Supplementary Material 1. Recently published data from patent foramen ovale closure in elderly patients

A systematic literature search was conducted to identify recently published outcomes from transcatheter patent foramen ovale (PFO) closure in patients of 60 years or older.

Design of the literature search

- Literature search performed in PubMed
- Published after January 1, 2020
- Search terms:
  - "patent foramen ovale"
  - "closure"
  - "elderly" OR "over 60" OR "over 65"
  - "old patients" OR "older patients" OR "old stroke patients" OR "older stroke patients"
- Inclusion criteria:
  - Including patients ≥60 years of age
  - Only PFO closure (i.e., excluding atrial septal defect closure)
  - Reporting on long-term outcomes (≥1 year)
  - Comparing outcomes in elderly versus younger patients and/or PFO closure versus medical therapy
  - Full papers on single study, excluding letters to the editor, meta-analyses, editorials, etc.

Results

A total of 78 unique references were identified. After review against the inclusion criteria, 8 studies were selected. A summary of these studies is provided in Supplementary Table 1.

Supplementary References

1. Alperi A, Guedeney P, Horlick E, Nombela-Franco L, Freixa X, Pascual I, et al. Transcatheter closure of patent foramen ovale in older patients with cryptogenic thromboembolic events. *Circ Cardiovasc Interv* 2022;15:e011652.
2. Chen PL, Wang CS, Huang JA, Fu YC, Liao NC, Hsu CY, et al. Patent foramen ovale closure in non-elderly and elderly patients with cryptogenic stroke: a hospital-based cohort study. *Front Neurol* 2023;14:1190011.
3. Eichelmann A, Kubini R, Nachoski D, Kosinski C, Becker M, Aljalloud A. Patent foramen ovale closure versus drug therapy in patients over 60 years and a follow-up of 5 years. *Clin Cardiol* 2024;47:e24251.
4. Farjat-Pasos JI, Guedeney P, Horlick E, Abtan J, Nombela-Franco L, Hibbert B, et al. Determinants of adverse outcomes following patent foramen ovale closure in elderly patients. *EuroIntervention* 2024;20:1029-1038.
5. Gili S, Calligaris G, Teruzzi G, Santagostino Baldi G, Muratori M, Montorsi P, et al. Patent foramen ovale occlusion in elderly patients: is it worth it? A large, single-center retrospective analysis. *J Clin Med* 2024;13:3514.
6. Lee PH, Kim JS, Song JK, Kwon SU, Kim BJ, Lee JS, et al. Device closure or antithrombotic therapy after cryptogenic stroke in elderly patients with a high-risk patent foramen ovale. *J Stroke* 2024;26:242-251.
7. Nachoski D, Schroeder J, Almalla M, Kubini R, Tchaikovski V, Kosinski C, et al. Dual-center experiences with interventional closure of patent foramen ovale: a medium-term follow-up study comparing two patient groups aged under and over 60 years. *Clin Cardiol* 2021;44:386-391.
8. Wintzer-Wehekind J, Alperi A, Houde C, Côté JM, Del Val D, Côté M, et al. Transcatheter closure of patent foramen ovale in patients older than 60 years of age with cryptogenic embolism. *Rev Esp Cardiol (Engl Ed)* 2020;73:219-224.

Supplementary Table 1. Overview of recently published studies on PFO closure including elderly patients

Study	Description	Treatment	Age [yrs]*	Outcomes	Notes
Alperi et al.[1]	Multicenter, non-randomized retrospective study. Inclusion: consecutive patients with a presumed PFO-associated stroke. Outcomes compared between patients ≤60 and >60 years of age.	All patients (n=1,271) underwent PFO closure.	≤60 years (n=883) 44±10 >60 years (n=388) 67±5	Both age groups had 99.9% rate of successful implantation and similar rates of in-hospital complications (<2%) including paroxysmal episodes of procedural AF. At a median follow-up of 3 years, patients >60 years had a significantly higher rate of the composite of TIA, stroke, and peripheral embolism, compared to younger patients (1.61 vs. 0.34 per 100 PY, *P*=0.001) and a higher incidence of AF (2.66 vs. 0.49 per 100 PY, *P*=0.001). The incidence of cerebrovascular ischemic events in patients >60 years was lower than expected according to their RoPE score, although higher than the observed incidences in younger patients.	- Older patients more frequently had a moderate/severe shunt (89.7% vs. 63%, *P*=0.001) and a higher ASA prevalence (61.4% vs. 43.3%, *P*=0.001).
Chen et al.[2]	Single-center, non-randomized cohort study, data from prospective stroke registry. Inclusion: Cryptogenic stroke/TIA, PFO. Outcomes compared between patients <60 and ≥60 years of age.	PFO closure and medical therapy (n=97) Medical therapy alone (n=76)	53.6±14.4 36.1% ≥60 60.2±14.9 56.6% ≥60	Rates of device-related adverse events and periprocedural AF were low overall, and non-significantly higher in patients ≥60 years. In both age groups, PFO closure was associated with a non-significantly lower rate of the composite of recurrent cerebral ischemic events and all-cause mortality at 2.5 years, compared to medical therapy. Relative benefits were greater in patients ≥60 years (23.3% vs. 8.6%). In patients ≥60 years, but not in patients <60 years, PFO closure was associated with significantly lower mRS at 180 days compared to medical therapy alone.	- Patients treated with PFO closure had larger shunts than those treated with medical therapy alone (moderate/large shunts: 80.4% vs. 29.0%). This was the case in patients <60 years (80.7% vs. 18.2%) and in patients ≥60 years (80.0% vs. 37.2%).
Eichelmann et al.[3]	Non-randomized, retrospective study. Inclusion: embolic stroke/TIA and PFO. All patients ≥60 years of age.	PFO closure and medical therapy (n=143) Medical therapy alone (n=199)	67±5 65±6	Non-significant difference in rate of new-onset AF (5.5% vs. 3% in patients undergoing PFO closure and medical treatment, respectively). Procedure-related adverse events in 4%. At mean follow-up of 5.5 years, PFO closure was associated with a significantly lower rate of recurrent stroke or TIA, compared with medical therapy (2% vs. 6%, *P*=0.021).	- No significant differences in PFO size between patients undergoing PFO closure and those treated with medical therapy alone. - Part of follow-up data was collected by phone calls with patients and physicians (recall bias).
Farjat-Pasos et al.[4]	Multicenter, non-randomized, retrospective study. All patients >60 years of age. Inclusion: diagnosed with cryptogenic thromboembolic event (ischemic stroke, TIA, peripheral embolism).	All patients (n=689) underwent PFO closure.	Median: 65 (IQR: 62–69)	Procedural success rate: 99.4%. Overall procedure-related complication rate: 2.6%. Procedural complications included major vascular complication (n=1), AF (8), stroke (1), MI (2), tamponade (1), device embolization (4), and in-hospital death (1). At a median follow-up of 2 years, the rate of stroke/TIA was 1.21 per 100 PY, stroke rate: 0.55 per 100 PY. 8/14 strokes were non-lacunar, of which 6 were cryptogenic. One non-lacunar stroke was attributed to late PFO closure device thrombosis. New-onset AF: 3.3 per 100 PY; 51.4% of AF episodes occurred during the month following PFO closure. Bleeding occurred at a rate of 0.77 per 100 PY. Mortality: 2.38 per 100 PY, most common cause of death was cancer-related.	

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Supplementary Table 1. Continued

Study	Description	Treatment	Age [yrs]*	Outcomes	Notes
Gili et al.[5]	Single-center, non-randomized, retrospective, observational study. Inclusion: indication according to clinical practice and consensus documents. Outcomes compared between patients <65 and ≥65 years of age.	All patients (n=462) underwent PFO closure.	Median: 45 years (IQR: 37–54) 64 (13.9%) patients ≥65 years had a median age of 69 years (IQR: 66.8–71.0)	Similar procedural characteristics between elderly and non-elderly patients, except for a significantly shorter procedure time for elderly patients (median: 21 vs. 24 min). Similar rates of peri-procedural events, including AF/SVT and device embolization (7.8% vs. 7.9% in elderly and younger patients, respectively). No recurrent events in patients ≥65 years, 2 TIAs in patients <65 years. New-onset AF in 3 and 8 patients <65 and ≥65 years, respectively. Significantly higher all-cause mortality in patients ≥65 years, largely attributable to age itself.	- Similar prevalence of moderate/severe shunts between elderly and non-elderly patients.
Lee et al.[6]	Multicenter, non-randomized, retrospective study. Inclusion: patients ≥60 years with cryptogenic ischemic stroke and a PFO.	PFO closure and medical therapy (n=161) Medical therapy alone (n=276)	66.2±5.2 69.2±6.7	PFO closure was associated with significantly lower incidence rate of ischemic stroke or TIA at median follow-up of 3.9 years, compared to medical therapy alone (3.98 vs. 2.24 per 100 PY, *P*=0.034). Atrial fibrillation was significantly more frequent in patients undergoing PFO closure compared to medical therapy alone (2.45 vs. 0.95 per 100 PY, *P*=0.030). Outcomes from a propensity score-matched analysis were similar to those from the overall cohort. Specifically in patients with a high-risk PFO, closure was associated with lower risk for both the composite of ischemic stroke or TIA and ischemic stroke alone.	- Compared to patients on medical therapy, patients undergoing PFO closure had a significantly higher prevalence of ASA (30.4% vs. 18.8%, *P*=0.008) and a higher prevalence of a large sized shunt (88.2% vs. 51.8%, *P*<0.001). - High-risk PFO: presence of ASA or a large shunt.
Nachoski et al.[7]	Retrospective, non-randomized observational study. Inclusion: PFO and ≥1 documented presumed paradoxical thromboembolic event. Outcomes compared between patients <60 and ≥60 years.	All patients underwent PFO closure (n=293)	<60 years (n=192) 47±6 ≥60 years (n=101) 67±4	Similar rate of periprocedural complications in patients <60 and ≥60 years (4% and 5%, respectively, *P*=0.772). At a mean follow-up of 3.6 years, patients <60 and ≥60 years had similar rates of recurrent thromboembolic events (1% and 2%, respectively, *P*=0.112) and new-onset AF (3.6% vs. 4.0%, *P*=0.662).	- Some data reported in this study may also have been included in the PFO-group reported by Eichelman et al.[3]
Wintzer-Wehekind et al.[8]	Retrospective, non-randomized observational study. Inclusion: cryptogenic embolism (stroke, TIA, peripheral embolism).	All patients underwent PFO closure (n=475).	≤60 years (n=385) 44±10 >60 years (n=90) 66±5	No statistically significant differences in procedural and in-hospital outcomes between the age groups. Patients >60 years: 100% successful device implantation, mild residual shunt at discharge in 14.4%. 1 in-hospital complication (major vascular complication). At median follow-up of 8 years: significantly higher all-cause mortality in patients >60 years (adjusted HR: 4.58). All deaths were non-cardiovascular. No significant differences in rates of other events between age groups (adjusted for risk factors), although there was a tendency toward a higher incidence of stroke/TIA in older patients, partially related to cardiovascular risk factor burden. In both age groups, the observed rate of stroke/TIA was lower than estimated by RoPE score.	- Some data presented in this study may have been included also in the multicenter study reported by Alperi et al.[1] - Patients >60 years have non-significantly higher prevalence of moderate/severe shunt (81.1% vs 76.1%) and presence of atrial septal aneurysm (41.1% vs. 32.2%).

PFO, patent foramen ovale; AF, atrial fibrillation; TIA, transient ischemic attack; RoPE, Risk of Paradoxical Embolism; PY, patient years; ASA, atrial septal aneurysm; mRS, modified Rankin Scale; IQR, interquartile range; MI, myocardial infarction; SVT, supraventricular tachycardia; HR, hazard ratio.
*Mean±standard deviation age, unless specified otherwise.