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Original Research

Comparison of Patent Foramen Ovale Sizing by Transesophageal Echocardiography and Balloon Sizing in Patients Undergoing Percutaneous Closure

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ABSTRACT

Background: A patent foramen ovale (PFO) has a complex anatomy, and evaluating the size before closure may be challenging. We aimed to investigate the correlation between preprocedural transesophageal echocardiography (TEE) and balloon sizing of PFO in patients undergoing percutaneous PFO closure.
Methods: A retrospective single-center study with analysis of 100 patients who, due to paradox thromboembolism in the left circulation, underwent percutaneous PFO closure. The PFO sizing was compared to measures attained by TEE and balloon sizing using linear regression analysis.
Results: PFO size measured by TEE occurred smaller than balloon sizing (2.19 mm [95% CI: 1.91 to 2.46] vs. 8.51 mm [95% CI: 8.02 to 9.00], $p < 0.001$). Additionally, neither the PFO channel length nor the atrial septal mobility measured by TEE correlated to the PFO size attained by balloon sizing, respectively (slope −0.018 [95% CI: −0.117 to 0.081], R = 0.036, $p = 0.719$) and (slope 0.049 [95% CI: ?0.043 to 0.141], R = 0.105, $p = 0.297$). Statistically significant difference in regression analysis but poor correlation was found between both TEE attained PFO and shunt size when compared to balloon sizing. Diverting patients according to the size of the PFO shunt was not statistically significant between PFO of moderate size compared, respectively, to a large and small PFO size. However, a difference was observed between a small and large PFO shunt size.
Conclusions: PFO defect and shunt size measured by TEE showed a poor correlation with balloon sizing. Neither PFO channel length nor septal mobility were correlated to the PFO size measured by balloon sizing.

ABBREVIATIONS

2D, two-dimensional; LA, left atrium; PFO, patent foramen ovale; RA, right atrium; TEE, transesophageal echocardiography.

Background

Patent foramen ovale (PFO) is a known cause of paradoxical embolism and ischemic stroke. Closure of a PFO effectively reduces the risk of recurrent strokes in selected patients with a prior ischemic stroke.[1–4] The size of a PFO, number of microbubbles shunted to the left atrium (LA), and presence of atrial septum aneurism are considered high-risk factors for occurrence of PFO-related ischemic stroke. Hence, it has been suggested that patients with these features benefit more from PFO closure than patients without high-risk PFO stigmata.[5–7]

Transesophageal echocardiography (TEE) is key in evaluating the presence and features of a PFO, and it is used in the procedural planning prior to percutaneous closure. However, a PFO is a complex anatomical structure, where evaluating the size of the PFO using standard two-dimensional (2D) TEE is difficult.[8] The shunt size is challenging to evaluate precisely due to dependency on the patient's ability to cooperate with the timing of Valsalva's maneuver and whether injection of agitated saline occurs from an upper extremity or lower extremity vein.[9–11] To ensure optimal device size selection for closure, periprocedural interrogation of the interatrial defect can be performed using a compliant

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balloon sizing catheter. This method is considered valid for evaluation of the anatomical PFO size since the compliant balloon makes a precise cask of the PFO channel. It is, however, unknown how well different PFO sizes evaluated by balloon sizing correlate to sizing and shunting evaluated by 2D TEE.

We aimed to investigate the correlation between PFO sizing and shunting by preprocedural 2D TEE and periprocedural balloon sizing using fluoroscopy in patients who underwent percutaneous PFO closure.

Methods

Study Design and Patient Eligibility

The study was designed as a single-center retrospective analysis based on a prespecified screening protocol with the inclusion of a total of 100 patients. Patients who underwent percutaneous PFO closure due to paradoxical thromboembolism were eligible for inclusion. Patients were excluded if TEE or fluoroscopy was unavailable or if TEE imaging quality was insufficient for the prespecified analysis. A total of 192 patients underwent PFO closure during the period from January 2017 through November 2018. Of these, 92 patients were excluded (Figure 1).

Data Collection

The patient's medical history was obtained from the electronic medical patient file. Analysis of TEE and fluoroscopy images was done in Impax Client 6.5.5.1608 (AGFA Healthcare N.V, Belgium) and/or EchoPAC (version 203 GE Healthcare, Horten, Norway). Furthermore, study variables obtained by TEE and fluoroscopy were evaluated by a single observer blinded to patient identification.

Echocardiographic Analysis

Analysis of the PFO anatomy was performed by 2D TEE during the Valsalva maneuver. The section plane was determined to best visualize the PFO channel. Subsequently, measurements of the PFO height and channel length were performed. The height or size was defined as the separation of the primum septum from the secundum septum at the LA end of the PFO channel during maximal septal bulge into the LA, while the channel length was measured when the interatrial septum was displaced into the LA, hence visible to its full extent. Another feature of a PFO is interatrial septal aneurysm, which is defined by a total excursion of the primum septum from the right atrium (RA) into LA of >15 mm or an excursion beyond the septal plane into either LA or RA of >10 mm.[12] Thus, to evaluate the mobility of the interatrial septum, measurements were conducted of the maximal excursion of the primum septum during a cardiac cycle. The shunt size of the PFO was examined through contrast echocardiography using intravenous administration of agitated saline injected into a cubital vein, followed by performance of the Valsalva maneuver. Initially, the contrast echocardiography was performed by transthoracic echocardiography with subsequent TEE repetition. Depending on the number of air bubbles passing through the PFO, the size of the shunt was classified into three sizes according to the classification used in the REDUCE trial, respectively small (1-5 bubbles), medium (6 to 25 bubbles), and large (>25 bubbles).[2] The maximal number of air bubbles appearing in the LA was counted during a single frame within three cardiac cycles, starting from the first appearances of air bubbles in RA.

All PFO closure procedures were guided by intracardiac echocardiography with sizing balloon inflated using the stop-flow method (Figure 2). Periprocedural measurements of the anatomical PFO size were conducted by fluoroscopy in anterior-posterior view. The size was defined as the minimum diameter of the sizing balloon (PTS Numed, 25 mm).

An interobserver variability test was performed by two observers, both blinded to patient identification, measuring all variables in 10 randomly selected patients.

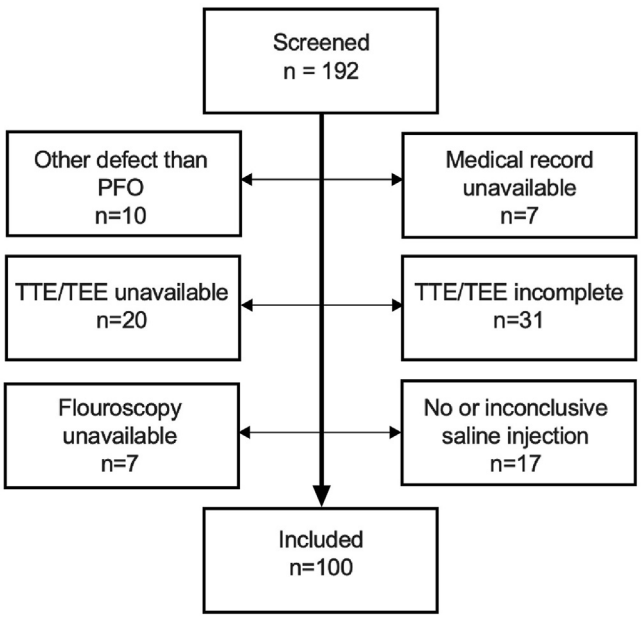

Figure 1. Flow chart of study inclusion.
Abbreviations: PFO, patent foramen ovale; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Statistics

The correlation between the measurements obtained by balloon sizing and the different parameters measured from TEE (length, height, interatrial septum mobility, and shunt size) was evaluated through linear regression and one-way analysis of variance using IBM SPSS version 26. Thus, with a 95% CI and correlation coefficient defined as Pearson's R, the results were expressed as slope and continued variables as mean with the correlation.

The assumption of homogeneity of variances between the prespecified shunt size was analyzed using Levene's *F* test. Subsequently, a boxplot comparing fluoroscopy and the three different PFO sizes defined by the numbers of bubbles occurring using saline contrast was created in Graph Pad Prism (version 7.0c) and analyzed using one-way analysis of variance as well as multi comparison t-test between each group.

Interobserver variability was tested for the TEE measurements regarding PFO channel length, height, and shunt size using Bland-Altman analysis plotted as difference vs. average.

Results

Patient Characteristics

As indicated in the flowchart (Figure 1), 100 patients fulfilled the inclusion criteria and had both TEE and fluoroscopy imaging available for analysis. The patient characteristics are presented in Table 1. There was a predominance of men and a mean age of 48.7 ± 11.3 years. The most frequently observed comorbidity was hypercholesterolemia (56%), whereas diabetes mellitus (5%), hypertension (27%), migraine (11%), previous myocardial infarction (4%), and current smoking status (18%) occurred to a lesser extent. The primary thromboembolic event was due to ischemic stroke (74%), while only 19% occurred as transient ischemic attack and 7% as a systemic embolism. Echocardiographic morphology of the interatrial septum

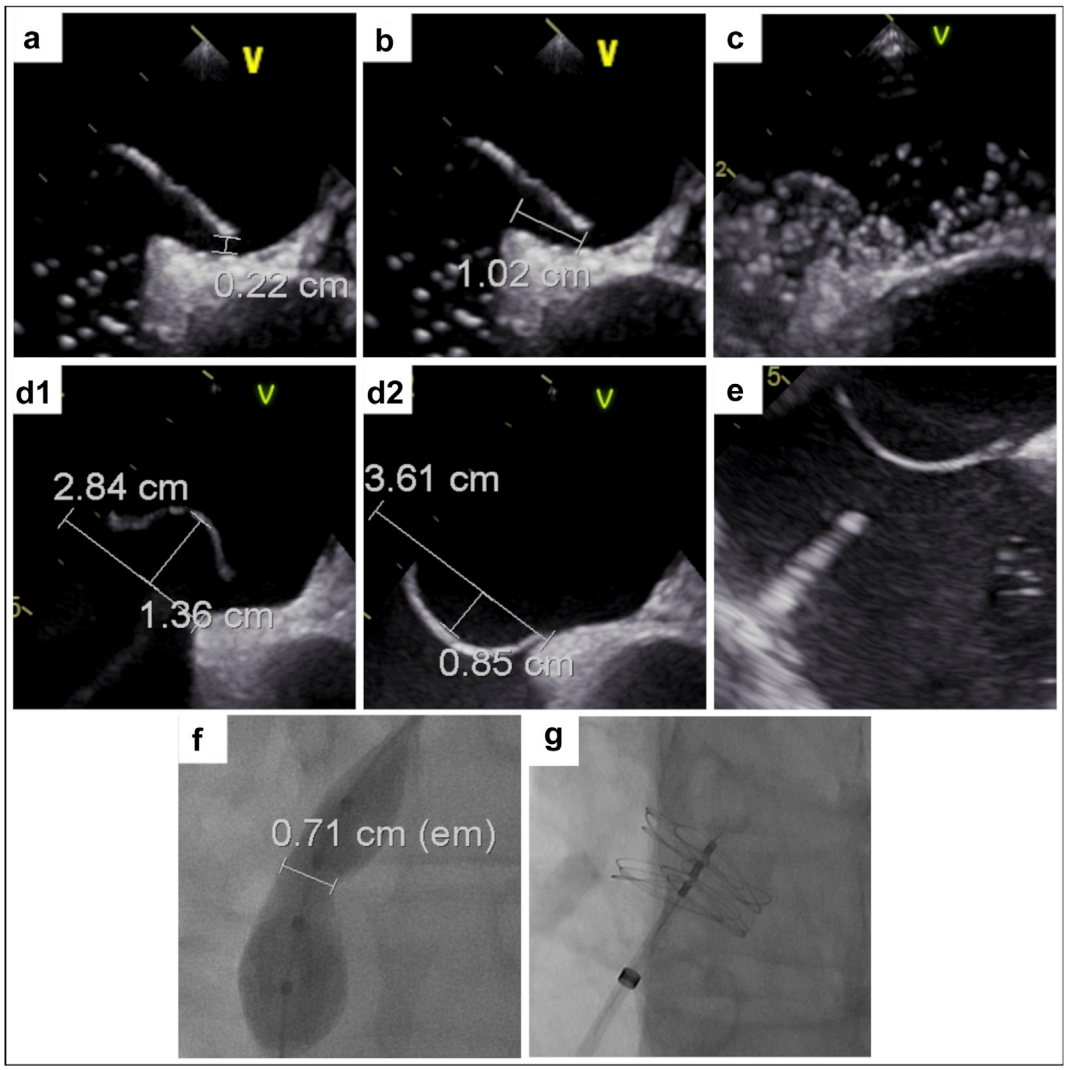

Figure 2. Echocardiography and fluoroscopy analysis. (a) PFO diastasis. (b) PFO length. (c) Bubbles shunted through a PFO. (d1 and d2) Atrial septum aneurysm with a combined deviation of 22 mm. (e) Large Eustachian valve inhibiting the contrast from reaching the septum. (f) Balloon sizing. (g) PFO occluder in situ. Abbreviation: PFO, patent foramen ovale.

observed included atrial septal aneurism (11%), fenestrations (2%), Chiari network (7%), and Eustachian valve (26%). PFO size attained by balloon sizing had a mean of 8.5 ± 2.5 mm, while size measured by TEE were smaller, 2.2 ± 1.4 mm. In 23 patients a small shunt was present, 45 patients had a medium shunt and 32 patients had a large shunt.

Device Selection and Closure

Device size was chosen based on balloon sizing and anatomy evaluated by intracardiac echocardiography. The devices used were mainly Gore Septal occluder (n = 86), ABBOTT Amplatzer PFO occluder (n = 8), or ABBOTT Amplatzer ASD occluder (n = 6).

The effect on closure was evaluated at a 3-month follow-up TEE, where a complete seal was found in 78 patients. Of the remaining patients, 15 patients had a residual shunting of 0 to 5 bubbles, 3 patients of 6 to 20 bubbles, and 4 patients had a shunt with more than 20 bubbles.

Balloon Sizing and Echocardiographic Evaluation of PFO Size

The PFO size measured by TEE was smaller than the corresponding measurements attained by balloon sizing (2.19 mm [95% CI: 1.91 to 2.46] vs. 8.51 mm (95% CI: 8.02 to 9.00), $p < 0.001$). Neither PFO channel length nor atrial septal mobility correlated with the PFO height (slope -0.018 [95% CI: −0.117 to 0.081], R = 0.036, $p = 0.719$) and (slope 0.049 [95% CI: −0.043 to 0.141], R = 0.105, $p = 0.297$). A difference was found between the PFO size measured by TEE and fluoroscopy. However, the correlation for the size between TEE and fluoroscopy was poor, which also occurred when comparing the shunt size to the balloon sizing (Figure 3a and b).

A difference was observed between the small and large PFO size (Figure 3c) but not between the large and small shunt size compared to the medium size when comparing the PFO size groups to balloon sizing (Figure 3c).

Interobserver Variability Analysis

Comparing the interobserver variability for the 2D TEE measurements using Bland-Altman plot analysis showed reasonable results for PFO channel length and shunt size. However, when looking at the PFO size, which was defined as the separation between septum primum and secundum, it showed tendency toward overestimation of the PFO size. The Bland-Altman plots of the interobserver variability analysis are presented in Figure 4.

Table 1
Patient characteristics

Patient Characteristics	n = 100
Age, years ± SD	48.7 ± 11.3
Male gender, n (%)	70 (70%)
Medical history	
Diabetes, n (%)	5 (5%)
Hypertension, n (%)	27 (27%)
Current smoker, n (%)	18 (18%)
Hypercholesterolemia, n (%)	56 (56%)
Migraine, n (%)	11 (11%)
Myocardial infarction, n (%)	4 (4%)
Tromboembolic Event	
Ischemic stroke, n (%)	74 (74%)
Transient ischemic attack, n (%)	19 (19%)
Systemic embolism, n (%)	7 (7%)
Morphology of the Atrial Septum	
Atrial septum aneurism, n (%)	11 (11%)
Fenestrations, n (%)	2 (2%)
Chiari network, n (%)	7 (7%)
Eustachian valve, n (%)	26 (26%)

Discussion

We found a poor correlation between PFO sizing and shunting evaluated by preprocedural 2D TEE compared to periprocedural balloon sizing using fluoroscopy in patients who underwent percutaneous PFO closure.

The patients included in the analysis were in their late 40s and with predisposition of a few cardiopulmonary risk factors of which hypercholesterolemia and hypertension were predominant. The primary reason for PFO closure was a result of a prior ischemic stroke and the shunt size of the PFOs were predominantly moderate or large. Compared to the REDUCE and RESPECT trials, these baseline features were very similar with the exception of a higher proportion of hypercholesterolemia in our population.[2,3] Hypercholesterolemia was defined based on concurrent treatment with statins and could merely reflect a prior stroke and the subsequent initiation of standard care including statin treatment.

Balloon sizing of the PFO revealed four times larger PFO size and poor correlation to the size of the PFO measured as separation height between the PFO septum primum and secundum septum by 2D TEE. This finding is in itself not surprising, since a PFO anatomically is a very complex structure and it is further supported by other studies, where advanced periprocedural three-dimensional TEE estimated a significantly larger anatomical PFO size than measured by 2D.[8,13,14] Despite that the separation height between the PFO septum primum and secundum septum measured by TEE has been used to measure PFO size in key clinical trials, these findings suggest that patient selection and procedural planning based on 2D TEE entity alone should be done very cautiously.[1–4]

The PFO ability to right-to-left shunting might be the most important risk factor, when considering the pathophysiology behind paradoxical embolism. The correlation between the shunt size and the anatomical size measured by fluoroscopy is poor, and hence emphasizing that the number of microbubbles shunted is not solely determined by the physical size of a PFO. It is well known, that the number of bubbles shunted are highly dependent on the patient's ability to perform and the timing of the Valsalva's maneuver, as well as whether the agitated saline injection is through an upper or lower extremity vein, of which the sensibility of detecting a PFO is greater when using the right femoral vein for saline administration.[9–12] To some extend the poor correlation can be explained by this.

Our findings support the findings by Kumar et al.[14] who also reported a clear difference between TEE and balloon sizing, but the differences we report are more modest. We find a 4x difference between TEE and balloon sizing (2.2 vs. 8.5 mm), whereas Kumar et al. reported a 7x difference (1.5 vs. 10.5 mm). Main difference between our studies and potential explanations are different imaging types for the included patients with a mix of TEE and intracardiac imaging by Kumar et al. and TEE only from our report as well as an inconsistent use of Valsalva maneuver by Kumar et al. vs. Valsalva in all patients in our report. Despite these differences, the overall conclusion of the studies is similar emphasizing the importance of caution in the planning of PFO closure based on TEE measurements only.

The mobility of the atrial septum and the length of the PFO channel evaluated by 2D TEE do not correlate with the anatomical balloon size, suggesting that these measurements are independent of the anatomical PFO size. This could support the recent results from the CLOSE and

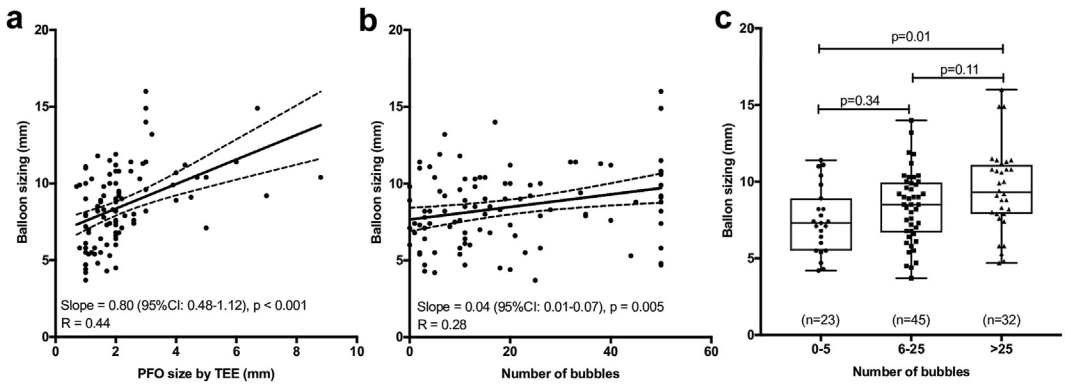

Figure 3. Correlation between PFO balloon sizing and respective PFO size and shunt size measured by TEE. Linear regression analysis of (a) PFO size and (b) shunt size measured by transesophageal echocardiography and balloon sizing. (c) Boxplot of shunt size and balloon sizing. Each column illustrates the mean and the quartile distribution of balloon sizing.
Abbreviations: PFO, patent foramen ovale; TEE, transesophageal echocardiography.

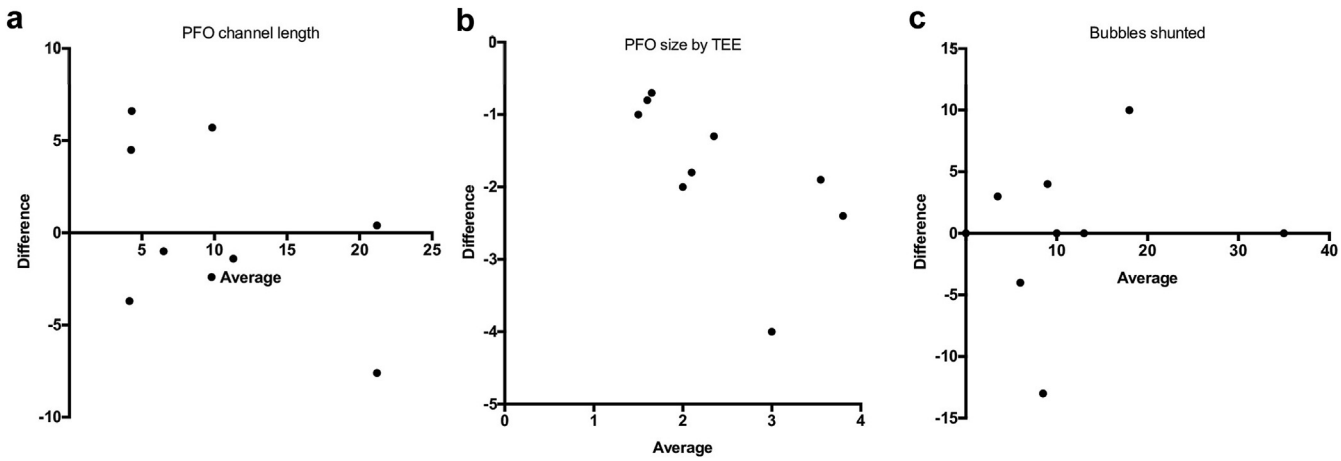

Figure 4. Interobserver variability. Bland-Altman plots of difference vs. average in assessment of echocardiographic interobserver variability of 10 randomly selected patients analyzed by two observers blinded to outcome. (a) PFO channel length. (b) PFO size by transesophageal echocardiography. (c) Bubbles shunted. Abbreviations: PFO, patent foramen ovale; TEE, transesophageal echocardiography.

DEFENSE-PFO trials, which showed that atrial septal aneurysm, not shunt size, was the most important predictor for recurrent stroke.[5] Even though, the recurrent stroke risk is reported to be 2.6% or 0.98 recurrent strokes per 100 patient years for patient undergoing PFO closure due to paradoxal embolism, it is still unknown how the true anatomical size of a PFO correlates to the recurrence of stroke.[15]

Limitations

All data were collected retrospectively. The echocardiographic parameters were measured from clinical scans without using a strict echocardiographic protocol. This detail may act as a confounder for the shunt size evaluation, since the ability for patients to perform proper Valsalva maneuver, presence of an Eustachian valve as well as the timing of agitated saline injection are important to optimize the visualization of the PFO shunting potential. Agitated saline was injected through a cubital vein in all patients, even though injection through a femoral vein has shown higher sensitivity for PFO detection, due to shunting of more microbubbles through the PFO compared to cubital veins.[12]

The interobserver variability found reasonable results for PFO channel length and shunt size but was not consistent in measuring PFO size defined as the separation between septum primum and secundum. Thus, emphasizing the importance of caution when using this parameter in the planning of PFO treatment.

Last but not least, the study was not powered to evaluate if prober sizing correlates to clinical outcomes.

Conclusions

Defect and shunt size of a PFO measured by TEE showed a poor correlation with PFO size determined by balloon sizing. PFO channel length and septal mobility did not correlate to the size of a PFO measured by balloon sizing.

Availability of Data and Material

The datasets used during the current study are available from the corresponding author on reasonable request.

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Ethics Statement

The study conformed to the Declaration of Helsinki and the Danish Data Protection Act and was approved by the institution Aarhus University Hospital according to local and ethical laws.

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Disclosure Statement

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References

1 Mas JL, Derumeaux G, Guillon B, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med.* 2017;377(11):1011-1021. https://doi.org/10.1056/nejmoa1705915
2 Sondergaard L, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med.* 2017;377(11):1033-1042. https://doi.org/10.1056/NEJMoa1707404
3 Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med.* 2017;377(11):1022-1032. https://doi.org/10.1056/NEJMoa1610057
4 Lee PH, Song JK, Kim JS, et al. Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial. *J Am Coll Cardiol.* 2018;71(20):2335-2342. https://doi.org/10.1016/j.jacc.2018.02.046
5 Turc G, Lee JY, Brochet E, et al, CLOSE and DEFENSE-PFO Trial Investigators. Atrial septal aneurysm, shunt size, and recurrent stroke risk in patients with patent foramen ovale. *J Am Coll Cardiol.* 2020;75(18):2312-2320. https://doi.org/10.1016/j.jacc.2020.02.068
6 Pristipino C, Sievert H, D'ascenzo F, et al. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. *Eur Heart J.* 2019;40(38):3182-3195. https://doi.org/10.1093/eurheartj/ehy649
7 Kent DM, Saver JL, Kasner SE, et al. Heterogeneity of treatment effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke. *JAMA.* 2021;326(22):2277-2286. https://doi.org/10.1001/jama.2021.20956
8 Rana BS, Shapiro LM, McCarthy KP, Ho SY. Three-dimensional imaging of the atrial septum and patent foramen ovale anatomy: defining the morphological phenotypes of patent foramen ovale. *Eur J Echocardiogr.* 2010;11(10):i19-i25. https://doi.org/10.1093/ejechocard/jeq122
9 Mojadidi MK, Bogush N, Caceres JD, et al. Diagnostic accuracy of transesophageal echocardiogram for the detection of patent foramen ovale: a meta-analysis. *Echocardiography.* 2014;31(6):752-758. https://doi.org/10.1111/echo.12462
10 Marriott K, Manins V, Forshaw A, et al. Detection of right-to-left atrial communication using agitated saline contrast imaging: experience with 1162 patients and

recommendations for echocardiography. *J Am Soc Echocardiography*. 2013;26(1):96-102. https://doi.org/10.1016/j.echo.2012.09.007

11 Hamann GF, Schätzer-Klotz D, Fröhlig G, et al. Femoral injection of echo contrast medium may increase the sensitivity of testing for a patent foramen ovale. *Neurology*. 1998;50(5):1423-1428. https://doi.org/10.1212/wnl.50.5.1423

12 Silvestry FE, Cohen MS, Armsby LB, et al. Guidelines for the echocardiographic assessment of atrial septal defect and patent foramen ovale: from the American Society of Echocardiography and Society for Cardiac Angiography and Interventions. *J Am Soc Echocardiogr*. 2015;28(8):910-958. https://doi.org/10.1016/j.echo.2015.05.015

13 Demulier L, Paelinck BP, Coomans I, et al. A new dimension in patent foramen ovale size estimation. *Echocardiography*. 2020;37(7):1049-1055. https://doi.org/10.1111/echo.14696

14 Kumar P, Rusheen J, Tobis JM. A comparison of methods to determine patent foramen ovale size. *Catheter Cardiovasc Interv*. 2020;96(6):E621-E629. https://doi.org/10.1002/ccd.28665

15 Sørensen H, Grove EL, Hojbjerg JA, et al. Recurrent ischemic stroke/transient ischemic attack after patent foramen ovale closure: A cohort study. *Int J Stroke*. 2024, 17474930241281120. https://doi.org/10.1177/17474930241281120