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The Brain's Heart – Therapeutic Opportunities for Patent Foramen Ovale (PFO) and Neurovascular Disease

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Abstract

Patent foramen ovale (PFO), a common congenital cardiac abnormality, is a connection between the right and left atria in the heart. As a “back door to the brain”, PFO can serve as a conduit for paradoxical embolism, allowing venous thrombi to enter the arterial circulation, avoiding filtration by the lungs, and causing ischemic stroke. PFO-related strokes affect more than 150,000 people per year in the US, and PFO is present in up to 60% of migraine patients with aura, and in one out of four normal individuals. So, in such a highly prevalent condition, what are the best treatment and prevention strategies? Emerging studies show PFO-related neurovascular disease to be a multi-organ condition with varying individual risk factors that may require individualized therapeutic approaches – opening the field for new pharmacologic and therapeutic targets. The anatomy of PFO suggests that, in addition to thrombi, it can also allow harmful circulatory factors to travel directly from the venous to the arterial circulation, a concept important in finding novel therapeutic targets for PFO-related neurovascular injury. Here, we: 1) review emerging data on PFO-related injuries and clinical trials; 2) discuss potential mechanisms of PFO-related neurovascular disease in the context of multi-organ interaction and heart-brain signaling; and 3) discuss novel therapeutic targets and research frontiers. Clinical studies and molecular mapping of the circulatory landscape of this multi-organ disease will both be necessary in order to better individualize clinical treatment for a condition affecting more than a quarter of the world's population.

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Keywords

Patent Foramen Ovale; PFO; Stroke; Migraine; CLOSURE I trial; RESPECT trial; Neurovascular Injury; Serotonin (5-HT)

Introduction

1.1. PFO - A Novel and Independent Stroke Risk Factor, and a Clinical Conundrum

Patent foramen ovale, a common congenital cardiac abnormality, has been described as a “back door to the brain.” (Latson, 2007) An opening enabling communication between the right and the left atria, PFO can serve as a conduit for paradoxical embolism, allowing venous clots and other embolic material, such as air, fat or infective agents, to travel directly to arterial circulation, avoiding filtration by the lungs and causing ischemic stroke to the brain.

Often discovered only after a stroke, PFO has been determined by multiple epidemiologic studies to be a novel and independent stroke risk factor, and most studies indicate that PFO, especially with certain high-risk features, is far more than an innocent bystander. (Hagen, 1984; Yip, 1997; Meissner, 1999; Petty, 1999; Woo, 1999; Grau, 2001; Jacobs, 2002; Schneider, 2004; Hara, 2005; Pinto, 2005)

PFOs are also found in approximately 20–30% of the general population. PFO-related strokes affect more than 150,000 people per year in the US, and are found in up to 40% of all cryptogenic strokes and 60% of all migraine-with-aura patients. (Kunitz, 1984; Foulkes, 1988; Lechat, 1988; Webster, 1988; Sacco, 1989; Pearson, 1991; Di Tullio, 1992; Adams, 1993; Cabanes, 1993; Agmon, 1999; Petty, 1999; Grau, 2001; Kolominsky-Rabas, 2001; Lee, 2001; Mattioli, 2001; Schulz & Rothwell, 2003; Mohr, 2004; Schneider, 2004)

PFO-related neurovascular injury certainly has a major impact on public health, and the high prevalence of PFO emphasizes the importance of proper identification and treatment of at-risk individuals. (Hagen, 1984; Sacco, 1989; Meissner, 1999; Petty, 1999; Kolominsky-Rabas, 2001; Lee, 2001; Schulz & Rothwell, 2003; Schneider, 2004; Hara, 2005; Pinto, 2005; Lloyd-Jones, 2009) But who should be screened to prevent future strokes? How to distinguish a “benign” from a disease-triggering PFO? How to treat PFO-related strokes and prevent recurrent strokes? What therapeutic targets and options are best for stroke and migraine patients? Since individual patients’ risks vary, preferred treatment is likely not one-size-fits-all for a disease that affects multiple organs, including the brain, heart, blood, and lungs.

Current treatments range from medical therapy utilizing anticoagulant and/or antiplatelet agents, endovascular PFO closure by meshed devices, or even surgical closure. Emerging data suggest that this anatomical gap also allows potentially harmful circulatory factors to travel directly from the venous (right atrial, deoxygenated) to the arterial (left atrial, oxygenated) side of the heart, a concept that may be important in finding novel therapeutic targets for PFO-related stroke and migraine. Here, we: 1) review the data on PFO-related injuries and summarize challenges in therapeutic options; 2) discuss potential targets and mechanisms of PFO-related neurovascular disease in the context of a largely unexplored territory of multi-organ interaction and circulatory heart-brain signaling; and 3) discuss novel therapeutic targets and research frontiers which are evolving into better clinical treatment for a condition affecting more than a quarter of the world’s population.

1.2. What is a PFO and how is it diagnosed?

The structure of PFO (Fig. 1) is best described as a dynamic tunnel (not just a “hole”) outlined by opposing myocardial flaps remnant from the fetal septum primum and secundum, which never fully fused to wall off the right from the left atrium. (Moore & Persaud, 2003; Calvert, 2011) In the fetal circulation, this enables maternal oxygenated blood pass directly to the fetus, bypassing the unaerated fetal lungs. At first breath, the lungs inflate, and within two years of birth, up to 70–75% of foramina ovale are fully closed. However, this anatomical communication between the right and left side of the heart – PFO persists in approximately one out of four human adults. (Hagen, 1984; Meissner, 1999; Moore & Persaud, 2003)

PFO is identified in approximately 27% of routine autopsy series (34% in those under 30 years old and 20–25% in older adults) and in 26% of the general population on trans-esophageal echocardiography (TEE) in community studies with potential stroke risk factors. (Hagen, 1984; Meissner, 1999) Structurally, the size of PFO tends to increase with age (Hagen, 1984), and due to its valvular nature (Figure 1b–c), PFO often facilitates more shunting in one direction, e.g., right-to-left against the heart’s natural gradient, especially during Valsalva’s maneuver (see Section 2.2.1). In contrast, an atrial septal defect (ASD) – most of the time a true “hole” or non-overlapping opening in the septum (wall) between the left and right atria (Figure 1d) – enables more bi-directional shunting which may result in right heart volume overload (from left-to-right shunting) and subsequent pulmonary hypertension, heart failure, arrhythmias and cyanotic disease. (Krasuski, 2007) ASD is beyond the scope of this review, it is worth noting that ASD’s relationship with stroke is less studied, in part because it tends to be diagnosed earlier and closed endovascularly or surgically at a younger age to limit its deleterious cardiac manifestations. In contrast, PFO is usually clinically silent for cardiac manifestation unless it is also coupled with ASD. PFO can however be a major contributor to injury in other organs – such as the brain – by allowing clots from the venous circulation to enter arterial circulation. PFO can also cause non-cerebral, paradoxical systemic embolic events such as coronary embolism leading to myocardial embolic infarction (MI), renal infarction, or limb ischemia. (Agarwal, 2010; Fazio, 2010a; Fazio, 2010b; Ramineni & Daniel, 2010; Iwasaki, 2011)

PFO is a very dynamic three-dimensional structure due to its derivation from the embryonic septum primum and secundum (Moore & Persaud, 2003). High-risk PFO features such as atrial septal aneurysm (ASA – Figure 1c) – an elongated and more redundant interatrial septum, implicated in PFO-related neurovascular injury either as the source of clotting itself or perhaps by enhancing PFO’s ability to shunt blood – are associated with higher incidence of stroke. PFO can be diagnosed by non-invasive contrast enhanced transcranial Doppler (c-TCD) or echocardiography (trans-esophageal echocardiography – c-TEE – and/or contrast-enhanced trans-thoracic echocardiography – c-TTE). (Teague & Sharma, 1991; Di Tullio, 1993; Meissner, 1999; Droste, 2002; Topcuoglu & Buonanno, 2003; Sloan, 2004; Pinto, 2005) These are relatively accurate, non-invasive, and only take about 15–20 minutes. In the US, “bubble contrast” by agitation of dissolved microbubbles in saline solution is usually used to visualize the PFO (Figure 2). These bubbles can either be detected to cross from the right to the left atrium (Figure 2c) or as sharp “hits” on TCD tracing (Figure 3) when the bubbles travel from the venous system to the intracranial arterial system. Valsalva maneuvers are performed to assess the ease with which the PFO opens and triggers shunting (Figure 2d). However, while diagnosis by bubble contrast echoes are safe and relatively reliable, since PFO is a highly dynamic structure, complex cases need complementary studies to confirm the presence of PFO and sometimes to rule out pulmonary shunting by intrapulmonary arteriovenous malformations (AVMs). In addition, cardiac magnetic resonance imaging, cardiac CT, and real-time three-dimensional echocardiography

(RT-3DTE) have all been investigated as adjunct diagnostic tools for the future. (Monte, 2010; Hamilton-Craig, 2011)

2. Stroke and PFO

2.1. Anatomy of PFO as it relates to heart-brain signaling – how are cardiac anatomical changes related to neurovascular diseases?

Every year nearly 800,000 people in the United States experience a new or recurrent stroke. Stroke accounted for nearly 144,000 deaths in 2005, and is also the leading cause of major disability. (Lloyd-Jones, 2009) PFO-related strokes constitute 40% of “cryptogenic” strokes – the 30–40% of strokes not attributed to well-established traditional etiologies such as large vessel atherosclerosis, hypertensive small vessel disease or cardioembolism related to atrial fibrillation. (Lechat, 1988; Webster, 1988; Sacco, 1989; Pearson, 1991; Di Tullio, 1992; Cabanes, 1993; Agmon, 1999; Mattioli, 2001; Mattle, 2010) Initially, PFO stroke patients were reported to be younger stroke patients, with fewer traditional stroke risk factors such as hypertension and coronary artery disease, but recently PFO has also been described to increase the risk in older individuals as well, especially in the setting of critical illness and venous clotting. (Yip, 1997; Petty, 1999; Jacobs, 2002; Schneider, 2004; Handke, 2007; Petrea, 2011) Clinical cohort studies and major case series have been summarized by comprehensive reviews and meta-analysis elsewhere. (Overell, 2000; Mattle, 2010)

Overall, regardless of age, numerous studies show that PFO has higher prevalence in stroke patients, and in particular among cryptogenic strokes – a finding unlikely to be incidental. (Handke, 2007; Force, 2008; Mattle, 2010) A summary of case studies over the last 20 years demonstrated that of 13 studies on PFO prevalence in stroke and non-stroke controls of all ages, 11 demonstrated positive association of PFO with ischemic stroke, and two showed no association. (Mattle, 2010) This meta-analysis found that stroke patients were 1.69 times more likely to have a PFO than non-stroke controls [CI 1.40–2.06]. In addition, of 29 studies over the last twenty years comparing prevalence of PFO in patients with cryptogenic strokes versus patients with phanerogenic (known) causes, 27 had positive association and two showed no association; overall, cryptogenic stroke patients are 3.32 times more likely to have PFO than stroke patients with known causes [OR 5.77, CI 3.65–9.13 for age <55; OR 2.69; CI 2.00–3.62 for age >55; OR 2.69, CI 2.00–3.62 for all ages]. (Mattle, 2010)

Various theories exist for the mechanism of stroke in patients with PFO, including: 1) paradoxical embolism, in which a venous clot (also, air, fat, infectious material) travels through the PFO into arterial circulation, avoiding filtration by the lungs and causing embolism in the brain; 2) primary thrombus formation within the PFO canal due to various high-risk anatomical features; 3) associated atrial arrhythmias related to the existence of PFO; and 4) concomitant hypercoagulable state that predisposes either to direct thrombus formation or venous clotting, setting the scene for paradoxical embolism. The index case of paradoxical embolism, first described in a young woman with stroke in 1877 (Cohnheim, 1877), likely also had concurrent hypercoagulable state.

Treatment for PFO-related injury has been under active investigation. Some experts advocate medical treatments targeting either platelets or coagulation cascades, and others are for obliteration of the PFO by endovascular closure – leaving little consensus regarding optimal clinical management. Ample good epidemiologic studies, and indepth reviews of these studies and their implications, have been published elsewhere. (Sacco, 1997; Mas, 2001; Donnan & Davis, 2004; Furlan, 2004; Tong & Becker, 2004; Ferguson, 2006; Bedard, 2007; Belvis, 2007; Furlan, 2007; Messe & Kasner, 2008; Windecker & Meier, 2008; Mazzucco, 2009; Mattle, 2010; Calvert, 2011) While establishing the “proper treatment” is beyond the scope of this review and current data, this lack of clinical consensus likely

originates from complexities of PFO-related injury itself, as a myriad of associated risks differ widely between individual patients, and further novel risk factors are just beginning to be recognized. (Yip, 1997; Petty, 1999; Jacobs, 2002; Schneider, 2004; Handke, 2007; Silver, 2007; Ning, 2008; Ning, 2009; Agarwal & Kapadia, 2010; Devendra & Krasuski, 2011; Haghikia, 2011; Lau, 2011; Petrea, 2011; Devendra, 2012; La Spina, 2012)

A more sophisticated understanding of this disease's multi-organ interactions and circulatory profile may help not only to better select patients for treatment, but also to define potential targets for future therapeutic options. We will review some of these advances in the following sections.

2.2. PFO-related neurovascular disease involves multiple organs

PFO allows interatrial right-to-left blood shunting during those periods of the cardiac cycle in which the right atrial pressure exceeds the left atrial pressure. In addition to paradoxical systemic embolism, an increasing number of pathological manifestations of PFO have been identified recently: platypnea-orthodeoxia, referring to both dyspnea (platypnea) and arterial desaturation in the upright position with improvement in the supine position (orthodeoxia); neurological decompression illness in divers, high altitude pilots and astronauts; migraine headache with aura; wake-up stroke/TIA's, and obstructive sleep apneas. (Bradley, 1985; Murray, 1991; Landzberg, 1995; Bakris, 1997; Shanoudy, 1998; Appelberg, 2000; Cheng, 2002; Guerin, 2005; Ozdemir 2008)

PFO-related stroke involves multiple organs. Clinical manifestations likely are related to high-risk cardiac features, circulatory predisposition to venous clotting, and acquired decreases in systemic compensatory mechanisms that predispose neurovascular mediators to traverse directly from the venous to the arterial side. Table 1 lists emerging acquired and inherited risk factors associated with PFO-related neurovascular events. Understanding the mechanism and the implication of these additional risks that heighten PFO-related injury will help individualize treatment and define novel therapeutic targets. Other organ-organ interactions related to PFO will be reviewed in the following sections.

2.2.1. Cardiac structural abnormalities—Several cardiac embryologic remnants, such as the Chiari network or Eustachian valve (valve of the inferior vena cava), have been reported to either increase the risk of *in situ* clot formation or of right-to-left shunting. (Schneider, 1995; Schuchlenz, 2004; Rigatelli, 2008) In particular, one of the strongest predictors of PFO-related stroke is the presence of atrial septal aneurysm (ASA) (Figure 1c) – a cardiac anatomical high-risk feature in which loose myocardial flaps adjacent to the PFO bow back and forth at each heartbeat, increasing shunting and arterial-venous mixing (Table 2b). The presence of ASA (with PFO) increases the risk of recurrent stroke by more than 20 fold in some studies. (Lechat, 1988; Pearson, 1991; Cabanes, 1993; Agmon, 1999; Mas, 2001; Mattioli, 2001; Lamy, 2002)

Prospective epidemiologic studies have been moving the field forward in establishing paradoxical embolic event as an independent stroke risk factor (Lechat, 1988; Webster, 1988; Pearson, 1991; Di Tullio, 1992; Cabanes, 1993; Agmon, 1999; Mattioli, 2001; Handke, 2007). However, variability in patient cohort, age, other stroke risk factors, methodologic variations and difficulties in quantifying PFO, and variable definitions in assessing PFO size and extent of ASA excursion, limit some studies in establishing the statistical significance for PFO alone and associated stroke recurrence. (Homma, 2002; Meissner, 2006; Di Tullio, 2007; Serena, 2008) These findings are not in conflict with the likely explanation that PFO, when lacking high-risk features such as ASA, or other provoking risks, may be just a back door to the brain, waiting for clot forming conditions to heighten stroke risk. From our experience, a PFO without high-risk features may serve as an

opportunistic conduit for both clinically apparent and clinically silent events if there is a “second hit.”

These “second hit” risks can be either anatomical or physiologic. For example, an important contributor to PFO-related events is the performance of Valsalva maneuver – an everyday voluntary or involuntary increase in intra-thoracic pressure triggered by coughing, sneezing, heavy lifting, core training during exercise, straining during a bowel movement, or any positional change that presses into the abdominal viscera. Patients are asked to perform Valsalva maneuver during echocardiography to enhance the diagnosis of right-to-left shunting in PFO. Since the right side of the heart is a lower-pressure system than the left, Valsalva maneuvers, which increase intra-thoracic pressure, help to forcefully open the PFO by increasing right-sided atrial pressure. This increases right-to-left shunting via PFO, allowing for more venous flow to bypass the filtering system of the lungs. (Langholz, 1991; Ning, 2008) A majority (>90%) of PFO-related stroke patients have right-to-left shunting with Valsalva, while more than 50% also have spontaneous shunting at rest. (Meissner, 1999) Valsalva maneuver preceding stroke onset has been reported in PFO-related stroke, with higher incidence in men (>15%). (Langholz, 1991; Ning, 2008)

2.2.2 PFO and the lung—There is an increased prevalence of PFO in patients with obstructive sleep apnea (OSA). (Shanoudy, 1998; Lau, 2011) Valsalva maneuvers to enhance PFO-related right to left shunting worsen OSA-related hypoxemia. Conversely, PFO-related right-to-left shunting occurs more frequently in patients with more severe obstructive sleep apnea, such that the number of microbubbles going to the brain on TCD increases in PFO patients with more severe OSA during sleep. (Shanoudy, 1998; Lau, 2011) As expected, treatment of OSA with continuous positive airway pressure (CPAP) decreases PFO-related right-to-left shunting. (Beelke, 2002; Pinet & Orehek, 2005)

Interestingly, even “asymptomatic” PFO contributes to pulmonary gas exchange inefficiency – the alveolar-to-arterial oxygen difference is significantly lower in PFO patients compared to controls (5.9 ± 5.1 vs. 0.5 ± 3.5 mmHg) – and hypoxia (10.1 ± 5.9 vs. 4.1 ± 3.1 mmHg) at rest. (Lovering, 2011) While this difference was not demonstrated during exercise in this particular study, another study showed that endovascular PFO closure improved exercise capacity and reduced exercise-induced hypoxemia. (Devendra & Krasuski, 2011) In this innovative study, “provoked exercise desaturation (PED)” was well characterized as “arterial desaturation during assessment of at least 8% to a value less than 90%” during ambulation up and down 4 flights of stairs. Of interest, one third of patients with PFO-related stroke had oxygen desaturation during stair exercise. At 3 months post PFO closure, oxygen saturation during exercise and clinical functional status dramatically improved for these patients with provoked exercise desaturation (oxygen saturation- $+10.1\%$ $\pm 4.2\%$, $p < 0.001$; NYHA functional $+1.5$ classes, interquartile range: 0.75 to 2, $p = 0.008$). (Devendra, 2012) Such a simple, inexpensive functional and physiological clinical assessment, which can be easily performed in the office, is highly promising in helping to refine patient selection for those who will benefit the most from PFO closure. Indeed, in the clinical setting, patients post-PFO closure frequently report improved general exercise tolerance and better vascular perfusion to the extremities.

The relationship of “asymptomatic” PFO with the severity of obstructive-sleep-apnea-related hypoxemia, resting pulmonary gas exchange and exercise-induced hypoxemia demonstrates the important physiologic association between PFO and pulmonary function. In addition to its importance for gas exchange, the lung’s enormous endothelial surface also plays a major role in detoxification of certain vasoactive and proinflammatory substances that may be procoagulable or may induce cerebrovascular dysregulation. PFO-related right-to-left shunting allows potentially vasoactive substances (such as 5-HT) to bypass the lung,

which may induce or aggravate injury to the brain – a new area in need of further investigation. (Fishman & Pietra, 1974b, 1974a; Ning, 2011)

2.2.3. PFO and peripheral vascular system—The importance of peripheral vascular pathology and PFO is well illustrated by “economy class stroke.” The term “economy class syndrome” was initially coined to describe the risk of pulmonary embolism (PE) in the setting of immobility of the lower extremities during air travel. (Cruickshank, 1988; Lapostolle, 2001; Perez-Rodriguez, 2003) While the baseline incidence of severe pulmonary embolism is low (approximately 0.01 cases per million passengers for <5,000 km traveled), the incidence increases 150 fold in those who travel by air for more than 5,000 km or spend approximately 6 hours or more in flight. (Lapostolle, 2001) Up to 10% of healthy air travelers develop asymptomatic deep vein thrombosis (DVT) after prolonged flights. (Scurr, 2001) In combination with the high prevalence (25% or higher) of patent foramen ovale (PFO) in the normal population, it is therefore reasonable to hypothesize an increased risk of PFO-related stroke among long-distance travelers. Indeed, literature supports the association of travel history and paradoxical cardio-embolic stroke associated with PFO, naming it “economy class stroke.” (Foerch, 2002; Isayev, 2002; Ayo-Martin, 2008)

Among patients with a history of long-distance travel prior to PFO-related stroke, the duration of daily travel (both land and air) is associated with risks of embolic events. The coexistence of additional risk factors, such as pelvic venous clots, pelvic venous abnormalities (May-Thurner Syndrome), hypercoagulable state, smoking, or migraine with aura, may increase the risk associated with immobilization and decrease the travel time required to lead to a stroke. (Greer & Buonanno, 2001; Florez, 2003; Cramer, 2004; Ning, 2008; Kiernan, 2009; Ning, 2009) For example, May-Thurner Syndrome is a pelvic anatomic abnormality found in more than 6% of patients with PFO-related stroke, predisposing patients to excessive or pathological compression of the left common iliac vein by the right common iliac artery, thereby increasing pelvic venous congestion and stasis which may lead to thrombi formation. (Kiernan, 2009) Patients with multiple risk factors may potentially benefit from pre-flight DVT prophylaxis. Since the optimal treatment for PFO-related stroke continues to be controversial, understanding the association between long-distance travel and other emerging PFO-related stroke risk factors is important in tailoring simple and low-risk prevention and treatment strategies such as education regarding travel health and low-risk short-term prophylaxis.

2.2.4 PFO and Blood—Since venous thromboembolism is a major part of PFO-related paradoxical embolic events, known inherited hematologic hypercoagulable states have been implicated in PFO-related stroke. Some of the known markers commonly tested as part of the PFO-related stroke evaluation include: factor V Leiden, low protein C or Protein S function; low antithrombin III; presence of activated-protein C resistance, various prothrombotic antibodies (including lupus anticoagulant, or anticardiolipin antibodies); and prothrombin gene mutation G20210A. Table 2.C. summarizes several retrospective cohort studies of various hypercoagulable states and their relationship to PFO-related neurovascular injury. Given the lack of reported data, or the very recent application to the human clinical situation, not further discussed in the present review are various other potential factors, such as Protein Z, phosphatidyl ethanolamine and phosphatidylinositol antibodies, increased levels of plasminogen activator inhibitor-1, alpha-2 antiplasmin, dysfibrinogenemias, hyperhomocysteinemia, or elevated lipoprotein(a).

Depending on the patient population, some studies suggest inherited hypercoagulable state such as protein C resistance, factor V Leiden mutation and elevated anticardiolipin antibodies hypercoagulability to be more prevalent in patients with PFO and stroke. (Cabanes, 1993; Chaturvedi, 1998; Steiner, 1998; De Castro, 2000; Overell, 2000; Mas, 2001; Bezzi, 2002;

Homma, 2002; Karttunen, 2003; Lichy, 2003; Pezzini, 2003; Schuchlenz, 2004; Botto, 2007) Since the combination of PFO and hypercoagulable state potentially increases the risk of recurrent stroke, some experts favor long-term anticoagulation in this population. However, several studies also show non-association of known hypercoagulable condition with PFO and point out important challenges such as the cost effectiveness of checking thrombophilic conditions and the risks associated with unnecessary anticoagulation. (Florez, 2003; Giardini, 2004; Weber, 2009; Morris) Various ethnicities in a patient cohort may also have lower yield and susceptibility to certain genetic testing, and the relative degree of hypercoagulability of heterozygous versus homozygous individuals may not merit the risk of systemic anticoagulation. From our clinical experience, however, it should be emphasized that PFO stroke patients harboring an occult hypercoagulable condition and additional risk factors (Table 2) may be at higher risk of recurrent embolic events, and that perhaps finding a thrombophilic condition to tailor anticoagulation therapy may improve the risk-benefit ratio in such higher-risk treatment.

Nonetheless, most studies show that only a small proportion of PFO-related stroke patients have any known hypercoagulable conditions. In fact, in PFO stroke patients the prevalence of known inherited hypercoagulable factors are reported to be relatively low, ranging from 2%–17%. (Florez, 2003; Cramer, 2004; Botto, 2007) While other risk factors discussed above such as May-Thurner anatomy (pelvic venous compression) also increase the risk of peripheral venous clot formation, these risks combined still account for only a small portion of PFO-related strokes, leaving the majority of patients without identifiable source of a clot.

If PFO primarily enables pre-existing venous clots to reach the brain, then where do clots originate in the 80–90% of PFO stroke patients without known clot-promoting conditions? Does PFO do more than just wait for pre-existing clots to traverse it? Are there hypercoagulable conditions yet unidentified and important known thrombophilic conditions not yet studied? These areas all need further investigation. Other neurovascular injuries related to PFO, such as migraine, may help to shed light on these questions.

3. Migraine and PFO

Migraine is a common disorder, affecting more than 13% of the US population. (Cerebral Embolism Task Force, 1986; World Health Organization, 2003) There is an important association of migraine with neurovascular and cardiovascular disease in both men and women. Migraine with aura is associated with various stroke subtypes, both ischemic and hemorrhagic. (Kurth, 2006; Kurth, 2007; Kurth, 2010) In particular, migraine with aura or neurological accompaniments is an independent risk factor increasing the chance of stroke by 6- to 8-fold for patients under the age of 45, somewhat lesser for older patients with meta-analysis indicating at least two-fold increase in risk of stroke for all ages. (Henrich & Horwitz, 1989; Lidegaard, 1995; Tzourio, 1995; Carolei, 1996; Merikangas, 1997; Musolino, 2003; Etminan, 2005) Transcranial Doppler studies demonstrate abnormalities suggestive of paradoxical emboli in about 45% of patients with migraine with aura. (Del Sette, 1998; Anzola, 1999) A large epidemiological study of cryptogenic stroke, PFO and migraine determined that 46% of patients had PFO, and migraine was twice as common in patients with PFO as compared to those without. (Lamy, 2002; Fuller & Jesurum, 2009) Why is migraine with aura associated with heightened risk of stroke? Can PFO be the missing link for this association or is it merely a coincidental finding of two common conditions?

Migraine is a highly prevalent and debilitating condition characterized by a heterogeneous array of symptoms and episodes of a recurrent unilateral disabling and often throbbing headache associated with gastrointestinal symptoms such as nausea or vomiting, sensory

sensitivities to light, noise, or odor, and can be associated with various neurological accompaniments such as visual or sensory/motor aura. (Headache Classification Subcommittee of the International Headache Society, 2004) More prevalent in women than men (12–25% vs 5–9%), migraines affect more than 300 million (11%) world wide and 28 million in US. (World Health Organization, 2007) A third of migraine patients experience aura at least on some occasion (Manzoni & Stovner, 2010) and it is also common in children. (Knezevic-Pogancev)

The relationship of migraine, neurovascular injury from stroke or silent white matter changes, and PFO is of great interest. It has long been observed incidentally that PFO closure for stroke seems to associate with lessened severity and intensity of migraine. (Wilmshurst, 2000; Post, 2004; Schwerzmann, 2004; Azarbal, 2005; Reisman, 2005; Giardini, 2006; Rigatelli, 2007; Slavin, 2007; Dubiel, 2008; Wahl, 2008) In most of these retrospective series, PFO was closed for indications other than migraine, such as recurrent paradoxical embolism. Based on the hypothesis that certain vasoactive substances such as serotonin may traverse PFO unfiltered by the lung and trigger migraines, ongoing clinical trials test PFO closure for the treatment of unrelenting migraines – especially in medical non-responders or patients who cannot tolerate the side effects of the medications. At the time of this review, the only prospective randomized controlled study completed (MIST) (Dowson, 2008) enrolled 147 subjects with intractable drug-resistant migraine. MIST did not reach its optimistic primary endpoints of complete cure at 6 months follow-up, and was complicated by a relatively high rate of post-closure residual shunting. Nonetheless, subgroup analysis showed greater reduction in total migraine headache days ($P=0.027$). Other clinical trials (PRIMA, in Canada/Western Europe; PREMIUM, in USA) are ongoing. (clinicaltrials.org) (Trabattoni)

However, the relationship between PFO and migraine remains a hotly debated issue with conflicting data. (Garg, 2010; Woods, 2010) In part these may suggest PFO and migraine are both prevalent and have highly heterogeneous presentations that are somewhat difficult to phenotype and streamline across various studies. Nonetheless the strong increased risk of stroke in migraine patients with neurological accompaniments (or aura) does make PFO an interesting link. Studies suggest it is less likely a coincidental finding, since experimental microemboli can lead to cortical spreading depression in animal models of migraine with aura, supporting the hypothesis that a subset of migraine with aura may represent a hypoperfusion microvascular embolic event and silent infarcts. (Nozari, 2010) This has also been shown in human subjects where air microemboli post TCD triggered migraine with aura. (Caputi, 2010)

Further studies are ongoing to probe these controversial associations. Genetically associated stroke syndromes such as CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), a hereditary microangiopathy caused by mutation in the Notch3 gene, also have migraine as symptoms – this suggests intrinsic cerebral endothelial vulnerability and susceptibility to injury in migraine states. A high prevalence of right-to-left shunt (by transcranial Doppler) was reported in CADASIL patients. (Angeli, 2001) While the association of PFO and CADASIL is variable, an interesting association between a very large shunt and presence of Arg141Cys mutation was noted. (Mazzucco, 2008; Zicari, 2008; Mazzucco, 2009) Thus, though CADASIL and PFO may not necessarily be related, a common association between the two conditions may reflect, at least in some cases, a link between genetic susceptibility to migraine and the brain endothelium's intrinsic vulnerability to either vasoactive or prothrombotic substances from right-to-left shunting. Ongoing studies in this area will not only help to understand migrainous phenomena, but also other PFO-related neurovascular injuries, whether it be

clinically apparent stroke or “silent” white matter disease concurrently found in many migraine patients.

4. Emerging Therapeutic Options for PFO

Treatment options for stroke in the setting of PFO are limited to medical therapy to prevent clot formation, and mechanical PFO closure. There is heated debate about whether PFO-related stroke patients should be treated with aspirin, with other platelet antiaggregants, with warfarin or low-molecular-weight heparin, fondaparinux, or the newer direct thrombin/Xa inhibitors, or should proceed to PFO closure. (Sacco, 1997; Donnan & Davis, 2004; Furlan, 2004; Tong & Becker, 2004; Ferguson, 2006; Furlan, 2007; Messe & Kasner, 2008; Windecker & Meier, 2008) The controversy in part arises from the lack of clinical trial data to support one treatment over another, and in part and perhaps more importantly, from the inherent complexity of this multi-organ disease. Observational studies with conflicting results are most likely driven by the heterogeneity of the patient population enrolled. In particular, there have not been systematic clinical efforts on risk stratification of PFO-related injury to tailor therapy and individualize treatment. The empiric use of antiplatelet and anticoagulation aims to prevent paradoxical embolic events, but clinical recommendations vary. (Orgera, 2001; Albers, 2004)

Data has been extrapolated from subgroup or post-hoc analysis from randomized trials aimed at other investigations. Decision analysis suggests anticoagulation or PFO closure is favored if estimated risk of PFO-related stroke recurrence is >0.8% per year. (Nendaz, 1998) Other efforts utilizing traditional risk factors to model the likelihood of PFO's contribution to cryptogenic stroke are ongoing. (Kent & Thaler, 2011) The Warfarin-Aspirin Recurrent Stroke Study (WARSS), a prospective trial that randomized ischemic stroke to either aspirin (325 mg/d) or warfarin (target INR, 1.4–2.8) found no difference in 2-year outcomes for the endpoints of recurrent stroke or death in cryptogenic stroke. (Mohr, 2001) The PICSS also found no difference between aspirin and warfarin. However, most studies did not take into account hypercoagulable state, age, or other novel risk factors unique to PFO-related stroke. The treatment outcomes are likely diluted by the heterogeneity of patient populations. The French PFO-ASA study and PICSS study found higher recurrent stroke on aspirin at 4 years at 15.2% (HR 4.2 compared to no high risk features), suggesting that perhaps anticoagulation may be indicated for a subgroup of patients with high risks.

In comparing the use of a percutaneously placed PFO occlusive device with best medical therapy alone for prevention of recurrent ischemic neurologic symptoms, several case series and meta-analyses report low rates of adverse effects and recurrence post PFO closure. (Hung, 2000; Martin, 2002; Wahl, 2008; Hammerstingl, 2011) Given the variability in the three-dimensional anatomy and the dynamic nature of PFOs, much effort has been devoted to making the appropriate endovascular closure devices, and several randomized prospective clinical studies are currently being sponsored and powered toward testing various devices for safety and efficacy compared to medical therapy. (www.clinicaltrials.gov) All current randomized clinical trials are industry funded for a single device and geared toward safety, without direct specification of individual medical treatment and most trials recruit a relatively low-risk population – excluding hypercoagulable states, intent for pregnancy (due to peri-partum hypercoagulable state or side effect of radiation exposure during procedure), or cardiac features such as atrial septal fenestration, with high risk for recurrent stroke. Table 3 shows currently ongoing trials listed in public domain in the United States.

Since most trials exclude patients with the highest risk (see exclusion criteria listed in Table 3), serious concerns have been raised that the existing randomized trials lack adequate power in trial design to detect a significant treatment effect between medical versus PFO

closure for the prevention of recurrent strokes. (Johnston, 2012) While these trials will provide important information in a subset of patients with relatively low risk, they are challenging to perform due to patient heterogeneity, limitation of using one single device for a dynamic cardiac structure that may require different devices, patient crossover, and difficulty with long-term followup.

For example, the CLOSURE trial, sponsored by NMT to test the STARFlex device, has been the first completed trial. (Furlan, 2012) For the CLOSURE I trial, while the PFO closure group had 22% less recurrent risk of stroke, this difference was not statistically significant (recurrent stroke/TIA rate of 5.5% in the closure group vs. 6.8% in medical-therapy group, adjusted hazard ratio, 0.78; $P = 0.37$). In their publication, the investigators summarized well the difficulties of conducting this trial:

Periprocedural major vascular complications occurred in 3.2% of patients in the closure group (13 of 402). Within 6 months, thrombus was found in the left atrium in 1.1% of patients in this group (4 of 366); 2 of the 4 patients with thrombus had a recurrent stroke... Our trial was designed to detect a two-thirds reduction in the risk of recurrent events in the closure group, which is an ambitious objective. Thus, it did not have the power to detect a smaller reduction in the event rate. It is also possible that adverse events and outcomes vary according to the specific device, an issue that was not addressed in our trial. Although the patients in our trial are representative of many patients who undergo closure with off-label devices, those who may be at highest risk for paradoxical embolism (e.g., patients with active deep-vein thrombosis or clinically significant hypercoagulability) were excluded from the trial because such patients require long-term warfarin therapy. Moreover, we do not know how many potential study participants underwent closure with the use of a device from another company... (Furlan, 2012)

As the CLOSURE investigators acknowledge, significant caveats hinder the study's ability to detect a treatment difference. These include: 1) potential issues with the device itself relating to high rate of thrombus formation and adverse events such as atrial fibrillation, which has been well documented in other studies for this particular device 2) a heterogeneous population (including TIA in order to enroll sufficient patients), 3) a very ambitiously set endpoint that is difficult to achieve, 4) exclusion of the highest-risk patients (hypercoagulable state) who would likely benefit the most, 5) a trend suggesting different baseline characteristics in the medical versus interventional cohorts, with patients who underwent closure being sicker, with more stroke risk factors such as hypertension (33.8 vs 28.4%; $p=0.08$) and hypercholesterolemia (47.4 vs 40.9%; $p=0.05$); and 6) a potentially biased cohort, with high dropout rate (16% in device arm; 19% in medical arm – largely due to patient without PFO, without stroke/TIA, inability to place device, no followup) in which participants in the medical arm may have undergone closure with other devices during the course of the trial. Therefore it is difficult to draw important conclusions from this study for current medical management of high risk individuals. These caveats led the CLOSURE investigators to note in conclusion that, "Our findings do not preclude a possible role for closure of a PFO in highly selected patient populations." (Furlan, 2012; Johnston, 2012)

The RESPECT trial compares PFO closure using the AMPLATZER PFO Occluder with all medical therapy including antiplatelet agents and anticoagulants. The primary endpoint was recurrence of ischemic stroke or early post-randomization death with power calculated for 25 adjudicated endpoints. The RESPECT trial had no study related deaths and achieved 93.5% effective closure rate (without shunting) at 6months post procedure. In raw numbers, the study had less events in the device arm (9 versus 16 events in the device versus medical arm). In contrast to the CLOSURE I trial, the RESPECT trial ($n=980$) showed significant risk reduction in PFO closure arm compared to medical arm in the per-protocol (63.4% risk

reduction in device arm; $p=0.032$) and as-treated analysis (72.7% risk reduction in device arm; $p=0.007$). (Carroll, 2012) However, a number of medical group patients underwent off-label closure and 3 out of 9 patients in the device group had strokes while awaiting device placement. Given the significant amount of patient crossover and spurious events while awaiting device placement, the RESPECT trial only demonstrated statistical significance in per-protocol and as-treated analysis rather than the primary intention-to-treat analysis (50.8% risk reduction in device arm, $p=0.083$). Despite the challenges in the trial, the investigators also provided thoughtful secondary analysis and found device was favored in patients who are on antiplatelet agents (rather than anticoagulant therapy), and for those who had “substantial” shunting and atrial septal aneurysms (a structure that promotes shunting). These important preliminary finding highlights the importance of right-to-left shunting in the mechanism of PFO related events. The study investigators concluded that the trial produced longer term outcomes than any other study and this becomes particularly important for younger PFO stroke as the benefit of PFO closure “became especially prominent 2–5 years after device placement.” (Carroll et al 2012)

While good clinical trials are making headway in evaluating the safety and efficacy of various endovascular closure devices as discussed above, larger clinical trials incorporating novel clinical risk factors and better translational understanding of PFO related stroke are needed in this multi-organ disease to help individualize appropriate therapy. Until more data and further understanding about PFO are available, open discussion with the patient explaining the pros and cons of each strategy is important. Patients need to be educated and informed about individual risks and modifying behavior, life style and stroke prevention strategies. Screening for PFO may be considered among frequent flyers with prior DVT or a high risk of DVT and other novel emerging risk factors discussed above. (Surmely & Meier, 2007) PFO patients with known inherited hypercoagulable state may need to be evaluated carefully for the risk-benefit of long-term anticoagulation. (Agarwal, 2010) Patients with high-risk occupational hazards such as divers, patients who are contemplating pregnancy, or patients who cannot tolerate antiplatelet or anticoagulation therapies may need intervention in addition to medical and behavior/occupational counseling. (Thaman, 2011)

5. Synthesis of Data and Concepts

5.1 Unanswered questions and Challenges

PFO is a dynamic and three-dimensional structure that changes over time and may confer signaling change via the circulation to other organs. Clinically PFOs can open and close over time, and this is supported by literature reporting that right-to-left shunting varies over time. (Anzola, 2003; Tanislav, 2010) Indeed, PFO is not only associated with clinically apparent injury, but also with “silent infarcts” on MRI. (Clergeau, 2009; Ueno, 2010) And many challenges exist in studying PFO-related neurovascular injury. The recurrence rate is relatively low in PFO without high-risk features, and therefore a well-powered trial will need perhaps thousands of patients. The time to event is long in younger patients, so trials will need long-term follow-ups to obtain sufficient events. Most current trials exclude the highest-risk patients with hypercoagulable states, which decreases the recurrence rate, and also makes the application of future results difficult to generalize to patients with hypercoagulable state – those patients most in need of risk management and preventive treatment. Individual PFOs have complex anatomical structure which may require different devices to ensure successful complete closure. So far trials have not yet assessed other PFO-related novel risk factors such as May-Thurner Syndrome, “silent infarcts,” long distance travel, provoked exercise desaturation etc.

Since PFO involves multiple organ systems, the complexity of organ-organ interaction needs to be studied as well. Indeed, it is not unusual to see that venous embolic events from

another part of the body predict cerebral embolism years later, or that cardiac endothelial dysfunction correlates to later stroke. (Boulanger, 2001; Sorensen, 2007) Since pulmonary embolism can predict stroke years in advance, and the brain can trigger sudden cardiac arrest (Samuels, 2007), organ-organ interaction may be bidirectional. Studying circulatory signaling from organ to organ would be of immense reward in the search for future therapeutic targets for PFO-related injuries.

Understanding that PFO-related neurovascular injury has a complex landscape involving multi-organ systems, and the current lack of clear evidence for therapeutic direction, patients need to be carefully evaluated individually and managed with multi-disciplinary input involving consensus from neurology, cardiology, hematology, peripheral vascular, pulmonary and other expertise. Very importantly, the patients themselves also need to be informed about the various approaches and the complexity of this disease, and to be actively involved in treatment decisions.

5.2 Novel Targets, Emerging Risks and Future Directions

PFO-related disease is an exciting and rapidly growing field. A Medline search of all articles related to “patent foramen ovale” yielded more than 2000 hits over the last decade, whereas the decade prior had fewer than 200 hits. Just what is so intriguing and complicated about PFO? At first glance, the mechanism of PFO-related neurovascular injury seems quite simple: a venous clot goes through a conduit in the heart to the arterial circulation and up to the brain. Unfortunately, this common-sense understanding has not been sufficient to guide clinical management. If that were the whole story, for example, then clinical risk should be largely predictable as a function of two variables: the size of the PFO (Table 2A) and the tendency to form dangerous venous clots (Table 2C) as listed in Table 2. While the “size” of PFO – understanding the difficulty of measuring “size” in such a dynamic structure – has been weakly correlated to stroke risk (Table 2a) (Di Tullio, 1993; Topcuoglu & Buonanno, 2003; Lopez-Haldon, 2008), the prevalence of patients with known prothrombotic states is still relatively low (2–17%), accounting for only a small percentage of PFO-related injuries. (Steiner, 1998; Homma, 2002; Florez, 2003) (Table 2C). So how do the 80–90% of PFO patients without known clot-forming conditions end up with embolisms? Might these patients have unknown underlying “procoagulant” states related to PFO?

Interestingly, the strongest predictor of PFO-related stroke is not related to PFO size or known prothrombotic states, but is the presence of atrial septal aneurysm (ASA) which increases the amount of shunting across the PFO and leads to more venous-arterial mixing (Figure 2C. Table 2.B.). In migraine with aura, it has long been hypothesized that the venous-arterial mixing from PFO-related right-to-left shunting may lead to more vasoactive substances in arterial circulation that trigger neurovascular reactivity. (Diener, 2007; Anzola, 2009) Just what are these vasoactive substances in blood? Do they have a role in stroke as well? Increased recognition of these brain-heart interactions has led to studies geared toward finding both inherited and acquired circulatory markers that predispose to PFO-related injury.

Serotonin (5-HT), a vasoactive prothrombotic substance that induces cardiac oxidative stress and a neurotransmitter carefully regulated and inactivated by the lung (Fishman & Pietra, 1974b, 1974a), is decreased post percutaneous closure of PFO, supporting the hypothesis that chronic right-to-left shunting may allow harmful vasoactive mediators to escape deactivation by the pulmonary vasculature, increasing the brain vasculature’s direct exposure to substances that elevate the risk of cerebrovascular injury. (Ning, 2011) These preliminary findings lead us to hypothesize that circulatory mediators may be responsive to the repair of chronic venous-arterial mixing, highlighting important brain-heart signaling

and the importance of the pulmonary vasculature's role in regulating vasoactive substances. (Fishman & Pietra, 1974b, 1974a; Ning, 2011)

So while the mechanical explanation of PFO facilitating paradoxical emboli by allowing venous clots to travel directly to the brain is logical, it is likely incomplete. The novel relationship of stroke and migraine, the implication of pre-clinical imaging as a risk predictor, the importance of organ-organ interaction, provoked exercise desaturation, and underlying hypercoagulable conditions resulting from venous-arterial mixing, are all important future directions to help select patients for the best therapeutic option.

6. Summary

PFO-related neurovascular injuries are multi-organ diseases that affect brain, heart, blood, lung, peripheral vasculature and circulation. Novel therapeutic targets and biomarkers are needed for better risk stratification and effective prevention and treatment. Organ-organ interactions are crucial. Indeed, a disease thought to be primarily affecting one organ likely also damages other organs in ways both clinically apparent and “silent,” and changes in circulatory profile may alter disease progression and recurrence in important ways. Other risk factors that enhance PFO's ability to trigger neurovascular injury are emerging, and likely involve anatomical, mechanical, physiologic, and molecular mediators. The molecular landscape of this multi-organ disease needs to be better examined in order to select optimal therapeutic treatments for individual patients. The pathophysiology of PFO-related disease is both anatomically and molecularly relevant. Studies are needed to explore whether medical management and/or mechanical closure may mediate molecular targets and signaling. Innovative clinical assessment, novel biomarkers, and alternative therapeutic targets are being actively investigated to address various aspects of the underlying mechanisms of a multi-organ disease affecting more than a quarter of the world's population.

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Abbreviations

ASA	Atrial Septal Aneurysm
ASD	Atrial Septal Defect
OSA	Obstructive Sleep Apnea
PFO	Patent Foramen Ovale
TTE	Transthoracic Echo
TEE	Transesophageal Echo
TCD	Transcranial Doppler
5-HT	Serotonin

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Figure 1.

Diagram of patent foramen ovale and atrial septal defect.

1A. normal fossa ovale, 1B. PFO; 1C. PFO with atrial septal aneurysm (ASA); 1D. Atrial septal defect (ASD) – PFO is a complex 3- dimensional structure that allows for right to left shunting, especially when ASA is present.

FIGURE 2. Trans-thoracic echo (TTE) bubble contrast study for the diagnosis of PFO

FIGURE 2a . TTE of normal heart without bubble contrast injection (right and left atrium labeled)

FIGURE 2b. Bubble contrast on right side of the heart only- note bulging of the atrial septal aneurysm (star) into the left atrium

FIGURE 2c. Bubble contrast crossing from right atrium - entering left atrium (star) as result of the PFO

FIGURE 2d. Enhanced shunting of bubble contrast into the left atrium and left ventricle (star) by valsalva maneuver.

Figure 2.

Trans-thoracic echo (TTE) bubble test for diagnosis of PFO. The heart is viewed “live” with echo-sonography as bubble saline contrast solution is injected into the arm vein. Figure 2a, TTE of normal heart without bubble contrast injection (right and left atrium labeled); 2b, Bubble contrast on right side of the heart only- note bulging of the atrial septal aneurysm (star) into the left atrium. 2c. Bubble contrast crossing from right atrium - entering left atrium (star) as result of the PFO. 2d. Enhanced shunting of bubble contrast into the left atrium and left ventricle (star) by Valsalva maneuver.

Figure 3. Transcranial Doppler (TCD) diagnosis and classification of PFO - TCD bubble contrast test for the screening of PFO.

Table 1

Emerging inherited and acquired risk factors associated with PFO-related stroke.

Organ Involved	Inherited	Acquired
Cardiac	Atrial septal aneurysm	
	Chiari's network	
	Eustachian valve	
		Valsalva maneuver (weight lifting, position change etc)
Circulatory	Hypercoagulable state	Hypercoagulable State
Pulmonary/Upper airway		Provoked exercise desaturation
		Obstructive sleep apnea
Peripheral vascular	May-Thurner's syndrome	DVT, pelvic clots, and venous catheter related
		Air/Long-distance travel
		Scuba Diving
Neurologic	Migraine with aura	Migraine with aura

Table 2

Literature on existing risk factors – PFO size, anatomy, and known hypercoagulable state.
Studies on PFO size, anatomy and hypercoagulable state.

Risk factor and study	Risk	P value
2. A. PFO Size (diameter >2mm)		
Steiner et al.	26% vs 6 % (cryptogenic vs other)	0.04
Homma et al.	HR 0.59 (PFO vs non-PFO pts)	NS
De Castro et al.	12.5% vs 4.3%	0.05
2. B. Coexisting Atrial Septal Aneurysm		
Cabanes et al.	OR 33.3 vs controls	0.0009
Overell et al. (meta)	OR 17.09 vs other stroke	95% CI 2.19–133.46
Schuchlenz et al.	OR 12 vs control	0.001
Mas et al.	OR 4.17 PFO w/or w/o ASA	0.007
2. C. Known Clotting factor mutations in PFO Patients (2–17%)		
Bezzi et al. 2002	11% vs 2% (Factor V Leiden)	NS
Pezzini et al. 2003	OR 10.09 (Prothrombin G20210A)	0.04
Lichy et al. 2003	OR 3.66 (Prothrombin G20210A)	0.01
Florez et al. 2003	17.3% (PFO) vs 22.1% (control)	NS
Karttunen et al. 2003	OR 13.99	0.022

Table 3
Ongoing trials of PFO closure versus medical therapy (www.clinicaltrials.gov)
Randomized clinical trials testing PFO closure device safety in US (data obtained from www.clinicaltrial.gov).

	Industry Sponsor (Device)	Time for Followup	N (Total in both arms)	Inclusion	Exclusion	Medical Group	Completion Date
CLOSURE I – “The primary objective is whether the STARFlex® septal closure system will safely & effectively prevent a recurrent embolic stroke/TIA and mortality in patients with a PFO and to demonstrate superiority of the STARFlex® device compared to best medical therapy.”	NMT (Starflex)	2 years	909	ALL-TIA and Stroke	NO Hypercoagulability	Any-ASA and/or Warfarin	Completed
RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) – “The purpose of this study is to investigate whether percutaneous PFO closure, using the AMPLATZER PFO Occluder, is superior to current standard of care medical treatment in the prevention of recurrent embolic stroke.”	AGA (Amplatzer)	2 years	980	Stroke	No Intention for Pregnancy No ASD	Any-ASA; Warfarin Plavix; Aggrenox	Completed
REDUCE – “The primary objective is to determine that PFO closure with the GORE HELEX Septal Occluder plus antiplatelet medical management is safe and effective and reduces the risk of recurrent stroke or TIA when compared to antiplatelet medical management alone in patients with a PFO and history of cryptogenic stroke or TIA.”	GORE (HELIX)	Not published	600's	ALL-TIA and Stroke	No hypercoag; No severe stroke; No high risk features of Atrial Septal Aneurysm	Antiplatelet et only (No Warfarin)	2008–2015