

Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix 1. The Extended PFO-Associated Stroke Causal Likelihood (PASCAL) Classification System

Risk Grade	Features	Casual Relatedness	
		Low RoPE Score ^a	High RoPE Score ^a
Very high risk	PFO + straddling thrombus	Definite	Definite
High risk	BOTH of: 1A. PFO + ASA, <i>or</i> 1B. Large shunt PFO, <i>AND</i> 2. PE or DVT preceding index infarct	Probable	Highly Probable
Medium risk	ANY of: 1. PFO + ASA 2. Large shunt PFO	Possible	Probable
Low risk	Small shunt PFO without ASA	Unlikely	Possible

^aThe 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.

PFO indicates patent foramen ovale; RoPE, Risk of Paradoxical Embolism; ASA, atrial septal aneurysm; PE, pulmonary embolism; DVT, deep vein thrombosis.

Comment

To further improve the identification of ischemic strokes due to patent foramen ovale, an international consensus group recently proposed the PFO-Associated Stroke Causal Likelihood (PASCAL) Classification System (1). Among patients with no major defined cause of ischemic stroke, the PASCAL classification system integrates information regarding: 1) presence of features that increase likelihood of PFO-stroke mechanisms (high risk PFO physiologic and structural features of large shunt or atrial septal aneurysm), and 2) absence of features that increase likelihood of an occult non-PFO stroke mechanisms (older age, vascular risk factors, and stroke topography features) as quantified in the RoPE score. Based on this combination of factors, the original, extended PASCAL Classification System algorithmically assigns a likelihood of causal relationship among

five levels: Definite, Highly Probable, Probable, Possible, and Unlikely. The PASCAL algorithm was developed using a mixed methods approach incorporating expert judgement, physiologic and epidemiologic data, and the validated RoPE Score. The original, extended PASCAL Classification system is shown above.

While data regarding many of the patient features used in the extended PASCAL Classification system were collected in the RCTs analyzed in the SCOPE project, two were not: 1) the presence of a thrombus straddling the PFO opening (supporting Definite causal relatedness), and 2) the occurrence of a PE or DVT shortly before or concurrent with the index ischemic stroke (supporting Highly Probable or Probable causal relatedness). Accordingly, for the current pooled analysis a simpler PASCAL classification system was developed by censoring those two uncollected patients' features and using the collected patient features to algorithmically assign patients to three levels of likelihood of causal relationship: Probable, Possible, and Unlikely. The SCOPE protocol prespecified as one of its primary aims testing for heterogeneity of treatment effect in the pooled RCT data based on patient PASCAL Probable, Possible, and Unlikely grades.

eAppendix 2. The Risk of Paradoxical Embolism (RoPE) Score

RoPE Score Calculator		
Characteristic		Points
No history of hypertension		1
No history of diabetes		1
No history of stroke or transient ischemic attack		1
Nonsmoker		1
Cortical infarct on imaging		1
Age, y		
18-29		5
30-39		4
40-49		3
50-59		2
60-69		1
≥ 70		0
Total RoPE Score (sum of individual points) =		_____
Abbreviations: RoPE = Risk of Paradoxical Embolism		

Comment

Patent foramen ovale (PFO) are randomly distributed in the general population in about 25% of adults, and not associated with other vascular risk factors. However, among patients with cryptogenic stroke (CS), the presence of a PFO is highly associated with the absence of conventional vascular risk factors and the presence of specific neuroimaging findings (a superficial cortical infarct). This negative association arises from index event (or “collider”) bias;¹ that is, it is induced because vascular risk factors and PFO are causes of the same outcome (i.e., cryptogenic stroke).

Based on this observation, we developed a model to predict the presence of PFO in patients with otherwise cryptogenic stroke and transformed this probability, using Bayes Theorem, into a “patient-specific” attributable fraction — i.e., the fraction of cryptogenic strokes that are attributable to PFO in a group of patients sharing a Risk of Paradoxical Embolism (RoPE) Score (1), according to the following equation:

$$\text{PFO Attributable Fraction} = 1 - \left(\frac{\text{Prevalence of PFO in controls} \times [1 - \text{Prevalence of PFO in CS cases}]}{\text{Prevalence of PFO in CS cases} \times [1 - \text{Prevalence of PFO in controls}]} \right)$$

We found that easily obtainable clinical characteristics can identify CS patients who vary markedly in the prevalence of PFO, reflecting substantial and clinically important variation in the probability that a discovered PFO is likely to be causally related to the stroke rather than an incidental present (eTable). For example, a PFO is discovered in just 23% of cryptogenic stroke patients in the lowest RoPE Score strata, which is approximately the same as the general population—indicating that PFOs in these patients are almost always an incidental finding. Conversely, PFOs are found in greater than 70% of cryptogenic stroke patients with a RoPE Score of 9-10, indicating almost a 90% probability that the stroke can be attributed to the presence of the PFO.

eTable. PFO-Attributable Fraction by RoPE Score.²

RoPE Score	Patients, N (n=3023)	Prevalence of PFO % (95% CI)	PFO-Attributable Fraction* % (95% CI)	Estimated 2-yr stroke/TIA recurrence rate (among those with PFO, n=1324)
0-3	613	23% (19% to 26%)	0% (0% to 4%)	20 (12-28)
4	511	35% (31% to 39%)	38% (25% to 48%)	12 (6-18)
5	516	34% (30% to 38%)	34% (21% to 45%)	7 (3-11)
6	482	47% (42% to 51%)	62% (54% to 68%)	8 (4-12)
7	434	54% (49% to 59%)	72% (66% to 76%)	6 (2-10)
8	287	67% (62% to 73%)	84% (79% to 87%)	6 (2-10)
9-10	180	73% (66% to 79%)	88% (83% to 91%)	2 (0-4)

*Based on the observed prevalence of PFO, rather than the predicted, and assumes a population prevalence of PFO of 25%.

PFO indicates patent foramen ovale; CI, confidence interval; TIA, transient ischemic attack.

The RoPE Score has been externally validated by independent teams to predict the presence of a PFO in the CS population^{3,4} and it is widely used in shared decision making. However, it is not intended to be used in isolation.

A higher RoPE Score, however, is associated with a lower recurrence risk. In the RoPE study the 2 year risk of stroke/transient ischemic attack (TIA) recurrence of patients with a RoPE Score of 0 to 3 was ~20 but was only ~2% in those with a RoPE Score of 9 to 10.¹

Further, the methods used to develop the RoPE Score (prediction of the presence of a PFO in cryptogenic stroke patients) did not permit high risk anatomic features of the PFO itself (such as the size of the left-to-right shunt and the presence of an atrial septal aneurysm) to be incorporated into the Score.

eReferences

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2. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology.* 2013;81(7):619-625.
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