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REVIEW TOPIC OF THE WEEK

Paradoxical Embolism

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ABSTRACT

Paradoxical embolism is an important clinical entity among patients with venous thromboembolism in the presence of intracardiac or pulmonary shunts. The clinical presentation is diverse and potentially life-threatening. Although the serious nature and complications of paradoxical embolism are recognized, the disease entity is still rarely considered and remains under-reported. This paper provides an overview on the different clinical manifestations of paradoxical embolism, describes the diagnostic tools for the detection of intracardiac and pulmonary shunts, reviews therapeutic options, and summarizes guideline recommendations for the secondary prevention of paradoxical embolism. (J Am Coll Cardiol 2014;64:403–15) © 2014 by the American College of Cardiology Foundation

Paradoxical embolism refers to the clinical phenomenon of thromboembolism originating in the venous vasculature and traversing through an intracardiac or pulmonary shunt into the systemic circulation (1). The clinical diagnosis requires a venous source of embolism, an intracardiac defect or a pulmonary fistula, and evidence of arterial embolism (2). Depending on the site of embolization, paradoxical embolism may result in neurological deficits related to ischemic stroke (3), chest pain and electrocardiographic changes indicative of myocardial infarction (MI) (4), acute abdominal pain due to gastrointestinal ischemia (5), back pain and hematuria as a result of renal infarction (6), or cold and pulseless extremities secondary to peripheral arterial occlusion (7) (**Fig. 1**).

EPIDEMIOLOGY

Cerebrovascular accidents constitute the most frequent relevant clinical manifestations of presumed paradoxical embolism. The majority of strokes are ischemic (87%) without identifiable cause, despite a comprehensive stroke work-up in up to 45% of patients. These strokes are commonly referred to as nondefined or cryptogenic (8). The prevalence of a patent foramen ovale (PFO) is increased more than 2-fold among patients with cryptogenic stroke compared with patients with conventional causes of stroke (odds ratio [OR]: 2.9, 95% confidence interval [CI]: 2.1 to 4.0) with differences in the prevalence between young (<55 years of age, OR: 5.1, 95% CI: 3.3 to 7.8) and older patients (≥55 years of age, OR: 2.0, 95% CI: 1.0 to 3.7) (9). The true prevalence of paradoxical embolism is unknown because the clinical diagnosis of proven or impending paradoxical embolism remains difficult (10), making it a presumptive diagnosis in most cases. There are likely additional mechanisms for stroke and transient ischemic attack (TIA), which remain undescribed and poorly understood. Among these, the pulmonary venous system remains a "black box" as a potential source of systemic embolism.

Among patients with transvenous, endocardial pacing leads, the presence of an intracardiac shunt has been associated with a 3-fold increased risk of systemic thromboembolism (hazard ratio [HR]: 3.30, 95% CI: 2.19 to 4.96, $p < 0.0001$), suggesting that paradoxical embolism is an underlying cause (11). Similarly, in the presence of a PFO, patients with deep venous thrombosis or pulmonary embolism have been found to have

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ASA = atrial septal aneurysm

ASD = atrial septal defect

CI = confidence interval

HR = hazard ratio

INR = international normalized ratio

MI = myocardial infarction

MSCT = multislice computed tomography

OR = odds ratio

PAVM = pulmonary arteriovenous malformation

PFO = patent foramen ovale

RCT = randomized controlled trial

TCD = transcranial Doppler

TEE = transesophageal echocardiography

TIA = transient ischemic attack

an increased risk of death and cardiovascular events in the wake of their acute illness, compared with control subjects without PFO (in-hospital mortality, OR: 11.35, 95% CI: 2.89 to 44.52) (12).

It has long been debated whether the presence of a PFO or another shunt in the context of cryptogenic stroke represents an association by chance or a true cause-effect relationship. Applying criteria developed by epidemiologists, numerous studies have established a strong and consistent association between the presence of PFO and the risk of cryptogenic stroke in support of paradoxical embolism as a responsible mechanism. Moreover, paradoxical embolism is biologically plausible, as evidenced by numerous case reports of thrombi trapped within a PFO and the typical temporal sequence of events beginning with venous thrombosis followed by arterial embolism. In addition, there is robust evidence documenting a physiological gradient with an increased risk of paradoxical embolism being related to shunt size and the additional presence of an atrial septal aneurysm (ASA) (13). In aggregate, these data have established PFO as an independent risk factor of cryptogenic stroke similar to other known risk factors, such as arterial hypertension, diabetes, or hypercholesterolemia.

PATENT FORAMEN OVALE. By far the most common intracardiac shunt is a PFO, which is formed by the left-sided interatrial septum primum and the right-sided interatrial septum secundum. A patent connection between the atria may be found in up to 30% of otherwise normal hearts. The prevalence of a PFO appears to decrease with increasing age, with an incidence of 34% during the first 3 decades, 25% during the third to seventh decade, and <20% among octogenarians. The observation of larger PFOs being present in the elderly (mean size 3.4 mm during the first decade and 5.8 mm during the 10th decade of life) suggests that there is an ongoing process of anatomical closure of the PFO during younger age (14). However, the assessment of PFOs in the elderly may be less diligent, and small PFOs are more likely missed; therefore, an alternate theory may be related to selective mortality by PFO.

Under physiological conditions, a pressure gradient is maintained between the left and the right atrium, which results in passive closure of the PFO. In the case of increased right atrial pressure exceeding left atrial pressure (as observed at the end of Valsalva maneuvers such as coughing, sneezing, squatting, defecation, or micturition), a transient right-to-left shunt may occur carrying particulate matter such as thrombi into the systemic circulation. A permanent increase in right-sided cardiac pressures, as observed after pulmonary embolism or other causes of pulmonary arterial hypertension, results in a significant and possibly permanent right-to-left interatrial shunt, thereby increasing the risk for paradoxical embolism (12). Patients with a larger PFO size (>4 mm) (15) and a greater degree of right-to-left shunt as assessed by crossing microbubbles are at particular risk to experience paradoxical embolism.

There are some additional anatomical variations that are frequently associated with PFO:

- A Eustachian valve (**Fig. 1**) is an embryonic remnant of the right valve of the sinus venosus that in utero directs oxygenated venous blood from the inferior vena cava to the foramen ovale. The Eustachian valve gradually disappears after delivery in the majority of individuals; however, residual and prominent remnants may direct venous blood to the fossa ovalis and cause significant right-to-left shunt in some individuals. This keeps the foramen patent. PFO and residual prominent Eustachian valves thus frequently coexist (70%) and constitute a common finding among patients with presumed paradoxical embolism (16).
- A Chiari network (**Fig. 2**) is another embryonic remnant of the right valve of the sinus venosus and is observed in approximately 2% to 4% of the general population. Whereas the Eustachian valve is a tenuous, valve-like ledge, the Chiari network contains a reticulated complex of threads and fibers in the right atrium that results from incomplete resorption during embryonic heart development. Although the Chiari network usually is an incidental finding on echocardiography, it is frequently associated with PFO (83%), a significant right-to-left shunt (55%), or an ASA (24%)—all facilitating paradoxical embolism (17).
- An ASA describes a floppy, undulating portion of the septum primum in the central region where it overlies the septum secundum. Defined as atrial septal excursion ≥10 mm with a base diameter ≥15 mm, it is as frequent as 2% in clinical studies (18). An ASA begets an adult PFO, and the majority of patients with an ASA indeed have a PFO. Typically, such a PFO is larger than a PFO without ASA (19), it may open with every heartbeat, and it is associated with an increased risk of paradoxical embolism.

ATRIAL SEPTAL DEFECT. According to their location, atrial septal defects (ASDs) are categorized as

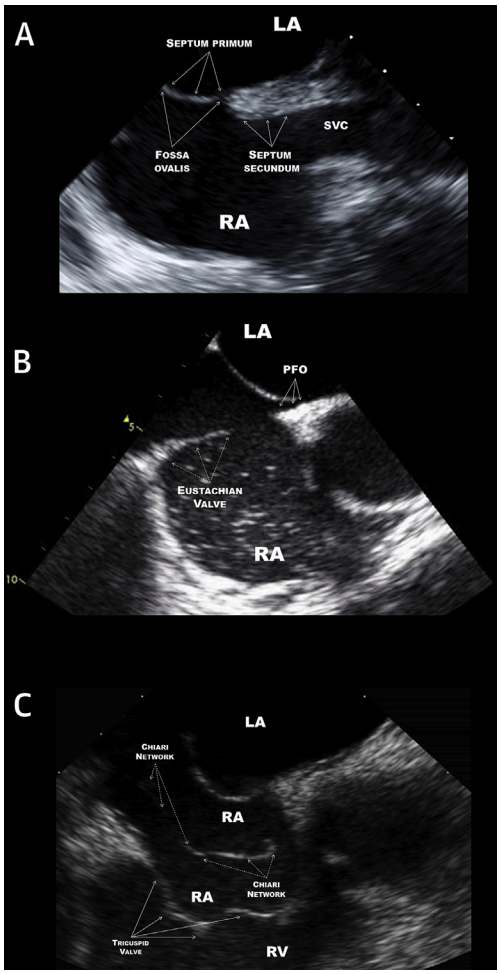


FIGURE 1 Anatomy of the Interatrial Septum and Anatomic Variations Associated With PFO

(A) Anatomic characteristics of the interatrial septum (transesophageal echocardiographic long-axis view, right side: cranial, left side: caudal). **(B)** Transesophageal echocardiography. Prominent Eustachian valve, which directs blood from the inferior vena cava toward the patent foramen ovale (PFO), as evidenced by the injected bubbles. **(C)** Transesophageal echocardiography. Prominent Chiari network in the right atrium (RA). LA = left atrium; RV = right ventricle; SVC = superior vena cava.

ostium primum, ostium secundum, sinus venosus, or coronary sinus defects. ASDs account for one-third of congenital heart defects in adulthood and are 2 to 3 times more common among females (20). Ostium secundum defects are the most frequent ASDs (75%) and are located in the area of the fossa ovalis. Regardless of the anatomic location, but depending on the size of the ASD and on its hemodynamic significance, patients may experience dyspnea on exertion and fatigue. Patients commonly present with atrial tachyarrhythmias. Patients with ASD have a relevant risk for paradoxical embolism, which has been reported with an incidence of up to 14% among patients referred for ASD closure (21,22).

OTHER SHUNTS. All intracardiac communications, including ventricular septal defects or cyanotic congenital heart defects, have a certain risk for paradoxical embolism. Although in most cases, a permanent left-to-right shunt is observed, a temporary or chronic increase in right atrial, right ventricular, or pulmonary pressures over left atrial, ventricular, or aortic pressures, respectively, may lead to shunt reversal and paradoxical embolism. By contrast, patients with pulmonary arteriovenous malformations (PAVMs) have a permanent right-to-left shunt permitting the passage of thrombotic or septic emboli into the systemic circulation.

PAVMs are abnormal vascular communications directly connecting a pulmonary artery and a pulmonary vein. PAVMs are rare, usually hereditary, and in most cases, associated with hereditary hemorrhagic teleangiectasias (23). PAVMs can present with a wide range of pathologies, including single or multiple, simple or complex, and unilateral or bilateral phenotypes of variable size. The physiological consequences are a permanent right-to-left shunt with the associated risk of hypoxemia and paradoxical embolism. Symptoms depend on size, number of PAVMs, and shunt volume, and range from asymptomatic to severely symptomatic with dyspnea, clubbing, and cyanosis during exertion or at rest. Observational studies suggest considerable morbidity, which is most frequently related to neurological complications including stroke, TIA, and cerebral abscess but can also include hypoxemia, hemorrhage, and migraine (24).

DIAGNOSIS

The diagnostic evaluation comprises screening for a thrombotic source, family history, arterial hypertension, diabetes mellitus, hypercholesterolemia, and tobacco abuse; the search for silent or overt atrial fibrillation (AF); imaging assessment of the intracranial and extracranial circulation; and transesophageal echocardiography (TEE) evaluation of the aortic arch and cardiac chambers. Blood sample analysis serves to screen for hematologic disorders and coagulation pathologies (25). In patients with cryptogenic embolism and a coexisting intracardiac communication at the atrial level, the presumptive diagnosis of paradoxical embolism should be seriously entertained. The work-up may be extended to an assessment of peripheral veins and evaluation for evidence of pulmonary embolism.

TABLE 1 Accuracy of Diagnostic Modalities for Shunt Detection

	Sensitivity	Specificity	First Author (Ref. #)
Transesophageal echocardiography	Reference method		
Transthoracic echocardiography	47%	100%	Di Tullio et al. (28)
Transthoracic echocardiography (harmonic imaging)	68%	93%	Clarke et al. (29)
MSCT (64-section)	66%	100%	Williamson et al. (31)
MRI	50%	100%	Nusser et al. (32)
Transcranial Doppler sonography	68%	100%	Di Tullio et al. (28)
Ear oximetry	76%	71%	Billinger et al. (34)

MRI = magnetic resonance imaging; MSCT = multislice computed tomography.

ECHOCARDIOGRAPHY. Transthoracic echocardiography or TEE provides information on cardiac and valvular function, as well as the presence of intracardiac masses (e.g., myxoma) or thrombus. They are the diagnostic method of choice for the noninvasive detection of intracardiac shunts and a patent ductus arteriosus. In addition to information on the localization of intracardiac shunts, echocardiography allows clinicians to assess the size of a defect and provides information on shunt quantity and direction. Finally, TEE is the preferred method to exclude large and mobile plaques in the ascending aorta and aortic arch, which have been associated with an increased risk of stroke.

The echocardiographic diagnosis of atrial or ventricular septal defects is made by the detection of a significant left-to-right shunt at rest, which can be detected by color flow Doppler. PFO diagnosis is more challenging, requiring additional tools. The thorough evaluation of the fossa ovalis, a shallow depression in the right atrium composed of the septum primum and secundum, is a prerequisite for detection of a PFO (**Fig. 1**). Most often, left atrial pressure exceeds right atrial pressure, thereby passively closing the interatrial communication. Accurate PFO detection requires peripheral injection of agitated saline or echocardiographic contrast medium at the end of a sustained and rigorous Valsalva maneuver. Transfemoral or pedal injection of contrast agents can increase the sensitivity and specificity of PFO detection (26). The echocardiographic criteria for PFO diagnosis include the early detection of contrast microbubbles in the left atrium within 3 cardiac cycles after opacification of the right atrium (27). PFO size is estimated using a semiquantitative score. Transesophageal visualization of the interatrial septum for PFO detection is generally considered to be more sensitive compared with transthoracic echocardiography (28). However, some studies suggest comparable sensitivity of transthoracic techniques with the use of harmonic imaging to visualize a right-to-left shunt through a PFO, in case of sufficient imaging quality (**Table 1**) (28,29). TEE typically underestimates defect size compared with invasive balloon measurements of the intracardiac defect.

TRANSCRANIAL DOPPLER SONOGRAPHY. Transcranial Doppler (TCD) is a noninvasive bedside test with a high sensitivity for the detection of a right-to-left shunt regardless of its location (**Table 1**). After peripheral injection of agitated contrast saline and adequate Valsalva maneuver, TCD detects microemboli in the middle cerebral artery and confirms the presence of a right-to-left shunt. Whereas TEE identifies the defect's site and size, concomitant intracardiac abnormalities (ASA, persistent Eustachian valve, or Chiari network), and other cardiac sources of embolism, TCD detects any kind of right-to-left shunt including pulmonary shunts (30). Microemboli also could be (but are not currently) assessed in an extracranial or limb artery.

COMPUTED TOMOGRAPHY/CARDIAC MAGNETIC RESONANCE. Multislice computed tomography (MSCT) provides high spatial resolution images, which allow a detailed assessment of the vasculature and cardiac structures during a resting state. Although the sensitivity and specificity of MSCT to detect a significant intracardiac defect and shunt is considered high (**Table 1**) (31), MSCT does not provide information on functional aspects of the intracardiac shunt and precludes Valsalva maneuvers. Moreover, MSCT is associated with exposure to ionizing radiation, which is of concern among young individuals in whom it should be avoided as a screening method.

The relevance of cardiac magnetic resonance imaging in the detection of intracardiac shunts remains controversial. Although small studies show adequate accuracy to detect intracardiac shunts and a good correlation with TEE, others question the spatial resolution during real-time evaluation (32). Again, Valsalva maneuvers are not possible. However, cardiac magnetic resonance is very useful for the noninvasive quantification of shunt volume.

EAR OXIMETRY. Ear oximetry is a noninvasive screening technique that can be applied ubiquitously and provides high sensitivity (85%; 95% CI: 72% to 93%) and specificity (100%; 95% CI: 88% to 100%) compared with TEE (33). Ear oximetry for the detection of intracardiac shunts is based on a simple principle. A significant shunt of desaturated venous blood from the right atrium into the left circulation causes a drop in arterial saturation within the first few seconds after a sufficient Valsalva maneuver. This transient fall in

systemic oxygen saturation can be noninvasively monitored in the peripheral circulation and with ear oximetry. However, a sufficient Valsalva maneuver is an important prerequisite for a diagnostically conclusive result (33,34).

CLINICAL MANIFESTATIONS

Embolic particles can be of different size and diverse origin and can become clinically relevant in various ways.

STROKE. Several observational studies have established a strong association between stroke and intracardiac shunts, particularly PFO (8,35,36). Young patients with cryptogenic stroke have been reported to have a higher prevalence of PFO alone (OR: 5.0; 95% CI: 2.4 to 10.4), as well as PFO associated with ASA (OR: 23.3; 95% CI: 5.2 to 103.2) compared with patients without stroke. Furthermore, in elderly patients (≥55 years of age) with cryptogenic stroke, the rate of PFO was found to be almost 3-fold increased (OR: 2.9; 95% CI: 1.7 to 5.0) and the rate of PFO and ASA was almost 4-fold increased (OR: 3.9; 95% CI: 1.8 to 8.5) when compared with patients with known cause of stroke (8). The association between ischemic stroke and PFO was confirmed in a meta-analysis on observational studies with a relative risk of 6.0 (95% CI: 3.7 to 9.7) for patients with PFO and cryptogenic stroke compared with those with known cause of stroke.

MIGRAINE. There is an association between migraine and paradoxical embolism. Small emboli originating from the venous circulation are usually filtered in the pulmonary circulation, but can enter the systemic circulation in the presence of a right-to-left shunt and provoke transient occlusion of the cerebral microcirculation (37). In addition, these small thrombi facilitate platelet activation and the release of vasoactive substances and proinflammatory markers from the trigeminal sensory neurons (substance P, calcitonin gene-related peptide, and neurokinin A), contributing to migraine attacks (38). The hypothesis of venous serotonin (usually metabolized in the lungs) reaching the brain through a PFO and triggering local vasomotion has also been raised.

Among patients with migraine, the prevalence of intracardiac right-to-left shunts has been reported to be as high as 50% (39). Controversy remains whether PFO closure reduces migraine frequency and severity. Although observational studies suggest a significant improvement of migraine attacks after PFO closure in up to 83% of patients (40,41), the prospective MIST (Migraine Intervention With STARFlex Technology) randomized controlled trial (RCT) failed to confirm this hypothesis (42). No significant difference was observed in the primary efficacy endpoint of migraine headache between patients undergoing PFO closure and sham control subjects 6 months after the intervention (4.1% vs 4.1%, $p = 0.51$). However, exploratory analyses revealed a significant reduction in total migraine headache days in the closure group ($p = 0.027$).

MYOCARDIAL INFARCTION. Paradoxical embolism causing acute MI in the presence of right-to-left shunt is a potentially fatal and likely under-reported phenomenon (4,43). Acute MI might be the consequence of paradoxical embolism, which should be entertained in the differential diagnosis (see **Fig. 2** for a case vignette). Histopathological evaluation of the thrombus aspirate is useful to further substantiate the origin of thrombotic material and to differentiate it from atheroembolism and rare other causes, such as myxomas. Additional clinical manifestations are described in the Online Appendix.

SECONDARY PREVENTION OF PARADOXICAL EMBOLISM

Therapeutic approaches include elimination of the pathway allowing paradoxical embolism to occur (percutaneous or surgical closure), medical treatment aiming to prevent recurrence of venous thrombosis, or its combination. Controversy remains as to the most effective treatment strategy.

MEDICAL TREATMENT. The most effective medical therapy for secondary prevention of recurrent events among patients with paradoxical embolism is unknown. Acetylsalicylic acid, oral anticoagulation, or a combination of both can be used. However, the best regimen to reduce thrombotic events while also avoiding bleeding complications remains undetermined. In observational studies, the rate of recurrent cerebrovascular accidents ranged from 3.4% (44) to 14.4% (45) per year using a treatment strategy of either acetylsalicylic acid or warfarin. Patients with PFO and ASA are at increased risk for recurrent ischemic stroke or TIA, and treatment with acetylsalicylic acid alone has been shown insufficient for secondary prevention (44,46).

WARSS (Warfarin Aspirin Recurrent Stroke Study) ($N = 2,206$) was a randomized, double-blind, multicenter trial comparing acetylsalicylic acid (325 mg/day) with warfarin (target international normalized ratio [INR]: 1.4 to 2.8) in the prevention of recurrent stroke (47). Irrespective of PFO presence, there was no significant difference in efficacy between warfarin and acetylsalicylic acid. Similarly, the multicenter,

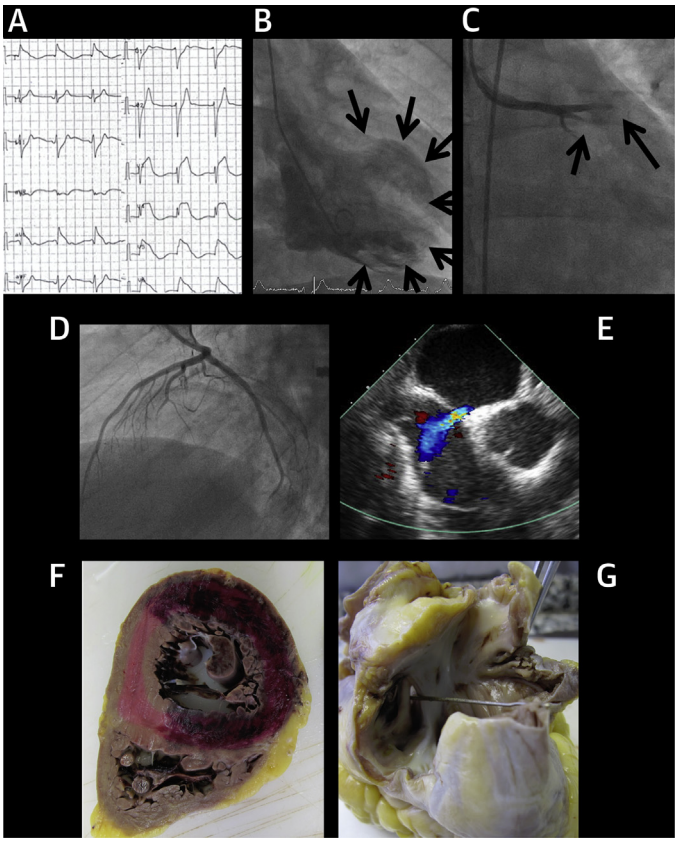


FIGURE 2 Clinical Case Vignette

A 34-year-old man was referred for primary percutaneous coronary intervention after cardiac arrest and resuscitation for ST-segment elevation myocardial infarction complicated by cardiogenic shock **(A)**. Angiography showed severe left ventricular dysfunction (the **arrows** indicate anteroapical left ventricular akinesia) **(B)** due to embolic occlusion of both the proximal left anterior descending and circumflex coronary arteries **(arrows) (C)**. After thrombus aspiration, balloon dilation under hemodynamic support of a left ventricular assist device (TandemHeart TM, CardiacAssist, Inc., Pittsburgh, Pennsylvania) and administration of abciximab, coronary flow was re-established **(D)**. Transesophageal echocardiography revealed a patent foramen ovale (PFO) with spontaneous bidirectional shunt, suggestive of paradoxical embolism, as the cause of embolic myocardial infarction **(E)**. The next day, treatment was discontinued due to brain death. Autopsy findings included hemorrhagic myocardial infarction **(F)**, a large PFO **(G)**, bilateral subsegmental pulmonary embolism, and a fresh thrombosis of the left femoral vein. Adapted and modified, with permission from Pilgrim et al. (43).

randomized PICCS (PFO in Cryptogenic Stroke Study) (N = 630) evaluating warfarin (target INR: 1.4 to 2.8) and acetylsalicylic acid (325 mg/day) in patients with PFO and stroke observed no significant difference between both treatment strategies, although the absolute risk for death or stroke was reduced almost by one-half with warfarin compared with acetylsalicylic acid in the subgroup with PFO (48). Of note, bleeding complications were more common among patients undergoing oral anticoagulation. In both the WARSS and PICCS studies, the rate of severe bleeding complications was similar (WARSS 1.5% vs. 2.2% per 100 patient-years, PICCS 1.8% vs. 1.9% per 100 patient-years), but minor bleeding was more frequent among patients receiving warfarin (WARSS 13% vs. 21% per 100 patient-years, PICCS 9% vs. 23% per 100 patient-years). The safety and efficacy of non-vitamin K antagonist oral anticoagulants in the secondary prevention of paradoxical embolism has not been studied so far. Given the available evidence investigating non-vitamin K antagonist oral anticoagulants among patients with AF, deep venous thrombosis, and pulmonary embolism (49–51), these agents may be considered a valuable alternative to warfarin among patients with paradoxical embolism.

PERCUTANEOUS TREATMENT OF INTRACARDIAC COMMUNICATIONS AND PAVMS. The percutaneous closure of ASDs was introduced in 1976 (52), followed by the first report of a percutaneous approach to PFO closure with the Rashkind Clamshell device in 1992 (53). Percutaneous PFO closure has evolved into a routine, low-risk intervention, which can be easily performed in an outpatient setting. Complications are rare but have been reported to include vascular injury at the puncture site (1.5%), device embolization (1.1%), cardiac tamponade (0.3%), TIA (0.2%) (54), and other device-specific complications, such as early and late device thrombosis and atrial arrhythmias. Significant residual shunt and incomplete closure, as well as thrombus formation around the device, may be the cause for recurrent neurological and peripheral embolic events (55). Overall, PFO closure bears the lowest risk of percutaneous cardiac interventions, with an overall risk <1% in an experienced center (56).

The treatment of choice of PAVMs is endovascular occlusion with intravascular coils or vascular plugs, whereas surgery (ligation, excision, or pulmonary segmentectomy) is limited to a few emergency cases to control bleeding. In the rare clinical scenario of the coincidence of pulmonary shunts and PFO, treatment recommendations are lacking, but a percutaneous approach consisting of PFO and simultaneous pulmonary shunt closure might be a reasonable option to reduce the risk of recurrent embolism.

SURGICAL TREATMENT. Surgical treatment of relevant shunts for secondary prevention of cryptogenic stroke is limited to patients undergoing cardiac surgery for other indications in view of less-invasive alternatives. Reports of surgical PFO closure have indicated closure success with rates of recurrent ischemic events comparable to those after percutaneous PFO closure, ranging between 0% and 14% (57,58).

RANDOMIZED EVIDENCE INVESTIGATING DIFFERENT TREATMENT STRATEGIES

Observational studies of percutaneous PFO closure using different devices among patients with presumed paradoxical embolism have suggested that there is a substantial benefit in the secondary prevention of recurrent stroke over medical therapy (59,60). A mortality benefit at 10 years of follow-up was demonstrated when comparing patients after device closure to those before or without device closure (59). Recently, results from 3 randomized, clinical trials investigating 2 different PFO closure devices (STARFlex, NMT Medical, Boston, Massachusetts, and Amplatzer PFO Occluder, St. Jude Medical, St. Paul, Minnesota) compared with medical therapy have been reported (61–63).

PFO CLOSURE VERSUS MEDICAL THERAPY. CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale) (61) was the first multicenter, randomized trial comparing the STARFlex closure device with medical therapy using either warfarin (target INR: 2 to 3) or acetylsalicylic acid (325 mg/day) among 909 patients with PFO and cryptogenic stroke enrolled between 2003 and 2008. The cumulative incidence of the primary endpoint (stroke or TIA within the first 24 months after the intervention, death from any cause during the first 30 days, and death from neurological cause after 30 days up to 24 months of follow-up) was 5.5% in the closure and 6.8% in the medical therapy groups (adjusted HR: 0.78, 95% CI: 0.45 to 1.35, $p = 0.37$). There were low rates of recurrent stroke (2.9% vs. 3.1%, $p = 0.79$) and TIA (3.1% vs. 4.1%, $p = 0.44$) and no deaths throughout the follow-up period. PFO closure was effective in 86% of patients after 6 months and 87% of patients after 24 months of follow-up. Device-associated thrombus was observed in 1.1% of patients and was considered responsible for recurrent stroke in 2 patients. PFO closure with the STARFlex PFO Occluder was associated with an 8-fold increased risk of new-onset AF (5.7% vs. 0.7%, $p < 0.001$), which occurred in the first week after the interventions in two-thirds of episodes.

The multicenter, randomized PC (Patent Foramen Ovale and Cryptogenic Embolism) trial compared the efficacy and safety of percutaneous PFO closure with the Amplatzer PFO Occluder with medical therapy among 414 patients with PFO and a history of cryptogenic stroke, TIA, or peripheral embolism (62). After a follow-up duration of 845 patient-years in the closure group and 835 patient-years in the medical therapy group, the pre-defined combined primary endpoint of all-cause death, recurrent stroke, TIA, or peripheral embolism had occurred in 7 patients in the closure group compared with 11 patients in the medical therapy group (3.4% vs. 5.2%, HR: 0.63; 95% CI: 0.24 to 1.62; $p = 0.34$). The incidence of recurrent stroke was low and was observed in 1 patient in the closure group and 5 patients in the medical therapy group (0.5% vs. 2.4%, HR: 0.20; 95% CI: 0.02 to 1.72; $p = 0.14$). Using the endpoint definition applied in the RESPECT trial, a numerical difference in recurrent stroke was observed between the closure ($n = 1$) and the medical therapy groups ($n = 7$), showing an 86% relative risk reduction by using the Amplatzer PFO Occluder compared with medical therapy (HR: 0.14; 95% CI: 0.02 to 1.17; $p = 0.07$).

Between 2003 and 2011, 980 patients with a medical history of cryptogenic stroke in the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial were randomly assigned to PFO closure with the Amplatzer PFO Occluder ($n = 499$) and medical therapy ($n = 481$) (63). Patients randomized to medical therapy alone were treated with acetylsalicylic acid (46.5%), warfarin (25.2%), clopidogrel (14.0%), or dual antiplatelet therapy using acetylsalicylic acid and clopidogrel (6.2%) or acetylsalicylic acid and dipyridamole (8.1%). The maximum follow-up duration was 8.1 years, with differences in follow-up duration between patients in the closure and medical therapy group (1,375 patient-years vs. 1,184 patient-years; $p = 0.009$), largely explained by differences in study withdrawal. PFO closure with the Amplatzer PFO Occluder was associated with a high rate of technical (99.1%) and procedural success (96.1%) and a low rate of periprocedural complications (closure vs. medical therapy: bleeding events 1.6% vs. 1.9%; $p = 0.81$). PFO closure was effective, showing complete PFO closure or trivial residual shunt in 94% of patients 6 months after the intervention.

The endpoint-driven study was stopped when 25 primary endpoints (recurrent stroke or death within either 30 days after the intervention or 45 days after randomization) were reached. They occurred in 9 patients in the PFO closure group compared with 16 patients in the medical therapy group (HR: 0.49, 95% CI: 0.22 to 1.11, $p = 0.08$). A significant difference in the primary endpoint was observed in the per-protocol analysis (HR: 0.37, 95% CI: 0.14 to 0.96, $p = 0.03$) and in the as-treated analysis (HR: 0.27, 95% CI: 0.10 to 0.75, $p = 0.007$). Of note, the treatment effect was particularly pronounced among patients with substantial shunt

TABLE 2 Meta-Analyses Comparing PFO Closure With Medical Therapy

First Author (Ref. #)	Overall Results (ITT)		Subgroup Analyses			Conclusions
	Recurrent Stroke (95% CI)	Composite Endpoint (95% CI)	Description	Recurrent Stroke (95% CI)	Composite Endpoint (95% CI)	
Wolfrum et al. (65)	RR: 0.66 (0.37–1.19)	NR	Per-protocol analysis	RR: 0.66 (0.32–1.38)	NR	Percutaneous PFO closure in patients with cryptogenic stroke does not appear to be superior to medical therapy.
			Amplatzer only	RR: 0.44 (0.20–0.94)	NR	
Hernandez and Moreno (70)	OR: 0.64 (0.37–1.10)	NR	Amplatzer only	OR: 0.46 (0.21–0.98)	NR	PFO closure with the Amplatzer Occluder may reduce the risk of recurrent stroke in patients with PFO and cryptogenic stroke.
Dentali et al. (71)	RR: 0.66 (0.37–1.19)	RR: 0.71 (0.48–1.06)	Atrial septal aneurysm	NR	RR: 0.71 (0.22–2.27)	There is insufficient evidence to establish the role of percutaneous PFO closure in patients with cryptogenic cerebrovascular events.
			Substantial shunt	NR	RR: 0.37 (0.09–1.45)	
Pandit et al. (72)	HR: 0.62 (0.36–1.07)	NR	Amplatzer only	HR: 0.44 (0.21–0.94)	NR	Percutaneous PFO closure with the Amplatzer Occluder is associated with a significant reduction in recurrent stroke.
Riaz et al. (73)	NR	HR: 0.66 (0.43–1.01)	Per-protocol analysis	NR	HR: 0.64 (0.41–0.98)	Percutaneous PFO closure provides a favorable trend toward improved outcomes compared with medical therapy in ITT analyses and confirms a benefit in PP analyses.
			Amplatzer only (ITT)	NR	HR: 0.54 (0.29–1.01)	
			Amplatzer only (PP)	NR	HR: 0.64 (0.44–0.97)	
Khan et al. (74)	HR: 0.67 (0.44–1.00)	NR	Per-protocol analysis	HR: 0.62 (0.40–0.95)	NR	Percutaneous PFO closure is beneficial compared with medical therapy in the prevention of recurrent cryptogenic stroke.
			As-treated analysis	HR: 0.61 (0.40–0.95)	NR	
			Amplatzer only	HR: 0.54 (0.29–1.01)	NR	
			Amplatzer only (PP)	HR: 0.48 (0.24–0.94)	NR	
			Amplatzer only (AT)	HR: 0.42 (0.21–0.84)	NR	
Zhang et al. (75)	RR: 0.66 (0.37–1.19)	NR	Amplatzer only	RR: 0.48 (0.23–1.02)	NR	Percutaneous PFO closure does not reduce the risk of recurrent ischemic stroke compared with medical therapy.
Hakeem et al. (76)	RR: 0.66 (0.35–1.24)	RR: 0.71 (0.48–1.06)	Per-protocol analysis	NR	RR: 0.66 (0.43–1.00)	While there is a trend towards improved outcomes with PFO closure, there is no statistical significance compared with medical therapy.
Nagaraja et al. (77)	OR: 0.65 (0.36–1.19)	NR	Atrial septal aneurysm	RR: 0.7 (0.21–2.33)	NR	Percutaneous PFO closure does not appear to confer an advantage over medical therapy.
			Substantial shunt	RR: 0.35 (0.09–1.41)	NR	
Rengifo-Moreno et al. (67)	HR: 0.62 (0.36–1.07)	HR: 0.67 (0.44–1.00)	Per-protocol analysis	NR	HR: 0.62 (0.38–1.00)	Percutaneous PFO closure may be beneficial in reducing the risk of recurrent vascular events compared with medical treatment.
			Substantial shunt	NR	HR: 0.35 (0.12–1.03)	
			Atrial septal aneurysm	NR	HR: 0.68 (0.32–1.42)	

Continued on the next page

(0.8% vs. 4.3%, p = 0.012) and associated ASA (1.1% vs. 5.3%, p = 0.016). Device-related thrombus was observed in none of the patients in the RESPECT or PC trials during echocardiographic follow-up. Patients in the closure group had a nonsignificant 2-fold increased risk for new-onset AF when compared with patients receiving medical therapy alone (3.0% vs. 1.5%, p = 0.13). In the RESPECT trial, the average number of patients that needed to be treated with the Amplatzer PFO Occluder to prevent 1 stroke amounted to 70 after 2 years and 24 after 5 years of follow-up.

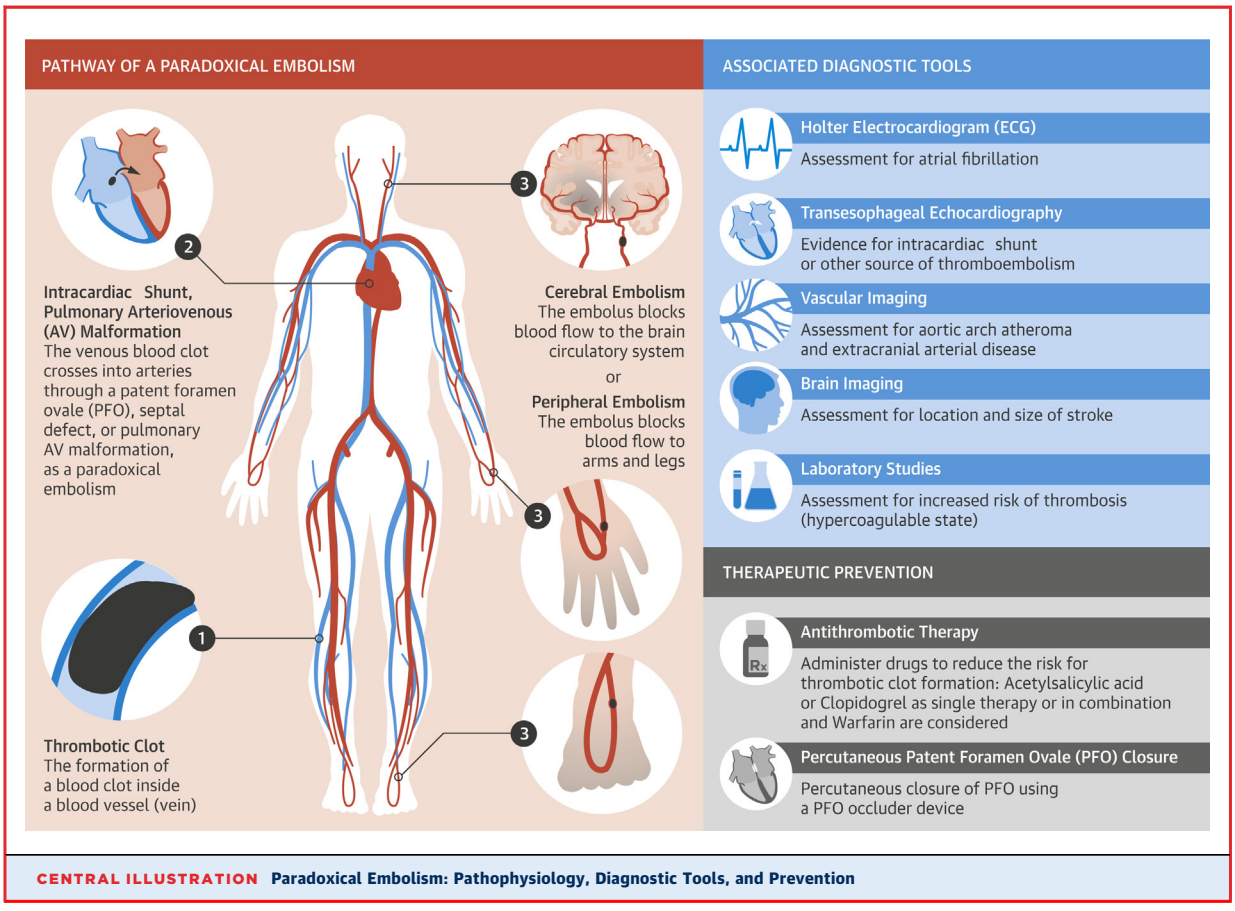
TABLE 2 Continued

First Author (Ref. #)	Overall Results (ITT)		Subgroup Analyses			Conclusions
	Recurrent Stroke (95% CI)	Composite Endpoint (95% CI)	Description	Recurrent Stroke (95% CI)	Composite Endpoint (95% CI)	
Pineda et al. (78)	OR: 0.65 (0.36–1.20)	OR: 0.70 (0.47–1.05)	As-treated analysis	NR	OR: 0.62 (0.41–0.94)	Percutaneous PFO closure may be associated with a decreased incidence of recurrent neurological events as compared with medical treatment alone.
Chen et al. (79)	NR	RR: 0.70 (0.47–1.04)	NR	NR	NR	Percutaneous PFO closure is competitive to medical treatment and should be offered to patients as a choice between a simple once-in-a-lifetime operation and lifelong medical therapy that might increase bleeding risk.
Ntaios et al. (80)	OR: 0.64 (0.37–1.10)	NR	Amplatzer only	OR: 0.46 (0.21–0.98)	NR	PFO closure compared with medical therapy fails to achieve a significant reduction in stroke. After pooling only trials using the Amplatzer PFO occluder, a significant reduction in stroke over medical treatment is observed.
Kwong et al. (81)	OR: 0.65 (0.36–1.20)	NR	Amplatzer only	OR: 0.47 (0.22–1.02)	NR	PFO closure compared with medical therapy fails to achieve a significant reduction in stroke.
Kitsios et al. (69)	HR: 0.55 (0.26–1.18)	HR: 0.67 (0.44–1.00)	Amplatzer only	HR: 0.38 (0.14–1.02)	HR: 0.44 (0.17–1.12)	PFO closure compared with medical therapy fails to achieve a significant reduction in stroke.
Capodanno et al. (68)	HR: 0.62 (0.36–1.11)	NR	Amplatzer only	HR: 0.44 (0.20–0.95)	NR	PFO closure compared with medical therapy fails to achieve a significant reduction in stroke. After pooling only trials using the Amplatzer PFO occluder, a significant reduction in stroke over medical treatment is observed.
Spencer et al. (82)	RR: 0.61 (0.34–1.07)	NR	Amplatzer only	RR: 0.44 (0.21–0.93)	NR	The available randomized evidence is insufficient to support PFO closure for patients with cryptogenic stroke.
Stortecky et al.* (83)	NR	NR	Amplatzer only StarFlex only Helex only	RR 0.39 (0.17–0.84) RR 1.01 (0.44–2.41) RR 0.71 (0.17–2.78)	NR NR NR	The effectiveness of PFO closure depends on the device used. PFO closure with the Amplatzer appears superior to medical therapy in preventing strokes in patients with cryptogenic embolism

Depicted are analyses from random effects models. *Results from network meta-analysis.

AT = as treated; HR = hazard ratio; ITT = intention to treat; NR = not reported; OR = odds ratio; PFO = patent foramen ovale; PP = per protocol; RR = risk ratio/rate ratio/relative risk.

DEVICE TYPE. A randomized trial compared clinical outcomes and device-specific differences between 3 different PFO occluders (Amplatzer PFO Occluder, STARFlex, or HELEX [W.L. Gore & Associates, Newark, Delaware]; 220 patients per group) among 660 patients with cryptogenic stroke and PFO (64). Although technical success was achieved in all patients, significant differences in effective PFO closure between devices were observed (Amplatzer 98.6% vs. STARFlex 96.8% vs. HELEX 91.8%; $p = 0.0012$). The primary endpoint of recurrent cerebral ischemia, death from neurological cause, or paradoxical embolism within 5 years after the index procedure was observed in 1.4%, 6.0%, and 4.0% of patients,



CENTRAL ILLUSTRATION **Paradoxical Embolism: Pathophysiology, Diagnostic Tools, and Prevention**

respectively (p = 0.04). Significant differences in device-associated thrombus formation (0% vs. 5.0% vs. 0.5%, respectively, p < 0.0001) and new-onset AF (3.6% vs. 12.3% vs. 2.3%, respectively, p < 0.0001) were observed during the observational period of 5 years.

META-ANALYSES. All 3 RCTs comparing PFO closure with medical therapy in the secondary prevention of cryptogenic stroke or embolism individually failed to show a statistically significant benefit of PFO closure according to the pre-defined endpoints (61-63). Several meta-analyses have scrutinized the available evidence including the RCTs (**Table 2**). Using a random effects model, Wolfrum et al. (65) reported a nonsignificant 44% relative risk reduction for the endpoint of stroke (pooled relative risk: 0.66, 95% CI: 0.37 to 1.19; p = 0.171) (65). In a time-to-event analysis, which considers the time to recurrent stroke (59,66), a significant risk reduction was observed (HR: 0.58, 95% CI: 0.33 to 0.99, p = 0.047). In another analysis, cerebrovascular events (composite endpoint of stroke and TIA, according to the intention-to-treat analysis) were significantly reduced (pooled HR: 0.59, 95% CI: 0.36 to 0.97; p = 0.04), as was the combined endpoint of death and vascular events (pooled HR: 0.67, 95% CI: 0.44 to 1.00; p = 0.05) (67).

Capodanno et al. (68) reported no significant difference between percutaneous PFO closure and medical therapy in the prevention of stroke in a random effects model, including all 3 RCTs (HR: 0.62, 95% CI: 0.34 to 1.11; p = 0.10). However, analyzing RCTs according to the implanted device resulted in a significant reduction of stroke (HR: 0.44, 95% CI: 0.20 to 0.95; p = 0.04) when restricting the meta-analysis to studies using the Amplatzer PFO occluder (62,63), suggesting a device-specific effect on clinical outcomes. Kitsios et al. (69) failed to show a significant reduction for the stroke endpoint using all 3 RCTs (HR: 0.55, 95% CI: 0.26 to 1.18), whereas a borderline significant effect was observed when analyzing the composite primary outcomes (HR: 0.67, 95% CI: 0.44 to 1.00) (69). These meta-analyses point to a potentially large treatment effect in favor of percutaneous PFO closure and suggest that there are device-specific differences in outcome potentially related to closure success and predisposition for thrombus formation and atrial arrhythmias.

CLINICAL DECISION MAKING

In advising individual patients of the treatment choice between medical treatment alone and percutaneous PFO closure, the physician needs to weigh the overall risk of stroke recurrence, anatomic details of the structural defect, evidence of venous or pulmonary thromboembolism, the risks and costs of lifelong antithrombotic therapy in case of medical treatment, the risks and costs in case of percutaneous PFO closure, outcomes with various PFO devices, the potentially large therapeutic benefit of PFO closure during long-term follow-up, and potential collateral benefits, such as improvement of headaches or exertional dyspnea. Of note, stroke is different from other adverse events owing to its impact on sensorimotor and neurocognitive functions. Available evidence suggests that PFO closure performed with devices achieving high closure rates reduces the risk of recurrent stroke compared with medical treatment alone and should be considered in patients with first-time cryptogenic stroke, particularly in those with high-risk criteria, such as presence of an ASA, large PFO, Eustachian valve, or Chiari network.

CONCLUSIONS

Paradoxical embolism is an important clinical entity among patients with venous thromboembolism and the presence of cardiac or pulmonary shunts. The clinical manifestations are serious but diverse and make the diagnosis challenging at times. The advent of TEE has greatly facilitated the detection of PFO, the most important mediator of paradoxical embolism. Although none of the 3 RCTs individually provided conclusive evidence in favor of percutaneous PFO closure over medical treatment alone, synthesis of the available evidence suggests a substantial treatment effect in favor of device closure and device-specific differences in outcome, which should be conveyed to patients and considered in the treatment allocation (**Central Illustration**).

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KEY WORDS embolism, paradoxical, patent foramen ovale, stroke

APPENDIX For additional information, including the genetics of intra-atrial defects, type and source of embolic particles, clinical manifestations of right-to-left shunt, and professional guidelines, please see the online version of this article.