# PATENT FORAMEN OVALE (PFO) CLOSURE FOR PREVENTION OF STROKE

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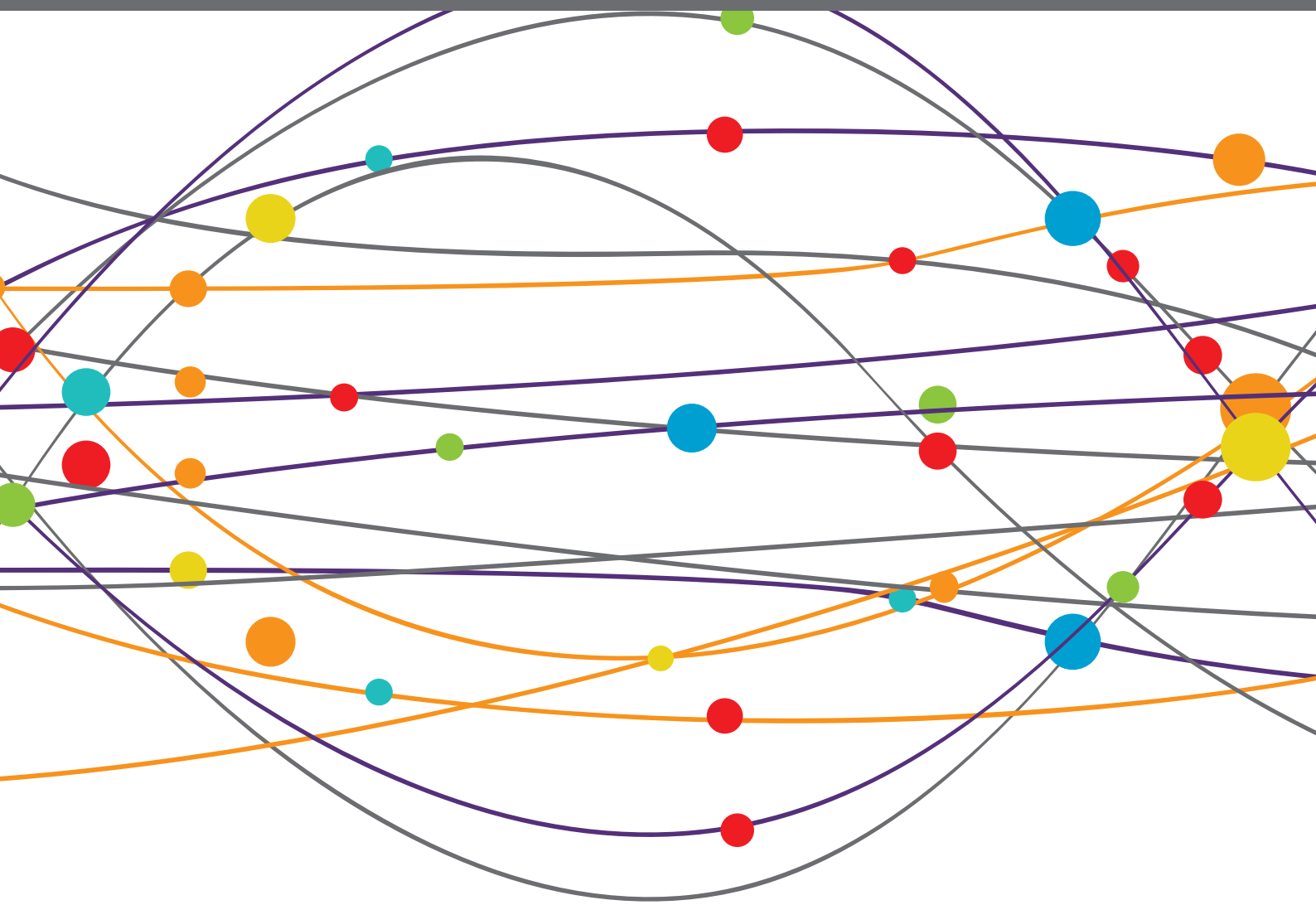

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# PATENT FORAMEN OVALE (PFO) CLOSURE FOR PREVENTION OF STROKE

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EDITORIAL
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# Editorial: Patent Foramen Ovale (PFO) Closure for Prevention of Stroke

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**Keywords: patent foramen ovale, stroke, cryptogenic stroke, PFO closure device, stroke prevention**

## Editorial on the Research Topic

## Patent Foramen Ovale (PFO) Closure for Prevention of Stroke

Stroke is the second leading cause of death worldwide and fifth leading cause of death in the United States (1). The term cryptogenic strokes is used to define strokes for which a cause cannot be identified and account for almost 40% of all the ischemic strokes. Patent foramen ovale (PFO) can potentially explain some of those strokes since it allows right-to-left shunting and was found to be more common in patients with cryptogenic strokes (40%) vs. the general population (25%). After the long-term results of the RESPECT trial and the publication of Gore REDUCE and CLOSE trials and multiple meta-analyses showing benefit from PFO closure in patients with history of cryptogenic stroke, PFO closure has regained a lot of popularity but is also attracting criticism when performed in patients with borderline indications (2–9). Our aim with this Research Topic was to collect a number of well-conducted primary studies, meta-analyses or state of the art narrative reviews on different questions and controversies regarding PFOs role in cryptogenic strokes. In this editorial, we present and put in context compared to the existing literature, the highlights of the studies of this Research Topic.

But what is the real prevalence of PFO? Koutroulou et al. conducted a systematic review of studies investigating the PFO rates according to different diagnostic imaging modalities. They found significant heterogeneity with prevalence rates ranging from 24.2% in autopsy studies to 23.7% in studies using transesophageal echocardiogram for the diagnosis vs. 31.3% in studies using transcranial doppler and only 14.7% in studies using only transthoracic echocardiogram. As expected, PFO prevalence was higher among patients with prior cerebrovascular events vs. those without prior cerebrovascular events, across all different diagnostic modalities and the autopsy series.

However, whether PFO (co)existence is the direct cause of stroke in patients with cryptogenic ischemic stroke remains an unanswered question. Ioannidis and Mitsias, in their state-of-the-art review, argue that PFOs can act as the direct cause vs. risk factor, or an even incidental finding in some patients with cryptogenic stroke. They provide an overview of the potential stroke mechanisms including paradoxical embolism, *in situ* clot formation or atrial tachyarrhythmias in the setting of a hypermobile atrial septum. Risk factors include the size and morphology of the PFO and the degree of the shunt. The authors present and explain the Risk of Paradoxical Embolism (RoPE) score and its use in patients with PFO. Low RoPE scores suggest low probability of pathogenic PFO and relatively higher probability of recurrent stroke events while higher RoPE scores suggest higher probability of pathogenic PFO but lower probability of recurrent events.



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The first of the mechanisms that Ioannidis and Mitsias proposed and analyzed is paradoxical embolism which originates from concomitant deep vein thrombosis (DVT). It seems that the prevalence of DVT and pulmonary embolism (PE) in those patients is higher than previously thought. Zietz et al. performed a systematic review of the association between DVT/ PE and PFO existence in patients presenting with cryptogenic stroke. They found eight eligible studies in total, with the DVT frequency ranging from 7 to 27% and the PE frequency ranging from 4.4 to 37%. They also examined the reversed association and they found that the presence of PFO in patients with PE was associated with higher rates of ischemic brain lesions. Given those findings, it is probably reasonable to maintain a lower threshold for DVT/PE screening in patients who present with stroke and are subsequently found to have a PFO.

On the other hand, the presence of PFO in the setting of ischemic stroke, was shown to be negatively associated with presence of AF, according to a meta-analysis conducted by Ze-Jun Chen and Thijs. The authors included 14 studies and 13,425 patients comparing AF rates in stroke patients with PFO vs. those without a PFO. They found that patients with a PFO were 48% less likely to have AF compared to those without a PFO. Their results remained significant after performing separate analyses for cross-sectional and longitudinal studies and in different age groups (>60 years old vs. <60 years old). Those findings -although potentially subject to detection bias- support that patients with PFO are not at an increased risk of arrhythmia compared to the general stroke population and may actually have a lower risk. Impaired left atrial (LA) mechanical function has been suggested to be one of the possible causes of cryptogenic strokes, since it can be associated with blood stasis and thrombus formation, while a few studies have even associated impaired LA function with presence of PFO. Speckle tracking is one of the non-invasive methods to evaluate the LA function. Gazagnes et al. studied the association between LA longitudinal strain and presence of PFO in patients who presented with cryptogenic stroke. Interestingly, no association was found, even in the subgroup of patients with PFO and atrial septal aneurysm. Their results were probably limited by their small size and future studies are anticipated.

Collado and Kavinsky discuss the need for a Heart-Brain team approach in PFO closure. The authors wrote a state-of-the-art opinion review presenting the relatively novel concept of the Heart-Brain team. They emphasize that after 2017, PFO closure for stroke preventions in young patients with prior stroke has resurrected and thus in order to avoid under-treatment or overenthusiasm about the invasive options, we should approach those patients with a multi-disciplinary Heart-Brain approach, including neurologists, general cardiologists and interventionalists among others. The Heart-Brain approach can probably provide the best possible consultation, decision making and outcomes for patients with PFO. Multidisciplinary discussion becomes of particular importance especially given the favorable outcomes even in the non-invasive, pharmacological arms of some of the RCTs and large registries on PFO closure. The explanation for this discrepancy might be explained by other non-PFO related risk factors for stroke which are concomitantly present in some of the patients who present with stroke and are found to have a PFO. In order to shed light into this theory, Kahles et al. analyzed data from the International PFO Consortium Study and tried to identify risk factors associated with prior stroke in patients with PFO. Their results were interesting suggesting that both PFO related (right-to-left shunt) and PFO unrelated (hypertension, diabetes, hypercholesterolemia, coronary artery disease, BMI, age) factors were associated with the likelihood of prior stroke and can potentially explain why there is heterogenous benefit among patients who receive a PFO closure device.

The discussion for PFOs role in cryptogenic stroke and the utility of PFO closure for given patient subgroups is still ongoing. We hope that our guest issue provides new insights to the existing literature and creates questions that might be answered in the future.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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# Epidemiology of Patent Foramen Ovale in General Population and in Stroke Patients: A Narrative Review

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**Introduction:** Percutaneous closure of patent foramen ovale (PFO) in selected patients with cryptogenic cerebrovascular ischemic events (CEs) decreases the risk of recurrent stroke; however, optimal patient selection criteria are still under investigation. Candidates for PFO closure are usually selected from the pool of CE patients with a high risk of Paradoxical Embolism (RoPE) score. The RoPE score calculates the probability that PFO is causally related to stroke, based on PFO prevalence in patients with CE compared with that in healthy subjects. The latter has been set at 25% based on the average of autopsy and transesophageal echocardiography (TEE) studies.

**Methods:** We conducted a comprehensive review of studies investigating PFO prevalence in general population and in patients with CE and non-CE using autopsy, TEE, transcranial Doppler (TCD) or transthoracic echocardiography (TTE). Studies were excluded if they (1) reported data from referred subjects with underlying cerebrovascular disease or (2) did not specify etiologically the events.

**Results:** In healthy/control subjects, PFO prevalence was 24.2% (1,872/7,747) in autopsy studies, 23.7% (325/1,369) in TEE, 31.3% (111/355) in TCD, and 14.7% (186/1,267) in TTE studies. All diagnostic modalities included PFO prevalence was higher in CE compared with healthy/control population [odds ratio (OR) = 3.1, 95% confidence interval (CI) = 2.5–3.8] and compared with non-CE (OR = 2.3, 95% CI = 2.0–2.6). In patients with CE, PFO prevalence in the young compared to the old was higher when the diagnostic modality was TEE (48.9 vs. 27.3%, $p < 0.0001$, OR = 2.6 with 95% CI = 2.0–3.3) or TCD (58.1 vs. 41%, OR = 1.9, 95% CI = 1.6–2.5), but not TTE (53.3 vs. 37.5%, $p = 0.16$). Regarding non-CE, PFO prevalence in the young compared to the old was higher when the diagnostic modality was TEE (20 vs. 12.9%, OR = 1.7, 95% CI = 1.0–2.8) but not TTE (10.4 vs. 7.8%, $p = 0.75$) or TCD (22.8 vs. 20.1%, $p = 0.56$).

**Conclusions:** Given the limitations of autopsy and TEE studies, there is good reason not to take a fixed 25% PFO prevalence for granted. The estimation of degree of causality may be underestimated or overestimated in populations with PFO prevalence significantly lower or higher than the established. Given the high sensitivity, non-invasive nature, low cost, and repeatability of TCD, future large-scale TCD-based studies should investigate potential heterogeneity in PFO prevalence in different healthy racial/ethnic populations.

**Keywords: PFO, epidemiology, stroke, TCD, review**

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## INTRODUCTION

In 1564, the Italian anatomist and surgeon Leonardo Botallo claimed in his publication "De catarrho commentarius" that he had discovered a "duct," which connected the right with the left atrium. He called it the "vena arteriarum nutria," which is nowadays known as foramen ovale or foramen Botalli (1). Three centuries later, Julius Cohnheim, a German professor of pathology, was the first to describe a case of fatal paradoxical embolism through a patent foramen ovale (PFO) to the middle cerebral artery (2). In 1880, Moritz Litten documented a second case of paradoxical embolism to the lower extremity (2). 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, pulmonary blood flow increases greatly because right heart pressure and pulmonary vascular resistance drop as pulmonary arterioles open in reaction to oxygen filling the alveoli. Left atrial pressure is increased resulting in functional closure of the foramen ovale. Anatomic closure occurs later in infancy in the majority of population, but sometimes the closure is incomplete and remains as PFO (3, 4).

Despite a thorough investigation, the etiology of cerebrovascular ischemic events remains undetermined in almost 10–40% of cases (5). Numerous case-control studies showed that PFO prevalence is remarkably high in patients with cryptogenic strokes (CSs) compared to the healthy population. It is considered that a part of these strokes may be attributed to paradoxical embolism or *in situ* thrombus formation in a PFO niche; therefore, PFO closure may be effective in secondary stroke prevention. The first three randomized controlled trials (RCTs) that addressed this issue (CLOSURE I, RESPECT, PC Trial) (6–8) failed to show superiority of PFO closure vs. best medical treatment (9). Despite the negative results, the suspicion that PFO was etiologically related with CS was strong. Four years later, three new RCTs (CLOSE, Gore REDUCE, DEFENSE-PFO) (10–12) and the extended follow-up results of the RESPECT trial (13) showed superiority of PFO closure compared to antiplatelet agents in appropriately selected patients using specific devices (14). Nevertheless, the optimal candidates for PFO closure are still not precisely known. The Risk of Paradoxical Embolism (RoPE) score (15) has been developed to facilitate the selection of CS patients who might benefit from PFO closure. The RoPE score applies Bayes' theorem and calculates the probability that PFO is causally related to stroke [PFO attributable fraction (PFOAF)], with higher scores implying greater possibility that a PFO is etiologically associated with a CS. Calculations are based on PFO prevalence in patients with CS compared with that in healthy subjects. The latter is considered to be 25% and the former is estimated at 40%, based on the RoPE database of 3,674 patients with CS (15). However, PFO prevalence in non-selected populations varies widely, and PFOAF may be "inflated" or "deflated," depending on numbers.

Therefore, we conducted a comprehensive critical review of the available epidemiological data on PFO prevalence in the general population and in stroke (cryptogenic and non-cryptogenic) stratified by diagnostic modality [autopsy, transthoracic (TTE) and transesophageal echocardiography (TEE), transcranial Doppler (TCD)] and by age (young vs. old). We provide a critical appraisal of each PFO screening modality, and we underscore methodological downsides of individual epidemiological studies that have impacted on the estimation of PFO prevalence in the general population and in distinct stroke patient subgroups and hitherto have been uncommented on.

## METHODS

We performed a detailed search in MEDLINE, SCOPUS, Cochrane Library, and Google scholar up to November 1, 2019, using the following terms in combination: "patent foramen ovale," "PFO," "right-to-left-shunt," "prevalence of patent foramen ovale," "prevalence of PFO," "frequency of PFO," "cryptogenic stroke," "cryptogenic stroke and patent foramen ovale," "autopsy studies and patent foramen ovale," "transthoracic echocardiography and patent foramen ovale," "transesophageal echocardiography and patent foramen ovale," "transcranial Doppler and patent foramen ovale," "PFO and cerebrovascular ischemic events," "PFO and migraine." We also searched the reference lists of all relevant articles. Both English and foreign language articles were reviewed. We included case-control, population-based, and cohort studies that examined PFO prevalence in patients with cerebrovascular ischemic events (cryptogenic or of known cause) and in the general population (healthy population or patients with diseases other than cerebrovascular disease), using autopsy or a validated ultrasound diagnostic modality (TEE, TTE, TCD). Patent foramen ovale documentation per diagnostic modality was as follows: (1) autopsy studies were conducted in patients with a cause of death other than cerebrovascular disease, and foramen ovale patency was demonstrated via a probe or a pencil; (2) in most TEE and TTE studies, investigations were evaluated by two different cardiologists and considered positive if one to five microbubbles were detected after the use of gelatin or saline contrast within three to five heart cycles after opacification of the right atrium, at rest and during Valsalva maneuver; (3) TCD examinations were also evaluated by one or two neurologists and considered positive if one to three microembolic signals were detected within 15–40 s after the injection of gelatin or saline contrast, at rest and during Valsalva maneuver.

Studies were included if (1) they reported data from a general population or from subjects of all ages without known cerebrovascular disease, who were referred for PFO detection; (2) they specified the etiologic type of ischemic cerebrovascular event as cryptogenic (CE) vs. event of known cause (non-CE); (3) they reported PFO prevalence in patients with transient ischemic attacks (TIAs) and stroke as a single group. In studies that separately reported PFO prevalence in patients with TIAs and stroke, only data from the latter were included in the analysis. Furthermore, we included data from studies in migraineurs that reported PFO prevalence in a non-migraineur population arm. Studies were excluded if (1) they reported data from subjects with an underlying cerebrovascular disease, who were referred for PFO detection; (2) they did not specify the type of ischemic cerebrovascular event. For duplicate studies, we included only

the updated article with the most informative data. We did not include review articles of previously included studies unless new data were reported. The extracted information was stratified and analyzed by diagnostic modality (autopsy, TEE, TTE, TCD), health status (healthy population/controls vs. stroke), CS status (yes vs. no), and age (young vs. old per authors' definition). Patent foramen ovale prevalence between different age and diagnostic modality subgroups was compared using the $\chi^2$ test. For the included studies, we calculated odds ratios (ORs) for PFO prevalence in CE compared with healthy/control population and also compared with non-CE, individually and cumulatively, stratified by diagnostic modality.

## RESULTS

Our search resulted in 1,032 studies, which were individually assessed. We identified 66 relevant articles, of which 54 were finally included in our review (**Table 1**) (16–69). We found 10 autopsy studies with 7,747 subjects (16–25). Patent foramen ovale was documented in 1,872 of them [24.2%, 95% confidence interval (CI) = 23.2–25.1]. We included 26 TEE studies in total (26–51). One study (29) was exclusively conducted on a healthy population. One study was conducted on a healthy population compared with migraineurs with aura (35). Twenty-four studies reported data from patients with cerebrovascular ischemic events (CE or non-CE), of which four studies also included TIAs (10–20% of the total events) (2, 31, 48, 49). Three studies also investigated a healthy population (27, 28, 34), and five studies also investigated control patients who underwent TEE for reasons other than ischemic cerebrovascular events (26, 30–33). Cumulatively, PFO was documented in 325 of 1,369 (23.7, 95% CI = 21.6–26.1) healthy subjects/controls, in 1,630 of 4,097 (39.8, 95% CI = 38.3–41.3) patients with CE and in 281 of 1,329 (21.1, 95% CI = 19.0–23.4) patients with non-CE. We included six TTE studies (52–57). One study was exclusively conducted on a healthy population (53). One study was conducted on a healthy population compared with migraineurs (54). Four studies (52, 55–57) reported data from patients with cerebrovascular ischemic events, of which one study also included TIAs in unknown percentage (55). One study (55) also investigated a healthy population, and one study (52) also investigated patients without cerebrovascular events who underwent TTE as a preparation for posterior fossa surgery. Cumulatively, PFO was documented in 186 of 1,267 (14.7, 95% CI = 12.8–16.7) healthy subjects/controls, in 66 of 131 (50.4, 95% CI = 41.9–58.8) patients with CE, and in 11 of 125 (8.8, 95% CI = 4.8–15.2) patients with non-CE. In our review, we included 12 TCD studies (58–69). Three studies were conducted in migraineurs compared to a healthy population (59–61), and nine studies reported data from patients with cerebrovascular events, of which five studies (63–67) also included TIAs (20–75% of the total events). Two studies also investigated a healthy population (58, 62). Cumulatively, PFO was documented in 111 of 355 (31.3, 95% CI = 26.7–36.3) healthy subjects/controls, in 706 of 1,591 (44.4, 95% CI = 41.9–46.8) patients with CE, and in 323 of 1,516 (21.3, 95% CI = 19.3–23.4) patients with non-CE.

**Tables 2**, **3** present the results of our review in young and old subjects, respectively. The age cutoff per individual study ranged between 40 and 60 years. In healthy/control population, there was no difference of PFO prevalence between the young and the old age groups, when the diagnostic modality was TEE (25 vs. 22.7%, $p = 0.35$) or TTE (11.4 vs. 14.9%, $p = 0.07$). Concerning TCD, a comparison was not possible because data were not available for the old age group. In patients with CE, PFO prevalence in the young compared to the old age group was higher when the diagnostic modality was TEE (48.9 vs. 27.3%, $p < 0.0001$, OR = 2.6 with 95% CI = 2.0–3.3) or TCD (58.1 vs. 41%, $p < 0.0001$, OR = 1.9 with 95% CI = 1.6–2.5), but not TTE (53.3 vs. 37.5%, $p = 0.16$). Finally, in patients with non-CE, PFO prevalence in the young compared to the old age group was higher when the diagnostic modality was TEE (20.0 vs. 12.9%, $p = 0.04$, OR = 1.7 with 95% CI = 1.0–2.8) but not TTE (10.4 vs. 7.8%, $p = 0.75$) or TCD (22.8 vs. 20.1%, $p = 0.56$).

**Figure 1** shows OR for PFO prevalence in CE compared with healthy/control population for eight TEE studies (26–28, 30–34), two TTE studies (52, 55), and two TCD studies (58, 62). Patent foramen ovale prevalence was higher in CE in TEE (OR = 3.2, 95% CI = 2.5–4.1, $p < 0.0001$), TTE (OR = 8.4, 95% CI = 4.2–16.7, $p < 0.0001$), and TCD studies (OR = 1.8, 95% CI = 1.2–2.8, $p = 0.008$). All diagnostic modalities included PFO prevalence was higher in CE compared with healthy/control population (OR = 3.1, 95% CI = 2.5–3.8, $p < 0.0001$). **Figure 2** shows OR for PFO prevalence in CE compared with non-CE for 14 TEE studies (26–28, 32, 36–38, 40–44, 50, 51), three TTE studies (52, 56, 57), and six TCD studies (58, 64, 66–69). Patent foramen ovale prevalence was higher in patients with CE in TEE (OR = 2.4, 95% CI = 2.0–2.8, $p < 0.0001$), TTE (OR = 9.7, 95% CI = 4.7–20.3, $p < 0.0001$), and TCD studies (OR = 1.9, 95% CI = 1.6–2.3, $p < 0.0001$). All diagnostic modalities included, PFO prevalence was higher in CE compared with non-CE (OR = 2.3, 95% CI = 2.0–2.6, $p < 0.0001$).

## DISCUSSION

Patent foramen ovale is not rare in the general population, but its detection has increasingly gained interest during the last two centuries, especially after its association with paradoxical embolism. Until late twentieth century, PFO detection relied exclusively on autopsy studies owing to lack of accurate *in vivo* diagnostic methods. However, even the more recent and better conducted studies admitted inherent limitations such as the use of formalin-fixed and not fresh specimens (16). The latter could have limited the detection of small-to-medium interatrial patency due to shrinkage of the fixed fibroelastic elements of the foramen ovale. Further possible disadvantages included the use of probes that could identify PFOs only larger than 1 mm and the inclusion of children. Interestingly, Hagen et al. (16) observed that PFO incidence was higher in younger subjects; conversely, PFO size was bigger in older subjects. They hypothesized that the former may be attributed to the increasing incidence of spontaneous anatomic closure of relatively small PFOs with advancing age, caused by age-related fibroelastic thickening of the valve of

**TABLE 1 |** List of included studies and PFO prevalence by diagnostic modality.

| Studies—all ages | Healthy/control population | Cryptogenic events | Non-cryptogenic events | |
|---|---|---|---|---|
| | PFO(+)/Total Prevalence (%) | PFO(+)/Total Prevalence (%) | PFO(+)/Total Prevalence (%) | Age (years) |
| **Autopsy Studies** | | | | |
| Hagen et al. (16) | 263/965 | | | >1 |
| | 27.2 | | | |
| Thompson and Evans (17) | 386/1,100 | | | All |
| | 35.1 | | | |
| Patten (18) | 683/3,277 | | | Mostly adults |
| | 20.8 | | | |
| Parsons and Keith (19) | 103/399 | | | All |
| | 25.8 | | | |
| Fawcett and Blachford (20) | 96/306 | | | >10 |
| | 31.4 | | | |
| Seib (21) | 85/500 | | | >20 |
| | 17 | | | |
| Wright et al. (22) | 113/492 | | | Mostly adults |
| | 23 | | | |
| Schroeckenstein et al. (23) | 50/144 | | | >20 |
| | 34.7 | | | |
| Sweeney and Rosenquist (24) | 20/64 | | | >10 |
| | 31.2 | | | |
| Penther (25) | 73/500 | | | Adults |
| | 14.6 | | | |
| **Total** | **1,872/7,747** | | | |
| | **24.2** | | | |
| **Transesophageal Echocardiography** | | | | |
| Cabanes et al. (26) | 9/50 | 36/64 | 7/36 | <55 |
| | 18 | 56.3 | 19.5 | |
| Jones et al. (27) | 2/19 | 4/14 | 3/12 | <50 |
| | 11 | 28.6 | 25 | |
| | 18/117 | 5/30 | 10/59 | 50–69 |
| | 15 | 16.7 | 17 | |
| | 11/66 | 5/27 | 8/78 | >70 |
| | 17 | 18.5 | 10.2 | |
| Job et al. (28) | 27/63 | 27/41 | 11/33 | <55 |
| | 43 | 65.8 | 33.3 | |
| Meissner et al. (29) | 148/581 | | | >45 |
| | 25.5 | | | |
| Mesa et al. (30) | 7/35 | 23/55 | | <50 |
| | 20 | 42 | | |
| Cerrato et al. (31) | 6/27 | 27/53 | | <50 |
| | 22.2 | 51 | | |
| | 7/51 | 16/53 | | >50 |
| | 13.7 | 30.1 | | |
| Hausmann et al. (32) | 2/18 | 9/18 | 0/1 | <40 |
| | 11.1 | 50 | 0 | |
| | 23/98 | 3/20 | 6/22 | >40 |
| | 23.5 | 15 | 27.3 | |
| van Camp et al. (33) | 11/28 | 19/24 | | All |
| | 39.3 | 79.1 | | |

*(Continued)*

**TABLE 1 |** Continued

| Studies—all ages | Healthy/control population | Cryptogenic events | Non-cryptogenic events | |
|---|---|---|---|---|
| | PFO(+)/Total<br>Prevalence (%) | PFO(+)/Total<br>Prevalence (%) | PFO(+)/Total<br>Prevalence (%) | Age (years) |
| Schuchlenz et al. (34) | 38/123<br>30.9 | 54/66<br>81.8 | | <60 |
| Schwerzmann et al. (35) | 16/93<br>17.2 | | | Young |
| Ranoux et al. (36) | | 31/54<br>57.4 | 1/14<br>7.1 | <55 |
| Homma et al. (37) | | 16/36<br>44.4 | 7/38<br>18.4 | All |
| Petty et al. (38) | | 22/55<br>40 | 15/61<br>25 | All |
| Mas et al. (39) | | 267/581<br>46 | | <55 |
| Homma et al. (40) | | 98/250<br>39.2 | 105/351<br>29.9 | All |
| Petty et al. (41) | | 33/133<br>24.8 | 27/158<br>17.1 | All |
| Handke et al. (42) | | 36/82<br>43.9 | 7/49<br>14.3 | <55 |
| | | 41/145<br>28.3 | 27/227<br>11.9 | >55 |
| Zahn et al. (43) | | 50/118<br>42.4 | 18/70<br>25.7 | All |
| Di Tullio et al. (44) | | 9/19<br>47.3 | 8/25<br>32 | All |
| Kim et al. (45) | | 76/245<br>31 | | All |
| Komar et al. (46) | | 69/88<br>78.4 | | <55 |
| De Castro et al. (47) | | 133/343<br>38.8 | | All |
| Weimar et al. (48) | | 376/1,126<br>33.4 | | All |
| Nighoghossian et al. (49) | | 27/79<br>34 | | <60 |
| Klötzsch et al. (50) | | 31/40<br>77.5 | 19/71<br>26.7 | All |
| Mesa et al. (51) | | 70/194<br>36 | 2/24<br>8.3 | <55 |
| | | 17/44<br>38.6 | | >55 |
| **Total** | **325/1369<br>23.7** | **1,630/4,097<br>39.8** | **281/1,329<br>21.1** | |
| **Transthoracic Echocardiography** | | | | |
| Lechat et al. (52) | 10/100<br>10 | 20/41<br>48.8 | 4/19<br>21 | <55 |
| Di Tullio et al. (53) | 164/1,100<br>14.9 | | | >39 |
| Tatlidere et al. (54) | 6/27<br>22.2 | | | All |

*(Continued)*

**TABLE 1 |** Continued

| Studies—all ages | Healthy/control population | Cryptogenic events | Non-cryptogenic events | |
|---|---|---|---|---|
| | PFO(+)/Total<br>Prevalence (%) | PFO(+)/Total<br>Prevalence (%) | PFO(+)/Total<br>Prevalence (%) | Age (years) |
| Webster et al. (55) | 6/40 | 19/34 | | <40 |
| | 15 | 55.9 | | |
| Di Tullio et al. (56) | | 10/21 | 1/24 | <55 |
| | | 47.6 | 4.2 | |
| | | 9/24 | 6/77 | >55 |
| | | 37.5 | 7.8 | |
| Jeanrenaud et al. (57) | | 8/11 | 0/5 | <50 |
| | | 72.7 | 0 | |
| **Total** | **186/1,267** | **66/131** | **11/125** | |
| | **14.7** | **50.4** | **8.8** | |
| **Transcranial Doppler** | | | | |
| Serena et al. (58) | 32/100 | 30/53 | 38/150 | All |
| | 32 | 56.6 | 25.3 | |
| Del Sette et al. (59) | 8/50 | | | <50 |
| | 16 | | | |
| Anzola et al. (60) | 5/25 | | | <55 |
| | 20 | | | |
| Domitrz et al. (61) | 16/65 | | | <55 |
| | 24.6 | | | |
| Koutroulou et al. (62) | 50/115 | 42/84 | | <55 |
| | 43.5 | 50 | | |
| Serena et al. (63) | | 162/229 | | <55 |
| | | 70.7 | | |
| | | 135/257 | | >55 |
| | | 52.5 | | |
| Mazzuco et al. (64) | | 29/74 | 16/52 | <60 |
| | | 39.2 | 30.8 | |
| | | 68/190 | 44/207 | >60 |
| | | 35.8 | 21.2 | |
| Palazzo et al. (65) | | 34/47 | | <55 |
| | | 72.3 | | |
| Yeung et al. (66) | | 16/27 | | <50 |
| | | 59.3 | | |
| | | 27/89 | | >50 |
| | | 30.3 | | |
| | | | 17/94 | All |
| | | | 18 | |
| Schminke et al. (67) | | 33/60 | 8/40 | All |
| | | 55 | 20 | |
| Consoli et al. (68) | | 77/327 | 170/797 | All |
| | | 23.5 | 21.3 | |
| Carod-Artal et al. (69) | | 37/90 | 5/40 | <45 |
| | | 41.1 | 11.1 | |
| | | 16/64 | 25/136 | >45 |
| | | 25 | 18.4 | |
| **Total** | **111/355** | **706/1,591** | **323/1,516** | |
| | **31.3** | **44.4** | **21.3** | |

*All ages are included.*

**TABLE 2 |** List of included studies and PFO prevalence by diagnostic modality in the young.

| Studies—young | Healthy/control population | Cryptogenic events | Non-cryptogenic events | Age (years) |
|---|---|---|---|---|
| | PFO(+)/Total<br>Prevalence (%) | PFO(+)/Total<br>Prevalence (%) | PFO(+)/Total<br>Prevalence (%) | |
| **Transesophageal Echocardiography** | | | | |
| Cabanes et al. (26) | 9/50<br>18 | 36/64<br>56.3 | 7/36<br>19.5 | <55 |
| Jones et al. (27) | 2/19<br>11 | 4/14<br>28.6 | 3/12<br>25 | <50 |
| Job et al. (28) | 27/63<br>43 | 27/41<br>65.8 | 11/33<br>33.3 | <55 |
| Mesa et al. (30) | 7/35<br>20 | 23/55<br>42 | | <50 |
| Cerrato et al. (31) | 6/27<br>22.2 | 27/53<br>51 | | <50 |
| Hausmann et al. (32) | 2/18<br>11.1 | 9/18<br>50 | 0/1<br>0 | <40 |
| Schuchlenz et al. (34) | 38/123<br>30.9 | 54/66<br>81.8 | | <60 |
| Schwerzmann et al. (35) | 16/93<br>17.2 | | | Young |
| Ranoux et al. (36) | | 31/54<br>57.4 | 1/14<br>7.1 | <55 |
| Mas et al. (39) | | 267/581<br>46 | | <55 |
| Handke et al. (42) | | 36/82<br>43.9 | 7/49<br>14.3 | <55 |
| Komar et al. (46) | | 69/88<br>78.4 | | <55 |
| Nighoghossian et al. (49) | | 27/79<br>34 | | <60 |
| Mesa et al. (51) | | 70/194<br>36 | | <55 |
| **Total** | **107/428<br>25** | **680/1,389<br>48.9** | **29/145<br>20** | |
| **Transthoracic Echocardiography** | | | | |
| Lechat et al. (52) | 10/100<br>10 | 20/41<br>48.8 | 4/19<br>21 | <55 |
| Webster et al. (55) | 6/40<br>15 | 19/34<br>55.9 | | <40 |
| Di Tullio et al. (56) | | 10/21<br>47.6 | 1/24<br>4.2 | <55 |
| Jeanrenaud et al. (57) | | 8/11<br>72.7 | 0/5<br>0 | <50 |
| **Total** | **29/140<br>11.4** | **57/107<br>53.3** | **5/48<br>10.4** | |
| **Transcranial Doppler** | | | | |
| Del Sette et al. (59) | 8/50<br>16 | | | <50 |
| Anzola et al. (60) | 5/25<br>20 | | | <55 |

*(Continued)*

**TABLE 2** | Continued

| Studies—young | Healthy/control population | Cryptogenic events | Non-cryptogenic events | Age (years) |
|---|---|---|---|---|
| | PFO(+)/Total<br>Prevalence (%) | PFO(+)/Total<br>Prevalence (%) | PFO(+)/Total<br>Prevalence (%) | |
| Domitrz et al. (61) | 16/65<br>24.6 | | | <55 |
| Koutroulou et al. (62) | 50/115<br>43.5 | 42/84<br>50 | | <55 |
| Serena et al. (63) | | 162/229<br>70.7 | | <55 |
| Mazzuco et al. (64) | | 29/74<br>39.2 | 16/52<br>30.8 | <60 |
| Palazzo et al. (65) | | 34/47<br>72.3 | | <55 |
| Yeung et al. (66) | | 16/27<br>59.3 | | <50 |
| Carod-Artal et al. (69) | | 37/90<br>41.1 | 5/40<br>11.1 | <45 |
| **Total** | **79/255**<br>**31** | **320/551**<br>**58.1** | **21/92**<br>**22.8** | |

fossa ovalis. Consequently, relatively larger PFOs remain in late adult life, and their size may undergo further modification by stretching (16).

The development of echocardiography (initially TTE and later TEE) during the second half of the twentieth century provided the first *in vivo* diagnostic tools for PFO. A second breakthrough in PFO detection happened after the development of TCD by Aaslid et al. (70) in 1982. Etiologic classification systems of ischemic stroke consider PFO as a medium-to-low or uncertain-risk emboligenic cardiac source (71, 72). Accordingly, the latest RCTs (10–12) documented spectacular superiority of percutaneous PFO closure only in carefully selected patients with CSs over best medical treatment, hence the need to detect reliably PFO in CS sufferers with the three available ultrasound modalities. Hitherto, TEE is considered the "gold standard" for the documentation of PFO (73, 74). A meta-analysis comparing TTE with TEE as a reference in 3,067 patients (75) evidenced the low sensitivity (45.1%) but very high specificity (99.6%) of TTE for PFO detection. The former can be attributed to several technical limitations: (1) atrial structures are located in the far ultrasound beam field and are subjected to acoustic interference by the chest wall; (2) during right-to-left shunt (RLS) provoking maneuvers, there is considerable lung interference, interrupting continuous imaging of the atria; (3) there is limited ability to document increased right-to-left atrial pressure gradient by visualizing movement of the septum toward the left atrium (73). Consequently, TTE even when performed with contrast agent and RLS provoking maneuvers is a poor screening tool for PFO: a negative examination should not rule out PFO presence, particularly if clinical suspicion is high.

The potentially causal relationship of PFO with some of cryptogenic ischemic events of the brain led vascular neurologists to incorporate contrast TCD in their routine workup for CS for more than 20 years, especially after the standardization of the technical protocol for the detection and quantification of RLS (76). Transcranial Doppler lacks direct visualization of atrial structures and documents RLS regardless of the subjacent pathology: PFO or (rarely) pulmonary arteriovenous malformations (PAVMs). However, it is the only diagnostic modality that (1) proves the emboligenic potential of RLS to the target organ (brain) and (2) quantifies the burden of embolism (number of microembolic signals corresponding to microbubbles) to the recipient (brain) and not to the source (left atrium). Furthermore, TCD is non-invasive, safe, and easily repeatable with low cost, and patients are alert and able to perform effective and calibrated Valsalva maneuvers. The latter may have significant impact on shunt quantification (77) and represents a major limitation of TEE because patients tend to perform ineffective Valsalva maneuvers owing to poor cooperation under sedation, dysphagia, or to the presence of the TEE probe in their esophagus. Additionally, TEE has certain esophagus-related contraindications (varices, diverticula, strictures, Barrett esophagus, Mallory-Weiss tear, important hemorrhagic risk) and may have rare but severe complications (aspiration, esophageal bleeding, or perforation).

Meta-analyses comparing TCD with TEE (75, 78) concluded that TCD has excellent diagnostic accuracy and should be used as a first-choice screening tool for PFO in patients with CS, reserving TEE to provide complementary anatomic details that may influence treatment decisions (PFO morphology, presence of atrial septum aneurysm). An updated meta-analysis of 2,751 patients by the authors of the European position paper on the management of patients with PFO (79) reconfirmed the excellent accuracy of TCD compared with TEE (sensitivity of 94%, specificity of 92%, area under the receiver operating characteristic curve of 0.97). Although TEE has been considered

**TABLE 3 |** List of included studies and PFO prevalence by diagnostic modality in the old.

| Studies—old | Healthy/control population | Cryptogenic events | Non-cryptogenic events | Age (years) |
|---|---|---|---|---|
| | PFO(+)/Total<br>Prevalence (%) | PFO(+)/Total<br>Prevalence (%) | PFO(+)/Total<br>Prevalence (%) | |
| **Transesophageal Echocardiography** | | | | |
| Jones et al. (27) | 29/183 | 10/57 | 18/137 | >50 |
| | 15.8 | 17.5 | 13.1 | |
| Meissner et al. (29) | 148/581 | | | >45 |
| | 25.5 | | | |
| Cerrato et al. (31) | 7/51 | 16/53 | | >50 |
| | 13.7 | 30.1 | | |
| Hausmann et al. (32) | 23/98 | 3/20 | 6/22 | >40 |
| | 23.5 | 15 | 27.3 | |
| Handke et al. (42) | | 41/145 | 27/227 | >55 |
| | | 28.3 | 11.9 | |
| Mesa et al. (51) | | 17/44 | 2/24 | >55 |
| | | 38.6 | 8 | |
| **Total** | **207/913** | **87/319** | **53/410** | |
| | **22.7** | **27.3** | **12.9** | |
| **Transthoracic Echocardiography** | | | | |
| Di Tullio et al. (53) | 164/1,100 | | | >39 |
| | 14.9 | | | |
| Di Tullio et al. (56) | | 9/24 | 6/77 | >55 |
| | | 37.5 | 7.8 | |
| **Total** | **164/1,100** | **9/24** | **6/77** | |
| | **14.9** | **37.5** | **7.8** | |
| **Transcranial Doppler** | | | | |
| Serena et al. (63) | | 135/257 | | >55 |
| | | 52.5 | | |
| Mazzuco et al. (64) | | 68/190 | 44/207 | >60 |
| | | 35.8 | 21.2 | |
| Yeung et al. (66) | | 27/89 | | >50 |
| | | 30.3 | | |
| Carod- Artal et al. (69) | | 16/64 | 25/136 | >45 |
| | | 25 | 18.4 | |
| **Total** | | **246/600** | **69/343** | |
| | | **41** | **20.1** | |

as the "gold standard" for PFO detection, there is good evidence to think that TEE is a standard of uncertain validity. Most of the studies that compared the two modalities did not verify the origin of presumed false-positive TCD results. Frequently, the latter were arbitrarily attributed to possible PAVMs, an entity considered particularly rare with a prevalence of 1 in 2,600 (80). Furthermore, PAVMs may sometimes be misinterpreted by TEE as well (78). A meta-analysis of 164 patients comparing TEE with autopsy, cardiac surgery, and/or catheterization as the gold standard showed a sensitivity of 89.2% and specificity of 91.4% to detect PFO and concluded that TEE should be complemented by highly sensitive screening tests, namely, TCD (81). Estimation of the degree of RLS in all patients undergoing cardiac catheterization for PFO closure could be used as an alternative gold standard and could be compared with preprocedural TEE and TCD data. The superior sensitivity of TCD has also been demonstrated in a study (82) where TEE failed to document RLS in 15% of patients with CS, and of those, 40% had large RLSs. Therefore, "false-positive" TCD results may, in fact, represent true PFOs that are missed because of TEE limitations, and a negative TEE should not negate the need for a complementary TCD investigation.

According to our review, PFO prevalence in the general population across all ages was roughly 24% in autopsy and TEE

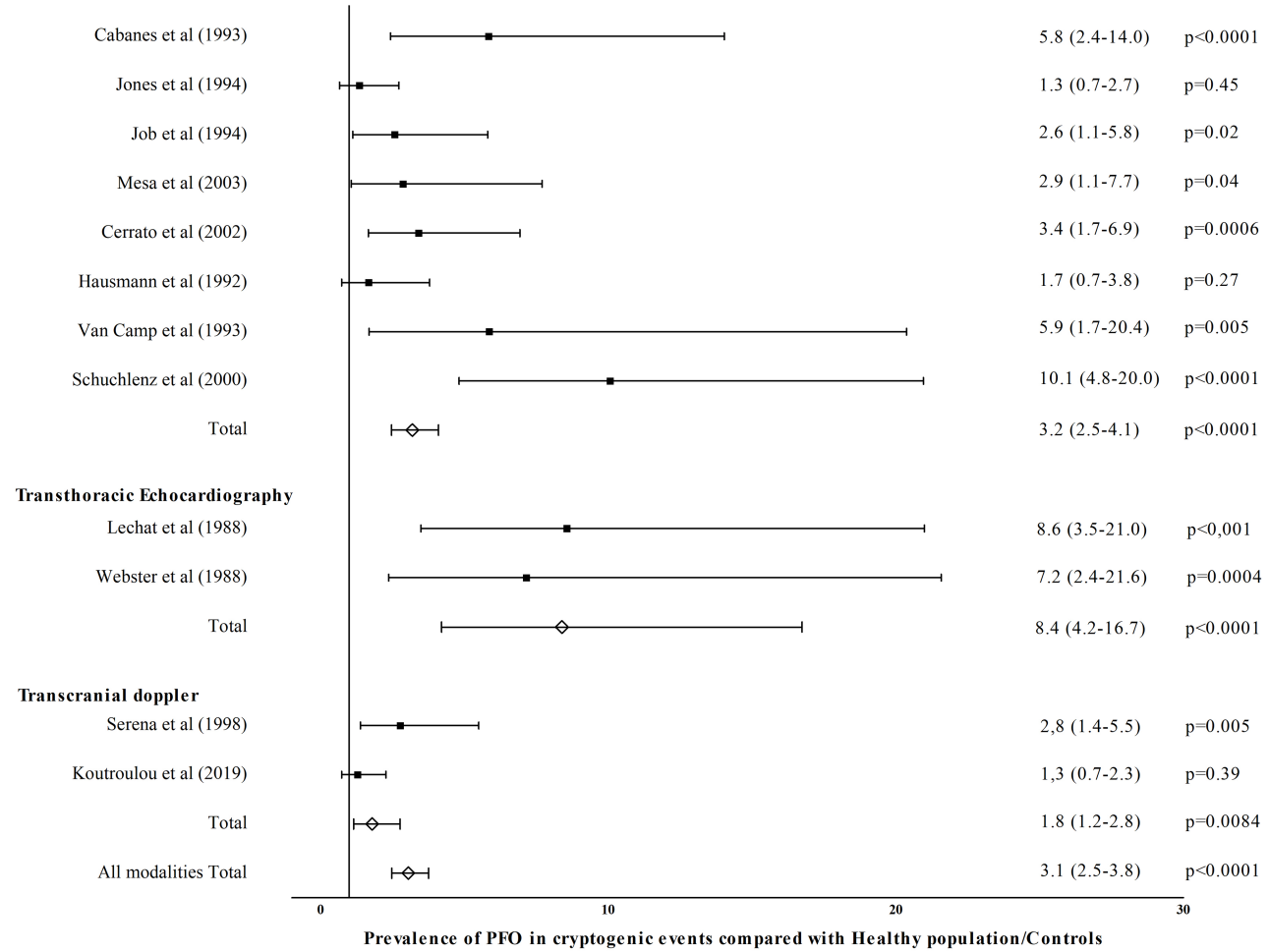


**FIGURE 1 |** Prevalence of PFO in cryptogenic events compared with healthy population/controls.

studies. As expected, this percentage was much smaller in TTE studies (15%), whereas in the highly sensitive TCD studies, PFO prevalence was higher (∼31%). The results were similar with small differences when subjects were stratified into young and old age groups. The results should be viewed under the limitations of the relatively small size (355 subjects) of healthy population in TCD studies and of the absence of TCD data in the old age group. Future TCD studies should focus on elderly general population and provide evidence regarding the differential PFO prevalence and magnitude of RLS with increasing age, as suggested by autopsy studies. Furthermore, in three of five TCD studies that estimated PFO prevalence (59–61), the healthy population comprised non-migraineurs, resulting in prevalence as low as 16% (59). Because migraineurs constitute 10–15% (83) of the general population and migraineurs are more likely to have a PFO (84), future studies on PFO prevalence in the general population should not exclude migraineurs.

Of note is the considerable variability in PFO prevalence among studies that used the same diagnostic modality. In autopsy studies, PFO prevalence ranged from 14.6 to 35.1%, in TEE studies from 11 to 43%, in TTE from 10 to 22.2%, and in TCD studies from 16 to 43.5%. The heterogeneous results could be attributed to (1) selection bias because in most ultrasound-based studies the reported "healthy population" consisted of patients who underwent an examination for a reason other than cerebrovascular event, and PFO detection was not the primary endpoint; (2) technical differences in PFO detection and RLS quantification; (3) different PFO

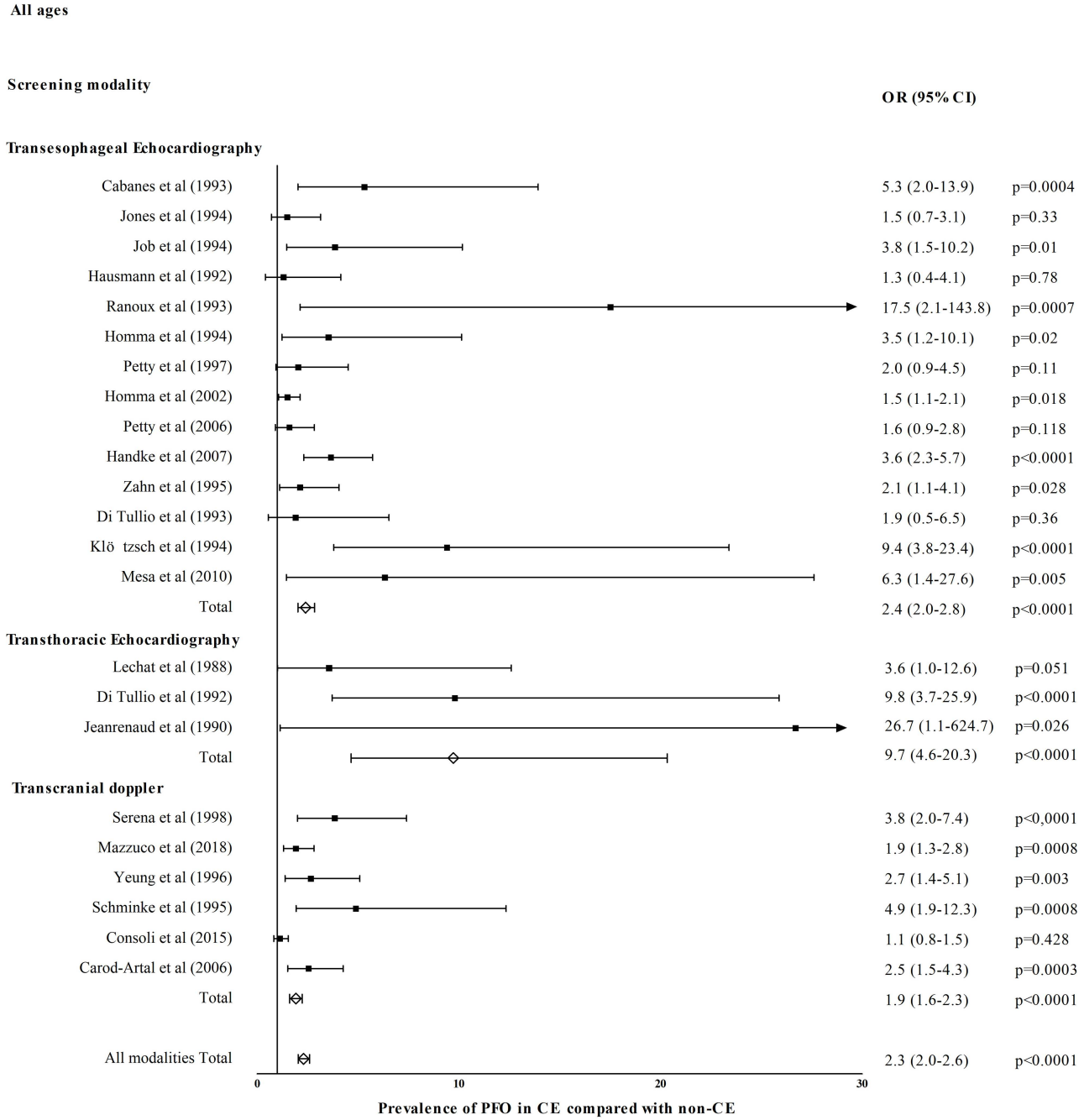


**FIGURE 2 |** Prevalence of PFO in cryptogenic events (CE) compared with events of known cause (non-CE).

prevalence in discrete ethnic/racial populations. Hitherto, the latter issue has not been addressed, and a "fixed" 25% (mainly based on autopsy and TEE studies) has been established as PFO prevalence across the general population and has been used for the calculation of PFOAF (15). However, given the limitations of autopsy and TEE studies, there is good reason not to take this percentage for granted. Interestingly, a recent TCD study conducted in a national population that comprised healthy Greek adults younger than 55 years and included subjects with migraine without aura (∼10% of the total population) found much higher PFO prevalence (43.5%) compared to previous TCD studies in other populations (62). Interest in optimal patient selection for PFO closure or possibly for long-term anticoagulation with direct oral anticoagulants (85) remains keen and the RoPE score may be useful in guiding patient management; albeit it lacks large

external validation studies, and it is heavily age weighted. Therefore, 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%.

Although this review is not systematic and does not include meta-analytic methodology, it has the advantage of including only studies with a clear etiologic classification of stroke (cryptogenic vs. non-cryptogenic). We excluded studies with a vague definition of CS or studies that included "pseudo" CSs, and we excluded data from patients with TIAs. Transient ischemic attacks are a "soft" and overused diagnosis, and TIA definition has evolved over the years from time-specific to tissue-specific (86). Reversible deficits, particularly in the elderly, may be caused by amyloid angiopathy, an easily missed diagnosis unless blood-sensitive magnetic resonance imaging sequences are performed (87). Accordingly, all recent successful PFO closure trials did not include patients with TIAs (10–12).

In our review, PFO prevalence was nearly 2-fold in CE compared with non-CE (OR ranging widely from 1.1 to 17.5 in individual studies) in accordance with previous random-effects meta-analyses that established the strong association between CS and PFO with OR in the order of 2.9 (88, 89). This marked difference persisted regardless of age confirming a meta-analysis in older patients with OR in the order of 2.5 (64). However, young patients with CE had higher PFO prevalence compared to older patients reflecting the stronger association of CE with PFO in younger ages (88, 89). Concerning non-CE, PFO prevalence across the board and particularly in older patients was numerically lower than in the general population possibly owing to the decreasing frequency and less implication of PFO in stroke mechanisms with increasing age (16). We showed that PFO prevalence across all ages was ∼3-fold in CE compared with healthy population/controls with OR ranging from 1.3 to 10.1. This is in accordance with random-effects OR from previous meta-analyses ranging from 2.1 to 2.9 (88, 89). The above association is mainly driven by TEE and TTE studies, whereas only two TCD studies compared PFO prevalence in CE with a relatively small non-selected general population of 215 subjects in total (58, 62). Given the high sensitivity, non-invasive nature, low cost, and repeatability of TCD, future large-scale TCD-based studies should investigate potential heterogeneity in PFO prevalence in different healthy racial/ethnic populations. The latter may have important implications in individualizing PFO-associated stroke risk assessment and management in the forthcoming era of precision medicine.

## AUTHOR CONTRIBUTIONS

IK and TK data acquisition, data analysis and interpretation, drafting of the manuscript. GT data interpretation, critical revision for important intellectual content. DT data acquisition, data analysis, and interpretation. DK and NG critical revision for important intellectual content.

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# Deep Vein Thrombosis and Pulmonary Embolism Among Patients With a Cryptogenic Stroke Linked to Patent Foramen Ovale—A Review of the Literature

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**Background:** Venous thromboembolism (VTE) can occur simultaneously with a cryptogenic stroke (CS) linked to patent foramen ovale (PFO), given paradox thromboembolism as potential stroke cause. However, little is known on the frequency of concomitant VTE and CS. We aimed to review the literature on the frequency of VTE in patients with CS linked to PFO (primary aim) and of ischemic stroke (IS) among patients with pulmonary embolism (PE) (secondary aim).

**Methods:** We performed a Medline search for cohort studies, written in English, with the following characteristics: (a) enrolling patients hospitalized for an acute ischemic stroke undergoing a work-up for deep venous thrombosis (DVT) and/or PE. To be included in this review, a study had to have at least a subgroup of patients with PFO; (b) the time interval between the index stroke and the work-up had to be within 40 days and the studies had to differentiate between DVT and PE. For the secondary aim, studies had to include patients with acute PE, known PFO-status and routine brain imaging on admission or within 1 year.

**Results:** We found eight studies reporting on the frequency of VTE after an acute CS linked to PFO. Concerning DVT, the reported frequency ranged between 7 and 27%; concerning PE, it lied between 4.4 and 37%. Six studies assessed the frequency of ischemic brain lesions among patients with an acute PE. In all studies, the presence of PFO was associated with ischemic brain lesions, both at baseline and follow-up.

**Conclusion:** VTE can be detected in patients with CS linked to PFO. While –based on the presented literature–routine screening for VTE in patients with CS linked to PFO does not appear justified, history taking, and clinical exam should consider concomitant VTE. Whenever clinically suspected, the threshold to trigger ancillary testing for VTE should be low. Among patients with an acute PE and PFO, vigilance for new neurologic deficits should be increased, with a low threshold for brain imaging.

**Keywords: cryptogenic stroke, patent foramen ovale, deep vein thrombosis, pulmonary embolism, venous thromboembolism**

## BACKGROUND

Up to date, ∼25% of ischemic stroke are described as cryptogenic (CS) (1). Even though a prospective follow up study did not describe a PFO as an independent risk factor for ischemic stroke in general (2), various studies demonstrated an association between PFO and CS (3–6). The suspected pathophysiological mechanism is paradox embolism, enabling a passage of the venous thrombus through the PFO into the arterial circulation (7). Imaging demonstrating the migration of a thrombus was also described (8). The source of venous thromboembolism (VTE) is often suspected in the peripheral venous system. An acute rise of the right atrial pressure—for example through a Valsalva maneuver—could facilitate the passage through a PFO. Ozcan et al. (9) described an association between Valsalva maneuver and a history of VTE with a PFO related ischemic stroke. Four trials demonstrated—after PFO closure—a reduced incidence of recurrent ischemic stroke compared to antithrombotic therapy (antiplatelet or anticoagulation) (10–13). However, none of the trials mandated screening for VTE, and all had anticoagulation as an exclusion criterion. In clinical practice, detection of VTE leads to anticoagulation, potentially postponing PFO closure as long as anticoagulation is needed, given the lack of data on concomitant anticoagulation linked to PFO closure.

In addition, patients with PFO and a diagnosed PE may be at increased risk for ischemic stroke, further underlying the role of paradox embolism (14).

In this work, we aim to review the literature on the frequency of VTE in patients with CS linked to PFO, and the frequency of ischemic stroke in patients with PE.

## METHODS

For this narrative review, we performed a Medline search using the keyword "deep vein thrombosis," "patent foramen ovale" and "ischemic stroke." Two reviewers (AZ, GMDM) evaluated the included studies. We searched for cohort studies, written in English after 1990, enrolling patients hospitalized for an acute ischemic stroke undergoing a work-up for deep venous thrombosis (DVT) and/or pulmonary embolism (PE). To be included in this review, a study had to have at least a subgroup of patients with PFO and had to differentiate between DVT and PE. The time interval between the index stroke and the work-up did not have to exceed 40 days, to increase chances of finding VTE linked to paradox embolism rather than secondary to immobilization due to the index stroke.

Concerning the secondary aim, we included cohort studies written in English who (a) enrolled patients with acute pulmonary embolism (b) performed a search for patent foramen ovale and (c) carried out a brain imaging after the diagnosis of an acute PE. In our Medline search we used the keyword "patent foramen ovale," "pulmonary embolism" and "stroke."

## RESULTS

Our review identified eight studies reporting the frequency of VTE in patients with CS linked to PFO. Six of these studies did not compare the frequency of DVT between CS and non-CS patients (**Table 1**) (15–20), two studies did (**Table 2**) (22, 23).

### Studies Not Comparing the Frequency of DVT in Patients With CS Vs. Non-CS

Investigation regarding the emergence of VTE were performed within 0 to 38 days after index stroke. Concerning DVT, the reported frequency ranged between 7 and 27%; concerning PE, it lied between 4.4 and 37% (15–20). Concomitant DVT in patients with PE were described in two studies: Lapergue et al. (17) found a DVT in 3 out of 5 patients with silent PE, Tanislav et al. (19) in 8 out of 56 patients. In a study by Osgood et al. (18) four pelvic DVT were diagnosed (8%), as well as 5 cases of May Thurner Syndrom. The latter describes an anatomical variation, in which the left V. iliaca communis is being anatomically narrowed by the right A. iliaca communis. This reduces venous blood flow, increasing the risk of DVT (21).

### Studies Comparing the Frequency of DVT in Patients With CS Vs. Non-CS

The prospective PELVIS study found—in patients with CS—more MR-venograms with pelvic DVT compared to non-CS (20 vs. 4%, $p = 0.025$), suggesting the source of paradox embolism may be located in the pelvic veins in a subset of patients with CS. Notably—when looking at the subgroup with PFO—there was no significant difference between CS and non-CS in the frequency of DVT (21 vs. 0%, $p = 0.30$) (22). In the retrospective study of Liberman et al. (23), contrast enhanced MR-venograms were used, and patients with CS vs. non-CS were compared. All patients, both CS and non-CS, had PFO. No significant difference in the frequency of DVT—both pelvic and lower extremity—was found between CS and non-CS (7.2 vs. 9.1%, $p = 0.71$), calling for further research before implementing routine pelvic MR-venograms. Clinical evidence of a PE was found in one patient with chronic lower extremity DVT.

### Studies on the Frequency of Ischemic Strokes in Patients With Acute PE and PFO

We found six studies; detailed analyses regarding population characteristics, diagnostic measures and time to interventions after admission are outlined in **Table 3** (14, 24–28). Overall, ischemic stroke was reported to be diagnosed within 2–22 days following after admission and was more frequent in patients with overt PFO with four studies revealing statistical significance (14, 25, 27, 28). In the study of Konstantinides et al. (27) all investigations were performed during the hospital stay (22 ± 17 days).

## DISCUSSION

Studies demonstrated a wide range in the reported frequency of VTE in patients with CS linked to PFO, likely because the diagnostic of lower extremity DVT depends on the investigator and expertise in using duplex sonography (15, 20). In asymptomatic patients, a lower sensitivity (60%) of venous duplex sonography is described (29).

**TABLE 1 |** Summary of studies on the frequency of DVT/PE in patients with CS linked to PFO.

| References | Patient with CS linked to PFO: % of the whole cohort (n) | Work-up for VTE | Days between Index stroke and VTE work-up | Frequency of DVT/PE in patients with CS linked to PFO |
|---|---|---|---|---|
| Lethen et al. (15) | 23% ($n = 53$) | Venography | 8 ± 3 | DVT: 9.5% (5/53)<br>PE: N/A |
| Cramer et al. (16) | 100% ($n = 37$) | Venography<br>MRV | 8 | DVT: 27% (10/37)<br>PE: N/A |
| Lapergue et al. (17) | 100% ($n = 114$) | Combined CT-Venography and pulmonary angiography | 4–9 | VTE: 10.5% (12/114)<br>DVT: 8.8% (10/114)<br>Silent PE: 4.4% (5/114) |
| Osgood at al. (18) | 100% ($n = 50$) | MRV | 4 ± 3 | DVT: 8% ($n = 4$)<br>May Thurner Syndrom*: 10% ($n = 5$)<br>PE: N/A |
| Tanislav et al. (19) | 100% ($n = 151$) | Ventilation perfusion scintigraphy | N/A | DVT: 7% ($n = 11$)<br>Silent PE: 37% ($n = 56$) |
| Ranoux et al. (20) | 19.1% ($n = 13$) | Venography | 0–38 | DVT: 8% ($n = 1$) in a plegic leg 14 days after index stroke<br>PE: N/A |

*PFO, patent foramen ovale; CS, cryptogenic stroke; PE, pulmonary embolism; DVT, deep vein thrombosis; VTE, venous thromboembolism; MRV, magnetic resonance venography; N/A, not available. *May Thurner Syndrome indicates an anatomical variation, in which the origin of left V. iliaca communis is being anatomically narrowed by the right A. iliaca communis. This reduces venous blood flow, increasing the risk of DVT (21).*

**TABLE 2 |** Summary of studies comparing the frequency of DVT among patients with cryptogenic vs. known-cause stroke.

| References | Population % (n) | Work-up for DVT | DVT prevalence in Non-CS vs. CS, % (n) | Time between Index stroke and DVT workup |
|---|---|---|---|---|
| Cramer et al. (22) | Non-CS: 52% ($n = 49$)<br>CS: 48% ($n = 46$, among them 61% with an PFO or ASD) | MRI Venogramm | Total patients<br>4% (2/49) vs. 20% (9/46); $p = 0.025$<br>Subgroup with PFO<br>0% (0/9) vs. 21% (6/28); $p = 0.30$ | 48.9 ± 16.1 h |
| Liberman et al. (23) | All Patients had PFO ($n = 131$)<br>CS: 74.8% ($n = 98$)<br>Non-CS: 25.2% ($n = 33$) | MRI Venogramm<br>LE duplex ultrasound | 9.1% (3/33) vs. 7.2% (7/98); $p = 0.71$ | 0–4 days |

*PFO, patent foramen ovale; CS, cryptogenic stroke; PE, pulmonary embolism; DVT, deep vein thrombosis; VTE, venous thromboembolism; MRV, magnetic resonance venography; N/A, not available.*

The two studies comparing the frequency of DVT between patients with CS vs. non-CS yielded conflicting results. In PELVIS (22)—but not in the study by Liberman et al. (23)—a higher frequency of DVT was observed among patients with CS than among those with non-CS. Differences in the DVT screening protocols as well as baseline characteristics may explain the conflicting results. In contrast to PELVIS, in the study of Liberman et al. (23) MR-venograms were contrast-based (i.e., less prone to artifacts), all patients had PFO, were older (mean age 46 years vs. 57 years, respectively) and had a higher burden of cardiovascular risk factors. To note, neither the subgroup of PFO patients in the PELVIS study nor the patients in the study of Libermann at al. (23) showed significant differences on the DVT frequency. Before implementing routine MR-Venography in clinical practice, further research is needed.

Liberman et al. (23) used the Causative Classification System to retrospectively classify the etiology of the ischemic stroke. Of note, patients with transient ischemic attacks were also included. In PELVIS, a stroke neurologist was responsible to identify and classify the cause of the ischemic stroke, based on the TOAST criteria.

In the three pivotal trials on PFO-closure (10, 11, 13), a search for VTE was not part of the routine diagnostic work up. In the follow up examinations, the occurrence of PE or DVT in the PFO closure group and the medical therapy group were reported as adverse events. Suspecting the frequency of underdiagnosed VTE, the risk of PE could even rise after PFO closure and without an effective oral anticoagulation. However, only the long-term evaluation of the RESPECT trial showed a higher detection rate of PE in the PFO closure group (24% vs 0.6%, $p = 0.03$) (12).

The CLOSE study compared PFO closure to oral anticoagulation. Three recurrent ischemic strokes were reported in the oral anticoagulation arm, whereas no recurrent stroke was described in the PFO closure arm (30). Since no trial allowed for PFO closure under concomitant oral anticoagulation, there are no data concerning PFO closure

**TABLE 3 |** Frequency of ischemic brain lesions among patients with an acute PE, with or without PFO.

| References | Study population | Diagnostic | Frequency of ischemic brain injuries (PFO vs. Non PFO) | Days to intervention after admission |
|---|---|---|---|---|
| Le Moigne et al. (24) | Acute PE ($n = 315$):<br>• PFO ($n = 42$)<br>• Non PFO ($n = 273$) | cMRI<br>TTE | Silent or symptomatic IBL<br>21.4% (9/42) vs. 5.5% (15/273)<br>Symptomatic IBL<br>9.5% (4/42) vs. 1.5% (4/273)<br>CS<br>16.7% (7/42) vs. 1.8% (5/273) | cMRI and TTE: 7 days |
| Vindiš et al. (25) | Acute PE ($n = 78$):<br>• PFO ($n = 31$)<br>• Non PFO ($n = 47$)<br>12 month follow-up ($n = 58$) | cMRI<br>TTE/TEE | At Baseline<br>64.5% (20/31) vs. 40.4% (19/47);<br>$p = 0.06$<br>At follow up<br>New IBL<br>33.3% (7/21) vs. 5.4% (2/37); $p = 0.008$ | TEE and TTE baseline<br>TTE: 12 month follow up<br>cMRI (baseline, 12 month follow up) |
| Doyen et al. (26) | Intermediate risk PE ($n = 41$)<br>• PFO ($n = 23$)<br>• Non PFO ($n = 18$) | cMRI<br>TTE/TEE | 17.1%<br>($n = 7$)<br>(PFO in all cases, 30.4% with PFO had an IBL) | TTE/TEE: 1–3 days<br>cMRI: 5 ± 4 days |
| Clergeau et al. (14) | Acute PE ($n = 60$)<br>• PFO ($n$ =15)<br>• Non PFO ($n = 45$) | cMRI<br>TTE | 33.3% (5/15) vs. 2.2% (1/45)<br>$p = 0.003$ | cMRI: 3 ± 1 days |
| Konstantinides et al. (27) | Acute PE ($n = 139$)<br>• PFO ($n = 48$)<br>• Non PFO ($n = 91$) | cCT or Autopsy | 13% (6/48) vs. 2.2% (2/91),<br>$p = 0.02$ | 22 ± 17 days |
| Goliszek et al. (28) | Acute PE ($n = 55$)<br>• PFO($n = 19$)<br>• Non PFO ($n = 36$) | cMRI<br>TTE | 21% (4/19) vs. 0% (0/36)<br>$P = 0.02$ | cMRI: 4.91 ± 4.1 days<br>TTE: N/A |

*PFO indicates patent foramen ovale; PE: pulmonary embolism; cMRI: cranial magnetic resonance imaging; TTE: transthoracic echocardiography; TEE: transesophageal echocardiography; IBL: ischemic brain lesions; N/A: not available.*

under oral anticoagulation. Thus, the diagnosis of DVT/PE—indicating oral anticoagulation for at least 3 months—could postpone PFO-closure leaving patients at risk of a stroke recurrence even under oral anticoagulation. To note, the early start of an oral anticoagulation could also lead to hemorrhagic transformation (7).

The reported association between PE and IS in patients with PFO further underlines the role of paradox embolism. Particularly in patients with intermediate-risk PE, PFO related ischemic brain lesions were frequent, up to 17.1% (26). Of note, none of these patients had a significant carotid stenosis or suspected cardioembolic source of ischemic stroke. Even under effective oral anticoagulation, Vindiš et al. (25) reported a significant difference in recurrent ischemic lesions in patients with PFO after PE, raising the question if PFO closure should be considered in some patients with PE (25).

## CONCLUSION AND CLINICAL IMPLICATIONS

Since VTE calls for therapeutic anticoagulation, the clinically important question arises if a baseline search for DVT in patients with CS linked to PFO is necessary. The reported frequency of DVT in two studies using MRI Venogram showed a large range of up to 20% (22, 23) while other studies described lower frequencies (15, 17). In patients with CS linked to PFO, the focus of medical history and physical exam should be intensified on the search for DVT/PE. The threshold for DVT/PE screening should be low, giving the potential subsequent indications for oral anticoagulation linked to PFO screening. Further prospective studies are needed to establish the optimal diagnostic work up for VTE/PE in patients with CS linked to PFO, as well as the safety of combining anticoagulation to PFO-closure.

## DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

## AUTHOR CONTRIBUTIONS

GD formulated the research question. AZ and GD summarized and extracted the data manually from published papers for this review. GD, AZ, and RS drafted the article and reviewed it critically.

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# Prior Stroke in PFO Patients Is Associated With Both PFO-Related and -Unrelated Factors

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**Background and Purpose:** To identify factors associated with prior stroke at presentation in patients with cryptogenic stroke (CS) and patent foramen ovale (PFO).

**Methods:** We studied cross-sectional data from the International PFO Consortium Study (NCT00859885). Patients with first-ever stroke and those with prior stroke at baseline were analyzed for an association with PFO-related (right-to-left shunt at rest, atrial septal aneurysm, deep venous thrombosis, pulmonary embolism, and Valsalva maneuver) and PFO-unrelated factors (age, gender, BMI, hypertension, diabetes mellitus, hypercholesterolemia, smoking, migraine, coronary artery disease, aortic plaque). A multivariable analysis was used to adjust effect estimation for confounding, e.g., owing to the age-dependent definition of study groups in this cross-sectional study design.

**Results:** We identified 635 patients with first-ever and 53 patients with prior stroke. Age, BMI, hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, and right-to-left shunt (RLS) at rest were significantly associated with prior stroke. Using a pre-specified multivariable logistic regression model, age (Odds Ratio 1.06), BMI (OR 1.06), hypercholesterolemia (OR 1.90) and RLS at rest (OR 1.88) were strongly associated with prior stroke.Based on these factors, we developed a nomogram to illustrate the strength of the relation of individual factors to prior stroke.

**Conclusion:** In patients with CS and PFO, the likelihood of prior stroke is associated with both, PFO-related and PFO-unrelated factors.

**Keywords: patent foramen ovale, PFO, right-to-left shunt, cryptogenic stroke, prior stroke, risk factor, hypercholesterolemia, International PFO Consortium**

## INTRODUCTION

The prevalence of patent foramen ovale (PFO) in the general adult population is 15–35% (1) and its association with cryptogenic stroke (CS) has been clearly established (2, 3). The higher prevalence of PFO in CS of all ages (3, 4) suggests a pathogenic role for PFO, at least in a substantial portion of these patients. Assuming that paradoxical embolism is the predominant pathogenic mechanism for recurrent strokes (5), PFO closure is a logical treatment option. However, recent RCTs comparing percutaneous closure with antithrombotic treatment revealed inconsistent results—some of them in favor of closure (6–9), whereas others without a significant advantage of closure (10–13). Low recurrence rates under both prevention regimens, non-PFO related recurrent stroke mechanisms, crossovers, procedure- and device-related complications as well as suboptimal patient selection—i.e., including some patients with non-PFO-related index strokes—might explain the inconsistency of the results (14–17). Hence, in patients with PFO and CS, the risk of stroke recurrence may be associated with both PFO-related and PFO-unrelated factors.

Previous strokes at presentation have been identified as a risk factor for stroke recurrence in patients with CS and PFO (18).

The aim of this study was to identify PFO-related and -unrelated risk factors associated with prior stroke in CS patients. Furthermore, we developed a nomogram to illustrate the strength of these associations.

## METHODS

### Patients

The International PFO Consortium is an ongoing academic trial, where researchers from currently nineteen stroke centers worldwide collaborate (NCT00859885). It was founded in 2008 and collects data of patients with ischemic stroke or TIA and PFO. Emphasis is placed on the evaluation of risk factors, PFO diagnosis, and secondary stroke prevention. It is a multicenter prospective study with a scheduled yearly follow-up. Database is expected to be closed after all patients reach a minimum of three years follow-up in 2021. Ethical approval was obtained from the local ethics committee of the corresponding center if legally required.

Patients older than 18 years with ischemic stroke or TIA $\leq$3 months and proven PFO on transesophageal echocardiography are eligible for the International PFO Consortium Study. There was no upper age limit. The whole International PFO consortium cohort included patients with different stroke etiologies. In the current study we addressed those with an undetermined stroke etiology, i.e., CS. Baseline data comprise demographic data, vascular risk factors, conditions predisposing to paradoxical embolism, previous medication, brain CT or MRI findings, echocardiographic PFO-features, and stroke etiology according to TOAST criteria (19). Annual follow-up visits assess secondary stroke prevention and stroke recurrence. Vascular risk factors include age, gender, arterial hypertension, diabetes mellitus, hypercholesterolemia, smoking, self-reported migraine, coronary artery disease, previous stroke, thrombophilia (factor V Leiden and prothrombin mutation, protein C and S deficiency, AT3 deficiency, and antiphospholipid antibodies). Echocardiographic features include atrial septal aneurysm (ASA) defined as hypermobility of the atrial septum with an excursion of $\geq$10 mm from midline, aortic plaques >4 mm thickness, and right-to-left shunt (RLS) at rest or under Valsalva maneuver (VM). Conditions predisposing to paradoxical embolism comprise VM at the time of stroke onset, deep vein thrombosis (DVT), and pulmonary embolism.

From September 2008 through December 2014, the International PFO Consortium enrolled 931 patients with CS and PFO. The present study focused on two patient subgroups: (a) 635 patients with first-ever stroke (i.e., neither radiological nor clinical evidence of prior stroke) and (b) 53 patients with prior stroke (i.e., both clinical and radiological evidence of prior stroke). Patients, who could not unambiguously assigned to the first-ever or the recurrent stroke group on the basis of past medical history and radiological signs, i.e., CS patients with clinical but no radiological evidence of prior stroke or vice versa ($n = 243$) were not included in the present study.

### Statistical Analysis

The distribution of quantitative data is described by mean $\pm$ standard deviation. Qualitative data is presented by absolute and relative frequencies. Corresponding hypothesis testing was performed by *t*-Test and the Chi-squared test or Fisher's exact test, as appropriate.

Missing values were imputed using a Random Forests model to account for possible interactions and high-dimensional relations of the data (20). Associations with prior stroke were estimated by Odds Ratios, with 95% confidence intervals, using univariate and multivariable logistic regression models. Any model contained age as an independent variable to adjust for confounding by the time-dependent stroke risk. Therefore, each estimated effect is conditioned on age, i.e., the assessment of PFO-related and—unrelated factors is valid for patients of the same age who are consequently at the same time-dependent stroke risk. The multivariable model was pre-specified to avoid bias and an increased risk of data-driven false-positive findings (21).

A nomogram was developed to illustrate the effect size of factors. Hypothesis testing was performed on exploratory two-sided 5% significance levels.

Of note, our main research goal was identification and effect estimation of potential risk factors rather than hypothesis testing. Moreover, the current study design did not allow for sample size calculation and thus might not have been adequately powered to test the multiple null hypotheses that the respective regression coefficients are zero.

All analyses were performed using the statistical software R 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria).

# RESULTS

## Factors Associated With Prior Stroke

Patient baseline characteristics are shown in **Table 1**. CS patients with prior stroke were significantly older (64.8 ± 10.8 vs. 53.3 ± 14 years), showed a higher body-mass-index (BMI, 27.8 ± 4.9 vs. 25.7 ± 4.5), were more likely to suffer from hypertension (59 vs. 32%), diabetes mellitus (19 vs. 6%), hypercholesterolemia (72 vs. 49%), and coronary artery disease (11 vs. 5%) and had a higher portion of right-to-left shunt (RLS) at rest (43 vs. 28%) compared to those with first-ever stroke. Adjusting for age, the odds ratio for these factors in the univariable model was 1.07, 1.09, 2.93, 3.37, 2.67, 2.57, and 2.00 for RLS at rest, respectively (**Table 2**). As expected, patients with prior stroke were frequently on antithombotic (72 vs. first-ever stroke 12%), antihypertensive (51 vs. 23%) and lipid lowering drugs (49 vs. 10%; all $p < 0.0001$).

The pre-specified multivariable logistic regression (**Table 3**) demonstrated that prior stroke was strongly associated with advancing age (OR 1.06, 95%CI 1.04–1.10, $p < 0.001$), RLS at rest (OR 1.88, 95%CI 1.00–3.47, $p = 0.046$), hypercholesterolemia (OR 1.90, 95%CI 1.00–3.73, $p = 0.055$) and BMI (OR 1.06, 95%CI 0.99–1.13, $p = 0.074$), reaching statistical significance for age

**TABLE 2 |** Association of baseline characteristics with prior stroke–univariate analysis (missing values were imputed).

| Predictor variable | OR | 95% CI | *P*-value |
|---|---|---|---|
| Age, years | 1.07 | 1.05–1.10 | < 0.001 |
| Male gender | 0.86 | 0.48–1.52 | 0.617 |
| Body-mass-index | 1.09 | 1.03–1.14 | 0.002 |
| Hypertension | 2.93 | 1.67–5.25 | < 0.001 |
| Diabetes mellitus | 3.37 | 1.51–6.96 | 0.002 |
| Hypercholesterolemia | 2.67 | 1.47–5.10 | 0.002 |
| Smoking | 0.73 | 0.35–1.40 | 0.365 |
| Migraine | 0.80 | 0.38–1.53 | 0.519 |
| Coronary artery disease | 2.57 | 0.93–6.11 | 0.045 |
| Aortic plaque | 2.32 | 0.53–7.26 | 0.192 |
| Valsalva maneuver | 0.22 | 0.01–1.04 | 0.138 |
| Deep vein thrombosis | 1.77 | 0.51–4.74 | 0.304 |
| Pulmonary embolism | 0.85 | 0.05–4.37 | 0.879 |
| Right-to-left shunt at rest | 2.00 | 1.12–3.53 | 0.017 |
| Atrial septal aneurysm | 1.18 | 0.65–2.10 | 0.568 |

*OR, odds ratio; CI, confidence interval.*

**TABLE 1 |** Baseline demographic, clinical and imaging data (missing values were imputed).

| | First-ever stroke *n* = 635 | Missing values | Prior stroke *n* = 53 | Missing values | *P*-value |
|---|---|---|---|---|---|
| Age, years | 53.3 ± 14.0 | – | 64.8 ± 10.8 | – | <0.001 |
| Male gender | 262 (41.3) | – | 20 (37.7) | – | 0.722 |
| Body mass index | 25.7 ± 4.5 | 29 | 27.8 ± 4.9 | 2 | 0.003 |
| Hypertension | 206 (32.4) | 1 | 31 (58.5) | – | <0.001 |
| Diabetes mellitus | 41 (6.5) | 2 | 10 (18.9) | – | 0.003 |
| Hypercholesterolemia | 309 (48.7) | 20 | 38 (71.7) | 2 | 0.002 |
| Smoking | 168 (26.5) | 16 | 11 (20.8) | 2 | 0.456 |
| Migraine | 157 (24.7) | 34 | 11 (20.8) | 4 | 0.631 |
| Coronary artery disease | 30 (4.7) | 8 | 6 (11.3) | 1 | 0.050 |
| Aortic plaque | 16 (2.5) | – | 3 (5.7) | – | 0.174 |
| Valsalva maneuver | 51 (8.0) | 57 | 1 (1.9) | 4 | 0.169 |
| Deep vein thrombosis | 27 (4.5) | 31 | 4 (7.7) | 1 | 0.298 |
| Pulmonary embolism | 14 (2.3) | 28 | 1 (1.9) | 1 | 1.000 |
| Right–to–left shunt at rest | 176 (27.7) | – | 23 (43.4) | – | 0.024 |
| Atrial septal aneurysm | 215 (33.9) | – | 20 (37.7) | – | 0.674 |
| **Medication on admission** | | | | | |
| Antithrombotic therapy | 77 (11.9) | | 38 (71.7) | | <0.001 |
| Antiplatelet | 66 | | 35 | | |
| Oral anticoagulation | 11 | | 3 | | |
| Antihypertensive drugs | 145 (22.5) | | 27 (50.9) | | <0.001 |
| Lipid lowering drugs | 65 (10.1) | | 26 (49.1) | | <0.001 |

*Values are mean ± SD or n (%).*

**TABLE 3 |** Association of baseline characteristics with prior stroke–multivariable analysis (pre-specified, missing values were imputed).

| Predictor variable | OR | 95% CI | *P*-value |
|---|---|---|---|
| Age, years | 1.06 | 1.04–1.10 | < 0.001 |
| Male gender | 0.78 | 0.41–1.46 | 0.446 |
| Body-mass-index | 1.06 | 0.99–1.13 | 0.074 |
| Hypertension | 1.06 | 0.53–2.11 | 0.872 |
| Diabetes mellitus | 1.45 | 0.58–3.42 | 0.413 |
| Hypercholesterolemia | 1.90 | 1.00–3.73 | 0.055 |
| Smoking | 1.35 | 0.61–2.82 | 0.439 |
| Valsalva maneuver | 0.28 | 0.02–1.39 | 0.218 |
| Deep vein thrombosis | 1.76 | 0.46–5.44 | 0.361 |
| Right-to-left shunt at rest | 1.88 | 1.00–3.47 | 0.046 |
| Atrial septal aneurysm | 0.98 | 0.51–1.84 | 0.959 |

*OR, odds ratio; CI, confidence interval.*

and RLS at rest. Moreover, the presence of a DVT (OR 1.76, 95%CI 0.46–5.44, $p = 0.361$) as well as an absent VM just before stroke onset (OR 0.28, 95%CI 0.02–1.39, $p = 0.218$) also hinted at a strong association with prior stroke, but was not statistically significant in this cross-sectional analysis.

Considering the weight of each predictor variable in the pre-specified multivariable model, reflected by its Odds Ratio, we developed a nomogram to illustrate the strength of each relation to prior stroke (**Figure 1**). Accordingly, age, BMI, hypercholesterolemia, RLS at rest, absence of VM directly preceding stroke onset and the presence of a DVT are the main factors associated with stroke recurrence.

For example, a 55-year-old (+40points) female (+10p) CS patient with PFO and an RLS at rest (+27.5p), BMI 30 kg/m$^2$ (+50p), presence of VM just before stroke onset (0p), sonographic proof of ASA (0p) and DVT (+25p), known hypercholesterolemia (+27.5p), no arterial hypertension (0p) or diabetes (0p) and non-smoker (0p) sums up to a total of 180 points, which corresponds to a likelihood of 7–8% that this women belongs to the patient group with prior stroke.

## DISCUSSION

The present analysis revealed associations of prior stroke with both PFO-related and -unrelated risk factors. Our study gives a novel insight into the nature and strength of the relationship of previous strokes at presentation and PFO.

Previous clinical and/or radiological stroke at presentation has been associated with higher risk of stroke recurrence in some studies (18) but not in others (22). In addition, recent data suggest that only CS patients with PFO in the high Risk of Paradoxical Embolism (RoPE)- Score strata, i.e., absence of classical vascular risk factors such as hypertension, diabetes mellitus and advancing age show an association of prior stroke with stroke recurrence (15). Age might play a dual role in the pathogenesis of stroke recurrence—both as a PFO-unrelated and PFO-related factor. It is usually considered a stroke risk factor that operates through PFO-unrelated pathogenic mechanisms. The increasing prevalence of classical vascular risk factors in older patients and the fact that stroke recurrence after PFO closure was higher in patients > 55 years of age than in younger patients underlines the relevance of PFO-unrelated contributors to stroke recurrence (23, 24). On the other hand, age might also increase the PFO-related stroke risk by prolonging the exposure time to Right-to-Left-Shunt. Prothrombotic conditions like endothelial damage, hypercoagulability, chronic inflammation, and venous stasis due to decreased regular exercise, which may not be addressed during routine stroke workup or may even be undetectable, accumulate with age and can predispose to paradoxical embolism in the long term (25).

The association of PFO-related factors with stroke recurrence has never been reliably established. Large PFOs have been positively associated with stroke recurrence in some studies (26–28) but not in others (14, 15, 29–31). The recent CLOSE and DEFENSE trials (7, 9) enrolled carefully selected cryptogenic stroke patients with large PFOs or concomitant atrial septal aneurysm. The studies showed that PFO closure was more efficacious in reducing the risk of stroke recurrence than antithrombotic treatment alone. The GORE-REDUCE trial included predominantly patients with moderate to large RLS and likewise demonstrated the superiority of PFO closure over medical treatment alone in preventing recurrent stroke (8). In addition, recent meta-analyses of RCTs comparing percutaneous PFO device closure with medical therapy in CS patients further support device closure in patients with certain PFO characteristics in particular moderate to large shunts (32, 33). Since PFO closure cannot prevent strokes of other possible etiologies, the findings of the above studies further emphasize the role of PFO-related factors in the pathogenesis of stroke recurrence.

Although our data suggest a strong association of prior stroke with conditions predisposing to paradoxical embolism such as DVT (OR 1.76) and VM directly preceding stroke onset (OR 0.28), the evidence is currently weak (DVT $p = 0.361$, VM $p = 0.218$) and needs confirmation in prospective, adequately powered trials. Briefly, the prevalence of DVT in the lower extremities, which was systematically captured in our database, was 4.4% in patients with first-ever stroke and 7.6% in patients with prior stroke. The findings are in keeping with the results of previous studies (34). However, we did not assess the prevalence of pelvic vein thrombosis in all patients. Paradoxical emboli originating from the pelvis have been recognized as an alternate source of stroke in this population (35). The missing data on pelvic vein thrombosis as well as the cross sectional study design may have obfuscated a statistical significant association between DVT and prior stroke.

VM at stroke onset was associated with a 72% reduced likelihood of a previous ischemic event. This could be best explained by the fact that VM increases RLS volume and supports a causal relationship between stroke and PFO, i.e. the stroke is most likely attributable to the PFO. PFO attributable strokes in turn demonstrated a low recurrence rate (36).

In terms of PFO-unrelated factors, our study identified hypercholesterolemia (OR 1.90, $p = 0.055$) and higher BMI

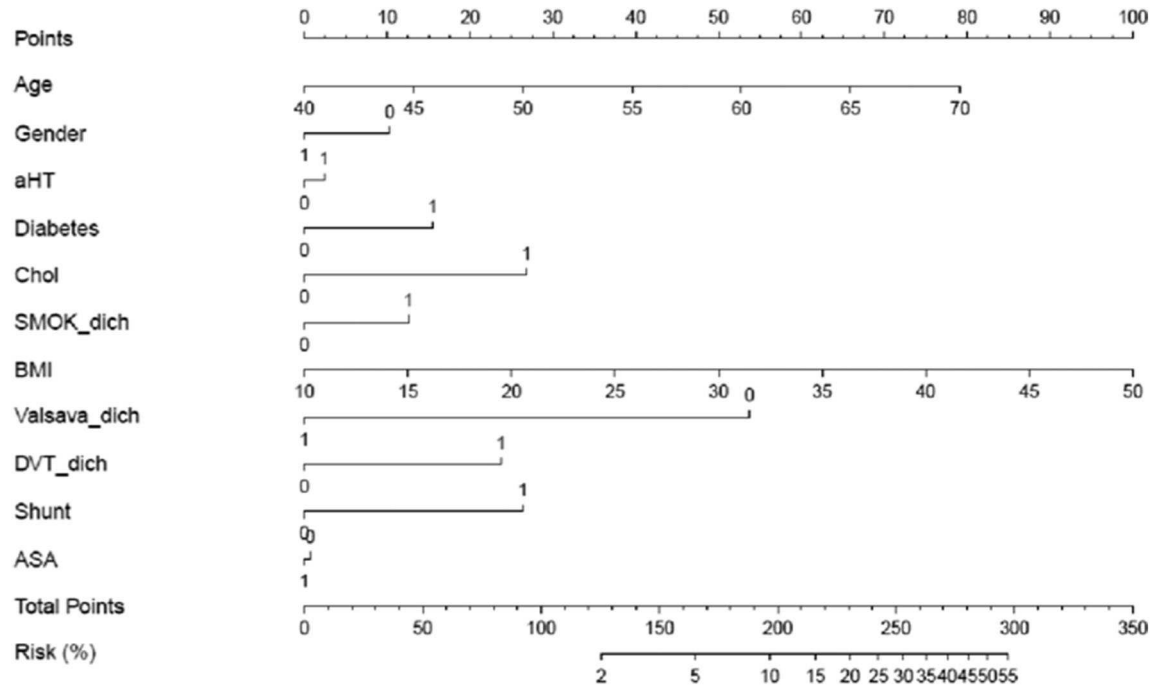


**FIGURE 1 |** Nomogram: Likelihood of prior stroke in patients with cryptogenic stroke and PFO. Draw a line up perpendicular from the corresponding axis of each predictor variable to the top line labeled "points." Sum up the number of points for all predictor variables to receive "total points. Now, draw a line descending from the "Total Points" axis until it intercepts the "Risk (%)" axis to estimate the likelihood of prior stroke.

(OR 1.06, $p = 0.074$) as being strongly associated with prior stroke, albeit not adequately powered to demonstrate statistical significance. Hyperlipidemia, especially an elevated ratio of ApoE/A1 or non-HDL/HDL levels, are known risk factors for ischemic stroke (37). Lipid-lowering drugs are firmly established in secondary stroke prevention (38). Just recently, it was shown that lowering LDL-levels below 1.8 mmol/l after stroke/TIA reduces the risk of a subsequent cardiovascular event compared to higher target LDL-levels (39), and the new ESC-guidelines recommend even lower LDL-levels in selected high-risk patients (40).

Several observational studies point to a lower rate of stroke recurrence in overweight or obese patients (41–44). However, recent studies in stroke patients receiving intravenous thrombolysis or patients with mild symptoms did not detect this relationship, thus challenging the "obesity paradox" (45, 46). Obesity was more common among patients with multiple CS and PFO in a single study, though the recurrence risk was not independently associated with BMI (18). Given these controversial findings, the impact of BMI on stroke recurrence needs further elucidation. Particularly in CS patients with PFO, elevated BMI and the presence of obstructive sleep apnea (OSA) might play a relevant role. Just recently, the coexistence of PFO and OSA in overweight men was suggested as a risk factor for wake-up stroke (47). Moreover, prolonged OSA episodes promoted RLS occurrence during sleep, which might increase the exposure time for paradoxical embolism (48).

The present study is limited by the missing assessment of OSA and other potentially high-risk PFO characteristics such as the presence of an Eustachian valve, a Chiari network or left atrial enlargement (49). In addition, the International PFO consortium study did not collect data on history of migraine stratified into those with aura or without. Furthermore, in patients with prior stroke, the PFO features were assessed at the time of the recurrent stroke only (i.e., at study enrollment). However, it is very unlikely that shunt size or presence of ASA would have changed substantially over time. Third, the process of screening for PFO across the 19 participating stroke centers was not standardized and thus might differ. Fourth, the effect of age cannot be separated from the time-dependent stroke risk. Therefore, age was mainly considered a confounder to allow adjusted effect estimation of other risk factors considered in the models.

Finally, we developed a nomogram to better illustrate the effect size of each risk factor and to easily estimate the probability of having suffered from a prior ischemic event at the time of the index stroke. Several studies suggest that prior stroke might also be associated with stroke recurrence (50, 51). Due to the cross sectional design of our study, we are currently not able to firmly establish those factors as risk factors for future events. However, the present study allows to identify promising "risk factor" candidates for recurrent stroke to be then tested in a longitudinal study design.

## CONCLUSION

In CS patients with PFO, RLS at rest, hypercholesterolemia and higher BMI were strongly related to prior stroke. The likelihood of prior stroke is associated with both, PFO-related and -unrelated factors. Based on the present findings, the impact of these factors on stroke recurrence in CS patients with PFO need to be further established in a longitudinal study design now.

## DATA AVAILABILITY STATEMENT

Data that is not available with the article will be provided in an anonymized form by the corresponding author upon reasonable request from any qualified investigator (subject to the provisions of the IRB).

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission Nordwest- und Zentralschweiz (EKNZ 2014-031). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

TK, M-LM, and KN contributed conception and design of the study. AH performed the final statistical analysis. TK and KN drafted the manuscript and all authors critically revised it for important intellectual content. All authors substantially contributed to the acquisition, analysis or interpretation of data and approved the final version of the manuscript.

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# Patent Foramen Ovale in Cryptogenic Ischemic Stroke: Direct Cause, Risk Factor, or Incidental Finding?

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Patent foramen ovale (PFO) has been associated with cryptogenic stroke. There is conflicting data and it remains uncertain whether PFO is the direct cause, a risk factor or an incidental finding. Potential stroke mechanisms include paradoxical embolism from a venous clot which traverses the PFO, *in situ* clot formation within the PFO, and atrial arrhythmias due to electrical signaling disruption. Main risk factors linked with PFO-attributable strokes are young age, PFO size, right-to-left shunt degree, PFO morphology, presence of atrial septal aneurysm, intrinsic coagulation-anticoagulation systems imbalance, and co-existence of other atrial abnormalities, such as right atrial septal pouch, Eustachian valve and Chiari's network. These may act independently or synergistically, multiplying the risk of embolic events. The RoPE score, a scale that includes factors such as young age, cortical infarct location and absence of traditional stroke risk factors, is associated with the probability of a PFO being pathogenic and stroke recurrence risk after the index stroke. Multiple investigators have attempted to correlate other PFO features with the risk of PFO-related stroke, but further investigation is needed before any robust conclusions are reached. PFO presence in young patients with cryptogenic stroke should be considered as etiologically suspect. Caution should be exercised in interpreting the relevance of other PFO features.

**Keywords: ischemic stroke, cryptogenic stroke, patent foramen ovale, atrial septal defect, right-left shunt, paradoxical embolism**

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## INTRODUCTION

The atrial septum is formed during the embryogenesis by two membranes growing from the atrial walls (septum primum and septum secundum), leaving an oval shaped fenestration (foramen ovale), which serves the right-to-left shunt (R-L shunt) of the fetal circulation (**Figure 1**). The foramen ovale is sealed during the first year of life by the fusion of the two membranes. The failure of this process leads to an interatrial slit-like channel, the patent foramen ovale (PFO) (1–3) (**Figure 1**). PFO is considered to be a subclass of ostium secundum defects (4). Other atrial septal defects include ostium primum defects, sinus venosus defects and coronary sinus defects. The size and morphology of the defect is individualized, depending on the structures which are involved (4).

PFO is present in ∼25% of the general population, tending to decline with increasing age, and is the most frequent cause of R-L shunt in adults (2, 5–7). Although most of the times PFO is "innocent," it has been associated with cryptogenic stroke (CS), migraine, peripheral embolism, and Alzheimer's dementia (1). The link between PFO and stroke was first described by Cohnheim

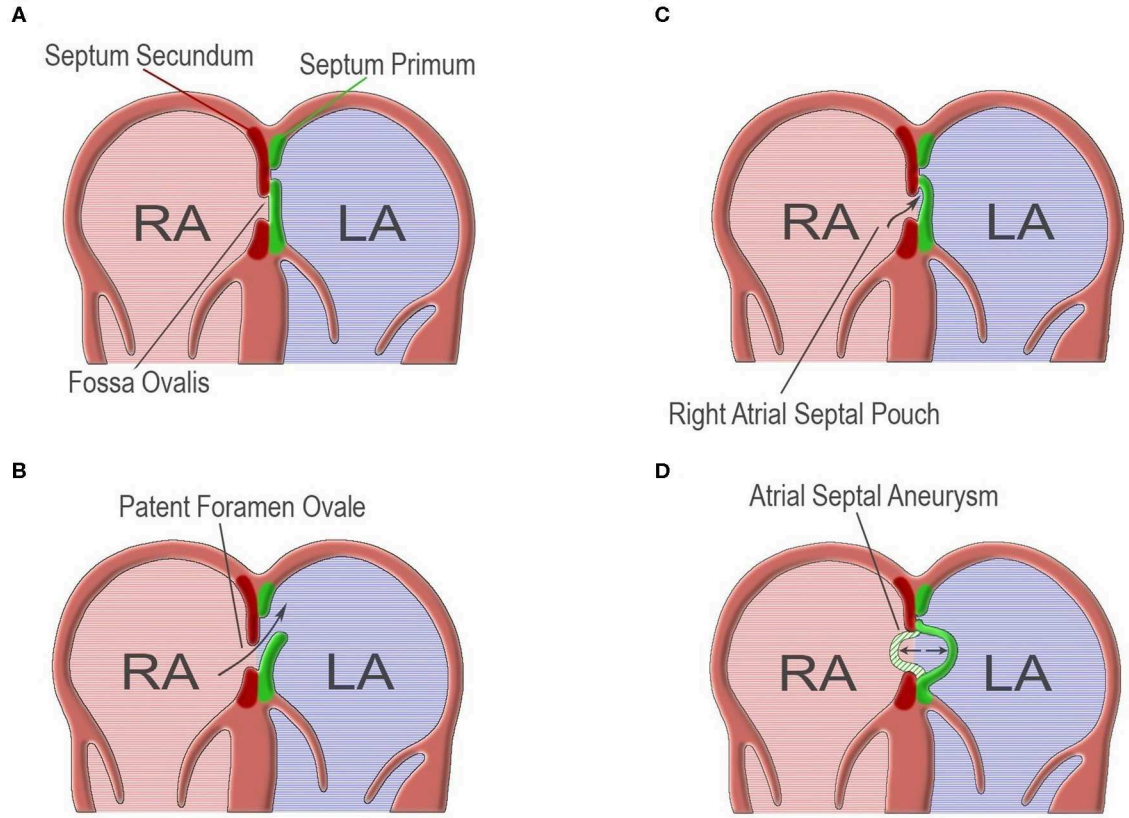


**FIGURE 1 | (A)** Normal atrial septum which results from the fusion of septum primum and septum secundum. **(B)** Failure of fusion of septum primum and septum secundum, leading to patent foramen ovale. **(C)** Right atrial septal pouch, resulting from malformation of atrial septum forming a blind-end socket. **(D)** Atrial septal aneurysm, the result of a hypermobile atrial septum. (Design and courtesy of Mr. Fotis G. Ioannidis).

in 1877 (8), and since then, a strong association has been established. The high PFO prevalence in the CS population (about 50%, 2-fold when compared with stroke patients of known cause) cannot be overlooked (5, 9).

The population affected by PFO-related embolic events is mostly young, and although the annual recurrence risk is relatively low, it tends to aggregate to a non-negligible total rate (6, 10). On the other hand, many PFOs in stroke patients represent incidental findings (11). Thus, it is essential to determine the high risk features of PFOs, as only PFO-related CS patients will potentially benefit from a PFO-closure procedure (6, 12, 13).

## PFO AND STROKE

CS comprises 15–40% of all ischemic strokes, and PFO occurs in 40–56% in patients <55 years old with CS or transient ischemic attack (TIA) (6, 12, 14). One has to distinguish between PFO being a direct cause of stroke and PFO being a risk factor for stroke. The relevant literature indicates that the strength of the association between PFO and stroke depends on the type of study. The role of PFO as a risk factor for ischemic stroke has mainly been demonstrated in case-control studies. In one of the original case-control studies, an ∼4-fold increase in PFO prevalence in stroke patients younger than 55 years and an ∼2-fold increase in older patients compared with controls of similar age was demonstrated (15). In a robust meta-analysis of case-control studies, Overell et al. reported an OR of 3.1 for PFO, 6.14 for atrial septal aneurysm (ASA), and 15.59 for PFO combined with ASA, when the examined population was younger than 55 years (16). On the contrary, the role of PFO as a risk factor for stroke and vascular events in the general population has not been demonstrated with certainty. Most studies suffered from inadequate sample sizes or short follow-up durations which may have masked possible associations. Di Tullio et al. (17) reported the results of a population study in which they followed a community cohort of asymptomatic individuals with and without PFO for an average of 11 years, and demonstrated that PFO was not associated with an increased risk of clinical stroke or silent brain infarcts (17).

Some PFOs likely are incidental findings. When they are pathogenic, it is still debatable whether they represent a risk factor for stroke or the true cause (5, 6). Moreover, the precise mechanism by which PFO causes a stroke is uncertain. Several PFO characteristics have been reported as high-risk features, such as hypermobile atrial septum, R-L shunt grade, R-L shunt at rest,

as well as non-PFO features, as young age and the coexistence of other atrial septal abnormalities (1, 16, 18).

## POTENTIAL STROKE MECHANISMS IN PFO

### Paradoxical Embolism

The most acceptable hypothesis currently is that of paradoxical embolism (19, 20). This phenomenon requires a venous thrombus to travel through a R-L shunt and cause arterial embolism (5, 6). This hypothesis is supported by studies reporting the PFO size and R-L shunt grade as risk factor for CS, case reports of thrombi stuck in PFO tunnel, and CS following deep venous thrombosis (DVT) (5, 19).

However, paradoxical embolism cannot stand as the only possible explanation (21). The existing data do not support an increased incidence of DVT or Valsalva-like activities prior to CS as compared to non-PFO CS patients, and a venous source of embolism is rarely identified (22). Moreover, some studies report increased risk of recurrence associated with smaller shunts (13). Thus, additional or alternative explanations are in order, perhaps related to PFO characteristics (18).

### *In situ* Clot Formation

Accumulated data support the notion that PFO is liable for *in situ* thrombus formation (13, 20–22). This hypothesis is empowered by the fact that specific features, such as long-tunneled PFO, concomitant presence of ASA or Chiari's network, increase the risk of stroke (1, 23–25). These findings do not favor the paradoxical embolism hypothesis, but the deceleration of flow, blood stagnation and thrombi formation within the PFO or ASA (20, 26).

Rigatteli et al. reported observations from computational anatomical models where he noted a pathologic pattern of left atrial (LA) blood flow due to permanent R-L shunt (27). Furthermore, a prospective study comparing pre-closure PFO patients with atrial fibrillation (AF) patients and healthy individuals, claimed that moderate-to-severe ASA was correlated with LA dysfunction (active and passive emptying, conduit function, LA ejection fraction), which reversed after PFO closure (28). These very interesting findings suggest LA dysfunction and AF-like flow, forming thrombi in the absence of the arrhythmia. Moreover, LA size has been correlated with ASA presence, multiple ischemic lesions and the RSL degree; LA diameter $\geq$43 mm and RoPE score>7 were significantly associated (29). Questions are also raised regarding the involvement of other R-L shunt sites (25).

### Arrhythmias

A very attractive hypothesis, supported by several authors, claims that embolic events in PFO are caused by atrial tachyarrhythmias and/or paroxysmal AF, especially in the presence of a hypermobile atrial septum (22, 30–33). Indeed, 20–42% of PFO and/or ASA patients are considered to have AF or atrial flutter (31).

The term of atrial vulnerability describes the electrophysiological trend to induce AF. Berthet et al. reported that inducible AF longer than 60 s in duration and abnormalities of effective refractory periods and atrial conduction time, were present in 58% of patients with PFO and/or ASA, as compared to 25% of patients without (31). Moreover, Cotter et al. reported increased interatrial block and atrial vulnerability in young CS patients with PFO; cases were also found to have longer P-wave duration, and proposed that stretch or pressure on the atrial septum is the causative mechanism (34).

It is believed that each one of the above mechanisms exists and that their synergistic action results in cumulative outcomes.

## AGE

Several studies support that one of the most powerful markers of a non-incidental PFO in stroke patients is young age, usually defined as age $\leq$ 55 years (1, 16, 35, 36). The incidence of PFO in the stroke population tends to decrease with increasing age (0–30 years: 34.3%, 30–80 years: 25.4%, 90–100 years: 20.2%),while other more traditional stroke risk factors, such as hypertension, dyslipidemia, smoking, and arrhythmias increase (2, 5, 22). The latter factors are also less frequent in populations with PFO-attributable embolic events (22).

In a meta-analysis, Overell et al. reviewed the literature with an eye toward the three-way association between PFO, CS and age heterogeneity of study populations, and concluded that when older patients were included, the strength of the correlation between PFO and CS was rather low (16). Specifically, when comparing stroke patients with controls, the positive association of PFO with CS was a function of younger age of the population (mean age of 44.8 years), while in the older population (mean age of 61.1 years) this association was not present (16). A similar pattern was detected when comparing CS to patients with stroke of known cause or healthy individuals (16, 35). Another meta-analysis reported similar findings, with OR of 5.1 for association of PFO with CS in young patients, while the association was weaker (OR: 2.0) for patients older than 55 years (36). According to these data, the presence of PFO in young CS patients should be strongly considered as etiologically suspect (16).

Nevertheless, it is worth noting that PFO-attributable strokes do occur in older patients as well, although data are scarce and further investigation is needed (24, 37). The population-based study of Mazzucco et al. is in line with this statement, and suggests transcranial Doppler testing as a feasible and cost-effective screening (38).

## HIGH-RISK ANATOMICAL FEATURES OF PFO

### Size

PFO diameter ranges from 1 to 19 mm, and tends to grow larger with advancing age (1, 2). Although PFO diameter is well established as a risk factor, the existing data are conflicting due to inter-operator variability and differences in the estimation methodology. It is worth mentioning here that the number of microbubbles crossing the atrial septum is not a reliable way for assessing the anatomic size of the PFO (18).

In most studies, size is an independent risk factor for stroke occurrence and recurrence (1, 5, 39, 40), with OR of 2.54 when the size is ≥2 mm (41). Moreover, CS patients tend to have larger PFOs, when compared to stroke patients of other known causes (13, 36). The impact of size on TIAs seems to be weaker (11).

On the other hand, some studies demonstrated that large PFOs were associated with increased risk for the index event or its severity, while smaller PFOs were associated with the risk of recurrence, indicating different pathophysiological mechanisms of embolism (13, 14).

## Shunt Degree

PFO may prevent shunting if its morphology favors a sufficient valvular mechanism; otherwise, it allows a shunt of varying degree (1, 3). The shunt is best estimated by transesophageal echocardiography. Transcranial doppler testing is highly sensitive but detects any R-L shunt, which includes intracardiac and extracardiac locations (1, 5). As for the transthoracic echocardiography, it is believed that it is more specific but less sensitive in detecting PFO, in comparison to transcranial Doppler ultrasonography (42).

Shunt degree is not defined exclusively by PFO size; (11) on the contrary, the right-left atrial pressure difference is one of the main factors affecting the degree of the shunt. For example, pulmonary hypertension favors patency of foramen ovale (2), while mitral regurgitation, left atrial dilatation, and left ventricular hypertrophy can raise the LA pressure and diminish the R-L shunt degree (43).

R-L shunt can be detected in up to 100% of patients with PFO and history of embolism; 10% of PFO-related CS have large-degree R-L shunt (44, 45). The shunt degree is significantly associated with stroke risk (both for index or recurrent event), as well as with TIA and migraines, while asymptomatic PFOs tend to be smaller (1, 9, 25, 36, 39, 41, 43). The incidence of stroke may be higher in the presence of significant shunt at rest (1). Moreover, smaller R-L shunts have been associated with greater recurrence risk (1, 13, 35, 46). It is also interesting that echocardiography features may predict recurrence risk only in those patients with higher RoPE scores (for RoPE score analysis, please, see below) (13). It has been suggested that when the RoPE score is ≥7 the presence of hypermobile interatrial septum and smaller shunts are predictive of stroke recurrence; if these data is confirmed, then we can consider that paradoxical embolism is responsible for only a fraction of the PFO-associated strokes, and that additional potential pathogenic mechanisms exist (13).

Interestingly, some studies report that the degree of R-L shunt is similar in PFO-related and other etiology stroke patients, and that it is not linked with risk of recurrence (18, 20). Nevertheless, one should keep in mind that shunt degree is a dynamic variable which can change because of pressure changes in the cardiac chambers, patient cooperation during the exam and operator's skills, indicating that its reliability and significance in clinical practice may be limited (18, 47). Moreover, the variability and controversies in the existing literature can be explained by the differences of the definitions of degree of R-L shunt and also of the population under study.

## Morphology

Other potentially high-risk features of PFO are: PFO length, tunnel-like morphology, height, thick fossa ovale rims, and low-angle PFO (14, 35, 41). Unfortunately, data are scarce, usually are the result of rather small studies, and often are conflicting.

One of the high-risk characteristics is the distance between septum primum and septum secundum, often named "PFO height." Some studies demonstrated increased embolic risk when the separation of the two membranes is large. Other studies report increased risk when the overlap between septum primum and septum secundum, often named "PFO length," is deficient (25, 35, 43). Tunnel-like morphology, defined as ≥8–10 mm in length, was also reported as a high-risk factor, with OR for CS in the region of 2.66 ($p = 0.017$) (1, 25, 35, 41). The discrepancy of whether a longer or shorter PFO is associated with embolic events may indicate differences in pathogenetic mechanisms.

Although the thickness of fossa ovale rims has not been linked with definite embolic risk, excessive thickness can be associated with poor closure devise stability (35).

Finally, the angle of PFO in relation to the inferior vena cava has been associated with the embolic risk. More specifically, a low-angle PFO (≤10°) corresponds to OR 3.74 ($p = 0.029$) for CS (41).

The above statements are made with a sense of caution as other studies failed to confirm these results (48).

# ATRIAL SEPTAL ANEURYSM

Atrial septal aneurysm (ASA) is an excursion of a hypermobile interatrial septum, which floats to either direction in the atria, and involves septum segments of variable size (5, 33) (**Figure 1**). Wide heterogeneity exists in the literature because of differences in the definition of ASA and study populations (16). The prevalence of ASA in the general population is 1–4% (15). Usually, ASA is combined with PFO (60–89%), and when it does, PFO tends to be of larger size (20, 40, 49). Several other abnormalities have been correlated with ASA, such as atrial septal defects and mitral valve prolapse (24, 33).

ASA is associated with increased stroke risk, especially in the presence of PFO, and is considered a stronger risk factor than PFO (5, 16, 24, 41, 50, 51). The incidence is even higher in younger patients and those with PFO-attributable stroke (16, 52). Moreover, atrial septal hypermobility has been identified as an independent predictor of embolism recurrence, and the risk rises by two to three times when it coexists with PFO (1, 11, 39, 46). Interestingly, the risk of recurrence for stroke or TIA within 4 years after the initial event was estimated at 19.2% for PFO combined with ASA vs. 5.6% for PFO alone (20). Furthermore, when PFO and ASA co-existed the OR for stroke was 4.96, compared with 1.83 for PFO or 2.35 for ASA in isolation (16). The risks seem to apply to older patients as well (37).

Besides the synergistic action of PFO and ASA, there is a size-dependent effect of ASA on stroke risk. Cabanes et al. reported that in young patients the OR for stroke was 8.5 when the ASA excursion was >10 mm, and only 1.2 for excursion 6–10 mm (26). A small study comparing symptomatic and asymptomatic ASA

reported median excursion of 7 mm in the patients group, in contrast to 4 mm in the healthy individuals group (14). Similar differences were also found in other studies, but these findings needs further investigation and validation (11).

It is important to mention here that in the general population ASA is associated with increased stroke risk, but the relative risk is still low, and therefore screening tests for asymptomatic individuals are not recommended (15).

## OTHER ATRIAL ABNORMALITIES

Several other atrial structural abnormalities have been considered to be associated with PFO and increased embolic risk, such as right atrial septal pouch (RASP), prominent Eustachian valve or ridge and Chiari's network (1, 23).

### Right Atrial Septal Pouch

Right atrial septal pouch (RASP) is a sack-shaped atrial septal malformation, detected on either side of the septum (1) (**Figure 1**). Scarce data propose RASP as a cause of blood flow disturbance and embolus formation, and there is coexistence with PFO arterial embolic events may occur (1).

### Eustachian Valve and Chiari's Network

Eustachian valve and Chiari's network are fetal features that interfere with the normal embryonic R-L shunt (1). Eustachian valve co-occurrence with PFO is estimated at 70%, while Chiari's network is related with PFO in 83% of cases (5).

While both can represent incidental findings, they have also been recognized as stroke risk co-factors in the presence of PFO (25, 40, 41). In particular, in a retrospective study, the OR for Eustachian valve or Chiari's network as factors related to CS was 4.47 in univariate analysis ($p = 0.002$) and 4.71 in multivariate analysis ($p = 0.009$) (41).

### Hybrid Defects

The term "hybrid defects" refers to a group of heterogeneous atrial septal abnormalities associated with PFO. (1) These combinations include ostium primum, ostium secundum, sinus venosus, and coronary sinus defects (5). Theoretically, all may result in paradoxical embolism, but their exact role and stroke risk associated with them still remain undetermined.

## VENOUS THROMBOSIS

Because paradoxical embolism is considered as one of the main mechanisms of PFO-related stroke, a clot in the venous system or conditions predisposing to venous clots are usually sought for. Deep venous thrombosis (DVT), pelvic vein thrombosis and hypercoagulable states are considered as risk factors for PFO-related stroke (35, 40).

In a rather small study increased incidence of lower extremity DVT was found in patients with probable paradoxical embolism (53). Similar findings were reported in a study of a young CS population (54). Moreover, DVT was associated with strokes >3 cm in diameter (55). Conditions such as immobilization, anesthesia, surgery and pregnancy prior to stroke events were found more often in CS patients with PFO (4.5 vs. 1.6%, $p = 0.05$) (22). However, other studies are not in line with these data, and claim that the source of venous thrombi is rarely detected (11, 40, 56). Of course, the discrepancy in the frequency of DVT and the usually low frequency of identifiable DVT among studies addressing PFO-related stroke may be in part due to the late timing of the diagnostic studies of the venous system after the index stroke.

Disruption of the balance of natural coagulation-anticoagulation mechanisms, such as Factor V Leiden mutation or prothrombin gene mutation, is also a co-factor for increased risk of stroke in the presence of R-L shunt. Karttunen et al. report OR 2.8 ($p = 0.021$) for prothrombotic states and 2.5 ($p = 0.037$) for common risk factors for venous thrombosis, in a case-control study of CS in PFO patients, aged 15–60 years (57). An underlying thrombophilia, either inherited or acquired, also predisposes to recurrence of embolism; this risk is decreased with PFO closure (58).

The risk of formation of venous clots seems to interact with age, as older people have more risk factors leading to this process. In the presence of a PFO, paradoxical embolism may occur, and recurrence rates tend to be higher (37, 59).

Of interest is the results of two clinical trials addressing the question of treatment with antiplatelet vs. anticoagulant drugs for second stroke prevention in patients with CS and underlying PFO. In the PICSS (patient foramen ovale in cryptogenic stroke study), a substudy to the WARSS (warfarin vs. aspirin for recurrent stroke study), there was no significant superiority of warfarin anticoagulation over aspirin; there was however a trend of toward warfarin being better than aspirin for secondary stroke prevention in this setting (HR = 0.52, $p = 0.28$); it should be noted that the follow-up period was 2 years (60). From the CLOSE trial, Mas et al. demonstrated that anticoagulants were not superior vs. aspirin for stroke prevention; this arm of the trial was underpowered (61). Based on the above and the knowledge that anticoagulants are the main treatment for venous thromboembolism, the lack of solid evidence that anticoagulants perform better than antiplatelet agents in preventing stroke, despite the methodological problems for each study, could raise suspicion that paradoxical embolism may not be the main or most frequent mechanism of stroke causation in the setting of PFO. Further study on this matter is desperately needed.

## THE ROPE SCORE AND PFO AS AN INCIDENTIAL FINDING

Many authors have attempted to answer which features of a PFO determine whether it is pathogenic or incidental finding in CS patients.

The Risk of Paradoxical Embolism (RoPE) score was designed for this reason, and also estimates the recurrence risk within 2 years after the index event (7). RoPE scale components include age, hypertension, diabetes mellitus, stroke or TIA history, smoking, and neuroimaging (large cortical infarct) to determine a 10-point score (7). Higher RoPE score results from young age, cortical infarcts and the absence of traditional stroke risk

factors; the higher the RoPE score the more likely that a PFO is pathogenic, and is usually associated with lower risk of stroke recurrence (7). RoPE score of 0–3 estimates 0% probability of pathogenic PFO and 20% probability of recurrent event, while a score of 9-10 estimates 88 and 2% probability, respectively (7). As emphasized above, PFO-attributable strokes may have low recurrence risk within the short period of 2 years, but because they occur in young patients, the overall risk within the lifespan of patients may be verysubstantial (6). It is worth noticing that R-L shunt degree, ASA and other PFO high-risk characteristics were not included in the RoPE score variables (47). Furthermore, in cases of stroke of known etiology, the RoPE score loses its prognostic value (7).

The RoPE score is a probability index; thus, low scores cannot exclude with certainty the possibility of PFO-attributable stroke, while higher scores cannot confirm the causative relationship (7, 25). Nevertheless, its efficacy has been tested in clinical practice; the fact that the risk of stroke recurrence was still high after PFO closure in patients with low RoPE score indicates that the stroke mechanism was indeed unrelated to PFO (62). A study in CS patients $\leq$50 years reported that RoPE score above 7 is the optimal limit for identifying a causative relationship of PFO and CS (63). It should be emphasized though, that the RoPE score does not characterize the risk of stroke associated with PFO individually, but it rather provides a guide to define whether the relationship of PFO with CS after the index event is causative or not (6).

Other high-risk echocardiographic features should not be underestimated. Recurrence risk seems to be heterogeneous within each RoPE score strata. Thaler et al. report an increased recurrence risk in patients with high RoPE score, associated with history of stroke or TIA, hypermobile atrial septum and small R-L shunt (13). Moreover, a meta-analysis defined that in the co-existence of ASA the probability of a PFO to be incidental was decreased (9% in younger and 26% in older patients) (36). The same study reported that when using the Bayesian approach one third of all PFOs in CS patients are incidental, and morphologic characteristics may alter these rates (36). A very interesting retrospective cohort study attempted to associate high-risk morphological features of PFO with the probability of CS (41). They identified: (a) long-tunnel PFO $\geq$10 mm, (b) hypermobile interatrial septum, (c) Eustachian valve/Chiari's network, (d) large R-L shunt during Valsalva maneuver, and (e) low-angle PFO $\leq$10°, as high-risk echocardiographic features and assigned one point to each creating thus a 5-point scale. PFO associated with a score $\geq$2 in this scale was strongly linked with CS (41). This study had several limitations, but it sets the basis for further investigation.

## CONCLUSIONS

PFO in stroke patients may represent an incidental finding, a risk factor for stroke occurrence or a robust cause. It is associated with CS through several mechanisms; most theories support paradoxical embolism, *in situ* thrombus formation, and arrhythmogenesis, while other possible, yet unknown, explanations cannot be excluded. Young age, PFO morphological characteristics and factors predisposing to venous thrombosis are essential features to determine a pathogenic PFO. Further investigation is needed in order to identify the role of these characteristics in the stroke pathogenesis.

## AUTHOR CONTRIBUTIONS

SI: review of literature, writing of manuscript draft, review of final draft manuscript. PM: review of literature, critical review of final draft of manuscript. All authors contributed to the article and approved the submitted version.

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OPINION
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# The Heart-Brain Team Approach in Patent Foramen Ovale Closure

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**Keywords: heart team approach, right to left cardiac shunt, stroke, interventional cardiac procedure, heart brain team, PFO closure device, embolic stroke, patent forame ovale**

Modern medicine mandates a multi-disciplinary approach in treating complex diseases. In cardiology, the heart team approach is often applied to the treatment of patients with complex cardiac diseases.

Cardiologists have long been collaborating with other specialists. Oncologists and cardiologists have already merged into a novel sub-specialty called cardio-oncology in treating patients with heart disease and cancer. Vascular surgeons and interventional radiologists have historically competed with cardiologists in treating peripheral artery disease. However, in the current era, a more collaborative environment is becoming more evident. Subspecialty training in medicine has diverged the entire medical field into different modalities with each specialist tackling a very specific disease process. However, these diseases are oftentimes too complex to be managed by a single specialist. To date, stroke in the setting of a patent foramen ovale (PFO) is one of the only few disease processes wherein stroke neurologists and cardiologists closely collaborate.

The history of managing PFO for stroke prevention endured a long and arduous journey. Contradictory opinions by cardiologists and neurologists in managing patients with PFO created an oppositional relationship between the two specialties. This schism was fueled by the conflicting results of multiple randomized clinical trials for percutaneous PFO closure.

The CLOSURE I trial in 2012 and the PC trial in 2013 demonstrated similar, albeit disappointing results. The results showed a non-statistically significant trend toward benefit with closure device for secondary prevention of stroke compared with current medical therapy. These two trials on PFO closure created a profound impact in the United States. Since then, PFO closure was largely forgotten and was not supported by stake holder societies and third party payers (1).

The conflicting results of these trials also created such an impact in the field of neurology that in 2016, the guidelines of the American Academy of Neurology (AAN) discouraged the use of PFO closure for cryptogenic stroke (2).

The relationship gap between stroke neurologists and interventional cardiologists widened after the inconsistent results of the CLOSURE I and PC trial. It also commonly led to frequent debates and difference in opinions between both specialists. On the other hand, patients with PFO and cryptogenic stroke continued to be treated with anticoagulation or antiplatelet therapy without any effective alternative.

After the AAN recommendation, the results of the landmark trials from the RESPECT (long term follow up) and REDUCE trials were released in 2017. Both trials resurrected the use of PFO closure for stroke prevention. Both trials demonstrated superiority of PFO closure device over medical therapy in secondary stroke prevention. The results of both the RESPECT and REDUCE trials ultimately led to the FDA approval of the Amplatzer PFO Occluder (Abbott Structural, Santa Clara, CA) and the Gore Cardioform Septal Occluder (W. L. Gore and Associates, Inc., Newark, DE), respectively.

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Since the 2016 AAN guidelines, there was an overwhelming consensus of the landmark PFO trials on the superiority of PFO closure over medical therapy alone in preventing recurrent ischemic stroke. Four years later, the AAN released a revised advisory regarding PFO closure. It states "*In patients younger than 60 years with a PFO and embolic-appearing infarct and no other mechanism of stroke identified, clinicians may recommend closure following a discussion of potential benefits (absolute recurrent stroke risk reduction of 3.4% at 5 years) and risks (periprocedural complication rate of 3.9% and increased absolute rate of non-periprocedural atrial fibrillation of 0.33% per year)*" (3). The release of this statement is both meaningful and historic. It not only acknowledged the results of the randomized clinical trials but also highlights the continued partnership between neurologists and cardiologists.

After the FDA approval of the two PFO closure devices, as well as the "blessing" of the AAN, it is anticipated that there will be a significant rise in PFO closure procedures in the next several years. However, cardiologists must be vigilant more than ever. Given that PFOs are present in approximately a third of the population, the risks of unnecessary procedures in patients who do not meet the indication for PFO closure should be strongly mitigated. Ensuring the appropriateness and delivery of patient-centered and quality care of our patients is critical. This goal, in our opinion, can only be achieved by the heart-brain team approach.

Patient selection is the single most important variable in effective and safe delivery of PFO treatment. Partnership with neurologists, specifically stroke neurologists, is a critical preliminary step in patient selection. A formal neurological consultation is mandatory prior to any PFO closure. In fact, no patient with PFO and stroke should undergo PFO closure without being evaluated by a stroke neurologist. A thorough evaluation of the possible etiology of stroke should be initiated. A battery of tests should be initiated by either the stroke neurologist or cardiologist including a transthoracic echocardiogram with a bubble study to rule out a right-to-left shunt, a heart rhythm monitor at least for 30 days to rule out atrial fibrillation, hypercoagulable work up, bilateral carotid ultrasound, and Doppler ultrasound to rule out lower extremity venous thrombosis.

Interventional cardiologists and stroke neurologists should borrow the heart team concept. Close collaboration between 2 different specialties in treating patients is not a novel concept in medicine. Cardiologists and cardiothoracic surgeons have long been working together since the inception of angioplasty in patients with coronary artery disease (CAD). The term "heart team" was popularized in the pivotal trial Synergy Between PCI With Taxus and Cardiac Surgery trial (SYNTAX). The SYNTAX trial paved the way for the collaboration between cardiac surgeons and interventional cardiologists in treating complex CAD. Each patient with complex CAD in the modern era is evaluated by an interventional cardiologist and a cardiac surgeon for possible percutaneous stent placement vs. coronary artery bypass graft surgery. As a result, decades of harmonious partnership between interventional cardiologists and cardiac surgeons have ensued. This unique teamwork has treated thousands of patients with complex CAD safely and effectively since the birth of angioplasty.

The efficiency and the success of the heart team approach once again was proven in transcatheter valvular therapies specifically transcatheter aortic valve replacement (TAVR). Historically, since Charles Hufnagel implanted the first artificial aortic valve and Charles Bailey and Dwight Harken performed their open commissurotomy in patients with mitral stenosis, the treatment of valvular heart disease has been exclusively been treated by cardiac surgeons. Now, patients with valvular heart disease are mandated to be seen by cardiothoracic surgeons and by an interventional cardiologist, mostly in an outpatient setting. The valve clinic was designed to deliver care to patients as fast and efficient as possible. A single visit of the patient in the valve clinic is comprised of an independent evaluation of the interventional cardiologist and a cardiac surgeon. After careful deliberation, patients are treated via either transcatheter or surgical therapies. Without question, the heart team approach is a proven concept and is now being used in the current era of transcatheter therapies.

The approach to PFO closure for stroke prevention should not be any different from the heart team concept. However, the clinical complexity of patients with PFO are completely different compared to patients with aortic stenosis (AS) and CAD. While the decision to treat patients with AS or CAD is often not a conundrum, patient selection is key in PFO closure patients. Often, it is very difficult to select patients for PFO closure since cryptogenic stroke is a diagnosis of exclusion. Only when no other etiology of ischemic stroke is evident, then closure may be indicated.

Placing a PFO closure device in a patient who does not meet the indication for closure may have drastic consequences. Prototypical PFO patients are young and healthy with many years or decades ahead of them. An implanted PFO closure device that is not indicated would expose the patient to lifelong risks of an intracardiac foreign body. To mitigate this dilemma, the decision to proceed with closure should not be decided by a single entity. The Society for Cardiovascular Angiography and Interventions (SCAI) expert consensus statement on institutional and operator requirements suggested a multi-disciplinary team composed of a stroke neurologist and an interventional cardiologist (4). The knowledge and expertise of a stroke neurologist in the diagnosis and management of PFO and stroke, especially in young, relatively healthy patients, is essential. Both entities should carefully evaluate patients not only for the indication for the procedure but also for the suitability of the patient even if it is indicated. One important goal of the heart-brain team approach is the avoidance of unnecessary and inappropriate PFO closures. The check and balance system between the two different specialties ensure that only patients with PFO-mediated strokes receive a PFO closure device after careful deliberation.

A strong PFO program must have a very rigorous selection process in order to offer the procedure to those who will benefit the most. Some institutions have already implemented a heart-brain team approach in PFO patients. The proven concept of a valve clinic for TAVR patients may be implemented in a "PFO

clinic." Stroke neurologists, general cardiologists, interventional cardiologists, interventional neurologists, electrophysiologists, hematologists, nurse practitioners, social workers, are some integral members of a heart-brain team. Bringing together expertise in all the fields in the same clinical setting allows complex clinical issues in PFO closure to be seamlessly addressed for the patients and their families in the most efficient and in the shortest amount of time.

SCAI has already established a PFO task force which includes representation from the AAN. This partnership is essential in ensuring the operator and institutional guidelines are thorough, evidence-based, and fair to both societies. Together, both societies with their members, can deliver safe and effective treatment to patients in the spirit of patient-centered care. Previously labeled as adversaries, stroke neurologists and interventional cardiologists are now considered invaluable partners in treating PFO-mediated strokes.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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# Left Atrial Function in Young Patients With Cryptogenic Stroke and Patent Foramen Ovale: A Left Atrial Longitudinal Strain Study

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**Background:** The study of left atrial (LA) longitudinal strain by speckle tracking is a reliable method for analyzing LA function that could provide relevant information in young patients with cryptogenic stroke (CS). The aim of this study was to investigate whether the presence of a patent foramen ovale (PFO) impacts the LA longitudinal strain in a population of young patients with first CS.

**Methods and Results:** Patients aged 18 to 54 years, treated consecutively in a university hospital for first CS, were included in this study. The presence of a PFO and an atrial septal aneurysm (ASA) was investigated using transesophageal echocardiography and transcranial Doppler. Speckle tracking analysis was performed on transthoracic echocardiography, allowing the measurement of global, passive, and active longitudinal LA strain, corresponding to the reservoir, conduit, and contractile function, respectively. A total of 51 patients were included in the study. In a multivariable analysis, overweight was associated with reduced global and passive LA longitudinal strain ($P = 0.013$ and $P = 0.018$, respectively), and hypertension was associated with reduced active LA longitudinal strain ($P = 0.049$). LA longitudinal strain was not different between patients with PFO or PFO plus ASA and patients without PFO.

**Conclusion:** LA longitudinal strain in young subjects with CS was impaired in the presence of overweight and hypertension, but not of PFO or PFO plus ASA.

**Keywords: cryptogenic stroke, stroke in the young, patent foramen ovale, left atrial function, speckle tracking**

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## INTRODUCTION

Stroke is far more common in the elderly than in the young. However, recent epidemiological studies have shown that the incidence of stroke is increasing in young subjects (1). The etiological spectrum of stroke in the young is different from those of older subjects. Moreover, between 30 and 50% of strokes in the young are classified as cryptogenic stroke (CS) despite extensive etiological workup (2, 3). Impaired left atrial (LA) mechanical function is one of the possible causes of seemingly CS (4). Impaired LA function may be a factor of blood stasis and thrombus formation (5). A large population-based cohort study showed that impaired LA function was associated withi

incident cerebrovascular events independent of known cerebrovascular risk factors and incident atrial fibrillation (6). Impaired LA function has been associated with age, hypertension, obesity, and diabetes mellitus (7–9). In addition, a few studies have suggested that impaired LA function may be associated with patent foramen ovale (PFO) or atrial septal aneurysm (ASA) in stroke patients (10, 11).

Speckle tracking is an ultrasound technique based on tracking the displacement of acoustic markers during the cardiac cycle, reflecting the myocardial deformation. This non-invasive technique has been validated for the assessment of LA function, allowing the measurement of global, passive, and active longitudinal strain, reflecting LA reservoir (storage of blood during left ventricular systole), conduit (passage of blood from the pulmonary veins to the left ventricle during early diastole), and contractile (filling of left ventricle through LA active contraction during end of diastole) functions, respectively (12, 13).

In this study, using speckle tracking analysis in young patients with first CS, we sought to determine whether PFO or PFO plus ASA were associated with LA function impairment.

# METHODS

## Study Population

Consecutive patients aged 18 to 54 years, treated for first-ever CS in a tertiary hospital, were included in this retrospective study. Patients with cerebral venous thrombosis, subarachnoid hemorrhage with secondary brain ischemia, or transient ischemic attack as defined by transient neurologic dysfunction without evidence of infarction on brain imaging were not included. Clinical, biological, and radiological data from all individual patients were reviewed using the electronic database. Hypertension, diabetes, and migraine were diagnosed by history. Overweight (including obesity) was defined as body mass index (BMI) >24.9. Hypertension was defined as persistent systolic blood pressure >130 mmHg or diastolic blood pressure >80 mmHg, as documented before stroke or treatment with antihypertensive drugs before stroke. Diabetes was defined as a previous diagnosis of type 1 or type 2 diabetes. Tobacco use was recorded in patients who were currently smoking. Hyperlipidemia was defined as elevated low-density lipoprotein cholesterol >1.6 g/L or hypertriglyceridemia >2.0 g/L.

The study conformed to the principles outlined in the Declaration of Helsinki. All patients were informed that clinical data collected during their hospitalization could be used for research purposes and gave their consent. The study was approved by our Institutional Review Board (internal reference RnlPH 2019-73).

## Stroke Diagnosis

Stroke was diagnosed according to current recommendations as an episode of acute neurological deficit corresponding with an acute ischemic lesion on brain magnetic resonance imaging (MRI). CS was retained after a negative complete diagnostic workup including brain MRI, ECG, 72-h telemetry, routine blood tests, and non-invasive angiography of cerebral and cervical vessels using MRI or computed tomography angiography, carotid duplex ultrasonography, and, in patients without a definite cause of stroke after an initial evaluation, transthoracic (TTE) and transesophageal (TEE) echocardiography. Additional investigations including 24-h Holter monitoring, cerebrospinal fluid analysis, and testing for thrombophilia were performed in selected patients with suggestive findings on initial evaluation or without a potential cause of stroke after completion of echocardiography.

The etiology of stroke was classified according to the ASCOD classification system (A, atherosclerosis; S, small-vessel disease; C, cardiac pathology; O, other causes; D, dissection). This classification system assigns a degree of likelihood of causal relationship to every potential disease (1 for potentially causal, 2 for causality is uncertain, 3 for unlikely causal but the disease is present, 0 for absence of a disease, and 9 for insufficient workup to rule out the disease) (15).

CS was diagnosed in patients without an ASCOD grade 1 cause of stroke. For the purpose of this study and in accordance with the ASCOD classification, patients with PFO as the only potential cause of stroke were classified as CS.

## Echocardiography

TTE and TEE were performed with a commercially available ultrasound Vivid E95 system (GE Vingmed Ultrasound AS, Horten, Norway) using either a 2.5-MHz transthoracic transducer or an 8-MHz transesophageal transducer, allowing a full-fledged analysis of archived sequences.

The presence of PFO and ASA were assessed by TEE with a contrast study performed at rest and during provocative maneuvers (Valsalva and cough test) according to guidelines (16). The contrast study was considered positive if ≥3 microbubbles appeared in the left atrium, either spontaneously or after provocative maneuvers, within three cardiac cycles after complete opacification of the right atrium (17). The degree of shunting was defined as small (grade 1; <20 bubbles) or large (grade 2; ≥20 bubbles). In case of negative TEE, PFO was to be diagnosed in the presence of a right-to-left shunt on transcranial Doppler, after eliminating other causes of right-to-left shunt. ASA was defined as excursion of the septal tissue of >10 mm from the plane of the atrial septum into the right atria or LA or a combined total excursion to the right and to the left of 15 mm (12).

Left ventricular (LV) ejection fraction was measured using the modified biplane Simpson's rule. Peak early (E) and late (A) waves were derived from pulse wave Doppler of mitral inflow.

LA volumes were measured in the apical four- and two-chamber views. The most suitable cardiac cycle was chosen for each view. The assessed parameters in each view included LA maximal volume ($V_{max}$), at mitral valve opening, minimal volume ($V_{min}$), at mitral valve closure, and pre-LA contraction volume ($V_{preA}$) at the onset of the P wave. The volumetric parameters of the LA function were calculated as follows (9, 18): total emptying volume (ml) = $V_{max}$-$V_{min}$, passive emptying volume (ml) = $V_{max}$-$V_{preA}$, active emptying volume (ml) = $V_{preA}$-$V_{min}$, total emptying fraction (%) = total emptying volume/$V_{max}$ × 100, passive emptying fraction (%) = passive

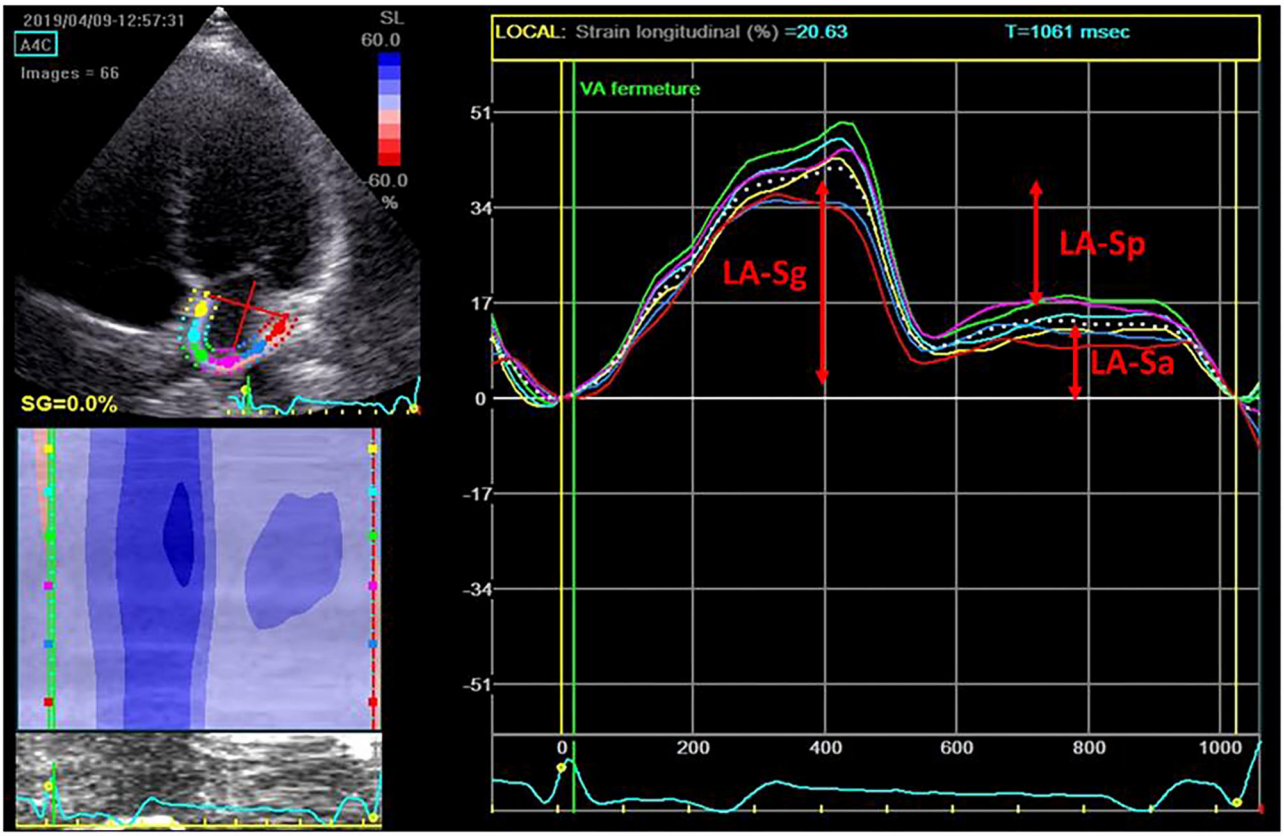


**FIGURE 1 |** Strain curve obtained after manual tracing of the left atrial (LA) border. LA-Sa, LA longitudinal active strain; LA-Sg, LA longitudinal global strain; LA-Sp, LA longitudinal passive strain.

emptying volume/$V_{max}$ × 100, and active emptying fraction (%) = active emptying volume/$V_{preA}$ × 100.

For speckle tracking analysis, the frame rate was set between 60 and 80 frames per second. The reference point was set at the beginning of the QRS complex. LA endocardial surface was manually traced in both four- and two-chamber views by a point-and-click approach (19). An epicardial surface tracing was then automatically generated by the system, thus creating a region of interest (13). The accuracy of tracking was visually confirmed throughout the cardiac cycle and confirmed from the morphology of the strain curves. If necessary, manual correction could be made or, if still non-acceptable, the segment was excluded from the analysis. Strain curves were generated for each segment. LA global longitudinal strain, active longitudinal strain, and passive longitudinal strain were measured by averaging the values observed in all available LA segments (12 when all four- and two-chamber segments were suitable), as shown in **Figure 1**.

## Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median and interquartile range. Intra- and inter-rater reliability for LA strain measurement were assessed by intra-class correlation coefficient from 10 randomly selected patients reanalyzed by two observers. Nominal values were expressed as numbers and percentages. We used Mann–Whitney rank sum test and Fisher exact test for comparison of continuous and nominal variables, respectively. A multivariable analysis was performed using logistic regression analysis. Reduced LA strain was defined as LA strain < median value. All tests were bilateral. Differences were considered as statistically significant for a $P < 0.05$. All analyses were performed using SPSS, version 20 (SPSS Inc., Chicago, IL, United States).

# RESULTS

Fifty-one patients were included in this study. The mean age was 42 ± 9 years; 34 (67%) patients were male. The patients' characteristics are summarized in **Table 1**.

Intra- and inter-rater reliability for LA global longitudinal strain were good or excellent with intra-class correlation coefficient (95% CI) of 0.903 (0.569–0.978; $P = 0.002$) and 0.889 (0.509–0.975; $P = 0.003$), respectively.

The associations of traditional cardiovascular risk factors with LA longitudinal strain in univariate analysis are summarized in **Table 2**. LA global longitudinal strain was reduced in older patients ($P = 0.009$) and in the presence of hypertension ($P = 0.002$), diabetes ($P = 0.049$), and overweight ($P = 0.001$). Older age ($P < 0.001$), overweight ($P = 0.004$), and non-smoking

($P = 0.034$) were associated with reduced LA passive longitudinal strain. LA active strain was not associated with any of the variables tested.

Twenty-one (41%) patients had PFO, including four patients with negative TEE but with a right-to-left shunt on transcranial Doppler. Ten (19.6%) PFOs were associated with an ASA. The patients with PFO were younger (38.8 ± 10.7 vs. 43.8 ± 6.8 years, $P = 0.101$) and had less hypertension (14.3 vs. 30%; $P = 0.315$) and diabetes (4.8 vs. 10%; $P = 0.634$) than the patients without PFO. However, none of these differences were statistically significant. BMI was similar in both groups (25.9 vs. 26.1; $P = 0.716$).

PFO and PFO plus ASA were not associated with any modification of global, active, or passive longitudinal LA strain. Large right-to-left shunt, defined as more than 20 bubbles on TEE and present in 12 patients (24%), was not associated with altered LA strain (**Table 3**). Among conventional LA function parameters, only LA total emptying volume was increased in patients with PFO ($P = 0.025$, **Supplementary File**).

**TABLE 1 |** Patient characteristics (values are numbers with percentages in parentheses unless otherwise indicated).

| **Age mean ± SD, years** | **42 ± 9** |
|---|---|
| Men | 34 (67) |
| Hypertension | 12 (24) |
| Overweight | 25 (49) |
| Smoking | 28 (55) |
| Dyslipidemia | 6 (12) |
| Diabetes | 4 (8) |
| PFO | 21 (41) |
| PFO-ASA | 12 (24) |
| Spontaneous R–L shunt | 18 (35) |
| Large shunt (grade 2) | 12 (24) |

A multivariable analysis using logistic regression showed associations of reduced LA global longitudinal strain with overweight (OR, 5.90; 95% CI, 1.45–23.99, $P = 0.013$), reduced LA active longitudinal strain with hypertension (OR, 5.95; 95% CI, 1.05–33.64, $P = 0.049$), and reduced LA passive longitudinal strain with overweight (OR, 6.87; 95% CI, 1.39–33.87, $P = 0.018$). Diabetes and dyslipidemia were not included in the models because there were too few patients with these risk factors and to limit the number of explanatory variables given the small sample size (**Table 4** and **Figure 2**).

## DISCUSSION

The present exploratory study using LA longitudinal strain measurement in young adults with CS showed associations of overweight with reduced LA reservoir function and reduced LA conduit function and of hypertension with reduced LA contractile function. In contrast, PFO, even in the presence of ASA or large right-to-left shunt, did not impact LA strain.

### LA Strain Measurement in Stroke Patients

Speckle tracking imaging, first developed for the analysis of LV deformation, has been validated by several studies for the assessment of LA function (12–14, 20). In addition to good reproducibility and angle independence, it detects a dysfunction at an earlier stage compared to classical parameters such as the size of LA, as functional changes precede morphological changes (9, 14). The measure of three different parameters is relevant as it corresponds to three components of LA function: reservoir, when LA fills with blood from pulmonary veins during systole; conduit, corresponding to the passage of blood into the ventricle during early diastole; and contractile, rising of LV stroke volume by LA contraction in late diastole. The use of LA longitudinal strain in this study was pertinent, as we expected a small degree of dysfunction, and LA longitudinal strain is easily obtainable in

**TABLE 2 |** Left atrial (LA) longitudinal strain values according to age, sex, and cardiovascular risk factors (values are mean ± SD).

| | | **LA global strain** | ***P*** | **LA active strain** | ***P*** | **LA passive strain** | ***P*** |
|---|---|---|---|---|---|---|---|
| Age, years[a] | ≥45 (*N* = 22) | 35.0 ± 8.4 | 0.009 | 16.5 ± 5.4 | 0.506 | 17.2 ± 5.1 | <0.001 |
| | <45 (*N* = 29) | 41.2 ± 7.7 | | 16.9 ± 4.4 | | 24.7 ± 7.2 | |
| Male sex | Yes (*N* = 17) | 37.6 ± 8.3 | 0.281 | 17.2 ± 5.2 | 0.549 | 20.7 ± 7.6 | 0.134 |
| | No (*N* = 34) | 40.4 ± 8.8 | | 15.9 ± 4.0 | | 23.3 ± 6.5 | |
| Overweight | Yes (*N* = 25) | 34.5 ± 8.4 | 0.001 | 15.9 ± 4.4 | 0.250 | 18.7 ± 7.3 | 0.004 |
| | No (*N* = 26) | 42.5 ± 6.5 | | 17.5 ± 5.1 | | 24.3 ± 6.3 | |
| Smoking | Yes (*N* = 21) | 40.6 ± 6.9 | 0.057 | 16.1 ± 4.1 | 0.592 | 24.3 ± 7.5 | 0.034 |
| | No (*N* = 30) | 37.1 ± 9.3 | | 17.2 ± 5.3 | | 19.7 ± 6.6 | |
| Hypertension | Yes (*N* = 12) | 31.9 ± 7.0 | 0.002 | 14.7 ± 4.0 | 0.065 | 18.4 ± 6.1 | 0.083 |
| | No (*N* = 39) | 40.6 ± 7.9 | | 17.4 ± 4.9 | | 22.6 ± 7.4 | |
| Diabetes | Yes (*N* = 4) | 30.6 ± 6.4 | 0.049 | 14.5 ± 4.9 | 0.405 | 16.0 ± 1.9 | 0.083 |
| | No (*N* = 47) | 39.2 ± 8.3 | | 16.9 ± 4.8 | | 22.1 ± 7.4 | |
| Hyperlipidemia | Yes (*N* = 6) | 34.8 ± 7.8 | 0.188 | 18.6 ± 6.1 | 0.366 | 16.4 ± 3.4 | 0.058 |
| | No (*N* = 45) | 39.0 ± 8.5 | | 16.5 ± 4.6 | | 22.3 ± 7.4 | |

[a]*Age was dichotomized according to median value.*

**TABLE 3 |** Left atrial (LA) longitudinal stain values according to patent foramen ovale (PFO) and atrial sepal aneurysm (ASA) (values are mean ± SD).

| | PFO | | | PFO–ASA | | | Severe shunt[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Present *N* = 21 | Absent *N* = 30 | *P* | Present *N* = 10 | Absent *N* = 41 | *P* | Present *N* = 12 | Absent *N* = 37 | *P* |
| LA global strain | 40.7 ± 8.4 | 37.0 ± 8.3 | 0.108 | 39.9 ± 7.3 | 38.2 ± 8.8 | 0.602 | 41.7 ± 6.0 | 36.9 ± 8.7 | 0.054 |
| LA active strain | 17.0 ± 3.9 | 17.5 ± 5.4 | 0.592 | 17.7 ± 3.9 | 16.5 ± 5.0 | 0.434 | 16.8 ± 3.5 | 16.5 ± 5.1 | 0.625 |
| LA passive strain | 23.5 ± 8.1 | 20.3 ± 6.5 | 0.117 | 21.3 ± 6.4 | 21.7 ± 7.6 | 0.794 | 24.7 ± 8.2 | 20.2 ± 6.8 | 0.109 |

[a]*Missing data in two patients.*

**TABLE 4 |** Logistic regression analysis of associations between cardiovascular risk factors and patent foramen ovale (PFO) and reduced left atrial (LA) strain (reduced LA strain was defined as LA strain < median value).

| | LA global strain | | LA active strain | | LA passive strain | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | *P* | OR (95% CI) | *P* | OR (95% CI) | *P* |
| Age | 1.01 (0.93–1.11) | 0.660 | 1.00 (0.93–1.08) | 0.884 | 1.10 (0.99–1.21) | 0.060 |
| Male | 1.25 (0.30–5.11) | 0.756 | 0.71 (0.19–2.63) | 0.616 | 1.39 (0.33–5.85) | 0.648 |
| Overweight | 5.90 (1.45–23.99) | 0.013 | 0.84 (0.22–3.19) | 0.802 | 6.87 (1.39–33.87) | 0.018 |
| Smoking | 0.56 (0.13–2.36) | 0.433 | 2.52 (0.66–9.66) | 0.175 | 1.10 (0.23–5.16) | 0.899 |
| Hypertension | 1.71 (0.29–9.95) | 0.299 | 5.95 (1.05–33.64) | 0.043 | 0.49 (0.07–3.17) | 0.457 |
| PFO | 0.62 (0.14–2.74) | 0.537 | 0.58 (0.15–2.17) | 0.421 | 0.292 (0.06–1.33) | 0.292 |

*LA, left atrial; OR, odds ratio.*

stroke patients, TTE being a part of the routine evaluation for cardio-embolic source.

Some previous studies used LA strain measurement in stroke patients. Most included older patients and focused on the link between LA dysfunction and cardiac diseases associated with a high risk of brain embolism such as LA thrombus or atrial fibrillation (5, 6, 21). Our study was not designed for analyzing this relationship, as only young patients with CS were included. We could find only one previous study of LA longitudinal strain in CS reporting reduced reservoir LA strain in patients compared to controls. Factors explaining this dysfunction were not explored but suggested to be linked to atherosclerosis risk factors (4).

## Association of Overweight and Hypertension With Impaired LA Strain

The finding of impaired LA function in the presence of hypertension and overweight is consistent with previous reports. The impact of hypertension and obesity on LA function are well-known in the general population, as they induce or contribute to atrial cardiomyopathy (22). These factors were associated with LA enlargement in earlier studies (23). More recent studies using the LA strain demonstrated impaired reservoir and conduit LA functions in patients with hypertension (24) in the absence of LA enlargement (7). A negative correlation between LA strain and body mass index was also reported (25). Our findings confirm the association of overweight with reduced reservoir and reduced conduit LA function and of hypertension with reduced contractile LA function in a selected population of young patients with CS.

## LA Function in Stroke Patients With PFO

PFO, especially PFO plus ASA or with large right-to-left shunt, is strongly associated with CS in young subjects (2, 17, 26). The prevalence of PFO and PFO plus ASA is higher in this population compared to the normal population and to patients with ischemic stroke of known etiology (27). The features of stroke associated with PFO are also different, both clinically, with younger patients less susceptible to have cardiovascular risk factors, and radiologically (26, 28). Several studies have now proven the benefit of transcutaneous PFO closure to prevent recurrent stroke in selected patients (29). However, the mechanisms of stroke associated with PFO remain unclear (30). Paradoxical embolism is often suspected but rarely proven. Other possible mechanisms include thrombus formation within the PFO or on the ASA surface and LA dysfunction. Two previous studies assessed LA function in stroke patients with PFO or ASA. Rigatelli et al. used conventional volumetric parameters in 98 stroke patients with PFO compared to 74 healthy subjects. They found significantly greater reservoir function and passive and active LA emptying, with significantly reduced conduit function and LA ejection fraction in patients with PFO compared to controls. Patients with PFO plus ASA had worse functional parameters than patients with isolated PFO (10). Na et al. compared 38 CS patients with isolated ASA to 38 age- and sex-matched healthy controls. The CS patients had significantly larger LA volume and lower active LA emptying fraction than the controls (11). In the present study of 51 CS patients using speckle tracking parameters, we found no evidence of impaired LA function in patients with PFO or PFO plus ASA compared to patients without. Among conventional LA function parameters,

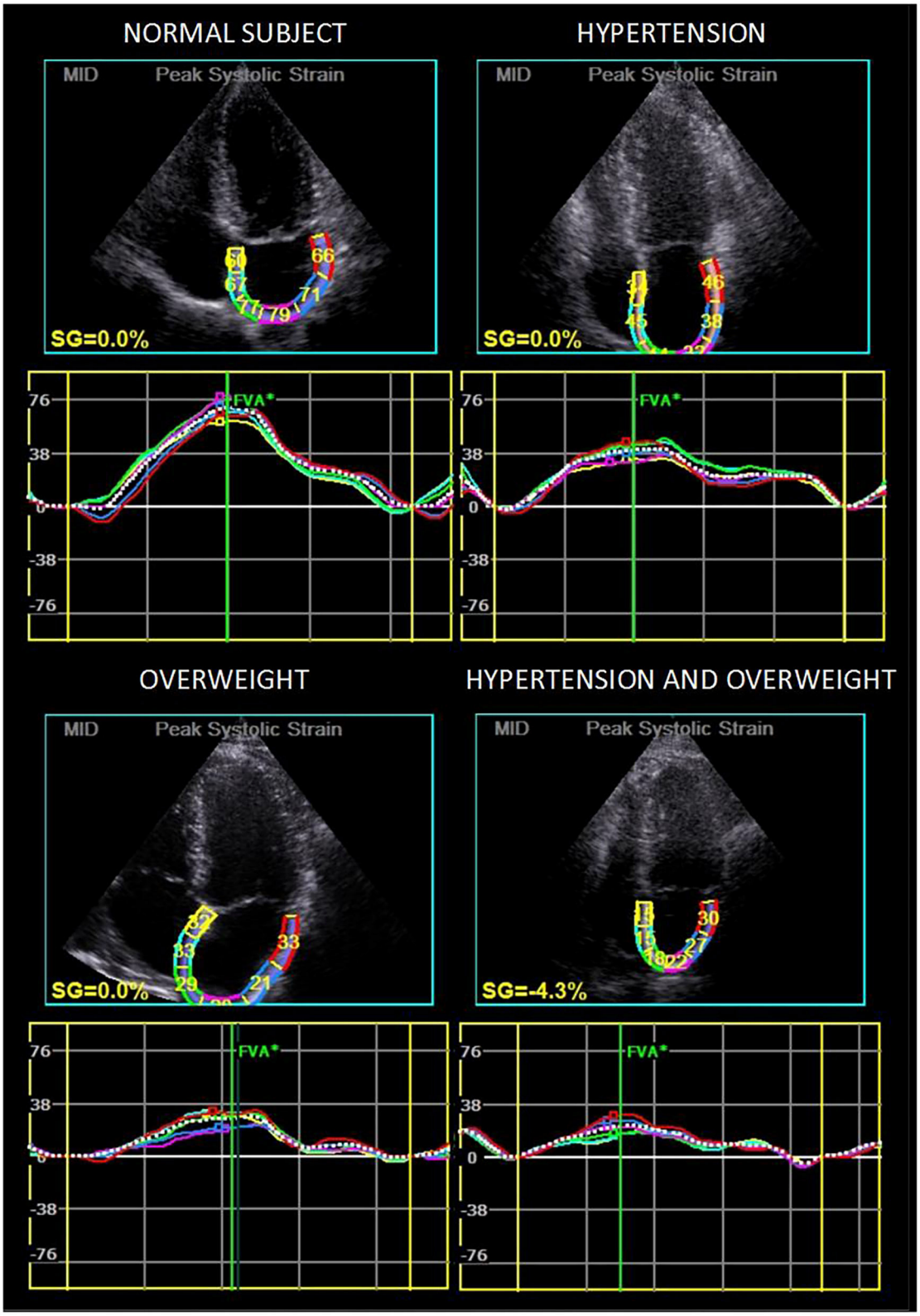


**FIGURE 2 |** Strain curves in four illustrative patients showing longitudinal strain reduction in overweight and/or hypertensive patients.

only LA total emptying volume was decreased in patients with PFO. It is possible that our negative findings were explained by a relatively small sample size. However, despite limited statistical power, we were able to confirm the association of LA dysfunction with hypertension and overweight. There are notable differences between the present study and the previous studies which may possibly explain the discrepant results. In the study by Rigatelli et al. the etiological workup of stroke was unspecified, and data on hypertension, diabetes, and overweight were not reported (10). Na et al. included only patients with isolated ASA (11). More importantly, stroke patients with PFO, or ASA were compared to healthy controls in both studies, whereas we compared CS patients with PFO to CS patients without PFO.

### Limitations

The present study has the general limitations of retrospective studies. Atrial fibrillation may have been overlooked in some patients, as we did not use long-duration recordings with implantable cardiac monitors. The measurement of the LA strain was performed with knowledge of the diagnosis of PFO in some patients. The large number of comparisons exposed to the risk of false positive results. In addition, the small sample size and the small number of patients with diabetes and hyperlipidemia did not allow these variables to be included in the multivariable analysis. However, the associations between overweight and hypertension and impaired LA function are consistent with the findings of previous studies. Finally, some of the negative results may have been due to insufficient statistical power. Therefore, our conclusions need to be confirmed on a larger sample.

## CONCLUSION

Impairment of LA longitudinal strain in young CS patients was not linked to PFO or PFO plus ASA but to overweight and hypertension. Further study is needed to confirm these findings in a larger number of patients.

## DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CHU de Toulouse Institutional Review Board (internal reference RnlPH 2019-73). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

JG, VL, and OL conceived the study. JG, CG, PF, and EC collected data. JG, VL, and OL analyzed and interpreted the data and drafted the manuscript. All authors contributed to the article and approved the submitted version.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.536612/full#supplementary-material

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SYSTEMATIC REVIEW
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# Presence of Atrial Fibrillation in Stroke Patients With Patent Foramen Ovale: Systematic Review and Meta-Analysis

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**Purpose:** Patent foramen ovale (PFO) is associated with ischemic stroke, especially in patients with embolic stroke of undetermined source. This study aims to evaluate the presence of atrial fibrillation (AF) in ischemic stroke patients with PFO.

**Methods:** We systematically searched EMBASE and MEDLINE databases on May 21, 2020 for studies that analyzed the presence of AF in patients with PFO. The primary outcome was the presence of AF in patients with PFO compared with those without. Outcomes were pooled using a random-effects model using the method of DerSimonian and Laird. We recorded demographic characteristics and the methods used for AF detection in the studies included (unspecified, history/medical records review, ECG, Holter monitor, or loop recorder).

**Results:** A total of 14 studies and 13,245 patients fulfilled the entry criteria. The average age was 61.2 years and 41.3% of the participants were female. There was a lower risk of AF in patients with PFO compared with those without (RR 0.52, 95% confidence interval, 0.41–0.63, $p < 0.001$). There was no evidence of heterogeneity. The lower risk of AF was found in cross-sectional and longitudinal studies and in studies stratified by average age (<60 or ≥60) and in cryptogenic stroke. Meta-regression by PFO detection technique suggested that studies using transoesophageal echocardiogram for PFO detection reported higher risk of AF (1.39, 95% confidence interval 1.14–1.70, $p = 0.004$).

**Conclusion:** The presence of a PFO in patients with ischemic stroke/TIA may be associated with a lower risk of AF. Few studies have estimated the risk of future AF in patients with PFO.

**Keywords: atrial fibrillation, patent foramen ovale, ischaemic stroke, transient ischaemic attack, cryptogenic stroke**

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## INTRODUCTION

A patent foramen ovale (PFO) is present in 20–25% of the general population and in up to 50% of younger stroke patients (1). Case-control studies have shown that PFO is strongly associated with ischemic stroke, especially in younger patients and in cryptogenic stroke (1–6). This has led to randomized controlled trials (7–11) that showed that percutaneous PFO closure reduces future stroke risk.

Before considering closure of PFO, the cryptogenic nature of the stroke needs to be demonstrated. Atrial fibrillation (AF) is an established risk factor for stroke. Although AF generally occurs in the elderly, it can occur in the age range where a PFO is considered an etiologic factor. Ruling out paroxysmal AF as an etiologic factor in this population is difficult.

The aim of this study was to perform a systematic review and meta-analysis of the available literature in order to determine the risk of AF in patients with ischemic stroke who have PFO as compared to those without PFO. Clinical variables that are associated with AF detection will be explored, as this may inform the selection of PFO patients for prolonged cardiac monitoring. AF associated with PFO closure is outside the scope of this review.

# METHODS AND MATERIALS

This systematic review and meta-analysis was registered with PROSPERO (The International Prospective Register of Systematic Reviews; CRD42019109505) and follows the PRISMA guideline for meta-analysis reporting.

## Search Strategy

Articles for review were retrieved by searching the databases MEDLINE and EMBASE (inception to 21st May, 2020), using the key terms "patent foramen ovale," "atrial septal defect," "atrial fibrillation," "atrial flutter," "atrial arrhythmias," "closure," "transcatheter closure," "surgical closure," "ischemic stroke," "cryptogenic stroke," and associated MeSH headings (**Supplementary Table 1**). The title and abstract screen were performed independently by V. T. and J. C., using the Rayyan tool (12). Full text review of the remaining articles was performed by J. C. This strategy was supplemented by a manual search of reference lists from key articles.

## Inclusion and Exclusion Criteria

We considered all original research, including prospective or retrospective cohort studies, case series, and comparative studies. We included cross-sectional studies that reported on the co-detection rate of PFO and AF, and studies that evaluated the rate of AF on longitudinal follow-up of ischemic stroke patients with and without PFO. Studies of AF post PFO closure were not included in this review. Studies with fewer than 50 patients were excluded. We excluded composite studies that examined both PFO and atrial septal defect closure, unless PFO-specific outcomes were separately reported and the PFO component contained 50 or more patients. We also excluded abstracts and studies in non-stroke populations. Publications were evaluated for duplicate or overlapping data, and only the most complete studies were included. Unpublished data were not sought.

## Quality and Bias Assessment

Assessment for study quality and bias was performed by J. C. and V. T. using the SIGN tool (13). Conflict was resolved by discussion and consensus.

## Data Extraction

Data extraction was performed by J. C. using a standardized Excel worksheet. We collected information on the principal author, year of publication, study design, sample size, methods for PFO detection—transcranial Doppler (TCD), transthoracic echocardiogram (TTE), transesophageal echocardiogram (TOE), and methods for AF detection (unspecified, medical records, history/questionnaire, electrocardiogram (ECG), Holter monitor of at least 24 h duration, or loop recorder). We also collected clinical variables known to predispose patients to AF, including average age, proportion of females, and proportion of patients with hypertension and diabetes.

## Statistical Analysis

For all analyses, we adopted a random effects model using the Der Simonian-Laird method. Additionally, we used the Sidik-Jonkmann method for sensitivity analysis (14). These methods assume that different studies are estimating different but related effect sizes and are a more conservative approach compared to fixed effects model when heterogeneity is present.

For the risk of AF in patients with PFO compared to those without, we performed meta-analysis of proportions using the Stata (ver 15.1, StataCorp, College Station, Texas) *metan* command. The pooled estimates were expressed as relative risk. All pooled estimates were presented with their 95% confidence intervals and 2-tailed $p$-values. A $p < 0.05$ was considered statistically significant.

Heterogeneity of the results was tested using the chi square, $I$ squared (15) and Tau-squared tests. Heterogeneity was considered low if $I^2 < 25\%$, moderate if $I^2$ is between 25 and 50%, and significant if $I^2 > 50\%$ (15). A $p < 0.10$ was considered statistically significant due to the lower power of these tests in meta-analyses where studies have smaller sample sizes or are few in number. Meta-regression was performed to assess the contribution of each pre-specified variable (i.e., age, proportion of females, proportion of patients with hypertension and diabetes, and methods of AF and PFO detection) to the overall risk of AF.

Publication bias was assessed graphically using the funnel plot and further assessed using Egger's regression asymmetry testing (16). The intercept of the linear regression line with the $y$-axis is used to measure asymmetry. If the intercept is significantly different from zero, this suggests the presence of publication bias.

# RESULTS

## Study Selection

The search strategy retrieved 2,088 abstracts for review, and 1,580 of these were considered inappropriate following title/abstract screen. The remaining 508 articles were reviewed in full. References of included articles were screened by J. C., and no additional study was identified for inclusion in the final analysis. The progress through each step of the review process resulted in a final number of 14 studies included (**Figure 1**).

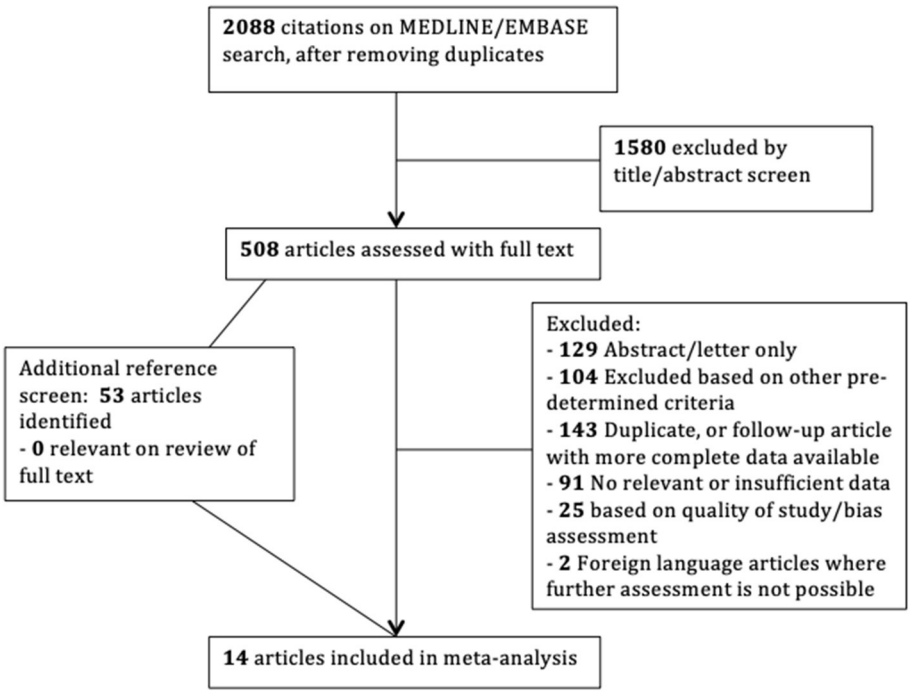


**FIGURE 1 |** Study selection flowchart.

## Bias Analysis

Bias analysis for studies included is summarized in **Supplementary Table 2**. Overall, studies minimized selection bias by including consecutive patients from the ischemic stroke population. Four studies (17–20) included consecutive stroke patients who were referred for echocardiogram. This could be a source of selection bias, as this population may be different from the unselected ischemic stroke population. However, while the indication for echocardiogram referral was not explicitly stated, both AF and non-AF patients were included in these studies. Attrition bias could not be assessed in some studies, as the completeness of follow-up was not reported. Detection bias was an issue for some studies, due to the use of only chart review or ECG to detect AF. This likely leads to significant under-detection of AF. Lastly, two studies (19, 21) suffer from confounding bias, as important AF risk factors such as hypertension were not reported.

## Risk of AF in Patients With PFO Compared With Those Without PFO

A total of 14 studies (17–30) and 13,245 patients were included in this part of the analysis. Six of these studies (21–23, 25, 26, 30) reported on the frequency of AF, frequency of PFO, and frequency of AF and PFO co-detection in an unselected ischemic stroke population that underwent a standard stroke etiology work-up, including a 24 h Holter. Four of these studies (17–20) reported on the same results but included only stroke patients referred for echocardiogram. One study (29) included patients in whom the initial in-hospital investigations, including continuous ECG monitoring, were unrevealing. Two studies (24, 27) reported patients who underwent more prolonged AF monitoring after initial negative investigations and reported on the risk of AF in those with PFO compared with those without. Full characteristics of each study are detailed in **Table 1**. The average age was 61.2 years, and 42.1% of the participants were female. There was a reduced risk of AF detection in patients with PFO compared to those without (RR 0.52, 95% confidence interval, 0.41–0.63, $p < 0.001$; **Figure 2**). There was no evidence of heterogeneity ($I^2 = 0\%$, $p < 0.001$). Sensitivity analysis using the Sidik–Jonkmann method yielded identical results.

Subgroup analysis based on AF detection techniques showed that the reduced risk of AF in PFO patients is seen across all subgroups. However, the effect estimate for the loop recorder subgroup has a wide confidence interval (RR = 0.83, 95% CI = 0.24–1.42), likely attributed to the small number of included studies. Four studies (24, 27–29), corresponding to 7,829 patients, specifically reported data on cryptogenic stroke. Subgroup analysis on these studies again showed reduced risk of AF in PFO patients (RR = 0.67, 95% CI = 0.38–0.96), as did studies that included all stroke subtypes (RR = 0.51, 95% CI = 0.37–0.65).

Univariable random-effects meta-regression by mean patient age, proportions of hypertension and diabetes, and method of AF detection did not detect an association with the risk of AF (**Supplementary Table 3**). Meta-regression by PFO detection technique suggested that studies using TOE for PFO detection reported higher risk of AF (1.39, 95% CI 1.14–1.70, $p = 0.004$).

**TABLE 1 |** Study characteristics—risk of AF in those with PFO compared to those without.

| References | Study type | Sample size | Average age | Female (*n*) | PFO detection | AF detection | Mean duration of AF monitoring | HTN (*n*) | Diabetes (*n*) | Non-index stroke/TIA (*n*) |
|---|---|---|---|---|---|---|---|---|---|---|
| Baher et al. (22) | Prospective cohort | 85 | 66 | 45 | 2 | 3 | N/A | 68 | 24 | 20 |
| Consoli et al. (23) | Prospective cohort | 1,130 | 68 | 453 | 1 | 3 | N/A | 793 | 234 | N/A |
| Cotter et al. (24) | Prospective cohort | 51 | 52 | 23 | 2 | 4 | Median duration prior to first episode of AF= 48 days. Mean duration in those without AF= 229 days. | N/A | N/A | N/A |
| Feurer et al. (25) | Retrospective cohort | 763 | 58 | 314 | 1 | 3 | Minimum 24 hours | 462 | 126 | N/A |
| Han et al. (21) | Retrospective cohort | 2,482 | 63 | 964 | 0 | 2 | N/A | N/A | N/A | N/A |
| Okura et al. (17) | Prospective cohort | 77 | 77 | 30 | 3 | 0 | N/A | 41 | 16 | N/A |
| Petty et al. (18) | Retrospective cohort | 116 | 63 | NA | 3 | 1 | N/A | 61 | 22 | 44 |
| Šanák et al. (26) | Prospective cohort | 98 | 40 | 42 | 3 | 3 | 3 weeks and 1 day. | 5 | 1 | NA |
| Warner et al. (19) | Retrospective cohort | 106 | 66 | 51 | 3 | 0 | N/A | N/A | N/A | N/A |
| Yasaka et al. (20) | Retrospective cohort | 426 | N/A | N/A | 3 | 0 | N/A | N/A | N/A | N/A |
| Thijs et al. (27) | Prospective cohort, *post-hoc* analysis | 221 | 62 | 79 | 3 | 3 | 3.69 years (total 815.5 patient-years) | 144 | 34 | 59 |
| Kasner et al. (28) | RCT, *post-hoc* analysis | 7,209 | 67 | 2,777 | 2 | 0 | N/A | 5,581 | 1,805 | 1,258 |
| Ohya et al. (29) | Retrospective cohort | 348 | 72 | 148 | 3 | 3 | Minimum 24 h | 271 | 103 | 68 |
| Yonemura et al. (30) | Retrospective cohort | 133 | 43 | 41 | 2 | 3 | 24 h | 54 | 19 | N/A |

*Categories for AF detection methods.*

*0 = Not systematically approached or unknown; 1 = History/medical records review/questionnaire; 2 = ECG ± symptom driven Ix (ECG/Holter); 3 = ECG + Holter (at least 24h); 4 = Loop recorder.*

*Categories for PFO detection methods.*

*0 = Not 100% patients had assessment; 1 = TCD ± TTE; 2 = TTE ± TOE; 3 = TOE.*

*HTN, hypertension; DM, diabetes mellitus; RCT, randomized control trial; N/A, not available.*

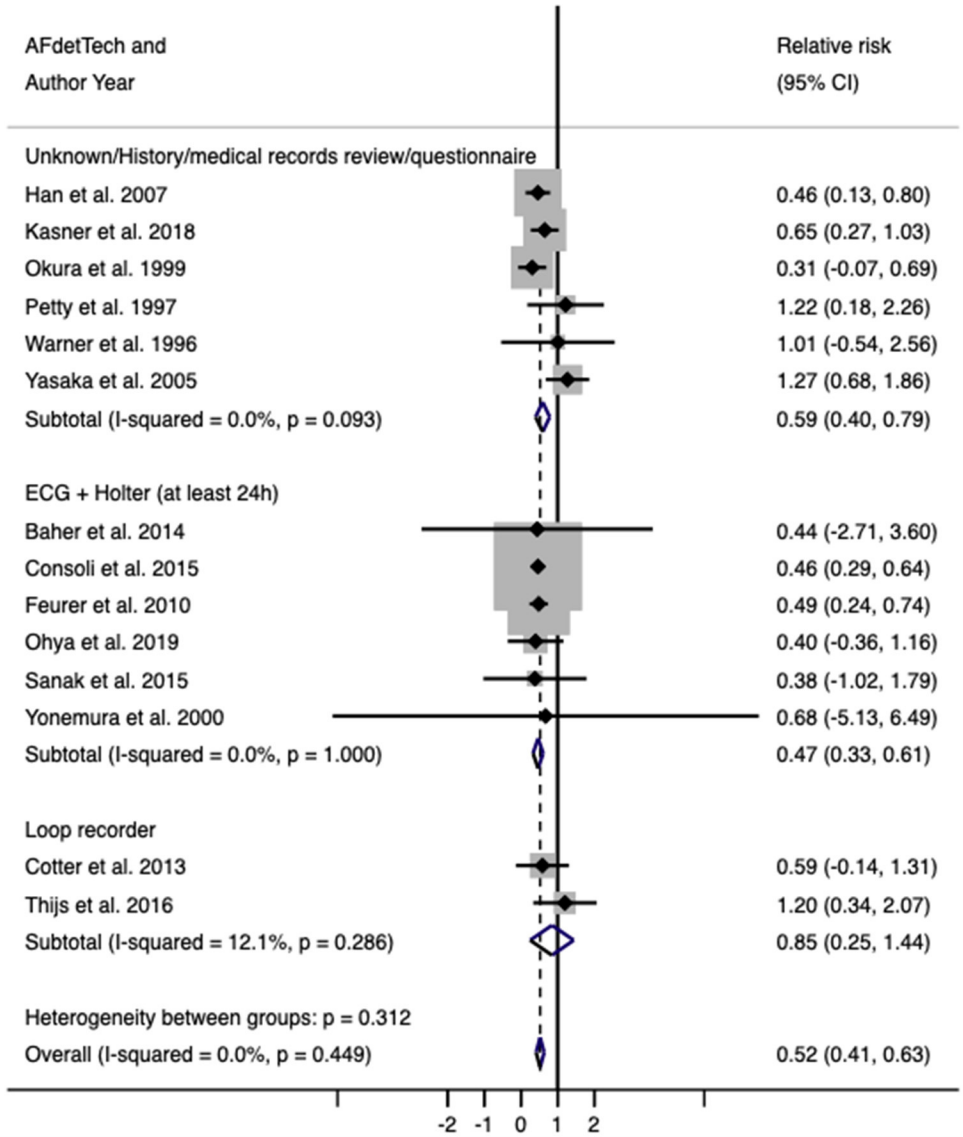


**FIGURE 2 |** Relative risk (with 95% confidence interval) of atrial fibrillation in patients with PFO compared with those without.

There is no statistical evidence of publication bias (intercept = −0.09, $p$ = 0.905), although the funnel plot suggested an absence of small studies reporting a higher risk of AF in those with PFO (**Figure 3**).

## DISCUSSION

This study-level meta-analysis found that the presence of PFO is associated with a lower risk of AF detection in patients with ischemic stroke/TIA.

The lower risk of AF in patients with PFO compared with those without is consistent with the general view that patients with PFO are not at an increased risk of arrhythmias compared with the general population (31). In addition, studies have also demonstrated that the presence of AF reduces the likelihood of right-to-left shunting through the PFO due to the elevation of left atrial pressure and the change in the pressure gradient across the PFO (32, 33). This in turn reduces the likelihood of PFO and AF co-detection. Studies that used TOE for PFO detection reported a higher risk of AF, although the magnitude of this effect was small. Whether use of TOE is a proxy for performing more thorough assessment and prolonged monitoring for AF is unknown. While age was not found to be a significant contributor to heterogeneity in this analysis, there was not a high degree of variability in mean age across studies. The relationship between age and risk of AF may be different within studies.

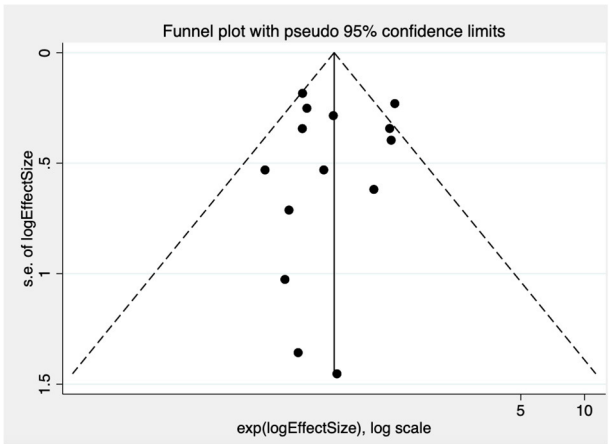


**FIGURE 3 |** Funnel plot test for publication bias in studies examining risk of AF in patients with PFO compared with those without. Treatment effect is on the *x*-axis, measure of study size on the *y*-axis. s.e. indicates standard error.

For example, the study by Yasaka et al. (20) which included patients of all ages, found that risk of AF was higher in PFO patients who were older. Lastly, a history of previous or recurrent cerebrovascular events may have been an important clinical factor that helps stratify the risk of AF. However, these data were reported in only three of the studies included and could not be examined adequately.

Our findings may have possible implications for diagnostic screening pathways after stroke and TIA. Knowing that a PFO is present, especially in a younger patient, may help determine the intensity of the monitoring regime for AF and avoid very prolonged monitoring. This may be particularly important in resource-limited settings.

There are several limitations to this study. First, two of the studies included (18, 21) suffered from detection bias (**Supplementary Table 2**), as they utilized routine ECGs, with or without once-off or symptom-triggered 24-h Holter monitoring for baseline and follow-up AF detection. Four studies (17, 19, 20, 28) did not explicitly state their method of AF monitoring. It is known that AF is often paroxysmal and asymptomatic, and these methods likely lead to under-detection of AF. This was illustrated by the CRYSTAL AF trial (34), which reported a much higher rate of AF of 12.4% at 12 months with insertable cardiac monitors. This is in contrast to the rate of 2% in the control group, where a mix of ECG and Holter monitoring were performed at the discretion of the clinician. The 2016 European Society of Cardiology Guidelines for the Management of Atrial Fibrillation (35) recommends that at least 72 h of continuous cardiac monitoring be performed for patients with ischemic stroke/TIA. In the 2014 American Heart Association/American Stroke Association guidelines, prolonged rhythm monitoring for 30 days is considered reasonable for patients who have had an ischemic stroke/TIA with no apparent cause (36). In the absence of adequate AF monitoring, the true incidence of AF may be higher.

Second, the methods for diagnosing PFO were heterogeneous, and there may be some detection bias if TTE is used as the sole modality to rule out a PFO. Third, all but four studies (24, 27–29) have reported data on an unselected ischemic stroke population. The inclusion of patients with a non-embolic stroke (such as a lacunar stroke), for whom a PFO is not considered a potential etiologic factor, may reduce the generalizability of the results. Furthermore, this is a study-level meta-analysis, and the relationships described are observational associations across trials and are prone to bias from unmeasured confounders. Adjusted summary statistics were available only for two studies (24, 27) and were included in all analyses. Examination of individual patient data will help to confirm these associations and offer valuable opportunities to study the impact of other important variables, such as PFO morphology, on the rate of AF. Lastly, there is a degree of publication bias resulting from the lack of small studies reporting a higher risk of AF in those with PFO.

## CONCLUSION

Stroke patients with PFO have a lower risk of AF compared with those without. Future research in this area should ensure adequate evaluation for AF over longer periods of cardiac monitoring and utilize a more rigorous AF follow-up protocol to determine the true incidence of AF.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

JC contributed to data collection, data analysis and interpretation, and drafted the manuscript. VT conceived and designed the analysis, contributed to data analysis, and critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.613758/full#supplementary-material

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