An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke

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ABSTRACT

Objective: We aimed to create an index to stratify cryptogenic stroke (CS) patients with patent foramen ovale (PFO) by their likelihood that the stroke was related to their PFO.

Methods: Using data from 12 component studies, we used generalized linear mixed models to predict the presence of PFO among patients with CS, and derive a simple index to stratify patients with CS. We estimated the stratum-specific PFO-attributable fraction and stratum-specific stroke/TIA recurrence rates.

Results: Variables associated with a PFO in CS patients included younger age, the presence of a cortical stroke on neuroimaging, and the absence of these factors: diabetes, hypertension, smoking, and prior stroke or TIA. The 10-point Risk of Paradoxical Embolism score is calculated from these variables so that the youngest patients with superficial strokes and without vascular risk factors have the highest score. PFO prevalence increased from 23% (95% confidence interval [CI]: 19%–26%) in those with 0 to 3 points to 73% (95% CI: 66%–79%) in those with 9 or 10 points, corresponding to attributable fraction estimates of approximately 0% to 90%. Kaplan-Meier estimated stroke/TIA 2-year recurrence rates decreased from 20% (95% CI: 12%–28%) in the lowest Risk of Paradoxical Embolism score stratum to 2% (95% CI: 0%–4%) in the highest.

Conclusion: Clinical characteristics identify CS patients who vary markedly in PFO prevalence, reflecting clinically important variation in the probability that a discovered PFO is likely to be stroke-related vs incidental. Patients in strata more likely to have stroke-related PFOs have lower recurrence risk. *Neurology*® 2013;81:619–625

GLOSSARY

auROC = area under the receiver operating characteristic curve; **CS** = cryptogenic stroke; **PFO** = patent foramen ovale; **RoPE** = Risk of Paradoxical Embolism.

Case-control studies suggest that patent foramen ovale (PFO) is a common cause of cryptogenic stroke (CS), likely through a paradoxical (venous-to-arterial) embolism.[1,2] However, CS has many potential causes, and PFO is a common anatomical variant found in approximately 25% of the general population.[3] Thus, a PFO discovered in the setting of a CS may be incidental or stroke-related.

Percutaneous mechanical closure of a PFO is frequently considered in patients with CS and PFO. The recently reported CLOSURE trial, however, found no benefit for this approach over medical therapy.[4] Nonetheless, stroke recurrence rates were low overall (limiting statistical power) and most stroke recurrence in both treatment groups was due to stroke of known mechanism, suggesting that many patients with incidental PFOs may have been enrolled.

The premise of the Risk of Paradoxical Embolism (RoPE) Study[3] is that only patients with a high attributable recurrence risk have the opportunity to benefit from PFO closure for secondary

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Supplemental data at www.neurology.org

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stroke prevention. Attributable recurrence risk can be thought of as the proportion of recurrent cerebrovascular events among those with a risk factor (i.e., PFO) that, in theory, would be avoided if the risk factor (PFO) was eliminated. Here, we estimate attributable recurrence risk as the joint probability of 2 risk dimensions: 1) the probability that the index event was related to the PFO (i.e., the attributable fraction among patients with PFO and CS); and 2) the risk of stroke recurrence. The analysis presented here seeks to develop an index that stratifies patients by the first of these dimensions, attributable fraction. Additionally, once the patients are stratified by their attributable fraction, by combining data from multiple large cohort studies, we estimate stratum-specific stroke/TIA recurrence risk.

METHODS Although it is rarely possible to establish in the individual patient whether a PFO discovered in the CS setting is incidental or stroke-related, one can estimate the attributable fraction among these CS patients with PFO using Bayes theorem. The derivation of this equation is described elsewhere.[2,5]

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

Accordingly, the attributable fraction is dependent on the prevalence of PFO in the CS population. Indeed, if one takes the prevalence of PFO in the general population as the control rate (i.e., the expected rate of finding a PFO in similar patients without CS), then the only value missing to estimate the probability that a discovered PFO is incidental (vs stroke-related) is the prevalence of PFO in CS cases. For example, in a sample of patients with CS with a PFO prevalence of 40%, approximately 50% of those would be incidental, if the prevalence in otherwise similar people is 25%.[2]

PFO prevalence among CS patients, however, is well known to vary based on other patient characteristics. For example, the prevalence is known to be higher in younger patients and patients without conventional stroke risk factors.[6–8] Thus, application of Bayes theorem would yield a more patient-specific estimate of attributable fraction by substituting a patient-specific prevalence of PFO in CS patients, conditional on the specific patient's characteristics. To apply Bayes theorem in this way, we make the following assumptions: 1) if not for those strokes that are PFO-attributable, the prevalence of PFO in a CS patient would be the same as in the general population (controls); 2) the rate of PFO-attributable strokes in PFO-negative CS patients is near-zero (i.e., false-negative rate with transesophageal echocardiography is low and any missed PFOs did not cause strokes); and 3) PFO prevalence in patients without CS is unrelated to those characteristics that determine its prevalence in CS patients (i.e., there is a constant control rate across strata).

Whereas we rely on face validity for the first 2 assumptions, the third assumption has both theoretical and empirical justification. In prior work, we have shown how the relationship between the presence of PFO and other risk factors (age, hypertension, diabetes, smoking) arises due to selection of a CS population—because CS is a common effect of both PFO and conventional stroke risk factors.[9] While the presence of PFO appears to "protect" CS patients from stroke risk factors (i.e., because those with PFO do not "need" these risk factors to become a CS case), there is no association between these factors and PFO in unselected "screened" populations.[10] In addition to this prior theoretical and empirical justification, herein we test the assumption by examining the relationship of PFO to stroke risk factors in a population of patients with stroke of known cause.

For the estimate of the PFO prevalence of the control rate, we use 25% in the base case, as there was consistency in PFO prevalence from 3 sources: that found in the largest population study of health volunteers (26%)[11]; the average seen in autopsy studies (26%)[12]; and that found in those with stroke of known cause among the RoPE component studies that included non-CS patients (26%).

Database. The RoPE database has been described in detail in a prior report.[13] Briefly, it was constructed from 12 component databases (table 1). The RoPE database contains information on 3,674 CS patients who have been investigated for PFO, where CS was defined by the TOAST (Trial of ORG 10172 in Acute Stroke Treatment)[14] classification. All RoPE subjects were studied with either transesophageal echocardiography or transcranial Doppler for PFO determination. For the analysis examining factors associated with PFO, only those 8 databases (n = 3,023) that include CS patients both with and without PFO were used; the 4 databases that enrolled only CS patients with PFO were not. As detailed in our prior report,[13] in all databases patients with PFO were medically treated with either antiplatelet or anticoagulant therapy at the physician's discretion, except for the French PFO/ASA (Atrial Septal Aneurysm) Study, where the protocol required antiplatelet therapy. A small minority of patients was treated with mechanical closure during follow-up.

Several component RoPE databases (PICCS,[15] APRIS,[16] Sapienza[17]) included patients with stroke of known mechanism who were investigated for PFO (n = 588). We used these patients to examine the assumption that PFO prevalence is similar across risk-factor strata among control patients, and for the estimate of the control rate of PFO.

Statistical analysis. To develop a predictive model for the propensity to have a PFO among CS patients, we explored crude associations (overall and within each database) between the presence of a PFO and clinical variables including the subject's age, sex, race, hypertension, diabetes, hyperlipidemia, history of coronary artery disease, smoking history, history of prior episodes of cerebral ischemia, and neuroradiologic variables (prior stroke on MRI or CT, small [<1.5 cm] vs large infarct, and deep or superficial location of infarct). Multivariable associations between predictors and the presence of a PFO were examined using logistic regression models. Selection of candidate variables for these models was based on clinical rationale and the published literature, as well as the consistency of variable definitions and availability across each of the 8 component databases.

Models were evaluated by conventional criteria, such as goodness-of-fit tests, calibration plots, and receiver operating characteristic curve areas. Multivariable regression models were run separately on each of the component datasets to assess the consistency of the results and model performance; interaction terms between indicator variables representing study and model predictors of PFO were used to further investigate variation in associations across study datasets.

For the final model, we reanalyzed the data using a generalized linear mixed model that included a random-effect term

Table 1 Component databases of the RoPE Study[a]

Database	No. of subjects	No. with PFO	No. without PFO
APRIS[16,b]	90	19	71
CODICIA[25]	485	300	185
French PFO/ASA[26]	581	267	314
German[27]	1,122	376	746
Lausanne	92	58	34
NOMASS[28]	60	23	37
PICSS[15,b]	250	98	152
Sapienza[17,b]	343[c]	133[c]	210
Bern (published)[29]	159	159	0
Bern (unpublished)	249	249[c]	0
Toronto[30]	121	121	0
Tufts[31]	122	122	0

Abbreviations: APRIS = Aortic Plaque and Risk of Ischemic Stroke; CODCIA = Prospective Spanish Multicenter Study; NOMASS = Northern Manhattan Stroke Study; PFO = patent foramen ovale; PFO/ASA = PFO/Atrial Septal Aneurysm; PICSS = PFO in Cryptogenic Stroke Study; RoPE = Risk of Paradoxical Embolism.

[a] Data within box rule were used for the PFO prevalence model.

[b] Database also contains patients with stroke of known mechanism investigated by transesophageal echocardiography, not represented in this table.

[c] Not used in recurrence risk estimation because of inadequate outcome ascertainment.

representing each component study to obtain final parameter estimates with their corresponding standard errors. We performed both complete case analysis and multiple imputation and present the multiple imputation model as the base case, because this provides less-biased parameter estimates.[18]

Based on the odds ratios of the variables, we created an easy-to-use point index. We examined the prevalence of PFO in each point stratum. For heuristic purposes, we used Bayes theorem to transform the stratum-specific PFO prevalence to a stratum-specific estimate of PFO-attributable fraction. As a check on the assumption of a constant control rate, we examined the relationship of the point score to PFO prevalence in patients with stroke of known cause.

We used Kaplan-Meier survival analysis to estimate the fraction of medically treated patients who developed a recurrent stroke or TIA among those patients with PFO at 1, 2, and 3 years, aggregating strata so that at least 100 PFO patients were included in each. Mechanical closure was treated as a censoring event. Two databases (Sapienza and Bern-unpublished) not meeting criteria for adequate follow-up were excluded from this analysis.[3] In the remaining RoPE databases, 93% of PFO patients had follow-up at 1 year or beyond.[13]

Standard protocol approvals, registrations, and patient consent. This study was approved by the Tufts Medical Center Internal Review Board.

RESULTS Of 3,674 patients in the combined database, 3,023 were in the dataset for modeling after excluding patients in the 4 databases that only included patients with PFO. Of these, 1,274 (42%) had PFO. The proportion of patients in each of the databases with PFO ranged from 21% (APRIS,[16] unique among databases for excluding patients younger than 55 years) to 63% (Lausanne). Table 2 shows the characteristics of patients with and without PFO. As can be seen, whereas the sex distribution was similar in CS patients with and without PFO, patients with PFO were considerably younger and were consistently less likely to have conventional vascular risk factors than CS patients with PFO. On neuroimaging, the infarcts were more likely to be large (>1 to 1.5 cm) and superficial in CS patients with PFO when compared to CS patients without PFO.

Multivariate model. On multivariate modeling, the presence or absence of a PFO was found to be predictable (area under the receiver operating characteristic curve [auROC] = 0.68). The odds of PFO presence were found to be diminished by older age, the presence of diabetes, coronary artery disease, hypertension, and hypercholesterolemia, as well as current smoking and history of stroke/TIA. The effects of these variables were consistent across databases (table e-1 on the *Neurology*® Web site at www.neurology.org), as was the overall performance of the model (table e-2). Table 3 shows the estimated effects for the multiply imputed database, but effects were similar in complete case analysis (table e-3).

The RoPE Point Score. Based on the similarity of the odds ratios in the model, we assigned a single point for the absence of each of the 3 vascular risk factors (diabetes, hypertension, smoking), the absence of a prior stroke or TIA, and the presence of a cortical stroke on imaging. Points were also assigned based on decade of life: from 1 point for those in their 60s to 5 points for those in their 20s. This yields a 10-point score (table 4). The performance of the RoPE Point Score was near-identical to the overall model (auROC = 0.68). Observed PFO prevalence ranged from 12% (in those with 0 or 1 point) to 82% (in those with 10 points). The attributable fraction, estimated using Bayes theorem and a control rate of 25%, is shown in table 5 truncated at a lower limit of 0%. Sensitivity analysis varying the control rate (i.e., general population prevalence of PFO) from the base case of 25% to 20% and to 15% (shown in figure e-1) had the same pattern but an overall higher estimate of attributable fraction, particularly in patients with lower scores. We also examined the distribution of RoPE scores in the group of patients younger than 60 years, an inclusion criterion for PFO closure trials (table e-4). Although extremely low point scores were absent from this group, there was still considerable variation in this overall higher RoPE score group, with more than one-third of these younger CS patients with PFO having a RoPE score of 6 or less. Model performance on these younger patients, as well as PFO prevalence and recurrence risks, was very similar to the overall cohort (auROC = 0.67). In contrast with its performance in patients with CS, the

Table 2 Comparison of patient characteristics with and without PFO[a]

	PFO (n = 1,274)	Non-PFO (n = 1,749)	*p* Value
Patient characteristics			
Male	58.9 (751/1,274)	59.3 (1,038/1,749)	0.8251
Age >65 y	21.5 (274/1,274)	35.9 (627/1,748)	<0.0001
White	86.1 (515/598)	79.3 (649/818)	0.0010
Diabetes	8.9 (113/1,269)	18.6 (325/1,746)	<0.0001
Coronary artery disease	6.7 (67/1,005)	12.0 (172/1,434)	<0.00001
Hypertension	32.7 (415/1,271)	53.2 (927/1,744)	<0.0001
Hypercholesterolemia	22.5 (195/866)	30.6 (425/1,387)	<0.0001
Current smoker	32.5 (410/1,263)	36.0 (622/1,727)	0.0435
History of stroke/TIA	11.9 (151/1,270)	18.0 (314/1,740)	<0.0001
Radiologic variables			
Prior stroke, % yes	22.6 (196/867)	31.1 (396/1,272)	<0.0001
No. of lesions	n = 901	n = 1,261	0.3255
Multiple	13.3 (120)	12.5 (158)	
Not multiple	72.5 (653)	75.2 (948)	
TIA	14.2 (128)	12.3 (155)	
Size	n = 930	n = 1,324	0.0189
Large	59.1 (550)	55.9 (740)	
Not large	27.1 (252)	32.4 (429)	
TIA	13.8 (128)	11.7 (155)	
Location	n = 907	n = 1,173	<0.0001
Superficial	54.1 (491)	44.9 (527)	
Deep	31.8 (288)	41.9 (491)	
TIA	14.1 (128)	13.2 (155)	

Abbreviation: PFO = patent foramen ovale.
[a] Data are % (n).

RoPE score was unrelated to PFO prevalence among patients with stroke of known cause (auROC = 0.53, $p = 0.3$; table e-5).

Kaplan-Meier stroke recurrence estimates. Follow-up data were available on 1,324 patients with PFO. Of these, 9% were closed within the first year after the index event and 11% were closed within the first 2 years. These patients were censored at the time of closure. Table 5 shows 2-year stroke/TIA recurrence rates in the subset of patients with PFO by strata, collapsed to include at least 100 PFO patients per strata. The data clearly show that recurrence rates decrease as the RoPE score increases, suggesting that patients with index events most likely to be PFO attributable are least likely to experience recurrent ischemic events. Similar results were seen for the outcome of stroke alone (table e-6). Kaplan-Meier estimates for years 1, 2, and 3 are shown in table e-7.

Table 3 Multivariate regression model predicting presence of PFO

Term in model[a]	OR (95% CI)	*p* Value
Age, per 10-y increase	0.72 (0.67–0.77)	<0.0001
Diabetes	0.65 (0.51–0.83)	0.0006
Hypertension	0.68 (0.57–0.81)	<0.0001
Current smoker	0.60 (0.50–0.71)	<0.0001
History of stroke or TIA	0.78 (0.62–0.99)	0.0375
Radiology, deep (vs superficial)	0.68 (0.54–0.84)	0.0006

Abbreviations: CI = confidence interval; OR = odds ratio; PFO = patent foramen ovale.
[a] Adjusted for sex and index stroke vs TIA.

DISCUSSION We present an index based on easily and reliably obtainable variables that may be useful to clinicians for predicting the probability of discovering a PFO in a patient with CS. In turn, this score can stratify patients by the related probability that a discovered PFO is incidental or stroke-related. Decreasing age, the absence of conventional vascular risk factors, and the presence of a superficially located lesion are strongly and consistently associated with

Table 4 RoPE score calculator

Characteristic	Points	RoPE score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	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 score (sum of individual points)		
Maximum score (a patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)		10
Minimum score (a patient ≥70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)		0

Abbreviation: RoPE = Risk of Paradoxical Embolism.

an increasing prevalence of PFO. Given the strength and the consistency of these effects, the presence/absence of these features should allow clinicians to identify sizable subgroups of CS patients who have a range in PFO prevalence from approximately 20% to 80%. This variation suggests a considerable and clinically important range among patients with CS and PFO in the probability that the PFO is stroke-related vs incidental. This is true even among patients who potentially meet inclusion criteria for the major PFO closure trials. The variables used in this model are frequently collected in the clinical and research settings and are clinically intuitive.

Our results also show that recurrence risk appears to be considerably lower in the strata of patients most likely to have PFO-attributable stroke. These results underscore the challenges of patient selection for PFO closure and the methodologic challenges facing PFO closure trials. Prior and ongoing trials of PFO closure vs medical therapy may be limited in power based on inaccurate assumptions of PFO-attributable recurrence rates. Additional work may permit the identification of variables capable of predicting higher recurrence rates among those with high RoPE scores, further improving patient selection. Such variables may include PFO characteristics such as spontaneous shunting at rest (i.e., not requiring Valsalva), shunt size, or an associated atrial septal aneurysm.

Although validation studies on populations not included in the RoPE Study have not been performed, the effects of each of the variables within the index were remarkably consistent across databases, as was the overall performance of the model. Thus, pooling across databases was a major strength of the study. However, heterogeneity of the databases was also a limitation. Because of inconsistent data collection across the component databases, we were unable to include in our predictive model several variables that may be predictive of PFO among CS patients.[6,8,19] These include obesity, index stroke severity, a history of deep venous thrombosis or pulmonary embolism, hypercoagulable states, prolonged travel/forced immobility, migraine, Valsalva at stroke onset, and "wake up" stroke/TIA.[20] Thus, further improvement in stratification and discrimination may be possible. Finally, because our approach was based on a model predicting PFO as an outcome, it was not possible to examine PFO characteristics (such as shunt size). However, we plan to measure such variables as markers of recurrence risk.

There are limitations related to the numerical estimation of attributable fraction from PFO prevalence.

Table 5 PFO prevalence, attributable fraction, and estimated 2-year risk of stroke/TIA by point score strata, using control rate of 25%

	Cryptogenic stroke (n = 3,023)			CS patients with PFO (n = 1,324)	
RoPE score	No. of patients	Prevalence of patients with a PFO, % (95% CI)[a]	PFO-attributable fraction, % (95% CI)[a]	No. of CS patients with PFO[a]	Estimated 2-y stroke/TIA recurrence rate (Kaplan-Meier), % (95% CI)
0–3	613	23 (19–26)	0 (0–4)	108	20 (12–28)
4	511	35 (31–39)	38 (25–48)	148	12 (6–18)
5	516	34 (30–38)	34 (21–45)	186	7 (3–11)
6	482	47 (42–51)	62 (54–68)	236	8 (4–12)
7	434	54 (49–59)	72 (66–76)	263	6 (2–10)
8	287	67 (62–73)	84 (79–87)	233	6 (2–10)
9–10	180	73 (66–79)	88 (83–91)	150	2 (0–4)

Abbreviations: CI = confidence interval; CS = cryptogenic stroke; PFO = patent foramen ovale; RoPE = Risk of Paradoxical Embolism.
[a] Note: 95% CI for PFO prevalence and attributable fraction based on normal approximation to the binomial distribution.

These estimations are dependent on model assumptions, which although clinically intuitive, are not always inviolate. Also, while the ranking of patients is not dependent on the assumed control rate of PFO in the general non-CS population, the parameter estimate of attributable fraction is sensitive to this rate, especially for strata with lower PFO prevalence rates. We chose a control rate of 25% because this was the average seen across a large number of autopsy studies,[12] and also closely approximated the rate seen among patients in the RoPE databases that obtained PFO data even in patients with known stroke mechanisms (26%, see table e-5). Our sensitivity analysis using the lower PFO prevalence estimates obtained in some case-control studies[2] yielded a similar pattern overall, except with a higher estimate of PFO-attributable strokes in lower score strata. The RoPE score thus cannot rule out a PFO-related stroke with certainty even in those patients with very low scores. Finally, use of the concept of attributable fraction assumes that there are separate PFO-dependent and PFO-independent mechanisms, and the distinction between attributable and etiologic fraction (in this case, the proportion of CS cases caused by PFO) is not necessarily trivial.[21,22] The causal mechanism of PFO-related stroke is assumed to be paradoxical embolism, but it is possible that other unknown mechanisms may account for the association. As is typical, we use attributable fraction as a proxy for etiologic fraction, because the latter is generally not estimable. Nevertheless, our estimates of attributable fraction have heuristic value, may be useful in designing trials, and may ultimately prove to have clinical value for treatment decisions.

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 stroke-related rather than incidental. Although patients in the high RoPE score strata are much more likely to have PFO-related strokes, the recurrence rates in these strata are relatively low. Further research is needed to investigate whether combining this index with predictors of recurrence risk, such as specific PFO features, may enable the selection of patients with a high attributable recurrence risk especially likely to benefit from PFO-specific treatments such as endovascular closure. A combined model might be useful for the planning and analysis of clinical trials[23,24] and subsequently for clinical care.

AUTHOR CONTRIBUTIONS

D.K.: designed and conceptualized the study, analyzed and interpreted data in the study, drafted the manuscript, revised, reviewed, and approved the manuscript. D.T.: designed and conceptualized the study, analyzed and interpreted data in the study, contributed study data, and revised, reviewed, and approved the manuscript. R.R.: analyzed and interpreted data in the study, supervised database management, revised, reviewed, and approved the manuscript. M.E., P.M., C.W.: contributed study data, analyzed and interpreted data in the study, revised, reviewed, and approved the manuscript. J.M., J.S., S.H., E.D., M.D., C.J., H.M., M.M., K.N., F.P.: contributed study data, revised, reviewed, and approved the manuscript. J.G., J.L.: revised, reviewed, and approved the manuscript.

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