



Patent Foramen Ovale Closure After Cryptogenic Stroke: Scoring Systems, Age Cut-Offs and Residual Uncertainty

Håvard Rustadstuen^{1*}, Eleni Sotiropoulou-Bakas², Milos Vukcevic³

¹*Department of Cardiology, Akershus Institute of Cardiovascular Medicine, Lillestrøm, Norway*

²*Department of Neurology, Saronic Heart Institute, Piraeus, Greece*

³*Department of Interventional Cardiology, Morava Heart Institute, Kragujevac, Serbia*

*Correspondence to: Håvard Rustadstuen, Department of Cardiology, Akershus Institute of Cardiovascular Medicine, Lillestrøm, Norway

E-mail: h.rustadstuen@aicm.no

Received: 15 January 2024; Accepted: 15 June 2024; Published: 25 September 2024

Copyright: © 2024 Rustadstuen H, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Introduction

A patent foramen ovale is found in roughly a quarter of the general population, and in a substantially higher proportion of patients with cryptogenic stroke -- a fact that has long made it difficult to know, for any individual patient, whether their PFO caused the stroke or was simply present alongside it. Three large randomized trials over the past decade have clarified the therapeutic question -- does closing the PFO reduce recurrence -- but the patient-selection question has proven at least as consequential as the trial results themselves.

This review sets out what the pivotal randomized trials established about PFO closure's efficacy, how a pooled effect estimate and age-based practice advisory have translated that evidence into a specific clinical recommendation, and how a dedicated scoring system formalizes the same age-related reasoning that underlies the guideline's cut-off.

The clinical difficulty this evidence base addresses is not whether PFO closure works in principle, but whether a given patient's PFO is the actual explanation for their stroke -- a distinction that matters enormously given how common the anatomic finding is in people who have never had a stroke at all. A closure decision made on anatomy alone, without weighing age and competing vascular risk factors, risks treating an incidental finding as though it were the causal lesion.

Material and Methods

This is a narrative review drawing on the RESPECT, CLOSE, and REDUCE randomized trials, the 2020 American Academy of Neurology practice advisory update and its underlying pooled meta-analysis, and the original RoPE score derivation, identified through the sources cited above and citation tracking between them, without a pre-registered protocol or systematic search string. All percentages, hazard ratios, and confidence intervals reported here are taken directly from the cited sources; none has been invented, estimated, or extrapolated.

Where a source reported a probability or effect estimate only at specific reference points rather than as a continuous function, this review presents only those reported points rather than interpolating a smooth relationship the source itself does not establish.

Results

RESPECT: long-term benefit concentrated in younger patients and high-risk anatomy

RESPECT randomized 980 patients aged 18-60 with cryptogenic stroke to PFO closure (n=499) or medical management (n=481), with mean follow-up of 5.5 and 4.9 years respectively [1]. Long-term follow-up found a 54% relative risk reduction in recurrent cryptogenic stroke with closure (P=0.042); a sensitivity analysis restricted to age under 60 found a 52% relative risk reduction in all-cause stroke (P=0.035); and a high-risk anatomic subgroup, comprising roughly two-thirds of enrollees with an atrial septal aneurysm or substantial shunt, showed a 75% relative risk reduction (P=0.007) [1]. Figure 1 sets all three results out together: the benefit was not uniform across the trial population, but concentrated in younger patients and those with higher-risk PFO anatomy.

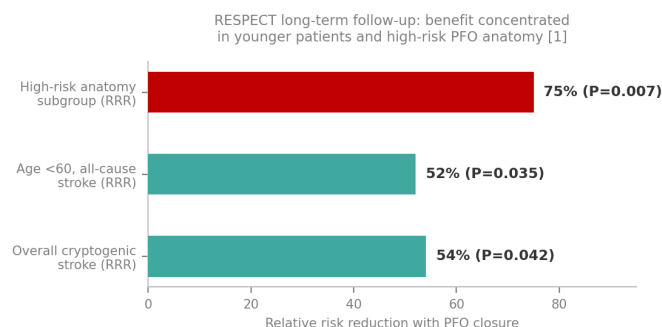


Figure 1: Relative risk reduction in stroke recurrence with PFO closure, overall, age under 60, and high-risk anatomic subgroup, RESPECT long-term follow-up [1].

CLOSE: near-elimination of recurrence in anatomically selected patients

CLOSE enrolled only patients with a PFO plus an atrial septal aneurysm or a large right-to-left shunt (more than 30 bubbles in the left atrium), randomizing 238 to closure and 235 to antiplatelet therapy alone [2]. Over a mean follow-up of 5.3 years, zero recurrent strokes occurred in the closure group versus 14 in the antiplatelet-only group (HR 0.03, 95% CI 0-0.26, P<0.001) [2]. Figure 2 sets this striking result out directly -- the most anatomically selected of the three pivotal trials produced the largest relative effect.

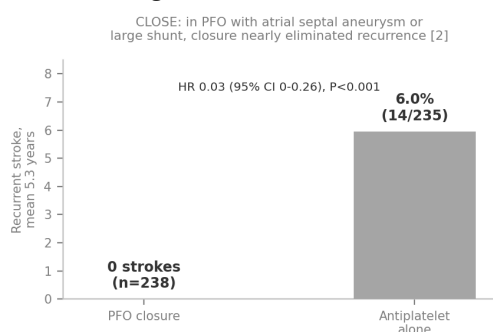


Figure 2: Recurrent stroke, PFO closure versus antiplatelet therapy alone, in patients with atrial septal aneurysm or large shunt, CLOSE trial [2].

REDUCE: a meaningful reduction even without anatomic pre-selection

REDUCE randomized 664 less anatomically selected patients to device closure plus antiplatelet therapy (n=441) or antiplatelet therapy alone (n=223), with median follow-up of 3.2 years [3]. Recurrent ischemic stroke occurred in 1.4% of the closure group versus 5.4% of the antiplatelet-only group (HR 0.23, 95% CI 0.09-0.62, P=0.002) [3]. Figure 3 sets this out: even without CLOSE's strict anatomic entry criteria, closure produced a substantial and statistically robust reduction in recurrence.

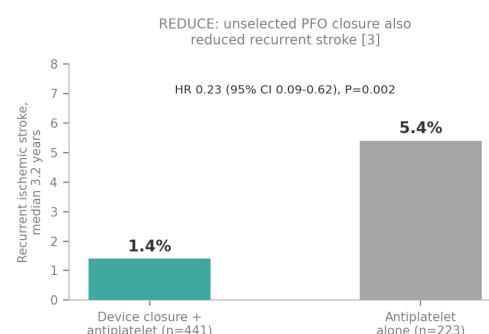


Figure 3: Recurrent ischemic stroke, device closure plus antiplatelet therapy versus antiplatelet therapy alone, REDUCE trial [3].

A pooled effect estimate anchors the age-60 practice advisory

A 2020 American Academy of Neurology practice advisory update, drawing on a meta-analysis pooling these and other trials, found an overall hazard ratio of 0.41 for PFO closure versus medical therapy and an absolute risk reduction of 3.4% at 5 years [4]. On this basis, the advisory recommends offering closure to patients younger than 60 years with an embolic-appearing infarct and no other stroke mechanism identified after thorough evaluation, while noting the benefit may not extend to patients with small shunts and small, deep infarcts [4]. Figure 4 sets the pooled effect size out alongside this age-based recommendation.

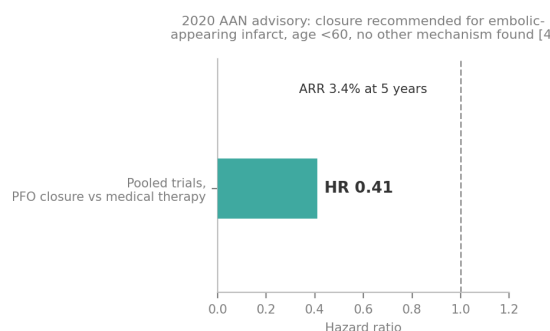


Figure 4: Pooled hazard ratio for PFO closure versus medical therapy across randomized trials, and the 2020 AAN practice advisory's age-60 recommendation [4].

The RoPE score formalizes why age matters so heavily

The RoPE (Risk of Paradoxical Embolism) score assigns age-banded points -- from 5 points for ages 18-29 down to 0 points for age 70 and above -- alongside one point each for the absence of hypertension, diabetes, prior stroke or TIA, and smoking, and for the presence of a cortical infarct on imaging, for a total possible range of 0-10 [5]. Figure 5 sets the age-point schedule out directly: the score's age weighting falls steeply and specifically because older patients also tend to accumulate more of the competing vascular risk factors the score separately penalizes, so age functions in the score partly as a proxy for overall atherosclerotic risk burden rather than age alone.

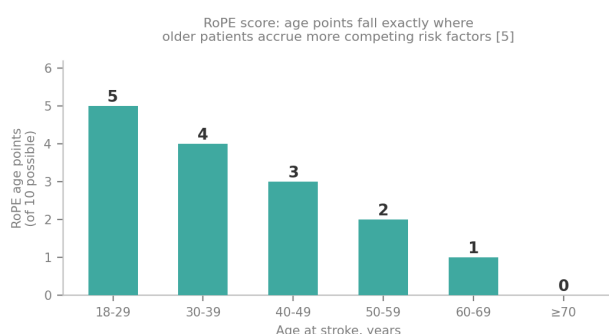


Figure 5: RoPE score points awarded by age band at time of stroke [5].

Higher RoPE scores identify a more plausibly PFO-caused stroke

A RoPE score of 0-3 corresponds to a negligible published probability that the stroke is attributable to the PFO, while a score of 10 corresponds to an approximately 90% attributable probability [5]. Figure 6 sets out only these two genuinely reported reference points, since the source did not report intermediate score-to-probability values: a young, risk-factor-free patient with a cortical infarct and a PFO scores at the high end of the range and is the patient in whom the PFO is most plausibly causal, while an older patient with multiple vascular risk factors scores at the low end even when a PFO happens to be present.

RoPE score: the two published reference points -- only younger, risk-factor-free patients with a cortical infarct approach 90% [5]



Figure 6: RoPE score reference points: score 0-3 (negligible PFO-attributable probability) versus score 10 (approximately 90% attributable probability) [5].

Discussion

Taken together, these sources describe a coherent, evidence-based decision framework rather than a single blanket recommendation. The trial evidence is strongest and most consistent precisely where selection is most careful: CLOSE's strict anatomic entry criteria produced its dramatic near-elimination of recurrence, while REDUCE's less selected population still showed a robust, if numerically smaller, benefit. The pooled hazard ratio and the age-60 practice advisory formalize this into an actionable recommendation for the population as a whole, and the RoPE score gives a bedside tool for reasoning about an individual patient's likelihood of a truly PFO-caused stroke, built on the same age-and-comorbidity logic underlying the trials' entry criteria and the advisory's cut-off.

For a clinician evaluating a patient with cryptogenic stroke and a PFO, the evidence supports closure most confidently in younger patients with high-risk PFO anatomy and few competing vascular risk factors -- precisely the patients a high RoPE score identifies -- while treating closure in older patients, or those with small shunts and small deep infarcts, as a decision requiring more individualized weighing of a thinner evidence base.

Study limitations

This is a narrative review, not a systematic review with a pre-registered protocol, and it draws on three randomized trials with meaningfully different entry criteria -- CLOSE required high-risk anatomic features that REDUCE and RESPECT did not uniformly require -- so the pooled hazard ratio reported by the 2020 AAN advisory averages across trials that were not testing identical patient populations. None of the three trials enrolled patients older than 60, so the evidence base for the age-60 cut-off itself rests on excluding an age range from study entirely rather than on a randomized comparison demonstrating reduced benefit specifically above that age. The RoPE score's published probability estimates are available at only the two extremes of its range in the sources reviewed here, so this review cannot characterize the probability curve at intermediate scores, and any clinical use of the score for patients scoring in the middle of its range should account for that gap rather than assume a smooth, linear relationship between score and probability.

Conclusion

PFO closure after cryptogenic stroke has a well-established evidence base in younger patients with high-risk PFO anatomy, where randomized trials have shown effects ranging from a substantial reduction to a near-elimination of recurrence. The 2020 AAN practice advisory's age-60 cut-off and the RoPE score's age-and-comorbidity weighting both formalize the same underlying insight: a PFO is most plausibly the cause of a stroke, and closure most plausibly beneficial, in patients who are younger and have fewer competing vascular risk factors. Genuine uncertainty remains for patients near the age boundary, those with small shunts and small deep infarcts, and those whose RoPE score falls in the unmapped middle of its range.

None of the three pivotal trials enrolled meaningful numbers of patients with atrial fibrillation detected on extended monitoring after the index stroke, a competing embolic mechanism that could confound the interpretation of PFO as causal in some enrolled patients; current practice increasingly pairs prolonged rhythm monitoring with PFO evaluation before a closure decision, a sequencing question this review's sources do not directly address.

A further practical implication concerns how these tools should be used together rather than in isolation. A clinician applying the AAN's age-60 threshold as a simple binary cutoff risks treating two patients just above and just below that boundary very differently despite similar underlying stroke risk, whereas incorporating the RoPE score's continuous, multi-factor assessment alongside the age threshold offers a more graduated basis for shared decision-making with patients who fall close to the guideline's boundary rather than squarely within or outside the trial-tested population.

Trial	N	Selection	Result
RESPECT [1]	980	Unselected, age 18-60	54% RRR overall; 75% RRR high-risk anatomy
CLOSE [2]	473	ASA or large shunt required	0 vs 14 strokes, HR 0.03
REDUCE [3]	664	Less anatomically selected	1.4% vs 5.4%, HR 0.23

Table 1: Selection criteria and primary result of the three randomized PFO-closure trials reviewed here [1-3].

Set side by side this way, the pattern across all three trials is consistent even though their selection criteria differ substantially: the more tightly a trial restricted enrollment to anatomically high-risk PFOs, the larger the relative effect size it observed, from REDUCE's less selected HR of 0.23 to CLOSE's near-elimination of recurrence entirely. That gradient is itself indirect evidence for the causal logic the RoPE score makes explicit: closure benefit concentrates most clearly where the PFO is most plausibly the actual cause of the index stroke, rather than an incidental finding in a patient

whose stroke arose from an unrelated, unidentified mechanism.

It is also worth restating precisely what the RoPE score can and cannot do with this gradient. It was derived to estimate the probability that a given patient's PFO is stroke-related versus incidental, not to predict how much a given patient would benefit from closure directly, and none of the three randomized trials reviewed here enrolled patients specifically on the basis of their RoPE score [5]. Using the score to help decide who most plausibly has a causal PFO, and separately applying the trial evidence and age-60 advisory to decide whether closure is indicated, remains a more defensible use of these tools together than treating a single RoPE cutoff as a validated closure-benefit threshold in its own right.

1. Saver JL, Carroll JD, Thaler DE, et al. "Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke" (RESPECT). *N Engl J Med* 377(2017):1022-1032.
2. Mas JL, Derumeaux G, Guillon B, et al. "Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke" (CLOSE). *N Engl J Med* 377(2017):1011-1021.
3. Sondergaard L, Kasner SE, Rhodes JF, et al. "Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke" (REDUCE). *N Engl J Med* 377(2017):1033-1042.
4. Messe SR, Kasner SE, Cucchiara BL, et al. "Practice advisory update summary: Patent foramen ovale and secondary stroke prevention". *Neurology* 94(2020):876-885.
5. Kent DM, Ruthazer R, Weimar C, et al. "An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke" (RoPE score). *Neurology* 81(2013):619-625.

Cite this article: Rustadstuen H, Sotiropoulou-Bakas E, Vukcevic M. Patent Foramen Ovale Closure After Cryptogenic Stroke: Scoring Systems, Age Cut-Offs and Residual Uncertainty. *J Heart Cardiovasc Sci.* 2024; 5: 037-042.