Appendix A2. RoPE Score Detail

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;[8] 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, 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 (**Appendix Table 2**). 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.

Appendix Table 2. PFO-Attributable Fraction by RoPE Score.[4] Cryptogenic stroke n=3023.

RoPE Score	Patients, N (n=3023)	Prevalence of PFO % (95% CI)	PFO-Attributable Fraction[a] % (95% CI)	Estimated 2-yr stroke/TIA recurrence rate (among those with PFO, n=1324)[4]
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)

[a]Based on the observed prevalence of PFO, rather than the predicted, and assumes a population prevalence of PFO of 25%.
CI, confidence interval; PFO indicates patent foramen ovale; 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[9,10] and it is widely used in shared decision making. However, it is not intended to be used in isolation. The premise of the RoPE Study was that mechanical closure will benefit patients with a high *attributable recurrence risk*, which can be thought of as the product of the attributable fraction (predicted by the RoPE Score) and the stroke recurrence risk. 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.[4]

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. For these reasons, recent consensus documents suggest that the RoPE Score should be part of a broader evaluation to help determine those patients whose PFO is most likely to be caused by a PFO-related mechanism who might benefit from closure.[11-13]