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The Frequency of Patent Foramen Ovale and Migraine in Patients with Cryptogenic Stroke

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Abstract

Background and Purpose—Individuals with migraine are at higher risk for stroke, but the mechanism has not been established. Based upon the association between migraine, and intracardiac right-to-left shunt (RLS), it has been proposed that stroke in migraineurs could be due to a paradoxical embolus passing through a patent foramen ovale (PFO) or pulmonary AVM. The aim of this study was to determine the prevalence of PFO with RLS in patients who presented with cryptogenic stroke and had a history of migraine.

Methods—Patients between 18 and 60 years old who presented with an ischemic stroke were characterized based on ASCOD phenotyping. A migraine diagnosis was identified by reviewing physician notes and frequent aura was defined if present in at least 50% of attacks. A PFO with RLS diagnosis was identified by the presence of a positive bubble contrast study with either transcranial Doppler, transthoracic or transesophageal echocardiography.

Results—Of the 712 patients who presented with ischemic stroke, 127 (18%) were diagnosed as cryptogenic; 68 patients had adequate testing for PFO and a documented migraine history. The prevalence of PFO in patients with cryptogenic stroke without migraine was elevated (59%) compared with the general population (18%). Patients with both cryptogenic stroke and migraine had a higher prevalence of PFO (79%). In patients with cryptogenic stroke who had migraine with

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frequent aura, the prevalence of PFO was 93%. Only five patients (4%) had a history compatible with migrainous infarction.

Conclusions—In patients with cryptogenic stroke who have migraine, there is a high prevalence (79%) of PFO with RLS. The timing of the stroke in migraineurs is usually not related to a migraine attack. These observations are consistent with the hypothesis that the mechanism of stroke in migraineurs is most likely due to a paradoxical embolus. Future cryptogenic stroke classification schemes should consider including PFO as a separate etiologic category.

Keywords

stroke; migraine with aura; migraine without aura; patent foramen ovale; shunt

Subject Terms (Journal List)

Cerebrovascular Disease/Stroke; Ischemic Stroke; Embolism

INTRODUCTION

Epidemiologic studies reveal that people who have a history of migraine headache with aura have a risk of developing a stroke that is 2.3 times higher than in people without migraine (1). This risk increases substantially in patients who smoke and/or use birth control pills, with an odds ratio for stroke as high as 13.9 (95% confidence interval 5.5 – 35.1) (2–4).

Based upon the association between migraine, particularly migraine with aura, and intracardiac right-to-left shunt (RLS), it has been proposed that stroke in migraineurs could be due to a paradoxical embolus passing through a patent foramen ovale (PFO) or pulmonary arteriovenous malformation (PAVM) (5).

The initial theory to explain the higher risk of stroke in migraineurs asserted that migraine was a "vascular headache" resulting from heightened cerebral arterial vasoreactivity (6–8).Ifthe cerebral arterial spasm was excessive, then persistent ischemia would result in a focal stroke. Although migraine attacks may be associated with cerebral oligemia, the reduction in blood flow (about 25%) rarely reaches the threshold for ischemia (9), and migrainous infarction is very uncommon (10). Migraine is no longer considered to be primarily a “vascular headache”, but rather it is a disorder of nervous system excitability where vascular alteration may occur, but is not the predominant mechanism responsible for migraine symptoms. The hypothesis for this study was that the majority of patients who presented with cryptogenic stroke and had a history of migraine, would also have a PFO withRLS.

METHODS

The authors declare that all supporting data are available within the article. Approval for this review study was granted from the UCLA Institutional Review Board (IRB). Informed consent was waived by the IRB. Patients between 18 and 60 years old who were diagnosed with stroke and came to the UCLA Comprehensive Stroke Center from January 1, 2008 to November 1, 2017 were identified. Cases of ischemic stroke were reviewed and clinically categorized based on ASCOD phenotyping by the neurology evaluation in the medical

records. ASCOD phenotyping categorizes the most likely etiology of the ischemic stroke as either A: atherosclerosis; S: small-vessel disease; C: cardiac pathology (other than PFO); O: other causes; D: dissection (11). Cryptogenic stroke was defined as those patients who had no other obvious cause for their stroke after an evaluation by neurology which included medical history, a brain MRI, evaluation of the carotid arteries and aortic arch, cardiac evaluation by transthoracic or transesophageal echocardiography, and monitoring for arrhythmias such as atrial fibrillation. A migraine diagnosis was identified by reviewing the neurology notes in the electronic medical record. A migraine with frequent aura diagnosis was defined in individuals experiencing aura in at least 50% of migraine attacks. A PFO with RLS diagnosis was identified by the presence of a positive bubble contrast study with either transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), or transcranial Doppler (TCD). TCD has been demonstrated to have higher sensitivity for detection of RLS when compared to contrast transesophageal echocardiography and is superior to transthoracic echocardiography (12, 13). It is important to note that although the TCD exam reveals the presence of a RLS, it does not distinguish between a PFO and PAVM. However, in our experience of 1500 TCDs the rate of PAVM is only 1% in patients referred without hereditary hemorrhagic telangiectasia (Tobis, unpublished data, 2017); similar results have been demonstrated in the literature and thus a positive RLS exam was used to define the prevalence of PFO (14, 15). Using passage of a guide wire across the atrial septum during cardiac catheterization with intracardiac echocardiography guidance as the standard for diagnosing a PFO, TCD ≥ grade 3 has 98% sensitivity for making the diagnosis of PFO (16). The degree of RLS was evaluated by TCD at rest and with the Valsalva maneuver. The Spencer logarithmic scale was used to grade the results, a grade of 2 or higher (> 10 embolic tracks/60 sec) was considered positive for a significant shunt, which has a 97% sensitivity and 100% specificity for the diagnosis of PFO (12).

Comparisons in PFO prevalence were made between patients with cryptogenic stroke without migraine, cryptogenic stroke with migraine, and cryptogenic stroke with migraine with aura using Fisher’s exact test. PFO prevalence in patients with cryptogenic stroke was compared to estimates of PFO in the general population. After identifying patients with both migraine and stroke, the frequency of a diagnosis of migrainous infarction was investigated. A migrainous infarction was defined as a typical migraine for that patient that begins with aura or their usual cephalgic pain but progresses into a clinical stroke that is documented with a lesion on brain MRI (10, 17).

RESULTS

A total of 1255 patients between 18 and 60 years of age were identified in the stroke database of the UCLA Comprehensive Stroke Center from January 1, 2008 to November 1, 2017. The upper age limit was set at 60 years as part of the definition of cryptogenic stroke. The stroke types were divided into ischemic 712/1255 (57%), intracerebral hemorrhage 293/1255 (23%), subarachnoid hemorrhage 183/1255 (15%) and transient ischemic attack 67/1255 (5%). Based on ASCOD phenotyping (11), the cause of the 712 ischemic strokes were further divided into the following categories: atherosclerosis 151/712 (21%), small artery disease 51/712 (7%), cardiac (other than PFO) 165/712 (23%), other 105/712 (15%)

and dissection 113/712 (16%). The remainder of the cases were considered cryptogenic in 127 of the 712 ischemic strokes (18%) (Figure 1).

Of the 127 patients with cryptogenic stroke, 68 (54%) had adequate testing to determine the presence of a PFO with RLS (by contrast TTE, TEE, or TCD) and a complete migraine history. Of the 68 cryptogenic stroke patients who had adequate testing for the presence of a RLS, 47 of 68 (69%) had a PFO. PFO with RLS was identified in 8 patients (17%) via TTE, 16 patients (34%) via TEE, 6 patients (13%) via TCD, and 17 patients (36%) via both TEE and TCD. All of the patients diagnosed via TCD had shunts that were Spencer grade 2 or greater.

Of the 68 cryptogenic stroke patients who had adequate testing for the presence of a RLS, 34 (50%) had migraine; and 15 of these 34 (44%) migraine patients had frequent aura (Figure 2). Of the 34 patients who had cryptogenic stroke and migraine, 27 (79%) had a PFO and of the 34 patients with cryptogenic stroke who did not have migraine, 20 (59%) had a PFO. Moreover, of the 15 patients with both cryptogenic stroke and migraine with frequent aura, 14 (93%) had a PFO (Figure 3). The difference in prevalence of PFO between patients with cryptogenic stroke without migraine, with migraine, and with migraine with aura was statistically significant ($p = 0.042$).

When compared to a control general population of 200 people where the prevalence of PFO was 18% as determined by a TCD ≥ grade 3, patients with cryptogenic stroke with or without migraine had significantly greater prevalence of PFO ($\chi 2$, $p < 0.00001$ and $\chi 2$, $p < 0.00001$, respectively)(18).

Five of the 128 (4%) patients who had cryptogenic stroke presented with a history that was compatible with a migrainous infarction. All 5 of these patients had a prior history of migraine. Two of the 5 (40%) patients with possible migrainous infarction had a PFO.

DISCUSSION

Our results from a database of all subjects who presented with a stroke to one academic medical center demonstrate a high prevalence of PFO (69%) in patients with cryptogenic stroke. Prior studies showed estimates of PFO in the cryptogenic stroke population between 38% and 48%, with slight differences based on patient age (19). Only transthoracic echocardiography was used to detect abnormalities in the atrial septum in these groups of patients, and thus a significant number of PFOs may have been missed. A subsequent meta- analysis found a broader range in the incidence of PFO in the cryptogenic stroke population, between 31% and 77%; these differences were largely attributed to differences in detection technique (20).

Additionally, our results show a high prevalence of migraine (50%) in patients with cryptogenic stroke. These results corroborate the findings of a study which demonstrated that migraine increased the odds of cryptogenic events, both TIA and stroke, with an odds ratio of 1.73 (95% confidence interval 1.38 – 2.16) relative to those without migraine(21).This effect may reflect an underlying association of both migraine and cryptogenic stroke with PFO (22).

The literature is mixed regarding the relationship between migraine and PFO. One large study did not find a significant association between PFO and increased prevalence of migraine (odds ratio 1.01, 95% confidence interval 0.63–1.61) or migraine with aura (odds ratio 1.01, 95% confidence interval 0.71–1.69) (23). It should be noted that this study excluded patients with a history of stroke. A meta-analysis, which did include patients with a history of stroke, found a significant bidirectional relationship between PFO and migraine (24): The prevalence of migraine in patients with PFO relative to those without PFO was characterized by an odds ratio of 5.13 (95% confidence interval 4.67 – 5.59), with significant results for the subgroup of patients who had migraine with aura; the prevalence of PFO in patients with migraine relative to those without migraine, independent of aura, was characterized by an odds ratio of 2.54 (95% confidence interval 2.01 – 3.08). These differences in the literature may be related to the inclusion of stroke patients in the study population, and what has been described as a “triad” of cryptogenic stroke, patent foramen ovale, and migraine with aura.

Wilmshurst, et. al. was the first to report that there was a high association of PFO in migraineurs who developed a stroke (5). In his study of 60 patients who presented with a stroke and had a history of migraine with aura, 84% had evidence of a PFO with a RLS. In our study, patients with both cryptogenic stroke and migraine had a high prevalence of PFO (79%), which is similar to the frequency that was reported by Wilmshurst. In the subset of patients with cryptogenic stroke who had migraine with frequent aura, the prevalence of PFO was also very high (93%). One explanation for this observation is that migraine with frequent aura may be a marker for the presence of PFO (25). The prevalence of PFO in patients with cryptogenic stroke without migraine was also elevated (59%), and the prevalence of PFO in each group was significantly higher than in a general population of 200 subjects at UCLA (18%) (18).

Many studies have highlighted the association between migraine with aura and PFO (24, 26, 27). The PREMIUM trial prospectively randomized 230 patients with PFO and medically- refractory migraine (with or without aura) to PFO closure versus a sham procedure.
Although the primary endpoint of 50% reduction of migraine attacks was not met, there was a significant reduction in mean headache days per month (−3.4 ± 4.4 days per month in the PFO closure arm versus −2.0 ± 5.0 days per month in the sham procedure arm, p=0.03) and a strong treatment response for the subgroup who had migraine with frequent aura (49% responded in the PFO closure group versus 23% in the sham procedure group, p=0.015,withresponse defined as at least a 50% reduction in migraine attacks per month) (28). Moreover, in all migraineurs, complete remission occurred in 8.5% of the closure group,

compared with only 1% of the sham group (p=0.01), suggesting that PFO may be causally related in some migraineurs.

The mechanism of migraine reduction via PFO closure is not entirely clear, though the association with cryptogenic stroke may provide insight into this relationship. Several theories have been proposed on the relationship between migraine and PFO due to right-to- left shunting of blood. Chemical triggers of migraine that are normally metabolized in the lung could bypass the pulmonary circulation through a PFO and thereby enter the cerebral circulation in higher concentrations. Alternatively, deoxygenated venous blood entering the

arterial system through a PFO could be sufficient to trigger a migraine in susceptible individuals (29, 30).

There is also evidence to suggest that release of platelet serotonin may play a role in the development of migraine in patients with RLS. It has been proposed that platelets, as a result of sheer stress, may become activated and release serotonin, ultimately leading to migraine; this process may be initiated by cardiovascular abnormalities, such as PFO (31, 32). There is also data that mitral valve prolapse (MVP) may similarly be implicated in migraine pathophysiology. It has been proposed that platelet damage from the mitral valve regurgitant jet could induce platelet damage and lead to release of serotonin (32). Interestingly, data has shown a significantly higher prevalence of MVP in patients with migraine versus control patients, with an odds ratio of 2.7 (95% CI 1.17 and 6.29) (33).

Microemboli have also been proposed as a migraine trigger. Small venous blood clots or platelet aggregates, which normally would be trapped by the lungs (and thus remain clinically silent), may act as a potential trigger for migraine when introduced into the arterial circulation through a right-to-left shunt (34, 35). Animal experiments support this hypothesis; mircoemboli have been shown to trigger cortical spreading depression (CSD), the slow cerebral depolarization underlying migraine with aura (36). Moreover, this theory of paradoxical microembolism provides a direct connection between PFO, migraine, and stroke, as larger emboli could attain a sufficient threshold of cerebral ischemia to produce an infarct.

Although more studies are needed to further elucidate these various theories, the relationship between stroke and migraine is unlikely to be explained primarily by vasoconstriction leading to infarction. Previous radiopharmaceutical scans have shown that cerebral blood flow only decreases by 25% from baseline during migraine, which would not be sufficient to cause tissue necrosis (9). Instead, the significant association between cryptogenic stroke, migraine, and PFO suggests that stroke in migraineurs may be mediated by a PFO pathway in the majority of cases. Our data support this latter hypothesis as the majority of patients in our study had overlap of cryptogenic stroke, migraine, and PFO but only 3 patients had a presentation consistent with migrainous infarction without the presence of a RLS.

Our results were limited by the adequacy of testing for PFO, and the selection bias inherent in a cohort of patients who underwent more thorough testing for RLS. Patients are often recommended for a TTE with bubble study to rule out PFO. Even at the UCLA Stroke Center of Excellence, in which stroke etiology is extensively investigated in all patients, TTE with bubble study was often the primary imaging modality

ordered, especially in the earlier years of this database. This can produce false negative results in over 50% of cases, as evidenced by a meta-analysis which included over 3,000 patients (37). In our study population, only 54% of patients with cryptogenic stroke had both sufficient PFO testing and a complete migraine history performed. It is possible that many patients had PFOs that went undiagnosed. These data suggest that when an etiology for stroke is not identified, prior to classifying a patient as cryptogenic, a TEE or TCD with agitated saline contrast should be obtained. This becomes particularly important in patients with a history of migraine, especially if they also experience aura. It should be emphasized that TCD saline

studies are not only more predictive than TEE for detection of RLS but also more predictive of recurrent events (38). Moreover, TEE misses 15% of RLS detected with TCD saline studies, and large shunts on TCD predict recurrent stroke better than the presence of a shunt on TEE (38).

The value of obtaining a thorough headache history in patients who present with cryptogenic stroke should be emphasized; a simple headache questionnaire, such as the Migraine Prevention Questionnaire 5 (MPQ-5), can be used for this purpose (39). Physicians must also be mindful of important clinical clues that are suggestive of paradoxical embolism in patients with cryptogenic stroke. Data have shown that individuals with paradoxical embolism are more likely to present with dyspnea or a Valsalva maneuver at the onset of stroke, waking up with stroke, a history of deep vein thrombosis, pulmonary embolism or the presence of varicose veins, or a history of sleep apnea(40).

The ultimate test for whether a PFO is present is not an agitated saline bubble study, but is a right heart catheterization with a guidewire to probe the atrial septum under intra-cardiac echo imaging or injection of contrast against the foramen ovale. In those patients who had a stroke and a history of migraine but do not have a positive study demonstrating a RLS, misdiagnosis is one possible explanation; migrainous stroke is another explanation, but if a PFO is not present, the etiology in these cases is truly cryptogenic.

Our results were also limited by a migraine diagnosis that was made without the consistent use of formal International Classification of Headache Disorders (ICHD) criteria (41).
Previous studies have found, however, that patient or physician-identified migraine is corroborated by ICHD criteria in the overwhelming majority of cases, such that the accuracy of diagnosis in our study is likely to be high (42). Nonetheless, migraine may be under- reported in our study based on lack of patient or physician reporting.

Another limitation of this study is its retrospective, observational nature without a comparison group, and the biases inherent in this design. Moreover, the associations we found do not prove causality; instead they are hypothesis generating and highlight relationships that exist between cryptogenic stroke, migraine, and PFO. The original Wilmshurst study that identified an increased incidence of PFO in migraineurs who developed a stroke focused on patients that were referred specifically for workup for paradoxical embolism (5). Our study instead started with a large, heterogeneous database of all stroke patients and then retrospectively identified those with migraine who were tested for a PFO. This strengthens the generalizability of the results in that this cohort represents the entirety of the stroke population at one referral institution and emphasizes the high incidence of undiagnosed PFO and migraine in

this group. Future studies should continue to target this population and further elucidate relationships in the triad of stroke, migraine, and PFO.

The current stroke classification scheme does not include a separate category for PFO. The “cardiac” subcategory that does exist excludes PFO and is reserved for clot originating on the left side of the heart. Based on our results of the high degree to which PFO is implicated in patients currently classified as “cryptogenic,” future stroke classification schemes should

consider including PFO as a separate etiologic category. If there is a stroke without an obvious ASCOD etiology but a PFO is present, it is no longer sufficient to define this as "cryptogenic", but could be categorized as a "PFO-associated stroke". Further support for having a PFO-associated stroke as a separate etiologic category comes from the RESPECT and REDUCE randomized trials, which demonstrated a significant reduction in recurrent stroke for subjects who had their PFO closed percutaneously: HR = 0.55 (95% CI 0.31 to 0.999; p = 0.046) and RR = 0.51 (95% CI, 0.29 to 0.91; P = 0.04), respectively, which provides evidence that PFO is causally related to cryptogenic stroke (43, 44).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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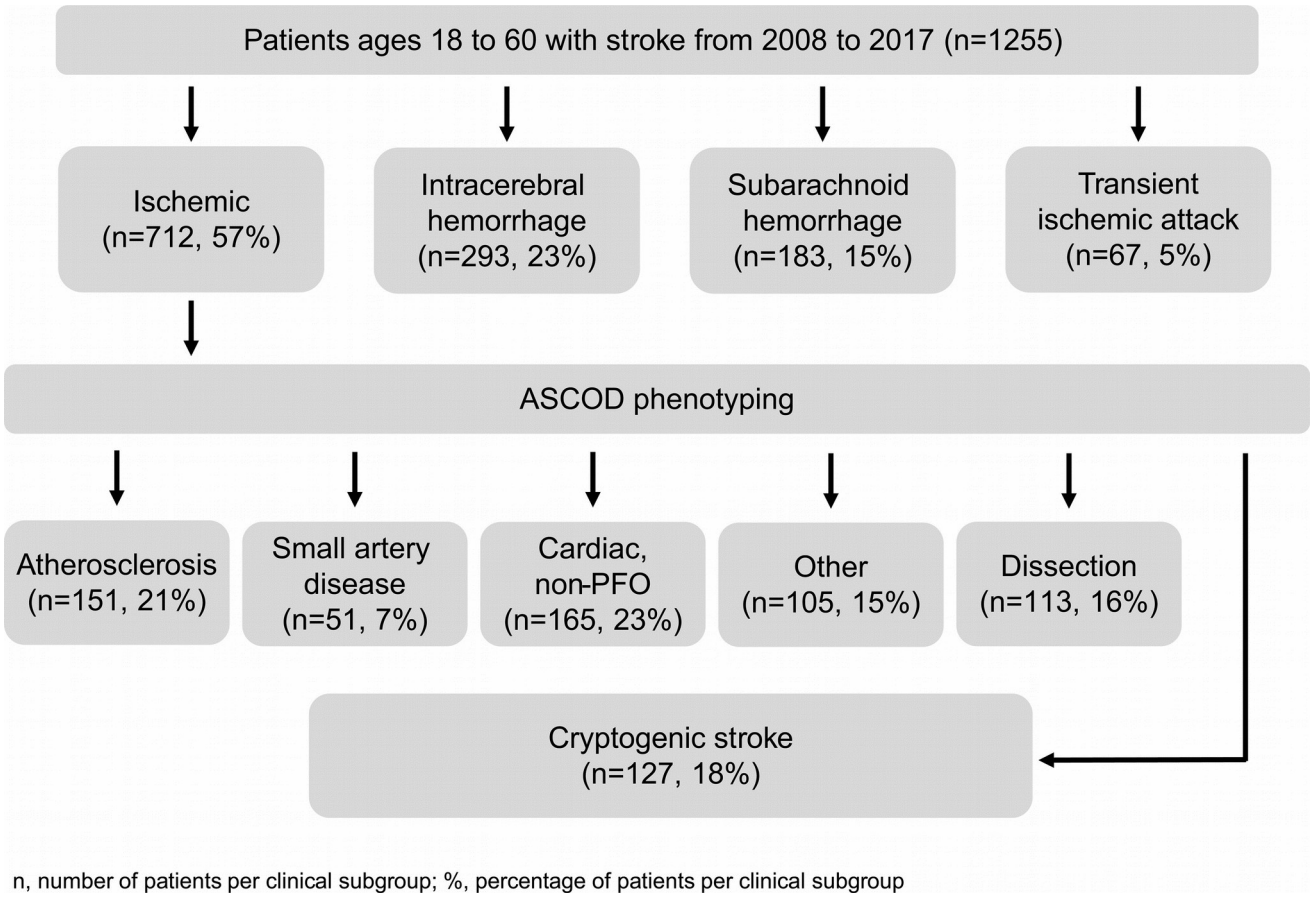


Figure 1.
Flow Chart for Patient Selection

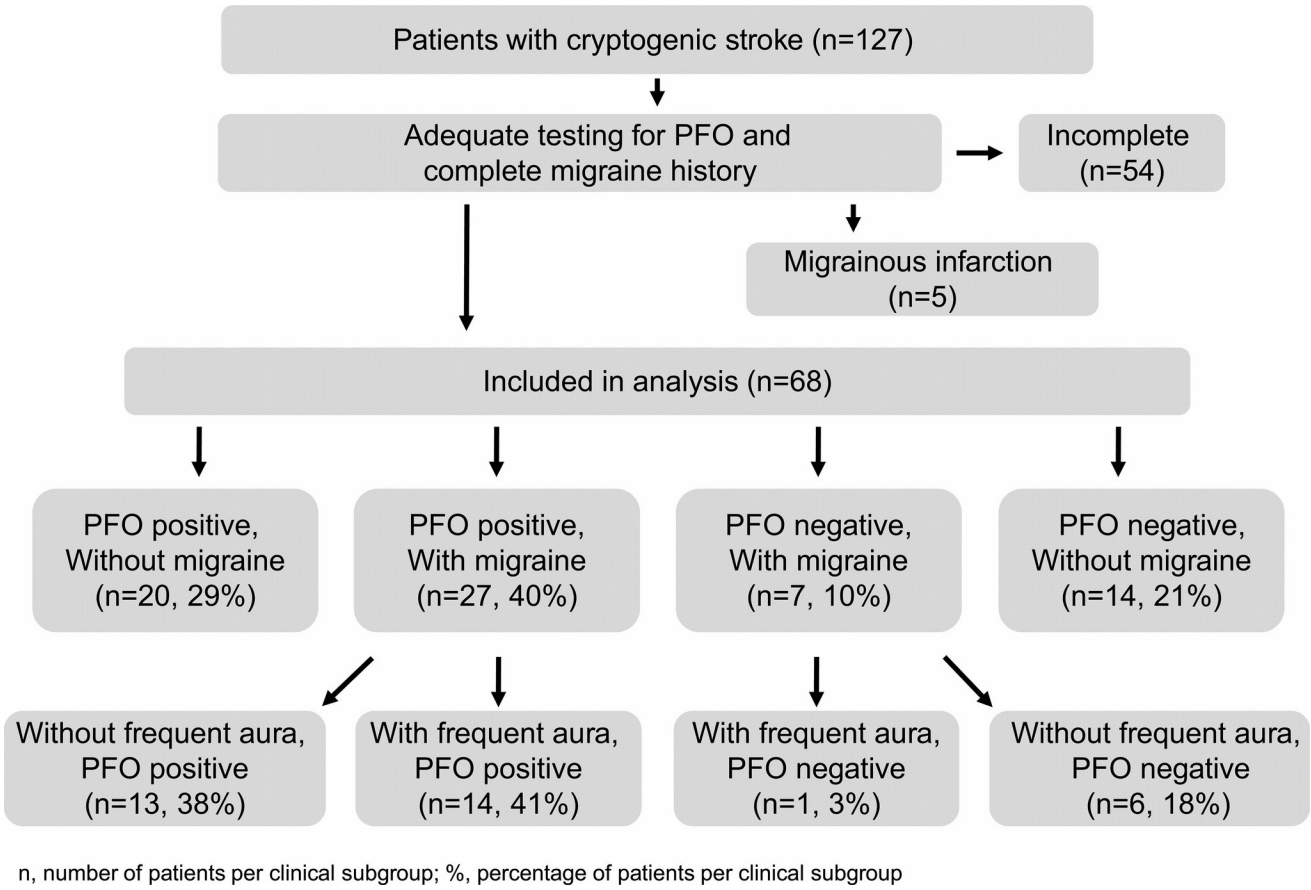
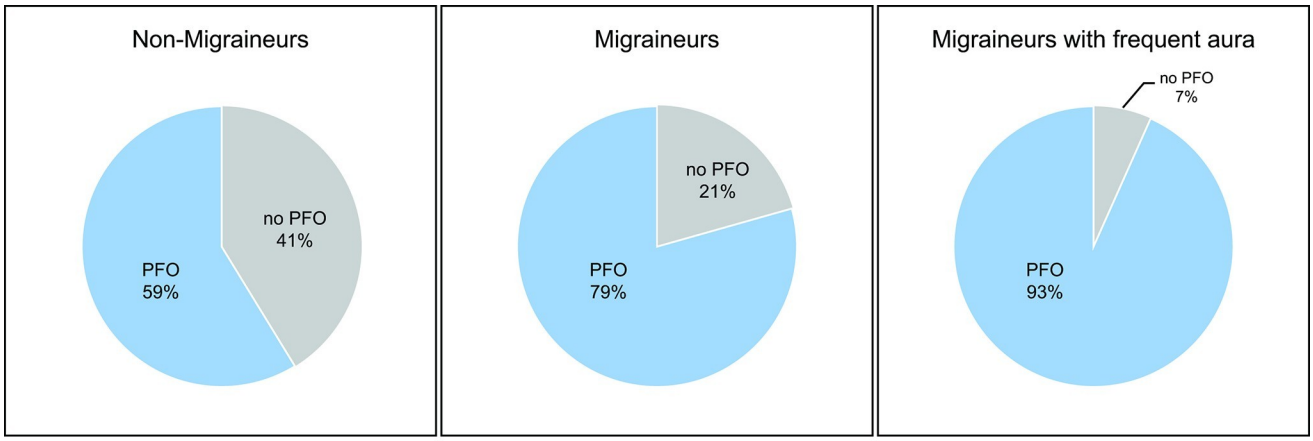


Figure 2.
Flow Chart for Patient Selection



%, percentage of patients with and without PFO in each clinical subgroup

Figure 3.
Prevalence of PFO in Patients with Cryptogenic Stroke