

Morphometric Features of Patent Foramen Ovale as a Risk Factor of Cerebrovascular Accidents: A Systematic Review and Meta-Analysis

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Keywords

Interatrial septum · Cryptogenic stroke · Ischemic stroke · Transesophageal echocardiography · Cardioembolic stroke

Abstract

Introduction: It is still disputable whether specific morphometric features of the patent foramen ovale (PFO) may stratify patients by the related probability that a discovered PFO is incidental or stroke related. **Objective:** We aimed to determine whether certain morphometrical characteristics of PFO are associated with an increased risk of cerebrovascular accidents, using a meta-analytical approach. **Methods:** We performed a systematic review of electronic databases for studies that compared morphometric parameters of PFO assessed by transesophageal echocardiography (TEE) in subjects with cryptogenic cerebrovascular accidents (Group 1) and control (Group 2). Data were extracted and pooled into a meta-analysis. **Results:** A total of 895 patients with PFO were reported (Group 1: 493, Group 2: 402). No difference was found in the PFO channel length (Group 1: 10.8 [8.6–12.9] mm vs. Group 2: 10.4 [9.1–11.7] mm), as well as in PFO height measured at rest (Group 1: 2.4 [1.5–3.3] mm vs. Group 2: 1.8 [1.4–2.2] mm). The PFO height measured during a Valsalva maneuver was larger in Group 1 (3.5 [2.8–4.1] mm) than in Group 2 (1.7 [1.2–2.2] mm). Also, the septal excursion distance was found to be larger in Group 1 (6.4 [5.1–7.8] mm)

than in Group 2 (3.1 [1.8–4.4] mm). The risk of cerebrovascular accident was higher in patients with PFO and concomitant septal aneurysm (OR 4.00; 95% CI 2.63–6.09; $p < 0.001$) and with large right-to-left shunt PFO (OR 3.81; 95% CI 2.21–6.55; $p < 0.001$), no such relationship was found for the presence of a Eustachian valve or Chiari's network (OR 1.90; 95% CI 0.90–4.05; $p = 0.094$). **Conclusions:** The TEE may help in identifying PFO that are of high risk of cerebrovascular accident. Greater PFO height during a Valsalva maneuver, larger septal excursion distance, concomitant atrial septal aneurysm, and large right-to-left shunt are associated with stroke-related PFOs.

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Introduction

The patent foramen ovale (PFO), which is one of the anatomical variants of the interatrial septum [1], may be responsible for ischemic cerebrovascular events in a paradoxical embolism mechanism [2]. A cryptogenic stroke is defined as an ischemic stroke in which its cause remains unknown even despite extensive diagnostic workup. Such embolic strokes of undetermined source are diagnosed in approximately one-third of all stroke patients [3]. Several studies have confirmed a significant association between cryptogenic stroke and the presence of PFO, suggesting

that paradoxical emboli may be the prevailing cause of cryptogenic cerebrovascular accidents [4]. Two therapeutic options are available for the secondary prevention of PFO-related strokes, which are antiplatelet therapy and invasive PFO closure [5]. Three recent randomized clinical trials and meta-analyses of all the available studies showed that in selected patients with cryptogenic stroke, PFO closure is superior to medical therapy for the secondary prevention of stroke [6–11]. Nevertheless, as approximately one-third of PFO discovered in patients with cryptogenic stroke are likely to be incidental and unrelated to the stroke, the selection of patients in whom closing the PFO will be justified is still an unresolved issue [2].

General risk factors that may help to stratify patients by the related probability that a discovered PFO is incidental or stroke-related are well established and included in the Risk of Paradoxical Embolism score calculator [12]. However, a fundamental question about PFO-related factors increasing the probability that a PFO in a patient with cryptogenic stroke is the prime causative factor rather than an incidental finding still has no clear answer. It is still disputable whether specific morphometrical features of the PFO identified in transesophageal echocardiography (TEE), such as channel length, height, or degree of shunt, may contribute to the ischemic cerebrovascular events [13–16]. Therefore, here we aimed to determine whether certain morphometrical characteristics of PFO are associated with increased risk of cerebrovascular accidents using a meta-analytical approach.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files (for all online suppl. material, see www.karger.com/doi/10.1159/000506433).

Search Strategy

A systematic literature search of the PubMed, EMBASE, Scopus, ScienceDirect, and Web of Science databases was conducted independently by 2 authors using PRISMA guidelines [17]. The PubMed search strategy is presented in online supplementary Table 1. The search was not restricted by either language or time. We subsequently reviewed and evaluated the reference lists of all eligible articles to ensure the identification of all relevant studies.

Eligibility Assessment and Data Extraction

We initially removed duplicate reports of the same studies. In the next step, we required that the papers fulfilled the following criteria: they (1) were TEE studies, (2) evaluated the morphology of PFO in humans with PFO-related cerebrovascular accidents or cerebrovascular accidents of unknown origin, and (3) compared those data with noncerebrovascular accidents control patients.

The cerebrovascular accident was defined as either ischemic stroke or transient ischemic attack (reversible ischemic neurologic deficit). Furthermore, we excluded following types of papers: case reports and case series, reviews and meta-analyses, editorials, conference abstracts, and articles with incomplete or irrelevant data. Afterward, all authors independently extracted data from the included studies. The extracted data included the year, country of origin, study design, samples size, and characteristics of each group. The PFO-related morphometrical characteristics were extracted and included into the analysis when at least 3 studies have reported the same parameter. Articles that were eligible for inclusion in the meta-analysis were assessed by all authors. Any disagreements were addressed by obtaining a consensus.

Statistical Analysis

The STATISTICA version 13.1 software (StatSoft Inc., Tulsa, OK, USA) with an additional Medical Bundle and MetaXL version 5.3 from EpiGear International Pty, Ltd. (Wilston, QLD, Australia) was used for the calculations. For the morphometric data, calculations were conducted using Comprehensive Meta-Analysis version 3.0 by Biostat (Englewood, NJ, USA). The statistical analysis was based on a random effects model. A p value <0.05 was considered to be statistically significant. Evidence of publication bias was investigated using a funnel plot and analyzed using the Egger method. We assessed heterogeneity among the included studies using the Cochrane Handbook's Q test and I^2 statistics. A $p < 0.05$ or $I^2 > 50\%$ was considered to indicate significant heterogeneity. Qualitative variables were compared using the χ^2 test of proportions for categorical variables. The comparison of confidence intervals of any 2 morphometric data indicated differences between 2 groups, and if they overlapped, the difference was considered as statistically insignificant [18].

Results

An overview of the study selection process is summarized in Figure 1. We initially identified 1,976 of records through the database and reference searching. Of these, 1,077 of the records remained after the removal of the duplicates. A total of 793 records were excluded due to not meeting the main established criteria, and the remaining 284 full-text articles were assessed for eligibility. In the subsequent step, 275 papers were excluded for not being original studies or not containing suitable data for the meta-analysis. Each step of the selection process was validated by 2 authors to avoid any discrepancies. In case of incompatibilities, studies were reassessed by both authors to achieve the final agreement. In summary, 9 studies that met our initial criteria were identified and included in the meta-analysis [19–27].

The characteristics of the included studies are presented in Table 1. All studies were TEE case-control studies with a Valsalva maneuver and contrast injection performed on adult patients, but there was a significant dif-

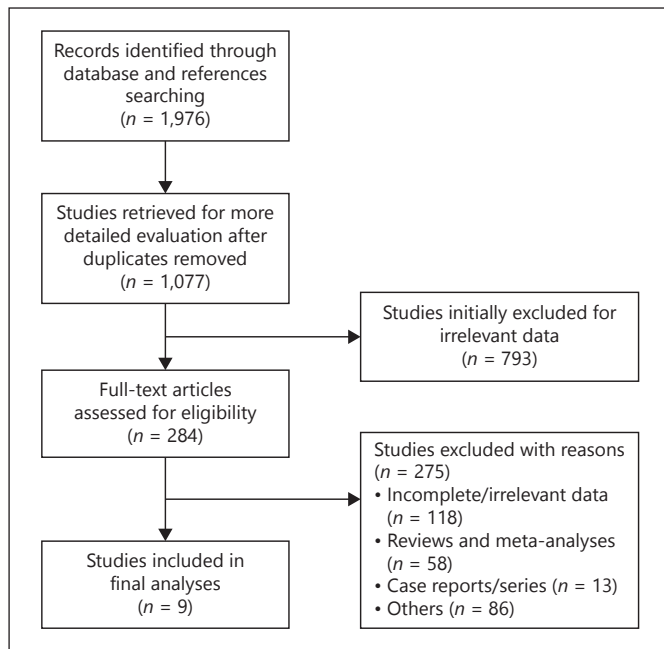


Fig. 1. Flow diagram demonstrating a selection of studies for meta-analysis. *n*, the number of records.

ference in patient age between studies. A total of 1,325 individuals were investigated in the included studies, among them 702 patients with cerebrovascular accidents (513 strokes, 189 transient ischemic attacks) and 623 control patients (without history of any cerebrovascular accident) were reported. All cerebrovascular accidents were defined as cryptogenic, but slightly different criteria were applied among included studies for this definition.

A total of 895 patients with PFO were reported. Two subgroups were distinguished in all the included studies: Group 1 – patients with cerebrovascular accident and with PFO identified in TEE; Group 2 – patients without any history of cerebrovascular accident and with PFO identified in TEE (Table 1). Group 1 included 493 patients and Group 2 included 402 individuals. All studies were reviewed to extract data regarding PFO morphology, especially: PFO channel length, PFO height, interatrial septum excursion distance, presence of atrial septal aneurysms, right-to-left shunt severity, presence of a prominent Eustachian valve, and presence of Chiari’s network, with their division into the abovementioned groups (online suppl. Table 2).

PFO Channel Length

Five studies have reported PFO channel length (maximum overlap between septum primum and septum secundum) [21, 24–27]. No statistically significant differ-

ence was found in the pooled mean length of the PFO channel between cerebrovascular accident and control groups (10.8 [8.6–12.9] vs. 10.4 [9.1–11.7] mm; Table 2).

PFO Height (Septum Primum and Secundum Separation)

The PFO height (or size) may be defined as a separation between the septum primum and secundum measured either at rest or during a Valsalva maneuver. Values for PFO height at rest were reported in 5 studies [22, 24–27]. No statistically significant difference was found in the pooled mean PFO height measured at rest between cerebrovascular accident and control groups (2.4 [1.5–3.3] vs. 1.8 [1.4–2.2] mm; Table 2).

The PFO height measured during Valsalva maneuver was given in 3 studies [19, 21, 25]. There was significantly larger pooled mean PFO height during a Valsalva maneuver in the cerebrovascular accident group than in the controls (3.5 [2.8–4.1] vs. 1.7 [1.2–2.2] mm; Table 2).

Septal Excursion Distance

The interatrial septum excursion distance (or mobility of the fossa ovalis), measured as a distance between the plane of the interatrial septum (septum primum) and the maximum bulging into the left or the right atrium, was reported in 3 studies [19, 22, 26]. A significantly larger pooled mean septal excursion distance was found in the cerebrovascular accident group than in the controls (6.4 [5.1–7.8] vs. 3.1 [1.8–4.4] mm; Table 2).

Presence of Atrial Septal Aneurysm

The cooccurrence of PFO and atrial septal aneurysm was reported in 7 studies [20–22, 24–27]. Definition of the aneurysmal interatrial septum was slightly different between studies (a total excursion cutoff value ranging from 11 to 15 mm). A total of 147 atrial septal aneurysms were identified among the cerebrovascular accident group, with a pooled prevalence of 35.4% (95% CI 25.8–45.7%; random-effects model, $I^2 = 76%$, $p < 0.001$), and 51 atrial septal aneurysms were identified in the controls, with a pooled prevalence of 14.3% (95% CI 9.9–19.3%; random-effects model, $I^2 = 32%$, $p = 0.18$). After meta-analysis, the risk of cerebrovascular accident was higher in patients with PFO and concomitant septal aneurysm than in patients with PFO, but without septal aneurysm (OR 4.00; 95% CI 2.63–6.09; $p < 0.001$; random-effect model; Fig. 2). No evidence of heterogeneity was found in the analysis ($I^2 = 14.63%$; $p = 0.318$). Funnel plot analysis does not reveal a significant publication bias influencing the data (Egger’s test: $p = 0.758$).

Table 1. Characteristics of studies included into meta-analysis

Study	Year	Country	Number of patients with cryptogenic CVAs (stroke/TIA) (% males)	CVA group characteristic	Age of CVA patients, years, mean \pm SD	Number of non-CVA control patients (% males)	Non-CVA group characteristic	Age of non-CVA patients, years, mean \pm SD	Total number of patients with PFO	Number of CVA patients with PFO (Group 1)	Number of non-CVA patients with PFO (Group 2)
Schuchlenz et al. [19]	2000	Austria	121 (66/55) (63.6)	Young (<60 years) consecutive patients with unexplained CVA referred for TEE	<60	123 (52.8)	Young (<60 years) consecutive patients with no history of any CVA and performed TEE, that was free of cardiac abnormalities, except for PFO or ASA	41 \pm 12	125	87	38
Cerrato et al. [20]	2002	Italy	175 (136/39) (50.3)	Consecutive patients with unexplained CVA referred for TEE	49.7 \pm 12	78 (51.3)	Consecutive patients with no history of any CVA referred for TEE	53.2 \pm 12	68	55	13
Natanzon et al. [21]	2003	USA	36 (31/5) (n/r)	Consecutive PFO patients with unexplained CVA referred for TEE	56.8 \pm 18.3	42 (n/r)	Consecutive patients with no history of any CVA referred for TEE with PFO as an incidental finding	58.2 \pm 17.6	78	36	42
Mesa et al. [22]	2003	Spain	55 (55/0) (50.9)	Young (<50 years) consecutive patients with clinical suspicion of stroke that was confirmed	40.1 \pm 10	35 (37.1)	Young (<50 years) consecutive patients with clinically suspected stroke in whom ischemia CVA was excluded	37.7 \pm 11.3	30	23	7
Fazlinezhad et al. [23]	2009	Iran	48 (31/17) (52.1)	Simple random sampling study evaluated young adult (15–45 years) patients with CVA	34.8 \pm 9.4	57 (47.4)	Young adult (15–45 years) consecutive patients who underwent TEE due to causes other than CVAs	33 \pm 9.8	39	25	14
Goel et al. [24]	2009	USA	58 (39/19) (53.4)	Patients selected from consecutive patients who undergone PFO closure and TEE	54 \pm 16	58 (63.8)	Consecutive patients with PFOs identified incidentally on TEE and without any histories of CVAs or any other embolic events	61 \pm 15	116	58	58
Komar et al. [25]	2012	Poland	88 (58/30) (45.5)	Consecutive PFO patients with unexplained CVA referred for TEE	36.1 \pm 16.2	88 (44.3)	Patients matched for gender and age who underwent TEE for other reasons than CVA in whom asymptomatic PFO was identified as the sole abnormality	36.1 \pm 16.2	176	88	88
Bayar et al. [26]	2015	Turkey	64 (40/24) (45.3)	Consecutive PFO patients with unexplained CVA referred for TEE	43.8 \pm 8.6	92 (54.3)	Patients with PFO diagnosed on TEE with no history of any CVA	37.8 \pm 9.3	156	64	92
Nakayama et al. [27]	2019	Japan	57 (57/0) (42.1)	Consecutive patients with PFO who were scheduled for transcatheter closure for cryptogenic stroke	50 \pm 14	50 (52.0)	Consecutive patients without CVA but with PFO who were scheduled for transcatheter closure for migraine	42 \pm 18	107	57	50

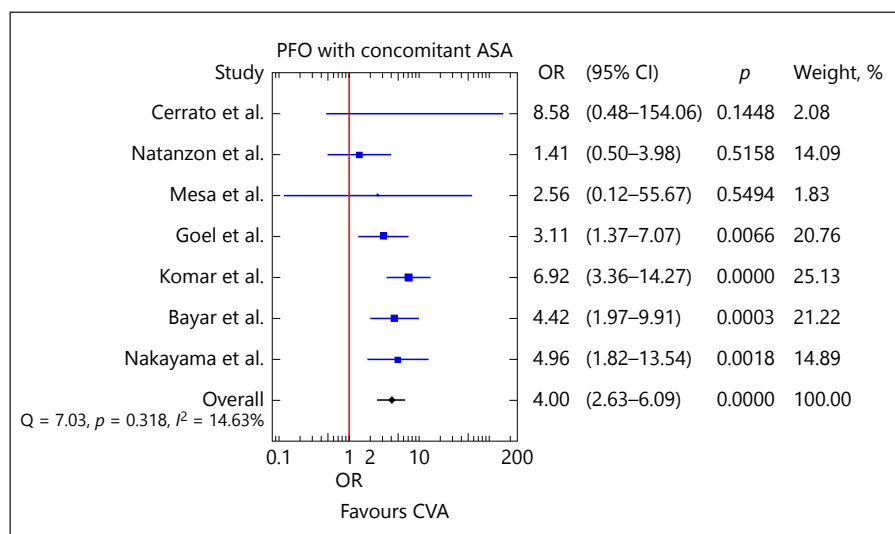
CVA, cerebrovascular accident; TIA, transient ischemic attack; PFO, patent foramen ovale; TEE, transesophageal echocardiography; ASA, atrial septal aneurysm; n/r, not reported.

Table 2. Pooled mean PFO-related dimensions in analyzed subgroups

Parameter	CVA patients with PFO (Group 1)	Non-CVA patients with PFO (controls) (Group 2)
PFO channel length		
Number of studies (number of patients)	5 (303)	5 (330)
Pooled mean length, mm (95% CI)	10.8 (8.6–12.9)	10.4 (9.1–11.7)
I^2 , %	31.9	11.4
PFO height at rest		
Number of studies (number of patients)	5 (290)	5 (295)
Pooled mean height at rest, mm (95% CI)	2.4 (1.5–3.3)	1.8 (1.4–2.2)
I^2 , %	3.9	55.1
PFO height during Valsalva		
Number of studies (number of patients)	3 (211)	3 (168)
Pooled mean height during Valsalva, mm (95% CI)	3.5 (2.8–4.1)	1.7 (1.2–2.2)
I^2 , %	43.7	0.0
Septal excursion distance		
Number of studies (number of patients)	3 (174)	3 (137)
Pooled mean excursion distance, mm (95% CI)	6.4 (5.1–7.8)	3.1 (1.8–4.4)
I^2 , %	21.8	0.0

CVA, cerebrovascular accident; PFO, patent foramen ovale.

Fig. 2. Forest plot representation of the results from the significant studies comparing presence of PFO with concomitant ASA in CVA patients and controls. Studies are displayed on the vertical and are marked with a square of proportional size to the study's calculated weight. The overall effect is lowermost and marked with a rhombus. PFO, patent foramen ovale; ASA, atrial septal aneurysm; CVA, cerebrovascular accident.



Right-to-Left Shunt Severity

Severity of right-to-left shunt via the PFO may be assessed based on counting the microbubbles passing to the left atrium. However, different quantitative criteria are adopted to determine the degree of shunt (online suppl. Table 2). Among all the included studies, 4 of them have used the same criterion and those were included in further calculations [20–22, 27]. If the number of crossing microbubbles was <20, the shunt was considered small; >20 microbubbles indicated a large shunt. A total of 110

patients with a large shunt were identified among the cerebrovascular accident group, with a pooled prevalence of 68.4% (95% CI 50.8–83.7%; random-effects model, I^2 = 81%, p < 0.001), and 42 individuals with a large shunt were identified in the control group, with a pooled prevalence of 37.8% (95% CI 29.0–46.9%; random-effects model, I^2 = 0%, p = 0.64). After meta-analysis, the risk of cerebrovascular accident was higher in patients with a large shunt PFO than in patients with a small shunt PFO (OR 3.81; 95% CI 2.21–6.55; p < 0.001; random-effect model;

Fig. 3. Forest plot representation of the results from the significant studies comparing shunt severity via PFO in CVA patients and controls. Studies are displayed on the vertical and are marked with a square of proportional size to the study's calculated weight. The overall effect is lowermost and marked with a rhombus. PFO, patent foramen ovale; CVA, cerebrovascular accident.

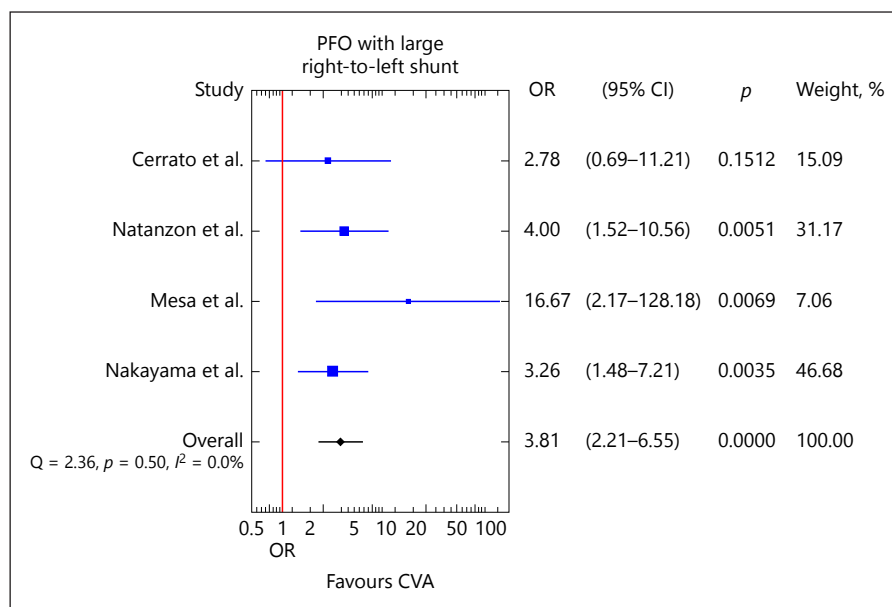


Fig. 4. Forest plot representation of the results from the significant studies comparing presence of PFO with concomitant Eustachian valve or Chiari's network in CVA patients and controls. Studies are displayed on the vertical and are marked with a square of proportional size to the study's calculated weight. The overall effect is lowermost and marked with a rhombus. PFO, patent foramen ovale; CVA, cerebrovascular accident.

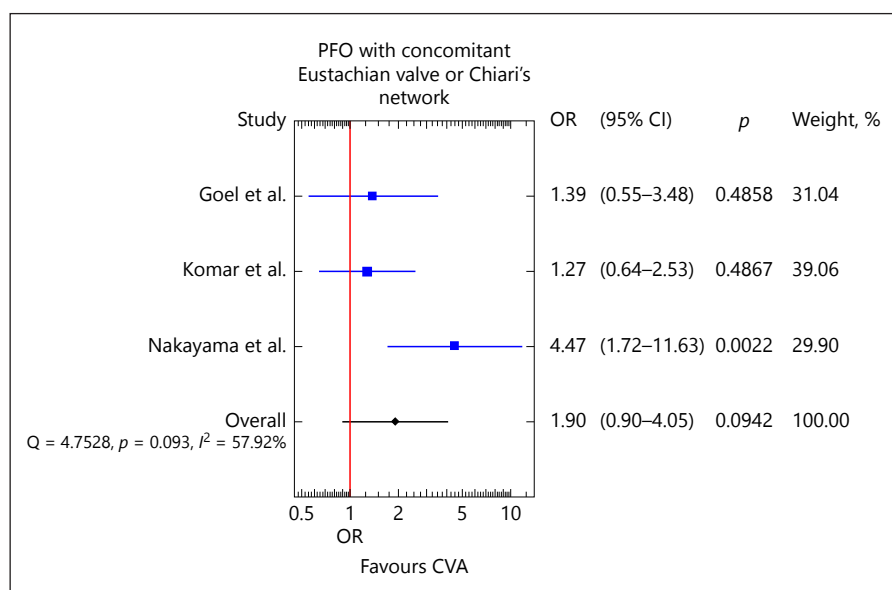


Fig. 3). No evidence of heterogeneity was found in the analysis ($I^2 = 0\%$; $p = 0.50$). Funnel plot analysis does not reveal a significant publication bias influencing the data (Egger's test: $p = 0.292$).

Presence of Eustachian Valve or Chiari's Network

The presence of prominent Eustachian valve or Chiari's network was reported in 3 studies [24, 25, 27]. Due to discrepancies in data reporting, we were unable to separate the presence of the valve and network into 2 independent analyses and thus those structures were merged

into 1 group. A total of 61 Eustachian valves or Chiari's networks were identified among the cerebrovascular accident group, with a pooled prevalence of 30.2% (95% CI 20.0–41.4%; random-effects model, $I^2 = 64\%$, $p = 0.06$), and 37 were identified in the controls, with a pooled prevalence of 19.1% (95% CI 13.9–24.9%; random-effects model, $I^2 = 0\%$, $p = 0.45$). After meta-analysis, no reliable association between the presence of Eustachian valve or Chiari's network and increased risk of cerebrovascular accident was found (OR 1.90; 95% CI 0.90–4.05; $p = 0.094$; random-effect model; Fig. 4). Significant heterogeneity

was present in this analysis ($I^2 = 57.92\%$; $p = 0.093$). Funnel plot analysis does not reveal a significant publication bias influencing the data (Egger's test: $p = 0.516$).

Discussion

In this study, we have attempted to systematize and reanalyze the results of currently available studies concerning the influence of PFO-related morphometric features on the occurrence of cerebral ischemic events, which has not been previously performed. As a result of our research, high-risk transesophageal echocardiographic features of PFO were identified, which are large PFO height measured during a Valsalva maneuver (≥ 2.8 mm), interatrial septum hypermobility (large septal excursion distance or concomitant atrial septal aneurysm), and large right-to-left shunt via the PFO (>20 microbubbles). Unexpectedly, the length of the PFO and the presence of the Eustachian valve or Chiari's network did not differ between the analyzed groups, which undermines many previous concepts trying to determine, hypothetically or based on single-center, small studies, characteristics of high-risk PFOs [27–29].

Factors identified by our meta-analysis seem to indicate the joint mechanism responsible for PFO participation in cerebrovascular ischemic events. The paradoxical embolism phenomenon is an indisputable causative agent in PFO-related embolisms [30]. Several specific conditions must coexist to allow thromboembolism originating in the venous vasculature to travel through the interatrial septum into the systemic circulation. First the thrombus must reach the vicinity of the right aspect of the interatrial septum. The presence of the Eustachian valve, which in fetal life helps direct the flow of oxygenated blood superiorly and anteriorly (to bypass the pulmonary circulation) may theoretically favor paradoxical embolism. On the other hand, the occurrence of the Chiari's network spanned in the right atrium, depending on its position within atrium, may either direct the blood flow (and thrombi) toward the interatrial septum or act as a filter retaining thrombi [31]. Second the thrombus must squeeze through the relatively small tunnel located in the septum to reach the left atrium. The PFO, when present, is functionally closed due to higher blood pressure in left than right atrium [32]. Temporarily increased right atrial pressure opens the PFO. Based on the results of our meta-analyses, it is reasonable to say that multiplane wider opening of the PFO channel, expressed by its larger height and larger shunt, may be the main paradoxical embolism facilitating mechanism. Moreover, the

presence of an atrial septal aneurysm causes drastic increase in PFO patency time, which in these cases opens not only during increased right atrium pressure, but practically every heartbeat. The hypermobile, less fixed, and more elastic septum that is associated with atrial septal aneurysm allows greater change in PFO channel dimensions and thus significantly contributes to the opening of the PFO [33].

The identification of high-risk PFO is crucial for choosing the right prevention or therapy strategies. It is well proven by the DEFENSE-PFO trial that PFO device closure in patients with high-risk PFO (defined as a concomitant presence of atrial septal aneurysm, septum hypermobility or PFO height measured at Valsalva ≥ 2 mm) resulted in significantly better outcomes than pharmacological therapy in secondary stroke prevention [34]. Such a beneficial achievement for secondary stroke prevention brings further questions about the legitimacy of closing the high-risk PFO not only in "cryptogenic" patients but also in those with the presence of other potential causes of ischemic accidents or even for primary cerebrovascular events prevention [35]. Moreover, closure devices should be designed and produced considering the specific morphometric features of the interatrial septum and PFO, which are different in high-risk patients. Finally, it is still debatable whether primary preventive PFO closure should be performed. Indeed, there are no strong data from randomized clinical trials that may support this strategy, but many points to the benefits of preventative PFO closure [36]. The PFO closure for primary prevention should be especially considered in certain high-risk patients, the majority of which are young people. Patients with high tendency for venous thrombosis, vocational or recreational activities fostering right to left shunts (e.g., deep or professional divers, mountain climbers and pilots), unfavorable PFO morphological features or those who can expect a collateral benefit (e.g., migraine patients) should be strongly considered for primary preventive PFO closure [37]. In those cases, early PFO closure is effective, relatively simple, and safe procedure without major adverse effects that may prevent death or permanent disability while being cost-effective in longer perspective [36].

Our meta-analyses are not without limitations, which are caused by the initial imperfections in study design and methods of data reporting of each study included. First, the definition of cryptogenic cerebrovascular accidents was slightly different among the included studies and some discrepancies in the study group and control selection processes might affect the final results (Table 1). Second, due to the way in which the data were reported by

the authors of identified studies, where strokes and transient ischemic attacks were mostly treated as 1 group, we were unable to separate data regarding only cryptogenic stroke; and thus all cerebrovascular accidents were analyzed in the current study. Moreover, our meta-analysis has investigated only those PFO-related parameters, which occurred in at least 3 different studies; therefore, it cannot be excluded that other features (such as septum primum thickness, septum secundum thickness and height, and ratios of selected measurements) may significantly affect an increased risk of cerebrovascular emboli. Additionally, the imaging method used (TEE), although it is recognized as a gold standard in interatrial septum evaluation, may affect the results of our meta-analyses due to potential differences in septum visualization and the views used, and thus modifications in measuring techniques between included studies [38]. Especially the definition of PFO shunt size varies significantly between studies and is highly subjective and poorly reproducible. Moreover, the mean age of the subjects included in each study group differed significantly between the groups and between studies. As the interatrial septum undergoes constant, lifelong remodeling, the size of the PFO may change over time and thus can influence the results of this study [39]. Also, we were unable to analyze for sex and ethnic differences in the PFO morphometry. Finally, the impact of other stroke risk factors (age, sex, comorbidity) and the mutual interaction of PFO morphological factors were not included in our one-factor analyzes, which should be considered in further studies.

In conclusion, our study demonstrated an association between PFO-related morphometric parameters and an increased risk of cryptogenic cerebrovascular accidents. Larger PFO height measured during a Valsalva maneuver and larger septal excursion distance are both associated with stroke-related PFOs. A PFO with concomitant atrial septal aneurysm and large right-to-left shunt via the PFO are risk factors that significantly increase the likelihood of ischemic cerebrovascular accidents.

Statement of Ethics

The ethical approval was not required for this type of study.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.K.H. and M.K.: conception and design of the work; data acquisition and analysis; drafting the manuscript; final approval of the article.

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