tests (full blood count, erythrocyte sedimentation rate, C-reactive protein, coagulation tests, biochemical profile). If, after the previously mentioned examinations, stroke etiology remained unclear, we proceeded to at least 24-h Holter monitoring, tumor marker tests, blood tests for autoimmune diseases and Fabry disease, and molecular tests for coagulation disorders. If the etiology of stroke still remained undetermined, we proceeded to full-body computed tomography (CT) scan (abdomen, chest) and CT angiography of the aortic arch. TEE was performed on all patients with CS and a RLS documented by TCD with bubble test, to confirm the existence of PFO and to obtain anatomic details for potential transcatheter closure.

Healthy general population. The group consisted of healthy subjects of Greek origin. They were recruited from the hospital personnel (doctors, nurses, paramedical staff, administration employees), patients' relatives and from the wider social circle. The subjects had had no history of stroke or serious cardiovascular disease, such as cardiomyopathy and valvular heart disease, and no serious systemic disease, such as pulmonary hypertension. Migraineurs without aura were allowed to participate. Personal and family medical history for potential vascular risk factors and medication use was obtained, and all subjects were submitted to Doppler ultrasound of the extracranial arteries and TCD with bubble test.

Exclusion criteria

Subjects were excluded from the study if: (1) they had had transient ischemic attack (TIA) as an index event; (2) they could not achieve an effective Valsalva maneuver (VM) of at least 40 cm H_2O lasting at least 5 s; (3) they did not have an adequate temporal bone window for TCD insonation; (4) they did not provide signed informed consent.

TCD protocol

Each subject underwent unilateral middle cerebral artery (MCA) TCD recording (Natus-SONARA/tek,) through the temporal bone window with a 2-MHz probe (depth range of 40–60 mm) after the bolus infusion of agitated saline, at rest, and after controlled VM. All examinations were conducted by three authors (IK, TK, GT).

The examination procedure for the detection of RLS was based on the instructions of the International Consensus Meeting,[16] modified regarding body position.[17] The subjects were prepared with an 18-gauge catheter inserted preferably into a left antecubital vein. The temporal bone window providing optimal insonation quality was selected and the subjects were placed in the upright sitting position (80–90°). Contrast agent was prepared using 9 ml isotonic saline solution and 1 ml air agitated through a three-way stopcock with the use of two 10 ml syringes. The examination was conducted three times at rest during normal breathing. The subjects were then asked to perform a testing VM while the MCA Doppler spectrum was recorded and the strain pressure was measured with a mouthpiece connected to a manometer. The VM was considered effective if a strain pressure of at least $>$40 cm H_2O for at least 5 s was reached,[18] along with a simultaneous reduction of at least 25% of the mean MCA velocity.[19] Next, the examination was conducted three times with VM. The VM was initiated 5 s after the end of contrast agent infusion and the monitoring for microembolic signals (MES) lasted at least 60 s.

MES were counted offline separately by two authors (IK, TK), and the mean number of the two counts was recorded. The appearance of at least one MES during rest or after VM within 15 s after agitated saline infusion was considered positive for PFO-associated RLS. According to the International Consensus Meeting, a time window for MES appearance that could reliably discriminate intracardiac from pulmonary RLS cannot be applied.[16] The use of a 15-s time window was based (a) on our previous research protocols and experience;[17,18] and (b) on the principle that, in presence of an intracardiac shunt, the passage time from a cubital injection site to the MCA is approximately 11 s at rest, subjected to a further delay of at least 5 s caused by the VM.[20] For each subject, the test with the

higher number of MES (with or without VM) was retained for analysis. RLS was classified using a modification of the ICC criteria as: (1) large (>20 MES or uncountable MES – "shower" or "curtain" pattern); (2) moderate (11–20 MES); and small (⩽10 MES).

RopE score calculation

The RoPE score was calculated for patients with CS.6 PFOAF was calculated for CS across the board and stratified per RoPE score stratum, using the following equation based on Bayes' theorem:

$$\textit{PFO Attributable fraction} = 1 - \frac{\textit{prevalence of PFO in healthy subjects} \times \textit{[1 - prevalence of PFO in CS patients]}}{\textit{prevalence of PFO in CS patients} \times \textit{[1 - prevalence of PFO in healthy subjects]}}$$

Statistical analysis

Chi-square test was used for the comparison of categorical variables and one-way ANOVA with Tukey method for pairwise comparisons was used for the comparison of continuous variables among the three groups of subjects. Using logistic regression adjusted for age and gender, odds ratios (OR) of PFO presence in stroke patients compared with healthy subjects were calculated. All results are presented as means ± SD unless otherwise stated. A p value of <0.05 (two-sided) was considered significant. 95% confidence intervals (CI) for PFO prevalence, and PFOAF were based on normal approximation to the binomial distribution.

Results

Baseline variables

Baseline characteristics of the study population are presented in Table 1. We included 124

Table 1. Baseline variables of the study population.

Variable	Healthy subjects, $n=124$	CS, $n=102$	nonCS, $n=56$	p
Age, mean (SD)				
All	37.2 (11)	42.1 (9.3)	45.7 (8.6)	<0.0001
Women	38.3 (11)	40.1 (8.8)	43.8 (8)	0.18
Men	35.7 (11)	43.7 (9.4)	46.3 (8.8)	<0.0001
Women, *n* (%)	69 (55.6)	46 (45.1)	13 (23.2)	0.0003
Migraine without aura, *n* (%)	13 (10.5)	7 (6.8)	3 (5.3)	0.53
Hypertension, *n* (%)	15 (12.1)	20 (19.6)	21 (37.5)	0.0004
Diabetes, *n* (%)	1 (0.8)	4 (3.9)	9 (16)	<0.0001
Coronary disease, *n* (%)	2 (1.6)	1 (0.9)	10 (17.8)	<0.0001
Current Smoking, *n* (%)	60 (48.4)	48 (47.1)	36 (64.3)	0.085
Hypercholesterolemia, *n* (%)	11 (8.9)	23 (22.5)	9 (19)	0.017
Prior stroke, *n* (%)	NA	14 (13.7)	14 (25)	0.076
Cortical location of index stroke, *n* (%)	NA	77 (75.5)	29 (51.8)	0.004
Stroke etiology, *n* (%)				
Cryptogenic	NA	102 (100)	0 (0)	
Cardioembolism	NA	NA	10 (17.8)	
Large artery disease	NA	NA	15 (26.8)	
Small artery disease	NA	NA	16 (28.6)	
Other determined etiology	NA	NA	15 (26.8)	

CS, cryptogenic stroke; NA, not applicable; nonCS, non-cryptogenic stroke; SD, standard deviation.

controls (mean age: 37.2 years; women: 55.6%), 102 patients with CS (mean age: 42.1 years; women: 45.1%), and 56 patients with non CS (mean age: 45.7 years; women: 23.2%).

Healthy subjects were 4.9 years younger than CS ($p=0.0008$), and 8.5 years younger than nonCS ($p<0.0001$), owing mainly to age differences in men. Women were numerically fewer in CS, and significantly fewer in nonCS ($p<0.0001$), compared with healthy subjects. The majority of participants in all groups came from northern Greece, since AHEPA University hospital was the lead study center. There was no difference in the prevalence of migraine without aura among the three study subgroups. As expected, cerebrovascular risk factors like arterial hypertension, diabetes mellitus, and hypercholesterolemia were more frequent in the two groups of stroke patients compared with healthy subjects. A total of 13.7% of CS had a previous event, also CS, and 25% of nonCS had a previous stroke, mostly of the same etiology as the index event. The infarction was localized cortically in three out of four patients with CS.

PFO prevalence

Table 2 presents PFO prevalence among study groups stratified by gender and by degree of RLS. TEE showed that, in all CS patients, a TCD-documented RLS was attributed to PFO. PFO in CS patients was numerically more frequent compared with the general Greek population [49% *versus* 42.7%; adjusted odds ratio (OR): 1.38, 95% CI: 0.8–2.4, $p=0.25$]. Conversely, PFO in non CS patients was significantly less frequent compared with the general Greek population (25% *versus* 42.7%, adjusted OR: 0.42, 95% CI: 0.20–0.89, $p=0.024$). Across the board, PFO was numerically more frequent in women than in men and significantly more frequent in women than in men with CS (60.8% *versus* 39.3%, $p<0.05$).

Large RLS was significantly more frequent in healthy subjects (19.4%, $p=0.036$) and CS patients (28.4%, $p=0.002$) compared with nonCS (7.1%) and numerically more frequent in CS compared with healthy subjects. Among subjects with large RLS, a "curtain" pattern was found in 50% (12/24) of healthy subjects, in 41.4% (12/29) of CS and in 75% (3/4) of nonCS patients. The prevalence of moderate and small degree RLS was not different among the three study groups.

RoPE score and PFOAF

In patients with CS, the median RoPE score was 7 (quartiles: 6, 8). The presence of PFO could be etiologically related with the index stroke only in

Table 2. PFO prevalence in the healthy Greek population and in stroke patients, stratified by gender and by degree of RLS.

PFO-associated RLS	Healthy subjects, $n=124$	CS, $n=102$	nonCS, $n=56$	p value
All degrees% (95% CI), *n/N*	42.7 (34.0–51.4), 53/124	49 (39.3–58.7) 50/102	25 (13.7–36.3) 14/56	0.013
Women	46.4 (34.6–58.1), 32/69	60.8 (46.8–75), 28/46	38.5 (12.0–64.9) 5/13	0.202
Men	38.2 (25.3–51.0), 21/55	39.3 (26.5–52.1) 22/56	20.9 (8.8–33.1) 9/43	0.110
Large; % (95% CI), *n/N*	19.4 (12.4–26.3), 24/124	28.4 (19.7–37.2), 29/102	7.1 (0.4–13.9), 4/56	0.006
Women	23.2 (13.2–33.1), 16/69	34.8 (21.0–48.5), 16/46	23.1 (0.2–46.0), 3/13	0.368
Men	14.5 (5.2–23.9), 8/55	23.2 (12.2–34.3), 13/56	2.3 (0.0–6.8), 1/43	0.013
Moderate; % (95% CI), *n/N*	8.1 (3.3–12.9), 10/124	8.8 (3.3–14.3), 9/102	3.5 (0.0–8.4), 2/56	0.456
Women	8.7 (2.0–15.3), 6/69	13.0 (3.3–22.8), 6/46	7.7 (0.0–22.2), 1/13	0.716
Men	7.3 (4.0–14.1), 4/55	5.4 (0.0–11.3), 3/56	2.3 (0.0–6.8), 1/43	0.548
Small; % (95% CI), *n/N*	15.3 (9.0–21.7), 19/124	11.8 (5.5–18.0), 12/102	14.3 (5.1–23.5), 8/56	0.738
Women	14.5 (6.2–22.8), 10/69	13.0 (3.3–22.8), 6/46	7.7 (0.0–22.2), 1/13	0.801
Men	16.4 (6.6–26.1), 9/55	10.7 (2.6–18.8), 6/56	16.3 (5.2–27.3) 7/43	0.632

CI, confidence interval; CS, cryptogenic stroke; nonCS, non-cryptogenic stroke; PFO, patent foramen ovale; RLS, right-to-left shunt.

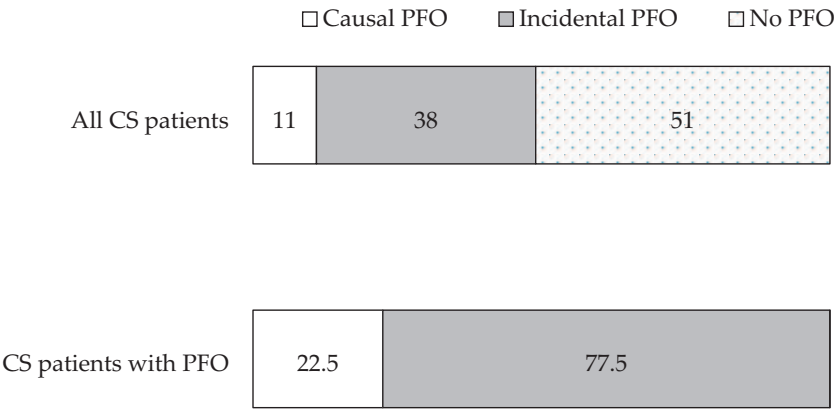

Figure 1. Prevalence (%) of causal and incidental PFO in patients with CS.
CS, cryptogenic stroke; PFO, patent foramen ovale.

Table 3. PFOAF stratified by RopE score in patients with CS and a PFO.

RoPE score	No. of CS patients, *n* = 102	No. of CS patients with a PFO, *n* = 50	Prevalence of PFO, % (95% CI)	PFOAF, % (95% CI)
0–3	0	0	NA	NA
4	2	1	50 (0.0–100.0)	25.5 (0.0–100.0)
5	9	4	44.4 (12.0–76.9)	6.7 (0–77.6)
6	23	7	30.4 (11.6–49.2)	0 (0–23.0)
7	27	14	51.9 (33.0–70.1)	31.0 (0–68.2)
8	19	10	52.6 (30.2–75.1)	32.8 (0–75.3)
9	18	13	72.2 (51.5–92.9)	71.3 (29.8–94.3)
10	4	1	25 (0.0–67.4)	0 (0–64.0)
0–8	80	36	45.0 (34.1–55.9)	8.9 (0–41.2)
9–10	22	14	63.6 (43.5–83.7)	57.3 (3.2–85.5)

CI, confidence interval; CS, cryptogenic stroke; NA, not applicable; PFO, patent foramen ovale; PFOAF, PFO attributable fraction; RopE, risk of paradoxical embolism.

one out of five patients with CS (PFOAF: 22.5%). This implies that, in our cohort of Greek CS patients, 51% did not have PFO, 38% had an incidental PFO, and only 11% had a stroke that could be attributed to PFO (Figure 1).

Table 3 presents PFOAF by RoPE score strata in patients with CS and a PFO. For any individual stratum up to RoPE score 8, the PFOAF was <33%. PFOAF exceeded 50% only in CS patients with a RoPE score of 9 (71.3%) or ⩾9 (57.3%). When the degree of PFO-associated RLS was taken into account, CS patients with a large RLS had a PFOAF of 39.7%, patients with a large or moderate RLS had a PFOAF of 36.6%, whereas patients with a small RLS had a null PFOAF. PFOAF by RoPE score strata in CS patients with large, large or moderate, and small PFO are presented in Tables S1, S2, and S3, respectively.

Discussion

This is the largest TCD study on PFO epidemiology in a general population, and the first study on PFO epidemiology in the Greek population. We

found that almost 43% of healthy younger adults have a PFO regardless of shunt size. This is the highest prevalence hitherto reported and seemingly contradicts with the results of autopsy and TEE studies. However, we believe that our results are valid and reflect the real prevalence of PFO in the Greek population for several reasons.

First, PFO prevalence in autopsy studies ranges widely between 15% and 35%.[21,22] Furthermore, even the more recent and better conducted studies used formalin-fixed and not fresh specimens,[23] thus limiting the detection of modest interatrial patency due to shrinkage of the fixed fibroelastic elements of the foramen ovale. Additional limitations were the use of probes that could identify PFOs only larger than 1 mm, and the inclusion of children.

Second, PFO prevalence in TEE studies varies equally widely with rates in subjects <55 years old as low as 11% and as high as 43%.[24,25] Although TEE is considered the "gold standard" for PFO detection, there is good evidence to support that TEE is a standard of uncertain validity because (i) it quantifies the burden of embolism to the source (left atrium) and not to the target organ (brain). (ii) Subjects are not able to perform e ective VM, resulting in shunt underquantification.[18] All subjects in our study achieved a calibrated VM $\geq$40 cm H_2O. (iii) It may miss even large PFOs in up to 15% of patients with CS.[8] On the other hand, TCD lacks direct visualization of atrial structures and documents RLS regardless of the subjacent pathology. However, meta-analyses comparing TCD with TEE confirmed the excellent diagnostic accuracy of TCD.[9,10] False-positive TCD investigations for PFO may be attributed to pulmonary arteriovenous malformations (PAVMs). Nevertheless, PAVMs are very rare, with a prevalence of 1 in 2600,[26] and may sometimes be misinterpreted by TEE as well.[27] Although timing of MES appearance on TCD or bubble visualization in the left atrium on TTE or TEE after contrast injection has been used to differentiate intracardiac from pulmonary RLS, this may be an elusive criterion.[28] PFO detection by TCD was corroborated by TEE in all our patients with CS, supporting the view that the increased PFO prevalence in the general Greek population is not driven by a high percentage of nonPFO RLS. Our TCD protocol regarding timing of MES appearance ($\leq$15 s), body positioning (sitting upright), and total number of agitated saline injections (six), favored optimal sensitivity for PFO detection. The prevalence of large or moderate-shunt PFO in the general population was 27.5% (95% CI: 19.6–35.3) – identical to the rates reported by autopsy and TEE studies.[7,23,29] The increased PFO prevalence across the board may be attributed to the increased sensitivity of our TCD protocol and to the diligence of the investigators to identify small PFOs, which otherwise would have been missed.

Third, since migraineurs constitute at least 15% of the European population,[30] our sample of the general Greek population comprised of migraineurs without aura in a similar percentage. Migraineurs with aura constitute up to 5% of the general population and are known to have higher prevalence of PFO compared with migraineurs without aura.[14] Therefore, the exclusion of migraineurs with aura from our study may only have decremented the actual PFO prevalence in the general Greek population.

Hitherto, etiologic classification systems of ischemic stroke consider PFO as a medium-to-low or uncertain-risk emboligenic cardiac source.[15,31] However, epidemiologic data suggest that PFOs may be causally implicated in stroke more commonly than previously thought. In fact, analyses of case-control studies suggest that in patients with CS $\leq$55 years-old, PFOs are causal in 42%, incidental in 14%, and absent in 44%.[32] Nevertheless, all previous assumptions rely on the premise that PFO prevalence in the general population is set at 25%. In our cohort of CS patients, PFOs were absent in a comparable rate of 51%. Conversely, causal (11%) and incidental (38%) PFOs differed considerably from the previously mentioned data, owing to the much higher PFO prevalence in the Greek population.

Interest in optimal patient selection for PFO closure or possibly for long-term anticoagulation with direct oral anticoagulants remains keen.[33] The RoPE score status (high *versus* low) has been integrated in a recently proposed flexible clinical practice approach to classifying PFO causal association in patients with embolic infarct topography and without other major stroke sources.[34] A high RoPE score shifts the level of causality from unlikely to possible in stroke patients harboring low-risk PFOs, and from possible to probable in patients with medium-risk PFOs. Albeit useful in guiding patient management, the RoPE score lacks large external validation studies and is heavily age-weighted. Our study underscores that the

estimation of degree of causality (PFOAF) may be underestimated or overestimated in ethnic/racial populations, with PFO prevalence significantly lower or higher than the established 25%. The median RoPE score in our cohort of CS patients was higher than the median score of the RoPE database (seven *versus* six). In our study, CS patients with a RoPE score of 9 had a PFOAF of 71%, which corresponded to patients of the RoPE database having a RoPE score of 7.[6] This implies that the threshold for high *versus* low RoPE score categorization is shifted upwards in populations with high PFO prevalence, necessitating a population-specific and not a universal causality evaluation formula.

PFO prevalence in our cohort of nonCS was lower compared with PFO prevalence in the general population. This finding may seem counterintuitive, but it has been replicated by previous studies. A TCD age-inclusive study reported 25% PFO prevalence in patients with stroke of known cause compared with 32% in the general population.[11] Another TEE study in patients <55 years old found lower PFO prevalence in patients with stroke of known cause (33%) compared with the general population (43%).[25] Interestingly, a large age-inclusive TCD study in another Mediterranean population found a relatively low PFO prevalence of approximately 22% both in patients with cryptogenic stroke and in patients with stroke of determined cause.[35] Furthermore, PFO prevalence in younger patients with nonCS varies widely depending on the diagnostic modality,[7] and values as low as 11% in TCD studies,[36] and as low as 7% in TEE studies have been reported.[37] The previously mentioned discrepancies may be attributed to heterogeneity among the relatively small populations of patients with stroke of known cause that have been included in different studies. On the other hand, potential interactions between a PFO and other established causes of stroke are hitherto unknown; an "incidental" PFO may favor or blunt the clinical impact of other stroke causes and vice versa, resulting in great diversity of PFO prevalence in these patient populations.

Our study has limitations. First, the sample of the general population is relatively small and may not be totally representative of the actual young and middle-aged Greek population. A sample size calculation prior to the study initiation was not possible owing to the complete lack of relevant data in Greek healthy subjects and in stroke patients $\leqslant 55$ years old. However, even the lower 95% CIs of PFO prevalence in our population are well above the established 25%. Furthermore, during interim evaluations after the recruitment of 20 new subjects, we constantly found PFO prevalence values above 40%, making it less likely for our results to reflect a play of chance. Second, age matching was not optimal resulting in a healthy population relatively younger than the stroke patients. However, there is no evidence to suggest that this age difference may have an impact on PFO prevalence in the general Greek population. On the contrary, autopsy data suggest that PFO prevalence is stable in persons spanning their fourth to seventh decade of life.[23] Third, the subgroups of patients with CS and nonCS were not numerically balanced. However, this was due to the fact that, as in other series, among younger patients with stroke, strokes of determined causes are harder to find than cryptogenic strokes.[1]

Conclusion

The prevalence of TCD-detected right-to-left shunt in the general Greek population seems to be much higher than the 25% prevalence reported by autopsy and TEE studies.

PFO may be the cause of stroke in one out of nine Greek patients with cryptogenic stroke. Among Greek patients with cryptogenic stroke who harbor a PFO, the latter is causal in one out of five patients.

The established RoPE score cutoff of $\geqslant 7$ for classifying PFO causal association in patients with embolic infarct topography and without other major stroke sources, may overestimate causality in patients deriving from populations with high PFO prevalence.

Author contributions

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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