The foramen ovale, while vital to our formative development, assumes mischievous potential if it persists post-utero. Similar to other vestigial structures, presence of a patent foramen ovale (PFO) appears to carry no physiologic or survival benefit for normal individuals. In states of abnormal right sided cardiac or pulmonary vascular capacitance or resistance, PFO has been implicated in worsening hypoxaemia caused by right to left intracardiac passage of deoxygenated blood (see box). More recently, a causative role of PFO in much more commonly occurring syndromes, including embolic ischaemic stroke, migraine with aura, and cerebral and cutaneous decompression disease, has been suggested. Highlighting cryptogenic embolic stroke associated with PFO, we will systematically review the evidence for these relations, discuss therapeutic potentials, and propose guidelines for therapeutic decisions as we await the completion of randomised controlled interventional trials.

CRYPTOGENIC STROKE AND PFO

Incidence
Stroke databases suggest that despite intensive evaluation, approximately 40% of all patients suffering ischaemic strokes (80% of all stroke victims) remain without clearly identifiable precipitant or cause (2002 heart and stroke statistical update, American Heart Association). In 1989, Webster and Lechat separately reported small case-control series with increased prevalence of PFO in patients with cryptogenic stroke (CS). To date, these descriptive series have been followed only by additional case-control studies, without prospective collection of primary occurrence of CS + PFO in a well defined population. While these case-control series have significant limitations, meta-analysis by Overell and colleagues suggested a strong correlation between PFO and primary occurrence of CS. In this analysis, prevalence of CS + PFO in persons of all ages was three times greater (95% confidence interval (CI) 2.0 to 4.3) than in non-stroke controls; this relation was even more compelling in persons with CS aged < 55 years of age, where PFO prevalence was five times greater (95% CI 3.2 to 8.3) than in healthy controls.

PFO and patient related risks
Attempts to risk stratify primary CS occurrence by anatomic features of PFO have had even greater limitation, due to smaller numbers of case-control studies including fewer patients. Most evaluation has focused on hypermobility (atrial septal aneurysm) of the septum primum. Most rigorous definition of atrial septal aneurysm requires ≥ 10 mm tissue sway in either direction from the septal plane (or ≥ 15 mm total sway) with a base of moving tissue that extends ≥ 10 mm. Anatomically, atrial septal aneurysm typically, if not invariably, is associated with either septal fenestrations or PFO. Case series meta-analysis points to a strong association between the presence of atrial septal aneurysm + PFO and primary occurrence of CS, with all ages, and those aged < 55 years with atrial septal aneurysm + PFO having five times greater (95% CI 2.4 to 10.4) and 16 times greater (95% CI 3.0 to 86.1) associative risk. This association was confirmed in a recent large case-control analysis. ‘‘High risk’’ PFO features of (1) atrial septal aneurysm, and (2) spontaneous intracardiac passage of bubble contrast without provocative manoeuvres have been applied to existing stroke databases and have been shown to carry several fold higher risk of stroke/transient ischaemic attack (TIA) recurrence when compared to CS + PFO patients without these features.

Causative mechanisms of association between CS + PFO remain speculative. Anecdotes of thrombi viewed passing from systemic venous circulation through PFO to the systemic arterial circulation have led to the suggestion of embolisation of systemic venous thrombus via PFO as a primary mechanism of disease. Such thrombi have generally appeared quite large, and would typically account for large vessel cerebro-occlusive disease and symptomatology. However, CS patients in primary occurrence trials and CS + PFO patients in secondary prevention trials have tended to present with smaller territory, or milder, neurologic events. This has led to speculation that smaller embolic material forms in situ within certain PFO. The two dimensional ‘‘tunnel’’, or
three dimensional “wind sock” nature of certain PFO suggests a plausibility of a pro-coagulant milieu with stagnation as well as potential for embolisation in people harbouring such PFO. However, direct evidence implicating such is lacking to date.

TREATMENT: MEDICAL, SURGICAL AND PERCUTANEOUS

Currently there are no consensus guidelines on treating patients with CS + PFO using available treatments including medical therapies (antiplatelet, anticoagulant), surgical PFO closure, and percutaneous closure.

Medical

Case series have suggested a significant risk of stroke/TIA recurrence (4–20%/year depending upon relative “high risk” features) for patients with CS + PFO using medical treatment. Use of warfarin, despite increased risk of associated haemorrhage, has been clinically favoured over aspirin, though confirmatory data are lacking. A prospective registry of CS patients aged 15–55 years treated with aspirin analysed recurrence over four years of stroke/TIA by presence or absence of PFO with/without atrial septal aneurysm. The authors suggested that there was notable attributable risk for future stroke/TIA of PFO with atrial septal aneurysm, with four year stroke/TIA recurrence of 15.2%/19.2% in patients with PFO + atrial septal aneurysm (hazard ratio 4.17). Of note, in this trial patients with PFO were significantly younger and had decreased additional stroke risks of systemic hypertension, diabetes, and higher body mass index.

The WARSS trial randomised patients aged 30–85 years with recent ischaemic stroke to use of either daily aspirin (325 mg) or warfarin (target international normalised ratio (INR) 1.4–2.8), assessing recurrence of ischaemic neurologic events or death. No statistical difference in occurrence of the primary end point at two years was noted between groups (16% v 17.6%, respectively). Subgroup analysis of a much smaller number of patients with PFO and ischaemic stroke (only some with CS) found similar risk of high stroke/TIA recurrence regardless of aspirin or warfarin treatment. In this trial as well, patients with PFO had decreased additional stroke risks of systemic hypertension, diabetes, and sedentary lifestyle.
Surgical

Surgical PFO closure appears a safe and effective means of eradicating PFO as a potential risk for stroke/TIA occurrence/recurrence, with limited supportive data. Ischaemic neurologic event recurrence rates of 4–17%/year, seen in surgical series of PFO closure for patients with index stroke, are likely to be distorted by limited and selected enrolment, as well as the single institutional nature of these case series.17–19

Percutaneous

Percutaneous PFO closure, first performed in 1989, is now possible with any of 5–7 different devices depending upon availability during various phases of investigational development (fig 1).20 In the USA, PFO may be closed percutaneously under Food and Drug Administration mandated humanitarian device exemption (HDE) guidelines in limited specific circumstances, both with CardioSEAL (HDE granted 2000) and the Amplatzer PFO Occluder (HDE granted 2002). PFO closure with all other devices remains limited to investigational trials: currently no device has FDA pre-market approval for this indication.

Assessing efficacy of percutaneous PFO closure for each device has been troublesome given the case series nature of existing studies, lack of randomised controlled trials, as well as a lack of defined and clinically meaningful end points for comparison. The oldest, continuous database examining percutaneous PFO closure safety and efficacy outcomes has suggested that, for progressive generations of double umbrella devices culminating in CardioSEAL and its modifications, annual recurrent combined stroke/TIA event rate following percutaneous closure has been consistently less than 4%.6 7 9 21 Complete PFO closure at follow up can be expected in 90–95% of patients utilising CardioSEAL (and its current STARFlex self adjusting modification) or the Amplatzer PFO Occluder.6 21 For all devices, choice, duration, and benefit and risks of peri-implant antiplatelet or anticoagulant strategies remain unclear and undefined, with current clinical practice mirroring post-coronary stent implantation pharmacologics (1–6 months clopidogrel, 75 mg daily, plus six months aspirin, 325 mg daily). Device related adversity has been documented with every occluder, with most notable occurrences including device embolisation, tissue erosion, pericardial inflammation, device related thrombosis, infection, device fracture or dislodgement, and stroke. Important other complications have included device related arrhythmia, transfusion requirement, and precipitation of migraine and chest pain. While exact incidences of such adversity are difficult to determine from limited available published series, clinically meaningful adversity most recently appears to occur in less than 1–3% of all patients undergoing percutaneous PFO closure.6 9 21 The incidence and clinical relevance of device related thrombosis and early and late post-implant atrial arrhythmias has yet to be determined and compared to other therapeutic modalities.

SYSTEMATIC REVIEW AND POOLED ANALYSIS

In a recent systematic review we chose to estimate the relative benefit of percutaneous PFO closure compared to medical therapy (tables 1 and 2, fig 2).22 Adjusting for attributable risk due to the higher prevalence of diabetes mellitus and smoking in medically treated patients with PFO, percutaneous PFO closure was shown to have a protective effect on stroke or TIA recurrence compared to medical treatment (annualised incidence 1.9% v 5.4%, relative risk 0.346, 95% CI 0.209 to 0.573; p < 0.0001). At one year follow up, PFO closure was associated with a relative risk of 0.385 (95% CI 0.252 to 0.589) and absolute risk difference of 4.4%. Otherwise expressed, after the first year of follow up, for every 23 patients who had their PFO closed percutaneously, one stroke or TIA was prevented compared to use of medical treatment.

RANDOMISED CONTROLLED TRIALS: THE TIME HAS COME

A number of attempts at randomised controlled trials (RCTs), including the percutaneous closure (PC) trial and the Paradoxical Embolism Prevention Study in Ischemic Stroke (PEPSIS) trial, occurred throughout the past decade, but failed largely due to a lack of: (1) neurologist–cardiologist–primary physician teamwork and coordination of goal and effort; (2) modern precise definition of ischaemic neurologic outcome; (3) data to generate realistic hypotheses and sample size requirements; (4) referring physician and investigator motivation to enrol all candidate patients into randomised expert care; (5) industry based sponsorship of a sufficiently sized trial to adequately address power concerns; and (6) a “tipping point” mentality that CS + PFO is a true and highly morbid disease, requiring study and relief. This milieu has radically shifted, setting the stage for current RCTs of percutaneous PFO closure and other treatments for persons affected by CS. The largest such trial, CLOSURE-1, is a > 1600 patient trial (neurologist principal investigatorship), testing superiority of CardioSEAL-STARFlex versus...
best medical treatment in persons with imaging confirmed index stroke, and evaluating similar hard neurologic end points as primary outcome. A second trial, RESPECT, is a 300 patient trial (primarily cardiologist principal investigatorship) evaluating equivalency of Amplatzer PFO Occluder PFO occlusion with clinician-determined “best medical therapy” in persons with “clinically symptomatic” index stroke, evaluating similar symptomatology as primary outcome. Both trials are projected to complete enrolment within 12–18 months.

In light of the above trials, we strongly advocate the following:

- Rapid investigation of patients with CS, including prompt assessment for and anatomic definition of PFO. When transthoracic echocardiography with Mueller manoeuvre (sniff forcing right atrial pressure to bow the atrial septum leftward) does not sufficiently define the presence of shunting or PFO anatomy, transoesophageal echocardiography is employed to provide greatest anatomic detail of intracardiac shunting, though likely with lesser sensitivity in diagnosis. While individual institutions may offer various “first line” testing for presence of intravascular shunting, including contrast echocardiography and transcranial Doppler sonography, we recommend standard transoesophageal echocardiography for all patients with CS and suspected PFO.

- Recognition of “high risk” patient (age < 55–60 years, (+) known circulating pro-coagulant) and PFO anatomic risk (“spontaneous echocardiographic shunting”, hypermobile septum primum, tunnel-like PFO) features potentially raising risk of recurrent neurologic ischaemic events.

- Patient education regarding association and particular risk features of CS and PFO, and removal or reduction of all potential procoagulant risks (trauma, obesity, inactivity, oral contraception, cigarette use, etc).

- In patients with new onset CS, enrolment of all eligible candidates into RCTs evaluating safety and efficacy of treatment arms. While we strongly favour data acquisition to answer questions regarding superiority of therapeutic choice in trials based upon most rigorous data analysis, both CLOSURE-1 and RESPECT remain reasonable enrolment options.

- Choice of primary PFO closure in patients:
  - with recurrent CS, not eligible for trial enrolment, despite compliant medical treatment or with inability to comply safely with medical treatment; while we favour percutaneous PFO closure, surgical closure is likely a reasonable, though rarely chosen, alternative, with fewer supportive data
  - with known circulating hypercoagulable states with recognised increased risks of thrombosis/embolism despite recommended warfarin treatment (lupus anticoagulant/antiphospholipid antibody syndrome)
  - with persistent procoagulant risk despite best medical treatment.

RIGHT SIDED CARDIAC DISEASE AND PFO

Persons affected by either compliance or capacitance abnormalities of right sided filling may have sufficient elevation of right atrial pressure so as to promote right-to-left shunting at the level of the foramen. Understanding the aetiology of the underlying muscle abnormality and targeting treatment to that, as is possible, is the mainstay of therapy for these patients. On occasion, control of cyanosis by means of PFO closure may be a reasonable acute and intermediate term palliation, with recognition that longer term worsening of muscle function caused by increased right sided volume may occur. In the adult patient with such disease, temporary PFO occlusion may offer some degree of mimicry of acute haemodynamic effects of closure, though there are no recognised manoeuvres that predict successful longer term outcomes with PFO closure. We advocate prolonged discussion of unknown intermediate and long term outcomes with such patients, and device implantation for PFO closure when indicated, at centres participating in closure registries.

DECOMPRESSION SICKNESS IN DIVERS AND PFO

Decompression sickness (DCS I—musculocutaneous; DCI II—neurologic) arises from nitrogen and oxygen gas formation in various body tissues at increased ambient pressure.

Gas passage from the systemic venous to arterial circulation can occur due to either pulmonary barotrauma or intravascular shunting.

Several studies have suggested increased incidence of PFO in divers with DCS. From initial recognition of association of PFO with DCS in 1986, to current reports of PFO closure for divers affected by DCS, differences in outcomes of case series highlight the differences in techniques used to: (1) select and enrol studied patients and controls; (2) clinically diagnose DCS; (3) diagnose PFO; and (4) image “neurologic events”. 26–32

In light of these limitations, general reviews suggests that: (1) regardless of presence of PFO, increasing numbers of divers may be associated with increasing incidence of DCS or asymptomatic neurologic events (ANEs); (2) occurrence of ANEs is likely to be common (25–50% of screened patients) in high volume divers; (3) multiple recurrences of DCS II, ANEs, and migraine headaches with aura may cluster in persons with “large shunt volume” PFO (atrial septal aneurysm or spontaneous shunting).

Standardisation of diagnosis and outcome remains a major obstacle for assessment of treatment for DCS prevention. Typically, more than 50% of high volume divers with ANEs remain asymptomatic, and there are no recognised risks predictive of future symptomatic events. In this context, nonetheless, previously symptomatic or high volume divers with ANEs or with “high risk” anatomic PFO features, who wish to continue diving may warrant closure in centres

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**Figure 2** Systematic review: stroke and TIA following transcatheter PFO closure compared to medically treated patients.

| Effect name | Event | Event-free | Effect | Lower | Upper | p Value | 0.1 | 0.2 | 0.5 | 1 | 2 | 5 | 10 |
|-------------|-------|------------|--------|-------|-------|---------|-----|-----|-----|---|---|---|---|
| Annualised rate of stroke | 5/1107 | 28/895 | 0.144 | 0.056 | 0.372 | 0.000 |
| Annualised rate of TIA | 16/1107 | 23/895 | 0.562 | 0.299 | 1.058 | 0.070 |
| Annualised rate of stroke or TIA | 21/1107 | 52/895 | 0.327 | 0.198 | 0.538 | 0.000 |
| Actuarial rate of stroke or TIA at 1 year | 30/1107 | 68/895 | 0.357 | 0.234 | 0.543 | 0.000 |
maintaining closure registries or participation in trials. Intervention for low volume sports divers with PFO without ANEs or symptoms of DCS, regardless of anatomic concerns, remains unfounded at the present.

Of interest, DCS, regardless of presence of PFO, has been noted in compressed air tunnel workers, high altitude aviators, and astronauts. Treatments offering potential for limiting the occurrence of DCS may carry particular import for such persons whose employment in high risk situations may place themselves and others at particular risk.

MIGRAINE SYNDROME AND PFO
The recognition of an association between migraine syndrome with aura (M+A) and PFO appears to have come “full circle” over the past two decades. Initial concerns from cardiologists focused on post-percutaneous PFO closure precipitation of migrainous events that mimicked original neurologic presentation. Effects from general anaesthesia, raised ambient catecholamines, and embolisation of metal or procoagulant microaggregates were all theorised as being related to occurrence.

**Indications for closure of PFO: key points**
- A 3 to 5-fold higher prevalence of PFO is noted in patients with cryptogenic stroke.
- Proposed “high risk” PFO features include: atrial septal aneurysm, spontaneous right-to-left shunting, and “tunnel-like” appearance.
- Although warfarin is often preferred over aspirin for secondary prevention of cryptogenic stroke, confirmatory data are lacking.
- Percutaneous transcatheter PFO device closure may be performed safely with a low incidence of recurrent neurologic events.
- Clinical trials comparing medical treatment versus transcatheter closure are underway.
- If ineligible for randomised trials, PFO closure may be considered in patients with recurrent events unable to safely comply with or despite medical treatment, “high risk” PFO feature, and/or “high risk” medical features (for example, hypercoagulable state, age < 55–60 years).
- High volume divers with decompression sickness or asymptomatic neurologic events who wish to continue diving may warrant PFO closure in appropriate centres.
- There is insufficient evidence to recommend PFO closure for the indication of migraine with aura.

Small epidemiologic studies have suggested a notably increased PFO prevalence in persons suffering M+A.23-24 The relation between this association and the recognition of M+A as a risk factor for ischaemic stroke in the young is unclear, though right to left passage of circulating factors has been postulated in both syndromes.25

Despite case series documenting PFO closure effects in persons with M+A, the competing concerns of both precapitation and reduction of M+A in persons with PFO lead to our recommendation not to pursue PFO closure at the present for persons with M+A without CS.26-27 We support improved basic aetiological and epidemiologic study of M+A, as well as study of the effects of various antiplatelet and anticoagulant agents as they are employed after percutaneous PFO closure.

**CONCLUSIONS**
Patency of the foramen ovale, occurring in 20–30% of persons, may be a commonly occurring intracardiac anatomic variation, yet our knowledge of even basic epidemiologic principles leading to association with disease remains lacking. This vestige of embryologic physiology has little if any relation to health and, on increasingly recognised occasion, harbours potential for association with catastrophic disease. Relative risks and benefits of treatments aimed at controlling or eliminating syndromes associated with PFO hinge upon study of the mechanisms of these diseases, the effects of specific planned treatments, and randomised controlled comparison trials to guide individual and population treatment recommendations. Current therapeutic options for control of PFO associated disease, including percutaneous PFO closure for recurrent stroke risk reduction as a model, have low adverse potential. While systematic review suggests a strong favour for percutaneous PFO closure when compared to medical treatments, these data are gleaned from case series. RCTs, including a large “superiority trial”, CLOSURE-1, and a smaller, “equivalency trial”, RESPECT, are active and ongoing, and will likely contribute to answering the necessary scientific and clinical questions to allow for improved patient care. We have been called “to arms” to recognise patients with PFO who are at risk of associated devastating disease, and to forcefully attack such by enrolling such patients, whenever possible, into RCTs testing risk limiting strategies. Until such study is completed, percutaneous PFO closure remains an effective and acceptable treatment for specific patients with high risk features falling outside protocol entry criteria.

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**Abbreviations**
- **ANE**: asymptomatic neurologic event
- **CS**: cryptogenic stroke
- **DCS**: decompression sickness
- **HDE**: humanitarian device exemption
- **M+A**: migraine syndrome with aura
- **PEPPIS**: Paradoxical Embolism Prevention Study in Ischemic Stroke
- **PFO**: patent foramen ovale
- **RCT**: randomised controlled trial
- **RESPECT**: Randomized Evaluation of recurrent Stroke comparing PFO closure to Established Current standard of care Treatment
- **TIA**: transient ischaemic attack
- **WARSS**: Warfarin-Aspirin Recurrent Stroke Study

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