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Proposal for Updated Nomenclature and Classification of Potential Causative Mechanism in Patent Foramen Ovale–Associated Stroke

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IMPORTANCE Recent epidemiologic and therapeutic advances have transformed understanding of the role of and therapeutic approach to patent foramen ovale (PFO) in ischemic stroke. Patent foramen ovale is likely responsible for approximately 5% of all ischemic strokes and 10% of those occurring in young and middle-aged adults.

OBSERVATIONS Randomized clinical trials have demonstrated that, to prevent recurrent ischemic stroke in patients with PFO and an otherwise-cryptogenic index ischemic stroke, PFO closure is superior to antiplatelet medical therapy alone; these trials have provided some evidence that, among medical therapy options, anticoagulants may be more effective than antiplatelet agents.

CONCLUSIONS AND RELEVANCE These new data indicate a need to update classification schemes of causative mechanisms in stroke, developed in an era in which an association between PFO and stroke was viewed as uncertain. We propose a revised general nomenclature and classification framework for PFO-associated stroke and detailed revisions for the 3 major stroke subtyping algorithms in wide use.

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Stroke is the second leading cause of death worldwide and among the most common debilitating diseases. Overall, 70% of strokes are ischemic and carry a high long-term recurrence risk.[1,2] Ischemic stroke is a heterogeneous disorder because numerous mechanisms produce vascular occlusion and infarction. *Cryptogenic ischemic stroke* (CIS), the term used when no causative mechanism has been identified, accounted for 40% of all ischemic strokes a half-century ago; however, with diagnostic advances, especially imaging, the proportion has declined to 15% to 30%.[3,4] Cryptogenic ischemic stroke occurs more frequently in young and middle-aged patients (<60 years old) who have fewer risk factors for atherosclerotic disease.[3,4] The most frequent pattern of CIS is a nonlacunar infarct (superficial, large, deep, or combined superficial and deep).[5]

As a diagnosis of exclusion, rendered when adequate workup has failed to identify a defined causative mechanism of stroke, CIS is a conceptual entity that requires continuous curation and pruning. When scientific advances unveil new causative mechanisms of stroke, patients with those conditions should no longer be characterized as cryptogenic but rather placed in the appropriate defined causation category. The most common, broad, defined categories are large artery atherosclerosis, cardioembolism, small vessel disease, and other causes. Three detailed classification systems to assign patients among these categories have gained wide acceptance: (1) Trial of Org 10172 in Acute Stroke Treatment (TOAST); (2) Causative Classification of Stroke (CCS); and (3) atherosclerosis, small vessel, cardioembolism, and other dissection (ASCOD).[6-9] Also influential has been the embolic stroke of undetermined source (ESUS) construct for the preliminary classification of patients.[4]

The most frequent advance requiring alteration in cryptogenic stroke classification is recognition of new, uncommon causative mechanisms that fall within the motley supraordinate category termed *other*. Examples of newly recognized or more easily diagnosed causative mechanisms since the first promulgation of formal causative classification systems in 1993[6] include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and reversible cerebral vasoconstriction syndrome.[10,11] Incorporation of these uncommon entities into diagnostic frameworks of causative mechanisms is straightforward; they become additional members of the category of other defined causative mechanisms of stroke. A less frequent and more challenging development mandating alteration to CIS classification is a change in status of a component entity within a defined category, such as cardioembolic stroke. When large-scale studies demonstrate a particular cardioembolic mechanism is more likely to be a genuine cause of stroke than was understood when classification systems were

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initially designed, the detailed algorithmic logic of the classification systems needs revision. Updated algorithms will appropriately classify more individuals as having defined causative mechanisms of stroke, and more patients will receive secondary prevention therapies appropriate for their specific causative mechanism, rather than generic therapies used for CIS.

Paradoxical embolism through a patent foramen ovale (PFO) is a mechanism of stroke appearing in the cardioembolic category in the formal classification systems for which scientific understanding has advanced substantially over the past decade. Paradoxical embolism is defined as the migration of thrombus from the systemic venous to arterial circulations via a right-to-left shunt, and may cause stroke, myocardial infarction, or peripheral embolism. The embolus is said to be paradoxical because a venous-origin thrombus is responsible for a systemic arterial event. Ordinarily, venous-origin thrombi pass through the right heart to the pulmonary circulation and are trapped in the pulmonary arterial-arteriolar-capillary tree. For paradoxical embolism to occur, there must be a direct connection between the otherwise distinct venous and arterial circulations, either intracardiac, such as a PFO or atrial septal defect, or extracardiac, such as a pulmonary arteriovenous malformation.[12,13] In addition to serving as a conduit for paradoxical emboli, it has been hypothesized that PFOs may less commonly produce stroke via in situ thrombus formation around the interatrial tunnel arising from slow or dyslaminar flow, but to our knowledge, no definitive evidence supports this mechanism.

Recent large-scale epidemiologic studies have indicated that PFOs are a more common stroke mechanism than was previously appreciated.[14-17] Furthermore, recent randomized clinical trials (RCTs) demonstrated the superiority of a PFO-specific therapy, percutaneous PFO closure, compared with a nonspecific stroke prevention strategy, antiplatelet medication alone, in averting recurrent ischemic stroke.[18-23] These results mandate the updating of classifications of the causative mechanisms of stroke. At a general conceptual level, it is no longer tenable to describe some patients who are found to have cerebral infarcts that are highly likely to have been causally associated with a present PFO as cryptogenic.[17,24,25] At a granular, operational level, revisions are indicated in the major stroke causation classification systems.[26] Classifying an otherwise-cryptogenic stroke in the presence of a likely causal PFO as being of uncertain cause hinders application of diagnostic and management strategies that are now recommended by guidelines and approved by regulatory bodies.[27,28]

In the current statement, we propose the term *PFO-associated stroke* as a distinct causative mechanism of ischemic stroke, applied in a graded manner based on a thorough patient evaluation. We synthesize evidence supporting this new nomenclature, which aligns PFOs with other well-characterized stroke causative mechanisms, facilitates causative mechanism–directed management, and can help guide further research to advance stroke diagnostics and therapeutics (the literature search strategy is in eAppendix 1 in the Supplement).

Evolution of Approaches to Identifying Causative Mechanisms of Ischemic Stroke

The modern era of investigation into causative mechanisms of stroke began in the 1960s through 1980s, with the advent of improved in vivo diagnostic technologies characterizing brain (computed tomography [CT] and magnetic resonance imaging [MRI]), cervical vessel (carotid ultrasound), cardiac structure (transthoracic echocardiography), and cardiac rhythm (Holter monitoring), and their application to large, consecutive populations of patients with stroke. Systematic use of these technologies, along with detailed history taking, physical examination, and laboratory testing, became standard diagnostic practice. Large-scale studies delineated the frequency of different ischemic stroke causative mechanisms in diverse age groups and racial/ethnic populations and revealed that patients with ischemic strokes often did not have any causative mechanisms identified. In the 1980s, the US National Stroke Data Bank collaborative study[29] introduced the term *stroke of undetermined cause*; in 1989, the rubric *cryptogenic stroke* was additionally introduced (in an editorial[30] discussing one of the first studies linking PFOs to strokes of otherwise unidentified source).

The increasing use of standardized diagnostic workups in clinical practice, clinical trials, and epidemiologic studies led to the development over the next 2 decades of formal systems for classifying ischemic stroke causative mechanism. Three systems for detailed causative mechanism ascription remain in wide use: TOAST,[6] CCS,[7] and ASCOD.[8] All algorithmically assign causation among 5 or 6 major categories of (1) large artery atherosclerosis, (2) cardioembolism, (3) small vessel disease, (4) other known causes (eg, nonatherosclerotic arteriopathies, hypercoagulable states), (5) dissection, and (6) cryptogenic stroke. All recognize patients may have evidence of more than 1 cause.

Three aspects of these classification systems[6-8] are most relevant to this article. First, all developed formal algorithms to assign likelihood ratings to potential ischemic stroke causative mechanisms (eg, probable, possible, present but unrelated). Second, these algorithms all included specific rules for assigning causal likelihood ratings to PFOs. Third, the PFO-association algorithms all reflected the perspective of the era in which they were developed, when the frequency of PFO causal participation in ischemic stroke was underappreciated and the distinctive therapeutic approaches dependent on recognizing PFO-associated stroke were not validated by RCTs. As a result, all developed algorithms for assigning a PFO association that, based on subsequent epidemiologic and clinical trial studies, are unduly conservative (**Table 1**).

Evolution of Epidemiologic Recognition of PFO as an Important Cause of Otherwise-Cryptogenic Stroke

Paradoxical embolism through a PFO that caused ischemic stroke was first described in 1877.[31] In 1972, 4 diagnostic criteria were advanced: (1) a cerebral/systemic embolism without a left-sided source; (2) a presence of venous thrombus or pulmonary embolus; (3) the demonstration of a right-to-left shunt; and (4) elevated right heart pressures, either constant, as in pulmonary hypertension, tricuspid valve disease, congenital right atrial hypoplasia, or transient, as from cough or Valsalva maneuver. However, prior to the advent of contrast echocardiography, the diagnosis of paradoxical embolism was infrequent, with only 128 cases reported worldwide through 1972.[32]

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Table 1. Original and Proposed Revised Classification Approaches to Assigning Cardioembolic Source Likelihood in Patients With Patent Foramen Ovale[a]

Original approach to PFO		Proposed revised approach to PFO	
TOAST			
Probable	Not assignable based on PFO	Probable	Both (1) cortical/cerebellar infarct or subcortical infarct >1.5 cm in diameter and (2) PFO and straddling thrombus; or all 3 of the following: (1) cortical/cerebellar infarct or subcortical infarct >1.5 cm in diameter, (2) recent preceding or concurrent VTE, and either (3a) a large-shunt PFO present or (3b) a small-shunt PFO plus an atrial septal aneurysm present
Possible	Both (1) cortical/cerebellar infarct or subcortical infarct >1.5 cm in diameter and (2) PFO present	Possible	All 3 of the following: (1) cortical/cerebellar infarct or subcortical infarct >1.5 cm in diameter, (2) a PFO present, and (3) probable criteria not met
CCS			
Evident	Not assignable based on PFO	Evident	A PFO and a straddling thrombus or a PFO and recent preceding PE or proximal DVT
Probable	Not assignable based on PFO	Probable	Either (1a) concomitant systemic embolism or (1b) multiple acute infarctions closely associated in time within 2 or more cerebral circulations in absence of severe arteriopathy of all relevant vessels, hypercoagulable state, or hemodynamic disturbance; plus either (2a) a large-shunt PFO present or (2b) a small-shunt PFO plus an atrial septal aneurysm present
Possible	A PFO present, with or without an atrial septal aneurysm	Possible	Both (1) a PFO present and (2) evident and probable criteria not met
ASCOD			
Potentially causal	Either (1a) bihemispheric or supratentorial and infratentorial territorial or cortical infarcts and signs of systemic embolism or (1b) single or no cerebral ischemic lesion and either (2a) a PFO and a thrombus in situ or (2b) a PFO and preceding PE or proximal DVT	Potentially causal	Either (1a) bihemispheric or supratentorial and infratentorial territorial or cortical infarcts and signs of systemic embolism or (1b) a single or no cerebral ischemic lesion, plus any of the following: (2a) a PFO with a thrombus in situ, (2b) a PFO plus an atrial septal aneurysm, (2c) a large-shunt PFO, or (2d) a PFO plus a recently preceding PE or proximal DVT
Causal link uncertain	Regardless of infarct pattern, either (1a) a PFO and an atrial septal aneurysm or (1b) a PFO and concomitant but not preceding PE or proximal DVT	Causal link uncertain	Regardless of infarct pattern, a small-shunt PFO plus a concomitant but not definitely preceding PE or proximal DVT
Causal link unlikely	A PFO present in isolation	Causal link unlikely	Both (1) a small-shunt PFO present in isolation and (2) criteria for potential or uncertain causality not met

Abbreviations: ASCOD, atherosclerosis, small vessel disease, cardiac pathology, other causes, and dissection; CCS, Causative Classification of Stroke; DVT, deep venous thrombosis; PE, pulmonary embolism; PFO, patent foramen ovale; TOAST, Trial of Org 10172 in Acute Stroke Treatment; VTE, venous thromboembolism.

[a] It is critical to note that each formal classification system has independent modules for grading several distinct categories of potential stroke mechanisms, including large artery atherosclerosis, cardioembolism, small vessel disease, and other mechanisms. This Table shows the original and proposed revised algorithms for the submodule for PFO within the cardioembolic mechanism category. The final output for each system will result from each framework's broader logical schema for integrating the PFO-specific findings from this submodule with the findings of presence or absence of other sources from the remaining modules. In general, under all 3 classification systems, when there is no competing source of stroke also present, the likelihood of a pathogenic role of a PFO is increased (examples in eAppendix 5 in the Supplement).

With the development of contrast echocardiography, PFOs became routinely detectable during life. In 1988, 2 influential case-control studies using contrast transthoracic echocardiography provided the first evidence that PFOs were strongly associated with otherwise-cryptogenic ischemic stroke: PFOs were present in 40% to 50% of patients who were young or had CIS vs 10% to 15% of control participants.[33,34]

Over the next 3 decades, multiple case-control and prospective cohort studies, using transthoracic or transesophageal contrast echocardiography or transcranial Doppler ultrasound for PFO detection, amplified these findings. A cumulative meta-analysis of 23 case-control studies enrolling 3364 patients demonstrated the odds of harboring a PFO were 2.9-fold higher in patients with CIS compared with control participants. The presence of PFOs was especially more frequent in young and middle-aged patients with CIS (age ≤55 years old; odds ratio, 5.1) but also more frequent among older patients with CIS (>55 years old; odds ratio, 2.0) (eAppendix 2 in the Supplement).[15]

The cumulative case-control data indicate PFOs play an important pathogenic role in otherwise-cryptogenic ischemic stroke.[15,17] The analysis estimates that, among young and middle-aged patients (≤55 years old) with CIS, PFOs are the cause of the stroke in 42%, present but noncausal in 14%, and absent in 44%. Among older patients with CIS (>55 years old), PFOs are the cause of the stroke in 15%, present but noncausal in 13%, and absent in 72%.[15,17] Given that cryptogenic strokes account for about 25% of all ischemic strokes,[4,6,17] these findings of association indicate that PFOs cause approximately 5% of all ischemic strokes and 10% of all ischemic strokes in young and middle-aged adults.

Modern epidemiologic and clinical studies have additionally identified demographic, history, imaging, and laboratory features that increase the likelihood that a discovered PFO is causally associated with an otherwise-cryptogenic ischemic stroke. Five broad categories of findings increase the probability that a PFO, when present, is pathogenic.

First, atrial septal aneurysms may potentiate stroke risk in patients with PFO. This is likely in part through association with larger defect size and longer patency time and also by hemodynamically facilitating access to the PFO of venous thromboemboli arriving in the right atrium.[16-18,20,28,35,36]

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Second is increased right-to-left shunt flow, permanently or transiently. The greater the volume of right-to-left flow across the PFO, the greater the chance a venous thromboembolus will cross the interatrial shunt rather than move directly from the right atrium to the right ventricle. Causes of greater right-to-left flow include a large PFO size, chronic right atrial hypertension, a Valsalva maneuver, and a Mueller maneuver attributable to obstructive sleep apnea.[17,18,20,28]

Third is the presence of, or disposition to, venous thrombosis. The likelihood of PFO complicity in ischemic stroke is increased when concurrent deep venous thromboembolism is documented on a lower-extremity ultrasonographic image, pelvic CT, or MR venography, or pulmonary embolism is documented on pulmonary CT arteriography performed within the first 2 to 3 days after stroke onset (before time for venous thrombosis to develop secondarily has elapsed). Circumstances promoting venous thrombosis are also suggestive, including recent immobility (such as extended plane or car travel, surgery, or illness), dehydration, laboratory findings of a venous hypercoagulable state, anatomic causes of venous congestion (eg, May-Thurner syndrome), or a history of prior venous thromboembolism.[17,37-42]

Fourth is a recipient brain artery or territory typical of embolism. Typical recipient sites in the cerebral circulation for emboli are large main arterial trunks (causing large combined superficial-deep infarcts or isolated, large, deep infarcts) and small distal arterial branches (causing isolated superficial infarcts). Emboli much less commonly veer into small, single, deep penetrator arteries (causing isolated, small, deep infarcts).[17,43]

Finally, there is the absence of risk factors for atherosclerosis. Because mild atherosclerotic disease is a frequent, competing potential cause of ischemic stroke, a PFO as a causative mechanism is supported by the absence of demographic and medical-history atherosclerotic risk factors, including a younger patient age and the absence of hypertension, hyperlipidemia, diabetes, and tobacco use.

The Risk of Paradoxical Embolism (RoPE) score uses absence of atherosclerotic risk factors and infarct topography, although not other features, to quantify likelihood of a PFO causal association to stroke in individual patients (eTable in the Supplement).[44,45] Among patients with cryptogenic stroke and a PFO and a RoPE score of 7 or greater, the fraction attributable to PFO is estimated to be 80%.[44]

Data Supporting Therapeutic Strategies for PFO-Associated Stroke

Medical Therapies: Anticoagulants vs Antiplatelets

The optimal medical treatment for secondary prevention of recurrent ischemic stroke in patients with an index ischemic stroke presumed to be attributable to PFO has not been completely clarified. To date, no individual RCT has shown superiority of oral anticoagulation, but meta-analyses of both observational and trial data are suggestive. A study-level meta-analysis of 20 primarily nonrandomized comparison studies and an individual participant–level data meta-analysis of 12 observational studies both suggested superiority of anticoagulation over antiplatelets in recurrent stroke reduction, although bleeding was increased.[28,46] Meta-analysis of 4 RCTs enrolling 1518 patients, including 2 recent trials testing direct oral anticoagulants, shows a nonsignificant trend favoring anticoagulation preventing recurrent ischemic stroke (3.1% vs 5.4%; relative risk, 0.68; $P = .10$) (**Figure 1**A).[47,48]

Percutaneous PFO Closure and PFO-Associated Stroke

Between 2012 and 2018, 6 RCTs[18-23] enrolling 3560 patients compared percutaneous PFO closure with medical therapy alone for secondary prevention of recurrent ischemic stroke after an index cerebral ischemic event attributed to PFO. While the trials had limitations (eAppendix 3 in the Supplement), they together provided consistent and reinforcing findings. Individually, 3 were positive for their primary end points,[18-20] and all 6 showed similar directionally favorable evidence of a benefit of device closure in preventing ischemic stroke. The RCTs differed in aspects that appeared to modulate the degree of benefit of device closure, including devices tested (with double-disk devices[18-21,23] more effective than double-clamshell devices[22]), medications tested (with antiplatelet agents less effective than anticoagulants),[17,18,28] permitted qualifying events (with greater device effect when entry was confined to nonlacunar ischemic strokes),[19,20] and permitted entry cardioanatomic features (with greater effect when entry required a concomitant atrial septal aneurysm or large shunt size).[18,20]

Study-level meta-analyses of all 6 RCTs demonstrate a reduction in recurrent ischemic stroke with PFO device closure.[17,28] In the meta-analysis that accounted for differential follow-up durations, therapy with currently available double-disk devices substantially lowered recurrent ischemic stroke over 5 years (6.0% vs 1.8%; hazard ratio, 0.20; $P = .001$; Figure 1B).[17] This 80% reduction corresponds broadly with the attributable fraction noted in epidemiologic studies.[44]

Across all trials, there were high procedural success rates and low risks of major complications.[12,17,28] The most common complication was atrial fibrillation, but the great preponderance of atrial fibrillation events were transient, self-limited episodes occurring in the first 4 to 6 weeks post procedure. Across PFO closure trials, over 2.5 years of follow-up, stroke associated with atrial fibrillation was infrequent and not different between device use and medical therapy (0.1% vs 0.09%).[49] **Figure 2** illustrates the timeline of development of acute ischemic stroke classifications and PFO closure trials.

Proposed Revisions in Classification Algorithms

Given the strengthened epidemiologic data that indicate PFO is an important cause of stroke, provides greater understanding of additional risk-stratifying features, and verifies that diagnosing a stroke as causally associated with PFO now triggers specific therapeutic interventions, updating of stroke causation classification systems is indicated.

At the technical level of formal classification systems, Table 1 shows suggested revisions in PFO-associated algorithms in TOAST, CCS, and ASCOD. Adding recognition of PFO and patient characteristics that increase likelihood of pathogenic association, including (1) a straddling thrombus through a PFO (to TOAST and CCS),

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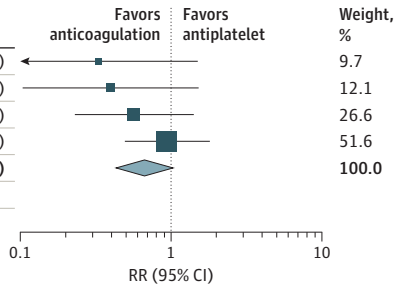
Figure 1. Forest Plots Showing Study-Level Meta-analyses of Randomized Clinical Trials of Strategies to Prevent Recurrent Ischemic Stroke in Patients With Patent Foramen Ovale (PFO)

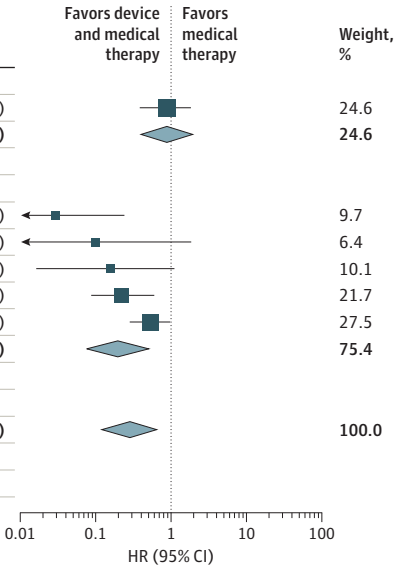
A Anticoagulation vs antiplatelet therapy

Study or subgroup	Anticoagulation Events	Anticoagulation Total	Antiplatelet Events	Antiplatelet Total	RR (95% CI)	Weight, %
PICSS, 2002	2	42	8	56	0.33 (0.07-1.49)	9.7
CLOSE, 2017	3	187	7	174	0.40 (0.10-1.52)	12.1
NAVIGATE ESUS, 2018	7	259	13	275	0.57 (0.23-1.41)	26.6
RE-SPECT ESUS, 2019	16	319	19	361	0.95 (0.50-1.82)	51.6
Total	**28**	**807**	**47**	**866**	**0.68 (0.42-1.08)**	**100.0**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.68$; $df = 3$; $P = .44$; $I^2 = 0\%$						
Test for overall effect: $z = 1.65$; $P = .10$						



B PFO closure and medical therapy vs medical therapy alone

Study or subgroup	log HR (SE)	Device and medical therapy Events	Device and medical therapy Patient-years (patients)	Medical therapy Events	Medical therapy Patient-years (patients)	HR (95% CI)	Weight, %
Umbrella-clamshell devices							
CLOSURE	-0.11 (0.40)	12	789 (447)	13	766 (462)	0.90 (0.41-1.98)	24.6
Subtotal		**12**	**789 (447)**	**13**	**766 (462)**	**0.90 (0.41-1.98)**	**24.6**
Test for overall effect: $z = 0.27$; $P = .79$							
Double disk devices (all or predominantly)							
CLOSE	-3.51 (1.11)	0	1231 (238)	14	1222 (235)	0.03 (0.00-0.26)	9.7
DEFENSE-PFO	-2.4 (1.47)	0	95 (60)	5	92 (60)	0.09 (0.01-1.62)	6.4
PC	-1.97 (1.09)	1	845 (204)	7	836 (210)	0.14 (0.02-1.17)	10.1
REDUCE	-1.47 (0.50)	6	1529 (441)	12	703 (223)	0.23 (0.09-0.62)	21.7
RESPECT-extended	-0.60 (0.30)	18	3080 (499)	28	2608 (481)	0.55 (0.31-0.99)	27.5
Subtotal		**25**	**6780 (1442)**	**66**	**5461 (1209)**	**0.20 (0.08-0.54)**	**75.4**
Heterogeneity: $\tau^2 = 0.61$; $\chi^2 = 9.46$; $df = 4$; $P = .05$; $I^2 = 58\%$							
Test for overall effect: $z = 3.20$; $P = .001$							
Total		**37**	**7579 (1889)**	**79**	**6227 (1671)**	**0.30 (0.13-0.68)**	**100.0**
Heterogeneity: $\tau^2 = 0.54$; $\chi^2 = 13.52$; $df = 5$; $P = .02$; $I^2 = 63\%$							
Test for overall effect: $z = 2.89$; $P = .004$							
Test for subgroup differences: $\chi^2 = 5.38$; $df = 1$; $P = .02$; $I^2 = 81.4\%$							



A, Anticoagulation vs antiplatelet therapy; PFOs were diagnosed by only transesophageal echocardiography in the PICSS and CLOSE trials, and by either transthoracic or transesophageal echocardiography in the NAVIGATE ESUS and RE-SPECT ESUS trials. B, PFO closure plus medical therapy vs medical therapy alone. CLOSE indicates Patent Foramen Ovale Closure or Anticoagulants vs Antiplatelet Therapy to Prevent Stroke Recurrence; HR, hazard ratio; NAVIGATE ESUS, the New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial vs ASA to Prevent Embolism in Embolic Stroke of Undetermined Source trial; PICSS, PFO in Cryptogenic Stroke Study; RE-SPECT ESUS, Randomized, Double-blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate vs Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source Trial; RR, relative risk.

(2) a large shunt size (to all 3 classification systems), and (3) a concomitant atrial septal aneurysm (to TOAST and CCS). The algorithmic logic chain is revised so that, when these features are present, a higher level of PFO causation likelihood is assigned (eFigure in the Supplement). In their original versions, both TOAST and CCS never classified a PFO with the terms *probably* or *evidently* associated with ischemic stroke, but rather only *possibly*[6,7]; in the revised version, both now classify PFOs with select features as probable or evident. Compared with its original version, the revised ASCOD system now would classify more PFOs with particular features with the terms *potentially causal* and *uncertainly causal*, rather than *unlikely related*.[8]

The Working Group also deliberated whether to recommend moving PFO-associated stroke from the systems' Cardioembolic group to the Other Defined Cause supraordinate group, because paradoxical emboli passing through a PFO are not technically of cardiac origin. After considering the advantages of each placement (eAppendix 4 in the Supplement), we suggest retaining the existing positioning but conceiving of the category more broadly as cardioembolic/transcardioembolic.

In addition, progress in understanding the magnitude and treatment of PFO-associated stroke has implications for the conceptual entity of ESUS. The ESUS construct collated into a single entity, for therapeutic management, patients with 20 diverse proximal sources of embolic stroke, including structural cardiac disease, cardiac dysrhythmias, paradoxical embolism, atherosclerotic disease, and tumoral emboli and did not encourage detailed

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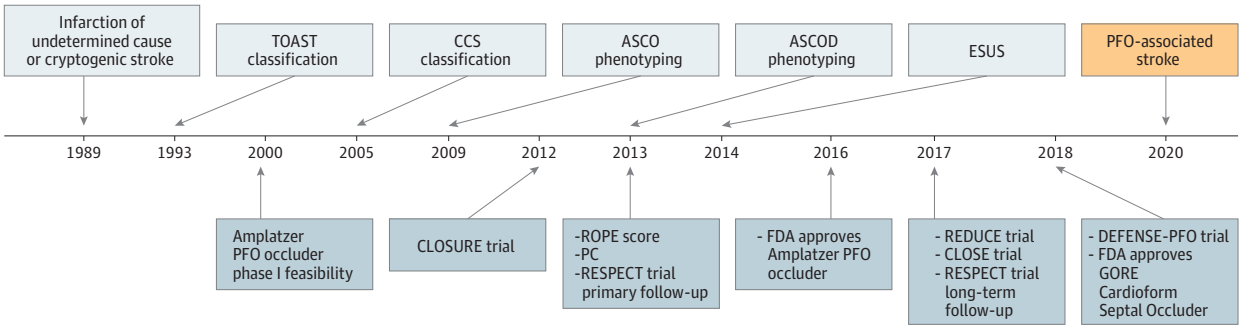
Figure 2. Timeline of Important Dates in the Development of the Current Acute Ischemic Stroke Classifications and History of Percutaneous Patent Foramen Ovale Closure



ASCO indicates atherosclerosis, small vessel disease, cardiac pathology, and other causes; ASCOD, atherosclerosis, small vessel disease, cardiac pathology, other causes, and dissection; CCS, Causative Classification of Stroke; CLOSE, Patent Foramen Ovale Closure or Anticoagulants vs Antiplatelet Therapy to Prevent Stroke Recurrence; CLOSURE, 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; DEFENSE-PFO Trial, Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale ; ESUS, embolic stroke of undetermined source; FDA, US Food and Drug Administration; PC, Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder With Medical Treatment in Patients With Cryptogenic Embolism; PFO, patent foramen ovale; REDUCE, Gore REDUCE Clinical Study; RE-SPECT, Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; RoPE, Risk of Paradoxical Embolism; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Table 2. Proposed Flexible Clinical Practice Approach to Classifying Patent Foramen Ovale Causal Association in Patients With Embolic Infarct Topography and Without Other Major Stroke Sources[a]

		RoPE Score	
Risk source	Features	Low[b]	High[b]
Very high	A PFO and a straddling thrombus	Definite	Definite
High	(1) Concomitant pulmonary embolism or deep venous thrombosis preceding an index infarct combined with either (2a) a PFO and an atrial septal aneurysm or (2b) a large-shunt PFO	Probable	Highly probable
Medium	Either (1) a PFO and an atrial septal aneurysm or (2) a large-shunt PFO	Possible	Probable
Low	A small-shunt PFO without an atrial septal aneurysm	Unlikely	Possible

Abbreviations: PFO, patent foramen ovale; RoPE, the Risk of Paradoxical Embolism Score.

[a] The algorithm in this table is proposed for use in flexible clinical practice, when application of an entire formal classification system is not being conducted.

[b] The RoPE score includes points for 5 age categories, cortical infarct, absence of hypertension, diabetes, prior stroke or transient ischemic attack, and smoking. A higher RoPE score (≥7 points) increases probability of causal association.

causative investigation to distinguish among them, including not requiring transesophageal echocardiography to identify and characterize PFOs.[4] Recognition that PFOs account for an important fraction of embolic strokes and merit distinctive therapeutic approaches argues against such a lumper approach. Instead, transesophageal echocardiography should be a component of the standard initial workup of patients with embolic distribution stroke, no major findings on (or no indication for) transthoracic echocardiography, and no major causative mechanism identified during initial extracranial and intracranial artery imaging and cardiac rhythm monitoring, especially in younger and middle-aged individuals.

In flexible clinical practice, we propose grading PFO-risk features according to the algorithm shown in **Table 2** in patients with cerebral or retinal infarcts of embolic topography. The greater the PFO-risk grade and the more complete the absence of even low-grade competition for other possible sources, the more likely the stroke is pathogenically associated with the PFO. In patients without other probable sources, the RoPE score, Valsalva at onset, and additional case-specific features enable the clinician to categorize ischemic strokes as of definite, probable, possible, or unlikely PFO origin.

Conclusions

While the pathogenic importance of PFO for stroke at the population level can no longer be in doubt, whether a PFO is causal in any particular patient is rarely certain. But this is true too for cardinal causes of stroke, such as severe carotid stenosis and atrial fibrillation; the causative mechanism of a stroke is almost always a probabilistic rather than definitive diagnosis. Yet both the epidemiologic data and the results of RCTs yield congruent results indicating that, in well-selected patients with a PFO and no other apparent cause, the PFO is likely to play a causative role in most cases. Thus, patients without other causes of ischemic stroke and

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with a medium-risk to high-risk PFO should no longer be designated as having a so-called cryptogenic stroke, implying a stroke of unknown causative mechanism. We propose the term *PFO-associated stroke* as a distinct entity of ischemic stroke for all patients presenting with superficial, large deep, or retinal infarcts in the presence of a medium-risk to high-risk PFO and no other identified likely cause. The diagnosis of PFO-associated stroke has intrinsic explanatory value for epidemiologic research, clinical trial design, and patients, families, and physicians regardless of any therapy outcome that might result.[50] In addition, it can inform therapeutic decision-making: patients with PFO-associated stroke who meet the regulatory device label criteria may benefit from PFO closure, additional patients may benefit from consideration for anticoagulation, and many patients may benefit from hydration and activity interventions to avert venous thromboembolism. Neurology and cardiology society guidelines should be updated to adopt nomenclature consistent with the evidence base to improve patient care and outcomes.

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