



Supporting Information

Supplementary material

This appendix was part of the submitted manuscript and has been peer reviewed.
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Appendix to: Cho KK, Khanna S, Lo P, et al. Persistent pathology of the patent foramen ovale: a review of the literature. *Med J Aust* 2021; doi: 10.5694/mja2.51141.

Appendix 1

Search strategy

We searched the literature for studies exploring the indications, approaches and complications of PFO closure using terms including patent foramen ovale, stroke, migraine, closure, complications, indications, through the databases PubMed, Medline, and the Cochrane Database of Systematic Reviews from database inception to May 2020. We searched the grey literature using Google Scholar. We also reviewed the reference lists of identified articles. For topics with numerous studies, emphasis was placed on larger trials and meta-analysis published in major journals within the last 5 years.

Table 1: Persistent pathology of the patent foramen ovale (PFO)

PFO-associated pathology	Mechanism of pathology and rationale for closure	Studies exploring indication	Details of studies	Main findings
PFO-associated stroke	▪ Mechanism: Occurs due to paradoxical embolism. ▪ Rationale: Closure to prevent further episodes of ischaemic stroke	▪ CLOSURE I¹ ▪ PC Trial² ▪ RESPECT trial³ ▪ CLOSE trial⁴ ▪ DEFENSE-PFO trial⁵	▪ CLOSURE I: control $n = 462$, intervention $n = 447$. Device: STARFlex Septal Closure System. This device is discontinued due to higher rates of residual shunt and thrombus formation. ▪ PC Trial: control $n = 210$, intervention $n = 204$. Device: Amplatzer PFO occluder. The inclusion of TIA as an endpoint may have resulted in dilution of effects. ▪ RESPECT trial: control $n = 481$, intervention $n = 499$. Device: Amplatzer PFO occlusion. High and unequal dropout. ▪ CLOSE trial: control $n = 235$, intervention $n = 238$. Device: all commercially available devices. Included only PFO with high risk features. ▪ DEFENSE-PFO trial: control $n = 60$, intervention $n = 60$. Device: Amplatzer PFO occlude. Included only PFO with high risk features	▪ CLOSURE I and PC Trial: PFO closure did not reduce rate of recurrent TIA or stroke, nor all-cause mortality ▪ RESPECT trial: In the intention-to-treat population PFO closure to be superior to medical therapy with number needed to treat of 42 patients to prevent a stroke in 5 years ▪ CLOSE trial: PFO closure superior to medical therapy for ischaemic stroke with number needed to treat of 20 patients to prevent a stroke in 5 years ▪ DEFENSE-PFO trial: PFO closure superior to medical therapy for ischaemic stroke with number needed to treat of 10 patients to prevent a stroke in 5 years
Migraine	▪ Mechanism: Unclear Rationale: Decrease symptoms	▪ PRIMA trial⁶ ▪ PREMIUM trial⁷ ▪ MIST trial⁸	▪ PRIMA trial: control $n = 54$, intervention $n = 53$ ▪ PREMIUM trial: control $n = 103$, intervention $n = 117$ ▪ MIST trial: control $n = 74$, intervention $n = 73$	▪ No differences in freedom from migraine from individual studies
Platypnoea-Orthodeoxia Syndrome	▪ Mechanism: worsening of right-to-left shunt on upright posture ▪ Rationale: improvement of platypnoea,	▪ Shah et al 2016⁹	▪ Case series, $n=56$	▪ Improvement in functional status and improvement in hypoxia

	orthodeoxia and functional status			
Decompression illness	▪ Mechanism: bubbles bypass pulmonary filtration through right-to-left shunt ▪ Rationale: closure of right-to-left shunt to prevent further episodes of decompression illness	▪ Billinger et al 2011¹⁰	▪ Non randomised trial, control $n = 39$, intervention $n = 26$, exploring neurological events post PFO closure	▪ PFO closure prevented neurological symptoms of decompression illness and reduced rates of ischaemic brain lesions on MRI imaging
Paradoxical embolism	▪ Mechanisms: right-to-left shunt causing embolism in non-brain areas of the body ▪ Rationale: closure of right-to-left shunt to prevent further embolic episodes	▪ Case reports¹¹⁻¹⁸	▪ Case reports	▪ Case reports suggest closure was undertaken to decrease risk for future episodes
Prior to neurosurgery	▪ Mechanism: Sitting leads to negative intracranial venous pressure, allowing air embolism to enter the venous system during surgery. A large PFO may cause right-to-left shunt, leading to stroke or myocardial infarction ▪ Rationale: Closure pre-neurosurgery to minimize the risk of air embolism	▪ Klein et al 2018¹⁹	▪ Meta-analysis of 4 observational studies exploring neurosurgery in the semi-sitting position: patients with PFO $n = 82$	▪ Air embolism occurred in 40.2% of patients with PFO during posterior fossa or cervical spine neurosurgery. Suggested PFO closure should be indicated if PFO is large or with right-to-left shunt
Associated carcinoid syndrome	▪ Mechanism: right-to-left shunt of substances such as serotonin causing left sided carcinoid heart disease and coronary spasm ▪ Rationale: to decrease progression of left sided heart disease and episodes of coronary spasm	▪ Mansencal et al 2008²⁰	▪ Case series, $n = 3$	▪ Improvements of ≥ 1 New York Heart Association class, improvements in 6 minute walk test and oxygen saturations
Post operative unexplained hypoxia	▪ Mechanism: right to left shunt	▪ Case reports²¹⁻²⁶	▪ Case reports	▪ Symptomatic improvement

TIA = transient ischemic attack; CLOSURE I trial = Evaluation of the STARFlex Closure System in Patients with a Stroke and/or TIA due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale; PC trial = Clinical Trial Comparing Percutaneous Closure of Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; RESPECT

trial = Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment trial; CLOSE trial = The PFO or Anticoagulation vs. Antiplatelets after Stroke trial; DEFENSE-PFO trial = Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients with High-Risk Patent Foramen Ovale trial; PRIMA trial = Percutaneous Closure of Patent Foramen Ovale in Migraine With Aura trial; PREMIUM trial = Prospective, Randomised Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management trial; MIST trial = Migraine Intervention with STARFlex Technology trial.

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