BRIEF COMMUNICATION

Clinicians’ Approach to Patent Foramen Ovale Closure after Stroke: Comparing Cardiologists and Neurologists

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BACKGROUND: Evidence from randomized trials and updated professional society guidelines supports patent foramen ovale (PFO) closure after cryptogenic stroke in select patients. It is unclear how this has been integrated into real-world practice, so we aimed to compare practice patterns between cardiologists and neurologists.

METHODS AND RESULTS: In March of 2021, a survey of cardiologists and neurologists who work or previously trained at the University of Pennsylvania Health System assessed practice preferences with respect to PFO closure after stroke. Clinical vignettes isolated specific variables of interest and used a 5-point Likert scale to assess the level of support for PFO closure. Stroke neurologists and interventional cardiologists were compared by Wilcoxon-Mann-Whitney tests. Secondarily, Kruskal-Wallis tests compared stroke neurologists, general neurologists, interventional cardiologists, and general cardiologists. We received 106 responses from 182 survey recipients (31/31 stroke neurologists, 38/46 interventional cardiologists, 20/30 general neurologists, and 17/77 general cardiologists). A similar proportion of stroke neurologists and interventional cardiologists favored PFO closure in a young patient with cryptogenic stroke, 88% and 87%, respectively (P=0.54). Interventionalists were more likely than stroke neurologists to support closure in the context of an alternative high-risk stroke mechanism, 14% and 0%, respectively (P=0.003). Stroke neurologists were more likely to oppose closure on the basis of older age (P=0.01).

CONCLUSIONS: There are key differences between how neurologists and cardiologists approach PFO closure after stroke, particularly when interpreting the stroke etiology and when considering closure beyond the scope of prior trials; this underscores the importance of collaboration between cardiologists and neurologists.

Key Words: closure • patent foramen ovale • PFO • stroke

Several clinical trials have recently demonstrated the efficacy of patent foramen ovale (PFO) closure for secondary stroke prevention in carefully selected patients.1-4 Despite differences in trial populations with respect to PFO anatomy, stroke topography, and comparative medical treatments, an exhaustive workup to exclude alternative stroke mechanisms was a critical commonality. While most trials excluded older patients (aged >60 years),1-3 one did not, in which approximately one fourth were at least aged 60 years.4,5 Several professional societies have published updated guideline statements emphasizing the importance of patient selection for PFO closure,6-9 but it remains unclear how this has been integrated into clinical practice. In 2005, a survey-based study revealed that cardiologists were more likely than neurologists to recommend PFO closure in young patients with cryptogenic stroke with PFO.10 In light of interval landmark trials and updated guidelines, we developed a survey to compare contemporary practice patterns between cardiologists and neurologists. We hypothesized that neurologists remain more conservative than cardiologists with respect to recommending PFO closure after stroke.

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METHODS

Design and Participants

The data that support the findings of this study are available from the corresponding author upon reasonable request. Stroke neurologists, general neurologists, interventional cardiologists, and noninterventional cardiologists were identified across the University of Pennsylvania Health System. University of Pennsylvania Health System is a multi-hospital regional system which includes a range of inpatient (6 hospitals) and outpatient healthcare facilities spanning community-based care to quaternary care. Additionally, stroke neurologists and interventional cardiologists that completed fellowship training at University of Pennsylvania Health System within the preceding 10 years were identified and included in the cohort of eligible survey recipients.

Survey creation, distribution, and data collection were managed in REDCap. The 19-question survey addressed provider demographics, PFO features, and brief clinical vignettes designed to isolate specific clinical or anatomic variables of interest, and a 5-point Likert scale assessed provider preferences with respect to PFO closure (Data S1). The survey was distributed to 184 eligible participants on March 16, 2021. Three weekly reminder emails were sent to participants that did not complete the survey. The survey closed on April 7, 2021.

This study was approved by the University of Pennsylvania Institutional Review Board and given the nature of the protocol, a waiver of informed consent was granted.

Statistical Analysis

Survey results were collected in REDCap after which the database was extracted to Stata 15.1 for analysis (StataCorp LLC, College Station, TX; 2017). Continuous variables were summarized by means (SD) or median (interquartile range) and categorical variables by proportions. For descriptive purposes, Likert-scale questions were consolidated into binary responses (i.e., the provider supports closure if they chose “strongly support closure” or “somewhat support closure”). For statistical analysis, the full Likert-scale range was assessed by Wilcoxon-Mann-Whitney tests when comparing stroke neurologists and interventional cardiologists. Similarly, Kruskal-Wallis tests compared the full range of survey responses across all 4 provider groups. In a secondary analysis, survey responses were consolidated into 3 categories: “support closure,” “neutral,” and “oppose closure” to more simply approximate clinical decision making (“strong” and “somewhat” were combined). With this consolidated data, Wilcoxon-Mann-Whitney tests were performed to compare stroke neurologists and interventional cardiologists.

RESULTS

Of 184 invitees, 106 responded, including 31/31 (100%) stroke neurologists, 38/46 (82%) interventional cardiologists, 20/30 (67%) general neurologists, and 17/77 (22%) noninterventional cardiologists. Four invitees initiated but failed to complete the survey in its entirety.

In the case of a carefully selected young stroke patient with cryptogenic stroke and PFO (Figure 1A), stroke neurologists and interventional cardiologists were similarly supportive of PFO closure ($P=0.54$). Between group differences were noted when all 4 specialties were compared ($P=0.011$), indicating general neurologists and noninterventional cardiologists may be less supportive of closure. In contrast, if a patient has a clearly identified high risk stroke mechanism (75% carotid stenosis; Figure 1B), stroke neurologists were more likely to oppose closure ($P=0.002$ versus interventional cardiologists; $P=0.003$ across all 4 specialties). Similarly, stroke neurologists were more likely than interventional cardiologists to oppose closure in a 55-year-old stroke patient with modifiable risk factors such as smoking and estrogen replacement therapy ($P=0.049$; Figure 2A). No intergroup differences were noted in the context of a low-risk potential alternative stroke mechanism such as nonstenotic carotid atherosclerosis (data not shown in figure). There were also no significant intergroup differences in considering a young patient with an indication for life-long anticoagulation (Figure 2B), although point estimates raise the possibility of that stroke neurologists may be less supportive of closure in this context ($P=0.14$ versus interventional cardiology; $P=0.09$ across all 4 groups). In the secondary analysis, the Likert scale was consolidated into 3 categories (support, neutral, or oppose), but this did not significantly alter the above reported differences between stroke neurologists and interventional cardiologists (Figures S1 and S2).

83% of interventional cardiologists reported referring patients to neurology for evaluation before pursuing PFO closure. Stroke neurologists were most likely to recommend against PFO closure based on older patient age (Figure 3A). In fact, substantial proportions of cardiologists support closure at any age, 28% of interventionalists and 36% of noninterventionalists. There was agreement between specialists about the appropriate duration of atrial fibrillation monitoring and the manner in which atrial fibrillation is interpreted; 96% of stroke neurologists and 92% of interventional cardiologists recommended at least 30 days of cardiac monitoring to rule out occult atrial fibrillation before pursuing PFO closure in a 55-year-old patient ($P=0.67$); and 85% of general neurologists and 88% of general cardiologists...
Figure 1. Patent foramen ovale closure in evidence-based scenarios.
(A) Stroke neurologists, interventional cardiologists, general cardiologists, and general neurologists were surveyed regarding their preference for patent foramen ovale closure in the case of a well-selected young patient with cryptogenic stroke after an extensive etiologic workup. Stroke neurologists and interventional cardiologists were equally supportive of patent foramen ovale closure ($P=0.54$), but differences were noted when comparing all 4 groups ($P=0.011$), indicating generalists are less likely to support closure. (B) In the case of a patient with a clear alternative stroke mechanism (severe carotid stenosis ipsilateral to the stroke), stroke neurologists were more likely than interventionalists to oppose closure ($P=0.002$), and differences were noted in comparing all 4 groups ($P=0.003$). Responses were provided based on a 5-point Likert scale. Gen Cards indicates general cardiologists; Gen Neuro indicates general neurologists; Interv Cards, interventional cardiologists; and Stroke Neuro, stroke neurologists.

Figure 2. Patent foramen ovale closure in scenarios lacking evidence.
(A) Stroke neurologists, interventional cardiologists, general cardiologists, and general neurologists were surveyed regarding their preference for patent foramen ovale closure in the case of a patient with modifiable stroke risk factors (estrogen replacement therapy and cigarette smoking). Interventionalists were more likely than stroke neurologists to support closure ($P=0.049$), but no significant differences were noted when comparing all 4 groups ($P=0.17$). (B) In the case of a patient with a lifelong indication for anticoagulation, stroke neurologists and interventionalists similarly opposed closure ($P=0.14$), and no differences were noted in comparing all 4 groups ($P=0.09$). Responses were provided based on a 5-point Likert scale. Gen Cards indicates general cardiologists; Gen Neuro, general neurologists; Interv Cards, interventional cardiologists; and Stroke Neuro, stroke neurologists.
similarly recommended at least 30 days of monitoring ($P=0.70$ comparing all 4 groups). The majority of each group considered any duration of atrial fibrillation sufficient to be considered a plausible stroke mechanism (Figure 3B).

**DISCUSSION**

The surveyed neurologists and cardiologists agree on several issues surrounding PFO closure, which is in contrast to a prior survey of PFO closure practice in 2005 where neurologists were much less likely to recommend PFO closure under any circumstance. However, this study does highlight important differences in the consideration of patient age, alternative stroke mechanisms, and modifiable risk factors. These results underscore the importance of collaboration between interventional cardiology and neurology, ideally stroke neurology, to ensure that an adequate evaluation is performed and that patients are provided with appropriate information and recommendations to facilitate shared decision-making.

Patient age is a potentially controversial variable when considering PFO closure after cryptogenic stroke. In this study, the majority of stroke neurologists did not recommend closure for those aged $>$65 years, whereas cardiologists were more willing to consider closure in older patients. In fact, 28% of interventional cardiologists and 36% of general cardiologists did not impose any upper age limit, assuming the patient is otherwise a good candidate. Three landmark trials excluded patients aged $>$60 years.1–3 One trial did not restrict enrollment based on age and included 28% aged $\geq$60 years and 9% aged $\geq$70 years. An analysis did not identify an interaction by age, dichotomized as greater or less than 60 years.5 However, this post hoc analysis was underpowered and updated professional society guidelines identify age as a critical consideration, indicating more data are needed to clearly establish the role of PFO closure in older patients.6–8 The different approaches to age may reflect varying interpretations of the literature or may suggest neurologists are generally more conservative in approaching PFO closure after stroke. As noted, a more conservative tendency was also evident in the 2005 survey-based study comparing cardiology and neurologists.10 This pattern was also observed when survey participants were presented with a 55-year-old woman who suffered a stroke in the context of active smoking and estrogen replacement therapy, after which the patient agreed to stop both. The majority of stroke neurologists preferred to forego closure in favor of addressing the modifiable risk factors, but the majority of interventional cardiologists supported closure. The clinical trials did not explicitly address these complex issues, so in the absence a definitive evidence-based decision, collaboration and shared decision-making is particularly appropriate.

When faced with a patient similar to those enrolled in the positive PFO closure trials, there was clear agreement between stroke neurologists and interventional cardiologists to pursue closure. However, general neurologists and general cardiologists are less supportive of closure, principally because of a larger proportion of survey respondents indicating they neither support nor oppose closure (ie, neutral). This may reflect a difference in comfort or confidence in this particular figure.
treatment decision among generalists. In this particular health system, it may reflect access to and reliance on subspecialists. A broader survey would be necessary to determine if this variability persists in other practice settings where subspecialists are less abundant.

In the case of a clear alternative stroke mechanism, such as carotid stenosis proximal to the index stroke, all stroke neurologists opposed closure while a portion of other providers recommended closure. Rather than suggesting nonstroke providers are more aggressive in pursuing closure, this may reflect their discomfort in identifying the likely stroke etiology (based on expected risk for each mechanism) or a lack of awareness that such a patient would have been excluded from the clinical trials. This finding underscores the importance of involving a neurologist to assess stroke mechanism before pursuing PFO closure, as required per the device labeling of both the Amplatzer PFO occluder (Abbott) and the CARDIOFORM Setpia Occluder (GORE) in the United States and elsewhere. Importantly, 17% of interventionalists indicated they do not routinely involve stroke neurologists before pursuing PFO closure.

When a young stroke patient has a lifelong indication for anticoagulation, the majority of stroke neurologists and interventional cardiologists recommend against closure ($P=0.14$), although point estimates raise the possibility that interventionalists may be somewhat more supportive of closure (27% versus 4%). The additional benefit of performing closure in such a case is unclear and controversial, but future trial data may provide clarity. Collaboration between neurology and cardiology may be particularly critical in scenarios where little data are available to guide clinical decision-making, such as patients with underlying hypercoagulable states, older patients, small PFOs, or modifiable risk factors. As the survey demonstrates, there may be a range of approaches, and until additional data become available, a collaborative effort likely better serves patients by bringing more perspectives to the process of shared decision-making.

The study has limitations. The questionnaire was relatively brief, but survey fatigue is a possibility despite the fact that only 4 participants failed it after initiation. The response rate was high, which may be perceived as a strength, but it is not typical of survey-based research and likely attributable to this being a relatively small, single-center study where some of the invited participants knew the investigators performing the study. The response rate was lower among general neurologists and general cardiologists, which may impact the comparison between specialists and generalists. The survey-based nature of this study raises the possibility of certain biases. There may be a central tendency bias among generalists who are less familiar with PFO closure. Acquiescence bias may artificially increase the reported degree of support in some responders. The single-center nature of the study also limits generalizability. Importantly, the study included providers from a range of practice settings within the health system and former trainees in interventional cardiology and vascular neurology who now work elsewhere. University of Pennsylvania Health System is a collaborative academic environment, which may blunt the between-group differences, and results may not be representative of other regions, community-based, or rural practices. A national/international survey would overcome this limitation. The sample size was relatively small, which yielded limited power to detect small differences between groups. In practice, clinical decisions are binary (close versus do not close), but the Likert scale reliably reflects the nuanced decision-making and recommendations with case vignettes.

CONCLUSIONS

Neurologists and cardiologists agree on several issues surrounding PFO closure after cryptogenic stroke, but key differences in the consideration of patient age, alternative stroke mechanisms, and modifiable risk factors highlight the need for collaboration and shared decision-making. Stroke neurologists were more likely to recommend against closure in clinical scenarios that did not reflect the patients enrolled in the landmark clinical trials. A national/international survey is needed to confirm these findings and more broadly reflect practice patterns.

ARTICLE INFORMATION

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Supplemental Material

Data S1
Figures S1–S2

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This page includes a list of references and a page number. The text is not directly related to the main content of the chapter.
SUPPLEMENTAL MATERIAL
Data S1. Supplemental Methods – Survey Tool

This supplement includes the complete survey instrument. Branching logic is described in italics.

1. What is your medical specialty?
   a. Stroke Neurology
   b. General Neurology
   c. General Cardiology
   d. Interventional Cardiology

   *If Q1=a – skip to Q4, otherwise continue with survey.*

2. Do you provide care for stroke patients as part of your clinical practice?
   a. Yes
   b. No *(if so, survey ends)*

   *If Q1=d – continue to Q3, otherwise skip Q3.*

3. Do you perform PFO closure as part of your clinical practice
   a. Yes
   b. No *(if so, survey ends)*

4. Do you routinely involve a neurologist before closing a PFO in your clinical practice?
   a. Yes
   b. No

5. A stroke patient has a PFO, but no other identified stroke mechanism and no traditional vascular risk factors – is there an age **above** which you would NOT consider PFO closure?
   a. 50 years
   b. 60 years
   c. 65 years
   d. 70 years
   e. 75 years
   f. 80 years
   g. no upper age limit
6. Prior to considering PFO closure in a cryptogenic stroke patient, how long do you recommend outpatient cardiac monitoring to rule out atrial fibrillation:

If the patient is 55 years old:
   a. Monitoring is not necessary
   b. 2 days
   c. 7 days
   d. 30 days
   e. Implantable loop recorder for greater than 30 days

7. If the patient is 30 years old:
   a. Monitoring is not necessary
   b. 2 days
   c. 7 days
   d. 30 days
   e. Implantable loop recorder for greater than 30 days

8. If atrial fibrillation is identified during post-stroke cardiac monitoring, what minimum duration of atrial fibrillation is necessary in order to consider it the stroke etiology?
   f. Any duration is sufficient (i.e. a few seconds)
   g. 30 seconds
   h. 6 minutes
   i. 6 hours

9. Which of the following factors make you more inclined to close a PFO? (Check all that apply)
   o Small shunt
   o Large shunt
   o Atrial septal aneurysm
   o Varicose veins
   o Chiari network
   o Prominent eustachian valve
   o Heterozygous factor V mutation
   o Elevated D-dimer
The next few questions will present concise clinical scenarios:

If Q1=a – skip Q9, Q10, Q11; If Q1=b or c – skip Q9, Q10, Q11; if Q1=d, continue.

10. A 35-year-old man underwent successful PFO closure after stroke. He has no other vascular risk factors. What antithrombotic therapy do you recommend immediately following closure?
   a. Single antiplatelet therapy
   b. Dual antiplatelet therapy
   c. Anticoagulation
   d. Antiplatelet plus anticoagulation
   e. No antithrombotic therapy

If Q9=e – skip Q10; if Q9=a, b, c or d, continue.

11. For how long do you recommend this immediate post-closure antithrombotic regimen?
   a. 1 month
   b. 2 months
   c. 3 months
   d. 6 months
   e. Lifelong

If Q10=e, skip Q11; if Q10=a, b, c or d, continue

12. After the completion of the post-closure antithrombotic regimen, what do you recommend for long-term antithrombotic therapy?
   a. Single antiplatelet therapy
   b. Dual antiplatelet therapy
   c. Anticoagulation
   d. Antiplatelet plus anticoagulation
   e. No further antithrombotic therapy is needed

If Q1=a, continue with Q12; if Q1=d, skip Q12

13. A 35-year-old man underwent successful PFO closure after stroke. He has no other vascular risk factors. After PFO closure, he completed a 6-month antithrombotic regimen as recommended by his cardiologist. Thereafter, what antithrombotic therapy do you recommend for long-term secondary stroke prevention?
a. Single antiplatelet therapy  
b. Dual antiplatelet therapy  
c. Anticoagulation  
d. Antiplatelet plus anticoagulation  
e. No further antithrombotic therapy is needed

14. A 50-year-old patient with no vascular risk factors suffered an embolic appearing stroke. PFO was identified on trans-thoracic and trans-esophageal echocardiogram. A thorough workup, including vessel imaging, thrombophilia testing, and prolonged cardiac monitoring, no alternative stroke etiology is identified.

Do you support or oppose PFO closure?

a. Strongly support closure  
b. Somewhat support closure  
c. Neutral  
d. Somewhat oppose closure  
e. Strongly oppose closure

15. If, instead, the CTA showed 30% ICA stenosis with an ulcerated plaque (in the territory of the stroke), do you support or oppose PFO closure?

a. Strongly support closure  
b. Somewhat support closure  
c. Neutral  
d. Somewhat oppose closure  
e. Strongly oppose closure

16. If, instead, the CTA showed 75% ICA stenosis (in the territory of the stroke), do you support or oppose PFO closure?

a. Strongly support closure  
b. Somewhat support closure  
c. Neutral  
d. Somewhat oppose closure  
e. Strongly oppose closure
17. A 50-year-old woman suffered a cryptogenic embolic appearing stroke 10 years ago. She has no known vascular risk factors. A thorough workup revealed no stroke etiology other than a PFO. PFO closure was not pursued. Now, 10 years after the stroke, she sees you in clinic to determine if she should pursue PFO closure.

Do you support or oppose PFO closure?

a. Strongly support closure
b. Somewhat support closure
c. Neutral
d. Somewhat oppose closure
e. Strongly oppose closure

18. A 37-year-old man with no vascular risk factors suffered an embolic appearing stroke. On echocardiogram, a PFO with atrial septal aneurysm was found. Vessel imaging is unremarkable. Prolonged cardiac monitoring is negative for atrial fibrillation. Lab work reveals high titers of beta-2-glycoprotein and anti-cardiolipin antibodies. After consultation with a hematologist, he is diagnosed with antiphospholipid antibody syndrome (APLS) and started on Coumadin.

Do you support or oppose PFO closure?

a. Strongly support closure
b. Somewhat support closure
c. Neutral
d. Somewhat oppose closure
e. Strongly oppose closure

19. A 55-year-old woman suffered an embolic appearing stroke. She smokes cigarettes and uses estrogen supplementation. Echo reveals a PFO. A thorough workup, including prolonged cardiac monitoring, reveals no alternative stroke etiology.

Do you support or oppose PFO closure?

a. Strongly support closure
b. Somewhat support closure
c. Neutral
d. Somewhat oppose closure
e. Strongly oppose closure
Figure S1. PFO closure in evidence based scenarios - simplified survey responses

A. In the case of a well-selected young patient with cryptogenic stroke after an extensive workup, a similar majority of stroke neurologists and interventional cardiologists were supportive of closure (p=0.86).

B. In the case of a patient with a clear alternative stroke mechanism (severe carotid stenosis ipsilateral to the stroke), stroke neurologists were more likely to oppose closure (p=0.03). P-values were calculated by Wilcoxon-Mann-Whitney tests.

Figure S1 Legend. PFO closure in evidence based scenarios - simplified survey responses: Stroke neurologists and interventional cardiologists were surveyed regarding their preference for PFO closure. Raw survey responses included five categories (strongly support, somewhat support, neutral, somewhat oppose, strongly oppose). Here, somewhat and strongly were consolidated to more simply demonstrate support or opposition. (A) In the case of a well-selected young patient with cryptogenic stroke after an extensive workup, a similar majority of stroke neurologists and interventional cardiologists were supportive of closure (p=0.86). (B) In the case of a patient with a clear alternative stroke mechanism (severe carotid stenosis ipsilateral to the stroke), stroke neurologists were more likely to oppose closure (p=0.03). P-values were calculated by Wilcoxon-Mann-Whitney tests.

Stroke neuro indicates stroke neurologists
Interv cards indicates interventional cardiologists
Figure S2. PFO closure in scenarios lacking evidence - simplified survey responses

A.

![Bar chart comparison between Stroke Neurologists and Interv Cardiologists for modifiable stroke risk factors (estrogen replacement therapy and cigarette smoking).](chart1.png)

B.

![Bar chart comparison between Stroke Neurologists and Interv Cardiologists for indication for lifelong anticoagulation.](chart2.png)

Figure S2 Legend. PFO closure in scenarios lacking evidence – simplified survey responses: Stroke neurologists and interventional cardiologists were surveyed regarding their preference for PFO closure. Raw survey responses included five categories (strongly support, somewhat support, neutral, somewhat oppose, strongly oppose). Here, somewhat and strongly were consolidated to more simply demonstrate support or opposition. (A) In the case of a patient with modifiable stroke risk factors (estrogen replacement therapy and cigarette smoking), there is no significant difference between stroke neurologists and interventional cardiologists, but point estimates suggest a larger proportion of interventionalists are supportive of closure (p=0.09). (B) In the case of a patient with an indication for lifelong anticoagulation, there is no significant difference between the two groups, but again the point estimates suggest a larger proportion of interventionalists are supportive of closure (p=0.06). P-values were calculated by Wilcoxon-Mann-Whitney tests.

*Stroke neuro indicates stroke neurologists*

*Interv cards indicates interventional cardiologists*