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Brief Title: **Long-term Outcomes After Percutaneous Closure of PFO**

Official Title: **Long-term Echocardiographic and Clinical Outcomes After Percutaneous Closure of Patent Foramen Ovale**

Study Protocol and Statistical Analysis Plan

1 September 2022

This is a single-centre observational study performed at MC Medicor International Center for Cardiovascular Diseases (Izola, Slovenia).

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia *(No. 0120-46/2022/9).* All procedures were performed in accordance with the Declaration of Helsinki.

Indications for percutaneous PFO closure were discussed by the institutional PFO team, comprising the referring physician, vascular neurologist, dedicated echocardiographer and interventional cardiologist, as described previously. Briefly, patients were eligible for percutaneous closure if they were aged ≥18 years, had CVI documented on CT or MRI, or TIA and PFO documented by TOE. Patients were routinely screened for other possible causes of CVI/TIA, including large vessel disease, such as aortic/carotid atherosclerosis, hypercoagulable state and paroxysmal AF, with 24-hour Holter monitoring if such events were suspected. If mechanisms other than paradoxical embolisation or lacunar infarct due to intrinsic small vessel disease were identified, PFO closure was not attempted.

PFO closure was performed in the cath lab by dedicated interventional cardiologists and echocardiographers. Conscious sedation without endotracheal intubation was used and the procedure was guided by fluoroscopy and TOE. After femoral vein access was achieved, a 6Fr multipurpose catheter (Cordis; Johnson & Johnson) was advanced over a J-tipped 0.035-inch guidewire (Cook Medical) into the right atrium and through the PFO into the left upper pulmonary vein. If PFO crossing was not successful with the J-tipped wire, a 0.038-inch hydrophilic wire (Radiofocus Guidewire M; Terumo) was used. After crossing the PFO, a weight-adjusted bolus of unfractionated heparin was administered and the wire was exchanged for a long, Amplatz Super Stiff guidewire (Abbott Vascular). Balloon sizing was left to the discretion of the operators. Different closure devices, including StarFLEX/BioSTAR (NMT Medical), FlatStent EF (Coherex), Occlutech (Occlutech) and the Amplatzer PFO occluder (Abbott Vascular), were used. Device selection was left to the discretion of the interventional cardiologist and echocardiographer and was based on the morphology of the PFO and adjacent structures, as well as the availability of a particular closure device. None of the patients received a dedicated occluder for atrial septal defect closure. Devices were implanted according to the manufacturers' instructions. Appropriate device shape and positioning were documented by fluoroscopy and TOE. After the procedure, patients received a loading dose of 300 mg clopidogrel, followed by 75 mg/day clopidogrel for 6 months and lifelong acetylsalicylic acid at 100 mg/day. Endocarditis prophylaxis was recommended for 6 months after device implantation.

Immediate postprocedural PFO closure was investigated by TOE with the patient still on the cath lab table using a bubble study during the Valsalva manoeuvre or by applying and releasing hand pressure at the right upper abdomen. The bubble study was performed by injecting 10 ml of a mixture of saline (8 ml), patient blood (1 ml) and room air (1 ml) through the femoral sheath. The degree of right-to-left shunting was graded

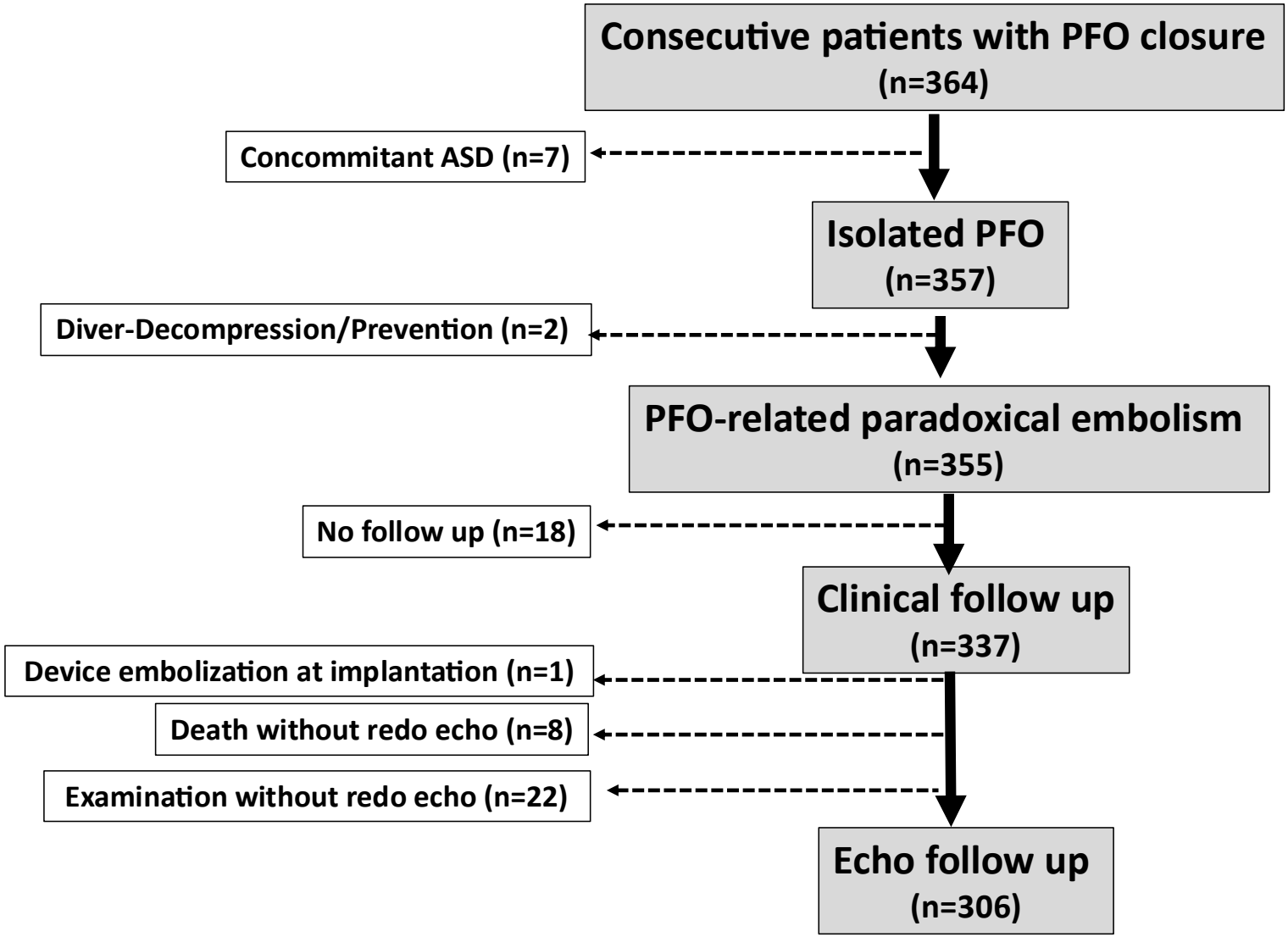
according to the appearance of bubbles in the left atrium within six cardiac cycles after right atrial opacification as large (>20 bubbles), moderate (10–20 bubbles) or small (<10 bubbles). Functional PFO closure was defined as ≤10 bubbles.

All patients underwent transthoracic echocardiography (TTE) with a bubble study at 6 months. **(Picture 1)** The TTE bubble study was performed by injecting 10 ml of the saline–blood–air mixture described above into the right cubital vein. At the time of the rapid injection, the patient's arm was raised. The appropriateness of the Valsalva manoeuvre was confirmed by the shift of the interatrial septum from the right to the left atrium. The degree of right-to-left shunting was graded as described above using a four-chamber apical view. The study was repeated at least three times. In addition to residual shunting, device position, morphology, possible thrombus formation and the presence of pericardial effusion were evaluated. Additional echocardiography (TOE or TTE) with a bubble study beyond 6 months was performed at the discretion of the patient's cardiologist or neurologist and with the patient's agreement. **(Picture 2)**

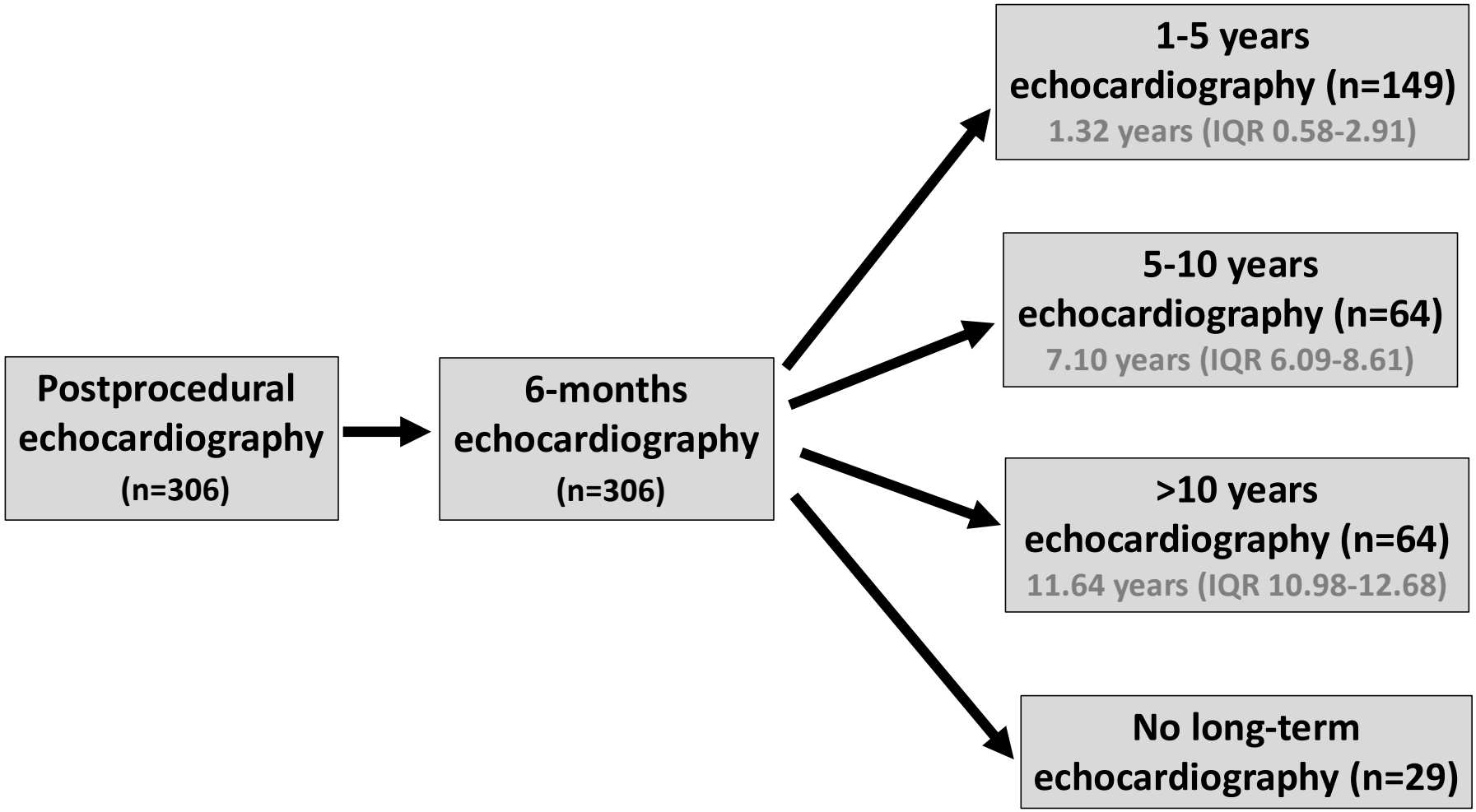
Patients with at least moderate residual shunt (>10 bubbles during the Valsalva manoeuvre) underwent further diagnostic investigations, starting with TOE to define device–interatrial septum morphology and interaction, as well as the site of eventual leakage. If TOE did not reveal the cause of right-to-left shunting, pulmonary CTA was performed to document possible pulmonary arteriovenous malformation.

Clinical events during follow-up were documented on the basis of patient interviews, examinations and review of outpatient and hospital records.

Continuous variables are presented as the mean±SD or as median with interquartile range (IQR) depending on their distribution. Categorical variables are presented as numbers with percentages. Continuous variables were compared using unpaired two-tailed t-tests, whereas categorical variables were compared using $\chi 2$ or Fisher's exact test. The McNemar Chi-squared test for dependent samples was used to compare echocardiographic closure rates at different time periods. In all cases, two-tailed $p<0.05$ was considered significant.



Picture 1. Enrollment of patients after percutaneous closure of patent foramen ovale with exclusion criteria.



Picture 2. Transthoracic echocardiography with contrast protocol after percutaneous closure of patent foramen ovale, with median and interquartile range.