

Prognosis of Cryptogenic Stroke With Patent Foramen Ovale at Older Ages and Implications for Trials

A Population-Based Study and Systematic Review

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 Supplemental content

IMPORTANCE Patent foramen ovale (PFO) closure may prevent recurrent stroke after cryptogenic transient ischemic attack (TIA) or stroke (TIA/stroke) in patients aged 60 years or younger. Patent foramen ovale is associated with cryptogenic stroke in the older population, but risk of recurrence is unknown. Data on prognosis of patients receiving medical treatment at older ages (≥ 60 years) are essential to justify trials of PFO closure.

OBJECTIVE To examine the age-specific risk of recurrence in patients with cryptogenic TIA/stroke with PFO.

DESIGN, SETTING, AND PARTICIPANTS A prospective study was nested in the population-based Oxford Vascular Study between September 1, 2014, and March 31, 2019, with face-to-face follow-up for 5 years. A total of 416 consecutive patients with a diagnosis of cryptogenic TIA or nondisabling stroke, screened for PFO at a rapid-access TIA/stroke clinic, were included. A systematic review and meta-analysis of cohort studies reporting on ischemic stroke recurrence after cryptogenic TIA/stroke in patients with PFO who were receiving medical therapy alone, or with PFO vs no-PFO was conducted. Sample size calculation for future trials on PFO closure was performed for patients aged 60 years or older.

EXPOSURES Patent foramen ovale and age as modifiers of risk of recurrent stroke after cryptogenic TIA/stroke in patients receiving only medical therapy.

MAIN OUTCOMES AND MEASURES Risk of ischemic stroke recurrence in patients with cryptogenic TIA/stroke and PFO receiving medical therapy only, and in patients with vs without PFO, stratified by age (<65 vs ≥ 65 years), as well as sample-size calculation for future trials of PFO closure in patients aged 60 years or older.

RESULTS Among the 153 Oxford Vascular Study patients with PFO (mean [SD] age, 66.7 [13.7] years; 80 [52.3%] men), recurrent ischemic stroke risk (2.05 per 100 patient-years) was similar to the pooled estimate from a systematic review of 23 other studies (9 trials and 14 observational studies) (2.00 per 100 patient-years; 95% CI, 1.55-2.58). However, there was heterogeneity between studies ($P < .001$ for heterogeneity), owing mainly to risk increasing with mean cohort age (meta-regression: $R^2 = 0.31$; $P = .003$). In the pooled analysis of 4 studies including patients with or without PFO, increased risk of stroke recurrence with PFO was seen only at age 65 years or older (odds ratio, 2.5; 95% CI, 1.4-4.2; $P = .001$ for difference; $P = .39$ for heterogeneity). The pooled ischemic stroke risk was 3.27 per 100 patient-years (95% CI, 2.59-4.13) in 4 cohorts with mean age 60 years or older. Assuming the more conservative 2.0 per 100 patient-years ischemic stroke risk in the PFO nonclosure arms of future trials in patients aged 60 years or older, projected sample sizes were 1080 per arm for 80% power to detect a 33% relative risk reduction.

CONCLUSIONS AND RELEVANCE The findings of this study suggest that age is a determinant of risk of ischemic stroke after cryptogenic TIA/stroke in patients with PFO, such that trials of PFO closure at older ages are justified; however, projected sample sizes are large.

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The causal role of patent foramen ovale (PFO) in patients with cryptogenic transient ischemic attack (TIA) and/or stroke (TIA/stroke) has been reinforced by randomized clinical trials showing that percutaneous closure reduces the risk of recurrent stroke, mostly in patients aged 60 years or younger.¹⁻⁵ However, older patients account for most strokes and PFO is associated with cryptogenic TIA/stroke in patients at older ages,^{6,7} with a substantial burden at a population level (approximately 6000 patients aged >60 years with large PFO and cryptogenic TIA/nondisabling stroke every year in the UK⁶). To our knowledge, there is no evidence from randomized clinical trials that PFO closure is effective in secondary prevention of stroke in patients older than 60 years.

In published trials of PFO closure, the risk of stroke recurrence is low even in the nonclosure arm (1.27 per 100 person-years),⁸ but this risk might be higher at older ages.⁹ However, PFO closure might be less effective and/or higher risk in older patients than in younger ones; therefore, new trials of PFO closure at older ages are required. Data on age-specific prognosis on medical treatment alone are warranted to justify trials of PFO closure at older ages and inform design of the trials.

We examined the age-related risk of ischemic stroke recurrence in a large, population-based cohort after cryptogenic TIA/nondisabling stroke in patients with PFO. We also performed a systematic review of cohort studies reporting ischemic stroke recurrence after cryptogenic TIA/stroke in patients with PFO receiving medical therapy alone or with PFO vs no PFO and pooled our data in a meta-analysis stratified by age, as well as in a meta-regression. We then estimated the sample size for future trials of PFO closure vs medical treatment alone in secondary prevention of cryptogenic TIA/stroke in patients with PFO aged 60 years or older.

Methods

OxVasc Study

This study was nested in the Oxford Vascular (OxVasc) Study, an ongoing, population-based study of the incidence and outcome of all acute vascular events in a population of 92 728 individuals, irrespective of age, registered with 100 primary care physicians in 9 practices in Oxfordshire, UK. Multiple methods of ascertainment are used for patients with TIA/stroke, as detailed elsewhere¹⁰ and summarized in the eMethods in the [Supplement](#), including a daily, rapid-access TIA/stroke clinic to which participating physicians and the local emergency department refer individuals with suspected TIA or nondisabling stroke. As part of the OxVasc Phenotyped Cohort, consecutive, eligible patients attending this clinic with an acute event or for 3-month follow-up after an inpatient admission were screened for PFO between September 1, 2014, and March 31, 2019, and followed up until December 1, 2019. The OxVasc study and TCD assessment were approved by the local ethics committee and written informed consent was obtained from all participants, or assent was obtained from relatives in the case of cognitive impairment or speech difficulty.

Key Points

Question Is the prognosis of cryptogenic transient ischemic attack and stroke in patients receiving medical treatment alone associated with the presence of patent foramen ovale and age?

Findings In this population-based study, risk of recurrent ischemic stroke (2.05 per 100 patient-years) was consistent with the pooled estimate from a systematic review and meta-analysis (2 per 100 patient-years). Risk increased with mean cohort age, and only in patients with cryptogenic transient ischemic attack and stroke aged 65 years or older was patent foramen ovale vs no patent foramen ovale associated with a higher risk of recurrent ischemic stroke.

Meaning The findings of this study suggest that a higher risk of stroke recurrence at older ages in patients with patent foramen ovale warrants trials of patent foramen ovale closure in older patients.

Patients were assessed by a neurologist or stroke physician, and all presentations and investigations were reviewed by the senior study neurologist (P.M.R.). Demographic data, history of atrial fibrillation, atherosclerotic risk factors (ie, male sex, as well as history of hypertension, diabetes, smoking, hypercholesterolemia, and coronary or peripheral vascular disease) were recorded during face-to-face interviews and cross-referenced with primary care medical records.¹¹ Patients routinely had 12-lead electrocardiography (ECG) and routine blood tests (ie, complete blood cell count, clotting profile, C-reactive protein, erythrocyte sedimentation rate, liver function, kidney function, thyroid function, electrolytes, and lipid profile) after the event. All patients underwent magnetic resonance brain and vascular imaging if not contraindicated (3-T magnetic resonance imaging with time-of-flight magnetic resonance angiography of the intracranial vessels and contrast-enhanced magnetic resonance angiography of the large neck arteries), or brain computed tomographic imaging with contrast-enhanced angiography or duplex ultrasonography if magnetic resonance imaging was contraindicated. Patients with cryptogenic TIA or stroke or those younger than 55 years also had thrombophilia screening, vasculitis screening, and genetic testing when appropriate. Clinical workup was completed with 5-day ambulatory ECG recording (R-test) and transthoracic echocardiography.¹¹

Contrast-enhanced transcranial Doppler (TCD) (bubble-TCD) sonography (Doppler Box; Compumedics DWL) was performed by 1 of 2 experienced operators (S.M. and L.L.) who were blind to the patient's clinical presentation. As a contrast agent, agitated saline was used in all cases according to accepted guidelines.¹² A large PFO was defined as a shunt with 20 or more microbubbles recorded. Since November 15, 2015, if a temporal bone window was not suitable for monitoring, the basilar artery was monitored through a transoccipital approach.¹³ Designation of PFO status was made at the time of assessment, and recordings were archived.

The OxVasc definition for stroke and TIA is given in the eMethods in the [Supplement](#). Cause of ischemic events was classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria.¹⁴ Events were classified as cryptogenic if

the diagnostic workup included at least brain imaging, ECG, and complete vascular imaging, and no clear cause was found. Patent foramen ovale alone was not considered as a criterion for cardioembolic stroke.¹¹

To identify any recurrent stroke, patients were followed up face-to-face or via telephone if they had moved out of the study area at 1, 3, 6, 12, 24, and 60 months. All recurrences during follow-up would be identified through additional sources, such as daily case ascertainment (hot pursuit as described in the eMethods in the Supplement) and review of primary care records. Deaths with underlying causes during follow-up were recorded by direct follow-up via primary care records and by centralized registration with the Office for National Statistics.

Systematic Review

We carried out a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline for meta-analyses.¹⁵ We searched MEDLINE and Web of Science for articles published from inception until March 31, 2020, using the terms *stroke*, *cryptogenic stroke*, *stroke of undetermined aetiology*, *embolic stroke of undetermined source*, *foramen ovale*, *PFO*, *atrial septal abnormality*, *interatrial septal abnormality*, *right-to-left shunt*, *prognosis*, and *recurrent stroke*. Full search strategy details are given in the eMethods in the Supplement).

We restricted the search to cohorts with more than 100 patients with cryptogenic TIA/stroke, reporting on stroke recurrence in patients with PFO who were receiving medical therapy alone. We did not limit the search to English-language studies. We also hand-searched reference lists of all articles identified, of the publications related to the component databases of the Risk of Paradoxical Embolism Study,¹⁶ and those of any previous systematic reviews. We contacted study authors to retrieve missing data as appropriate.

Eligible studies included case-control, cohort, population-based studies or randomized clinical trials reporting on recurrent ischemic stroke after cryptogenic events in patients with PFO who were receiving medical treatment alone. Two of us (S.M. and L.L.) independently screened the references and identified eligible studies. Any discrepancy was solved via discussion or involving another one of us (P.M.R.). In case of duplicate studies, we included only the report with the most informative and complete data.

Two of us (S.M. and L.L.) independently extracted data from eligible articles using a standardized data extraction form. Information obtained included study type, setting of enrolment, years of enrolment, number of patients with cryptogenic stroke vs stroke of known causes, number of patients with cryptogenic stroke with vs without PFO, age cutoff and mean age, follow-up duration, type of index event, stroke subtype classification (Trial of Org10172 in Acute Stroke Treatment¹⁴ vs other); assessment for index event (complete, incomplete, or unreported), PFO screening modality (transthoracic echocardiography, transesophageal echocardiography, or bubble-TCD), prolonged ECG monitoring, baseline modified Rankin scale, medical treatment after index event (antiplatelet agents or anticoagulation), intracranial hemorrhages, assessment for

recurrent event (direct, indirect, or unreported), type of recurrent event, and number of patients with ischemic stroke recurrences with vs without PFO.

The definition of PFO was based on the demonstration of right-to-left shunt both for studies using TCD¹² or transthoracic or transesophageal echocardiography,¹⁷ the definition of right-to-left shunt size in the latter examination usually being based on the maximum number of microbubbles reported in the left atrium during the first 3 cardiac cycles after detection in the right atrium; a large right-to-left shunt usually comprised more than 20 to 25 microbubbles.^{2,4} Assessment of the index event was considered complete if the diagnostic workup included at least brain imaging, ECG, and extracranial imaging.¹¹ Face-to-face assessment with study physicians in the acute phase of a possible recurrent event was considered as direct assessment for recurrent events. To assess study quality, we used the Newcastle-Ottawa Scale.¹⁸

Outcomes

First, we aimed to estimate the absolute risk of ischemic stroke recurrence (or ischemic and hemorrhagic stroke when ischemic only was not reported) per 100 patient-years in patients with cryptogenic TIA/stroke and PFO receiving medical therapy only, and its association with mean study age, both in the OxVasc Study cohort and in cohorts from the systematic review. Second, we aimed to determine any excess risk of recurrent stroke in patients with vs without PFO, stratified by age (<65 or ≥65 years), by pooling OxVasc data with data from the systematic review. Third, we aimed to calculate the desirable sample size for future trials of PFO closure and medical treatment after cryptogenic stroke/TIA in patients aged 60 years or older.

Statistical Analysis

Absolute risk of ischemic stroke recurrence per 100 patient-years was calculated in the OxVasc Study cohort and for each of the included studies in the systematic review (or ischemic and hemorrhagic stroke when ischemic only was not reported) on the basis of the data provided in the main article, the supplemental material, or by the author on request. Pooled estimates of absolute risk were obtained by meta-analysis with the 95% CI of the pooled risk estimate calculated to allow for extrabinomial variation,¹⁹ to avoid artificially narrow intervals produced by standard methods of calculating 95% CI in case of heterogeneity between studies. To test for age as a potential source of between-study heterogeneity, we regressed the ischemic stroke recurrence rate against study mean age, weighted by the inverse variance of risk estimate.²⁰

In the OxVasc Study cohort and in studies that reported on both groups, meta-analysis with Mantel-Haenszel-Peto methods was used to determine excess risk of recurrent stroke in patients with PFO vs those without PFO by calculating the odds ratio (OR) with 95% CI for ischemic stroke recurrence in patients with cryptogenic events and PFO vs patients without PFO stratified by age (<65 or ≥65 years).

We estimated the projected sample size for trials of PFO closure vs medical treatment only after cryptogenic TIA/stroke in patients aged 60 years or older with 80% power to

Table. Baseline Characteristics of Cryptogenic Events in the Oxford Vascular Study Cohort, Stratified by Age

Characteristic	All Patients			≥65 y		
	No. (%)			No. (%)		
	PFO (n = 153)	No PFO (n = 263)	P value	PFO (n = 98)	No PFO (n = 180)	P value
Age, mean (SD), y	66.7 (13.7)	69.3 (12.7)	.06	75.1 (6.4)	76.4 (6.6)	.09
Male sex	80 (52.3)	126 (47.9)	.39	47 (48.0)	78 (43.3)	.46
Index event						
Transient ischemic attack	110 (71.9)	193 (73.4)	.74	45 (79.6)	135 (75.0)	.39
Ischemic stroke	43 (28.1)	70 (26.6)		20 (20.4)	45 (25.0)	
Previous vascular event						
Myocardial infarction	6 (3.9)	9 (3.4)	.79	5 (5.1)	7 (3.9)	.63
Peripheral vascular disease	3 (2.0)	5 (1.9)	.97	3 (3.1)	1 (1.7)	.45
Transient ischemic attack	14 (9.2)	15 (5.7)	.18	12 (12.2)	14 (7.8)	.22
Stroke	12 (7.8)	22 (8.4)	.85	7 (7.1)	17 (9.4)	.51
Known vascular risk factors						
Hypertension	72 (47.1)	152 (57.8)	.03	58 (59.2)	122 (67.8)	.15
Diabetes	22 (14.4)	34 (12.9)	.68	14 (14.3)	27 (15.0)	.87
Hyperlipidemia	61 (39.9)	91 (34.6)	.28	49 (50.0)	71 (39.4)	.09
Valvular heart disease	5 (3.3)	11 (4.2)	.64	3 (3.1)	8 (4.4)	.57
Cardiac failure	3 (2.0)	2 (0.8)	.28	3 (3.1)	2 (1.1)	.24
Venous thrombosis	4 (2.6)	9 (3.4)	.65	3 (3.1)	7 (3.9)	.72
History of smoking	87 (56.9)	130 (49.4)	.14	52 (53.1)	84 (46.7)	.31
PFO size						
Small (shunt with <20 microbubbles)	92 (60.1)	NA	NA	63 (64.3)	NA	NA
Medium-large (shunt with ≥20 microbubbles)	61 (39.9)	NA	NA	35 (35.7)	NA	NA
Medication at discharge						
Warfarin alone	0 (0)	2 (0.8)	.54	0 (0)	1 (0.6)	.73
DOACs alone	0 (0)	1 (0.4)		0 (0)	0 (0)	
Antiplatelet	152 (99.3)	257 (97.7)		97 (99.0)	177 (98.3)	
Antiplatelet plus warfarin	1 (0.4)	1 (0.7)		1 (1.0)	1 (0.6)	
Antiplatelet plus DOACs	0 (0)	2 (0.8)		0 (0)	1 (0.6)	

Abbreviations: DOACs, direct oral anticoagulants; NA, not applicable; PFO, patent foramen ovale.

detect either a 66% risk reduction for the interventional closure arm, which was expected on the basis of trials predominantly on antiplatelet treatment in the younger population, or a more conservative 33% reduction to allow for the higher background risk of stroke in the older population or a comparison with anticoagulation.²¹

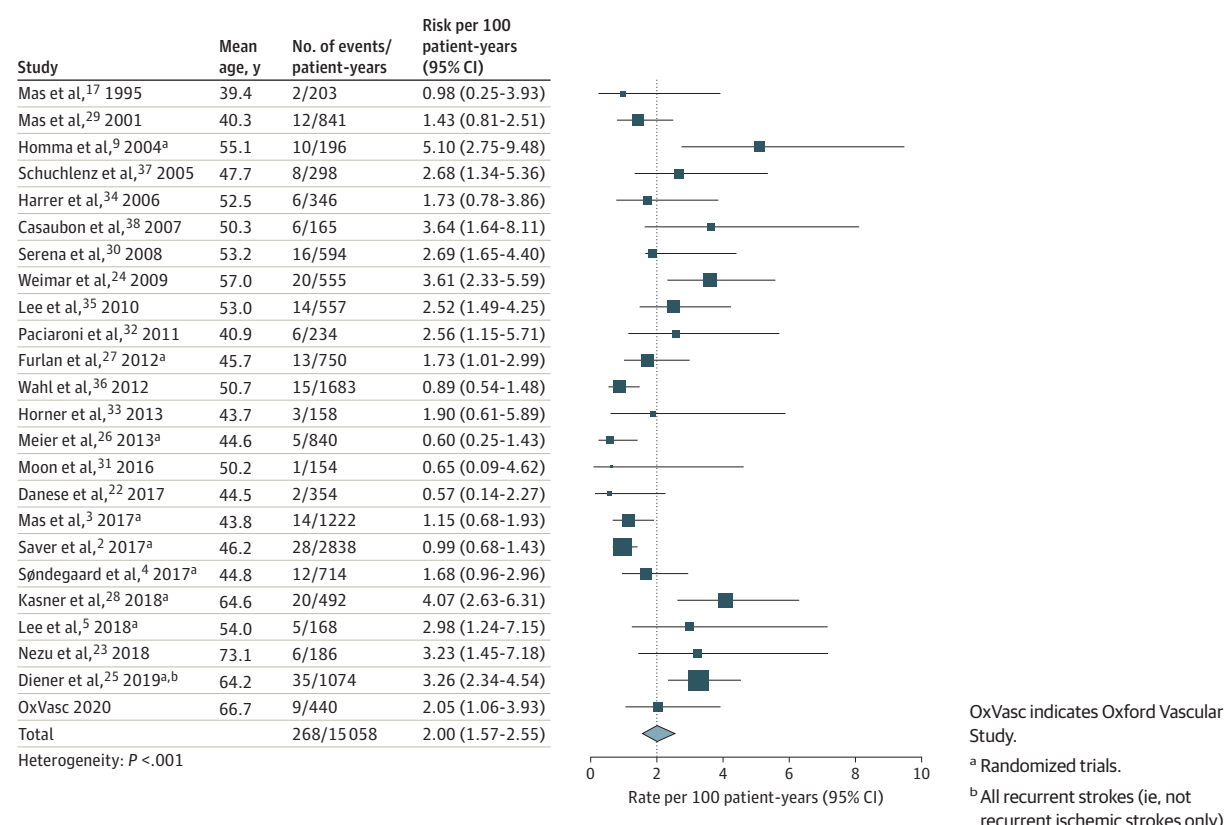
Results

Of 456 consecutive patients in the OxVasc Study with a diagnosis of cryptogenic TIA/nondisabling stroke, bubble-TCD was obtained in 416 patients, with intolerance to supine position, lack of bone window, and cannulation issues being the most common reasons for lack of scanning. Of the 416 scanned patients, 153 had a positive bubble-TCD (36.78%, mean [SD] age, 66.7 [13.7] years). Characteristics of patients with cryptogenic TIA/nondisabling stroke with and without PFO, stratified by age (<65 or ≥65), are reported in the **Table**.

Of 577 potentially eligible records identified for the systematic review, we identified 28 eligible articles reporting

on 23 studies^{2-5,9,17,22-38} (9 trials and 14 observational studies) including 4889 patients with cryptogenic TIA/stroke and PFO who were receiving medical treatment alone (eFigure 1 in the **Supplement**). Noneligible studies included observational studies³⁹⁻⁴⁴ and 1 randomized clinical trial (47 patients with cryptogenic stroke/TIA randomized to either warfarin or aspirin)⁴⁵ with a population below the threshold for inclusion (<100 patients with cryptogenic TIA/stroke enrolled); observational studies on an unsuitable population (mostly retrospective studies selecting patients on the basis of echocardiographic finding of a PFO, where the analysis included patients without stroke, or patients with both cryptogenic and noncryptogenic TIA/stroke)⁴⁶⁻⁵⁴; secondary publications of an included study^{55,56}; and a study that reported only composite outcomes of TIA/stroke and peripheral embolism.⁵⁷ We contacted 8 authors and obtained unpublished data from 4 individuals.^{9,22-24,58} Study characteristics are detailed in the eResults and eTable 1 in the **Supplement**. The quality assessment of the studies is reported in eTable 2 in the **Supplement**.

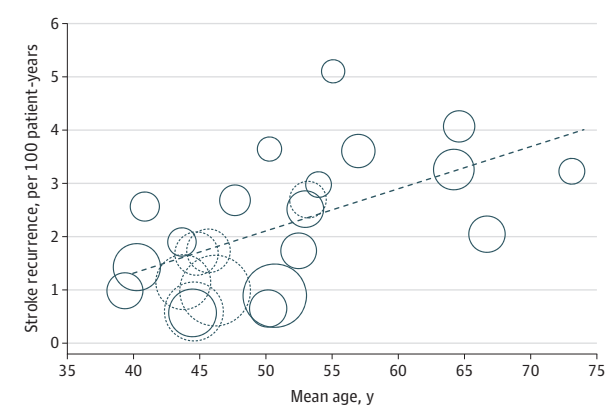
In OxVasc patients with cryptogenic TIA/stroke and PFO, a total of 9 recurrent ischemic strokes occurred during 440

Figure 1. Absolute Risk of Recurrent Ischemic Stroke in Patients With Patent Foramen Ovale Receiving Medical Treatment Alone

patient-years, with an absolute risk of 2.05 per 100 patient-years (Figure 1). Of these, 5 patients per 329 patient-years had TIA as an index event (risk, 1.5 per 100 patient-years) and 4 per 111 patient-years had a stroke (risk, 3.6 per 100 patient-years). On pooling with the 23 other eligible studies from the systematic review, risk per 100 patient-years of ischemic stroke was 2.00 (95% CI, 1.57-2.55) (Figure 1), based on 268 recurrent events during 362 324 patient-years. One included study with patient mean age of 64.2 years reported the risk of all strokes rather than ischemic strokes only,²⁵ contributing to the analysis with 6 of 268 events overall. A sensitivity analysis excluding this study is shown in eFigure 2 in the Supplement.

There was substantial heterogeneity between studies ($P < .001$ for heterogeneity) in the risk of ischemic stroke, which was partly explained by higher risk with increasing mean age of the study cohort (meta-regression: $R^2 = 0.31$; $P = .003$), with absolute risk increasing by about 50% in relative terms for every 10 years of age (Figure 2). The pooled ischemic stroke risk at age 60 years or older was 3.27 per 100 patient-years (95% CI, 2.59-4.13).

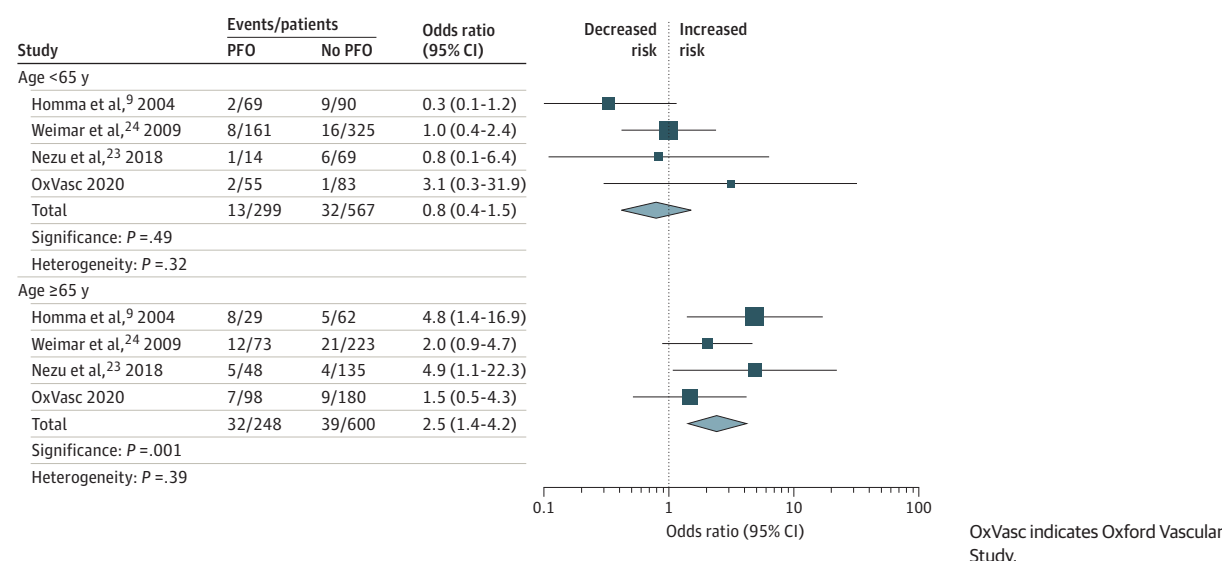
Pooled recurrent ischemic stroke risk was 1.26 per 100 patient-years (95% CI, 0.91-1.75) among the randomized clinical trials of PFO closure (mean [SD] age, 46.51 [9.55] years),^{2-5,26,27} and 2.37 per 100 patient-years (95% CI, 1.84-3.05) for the other cohorts (mean [SD] age, 51.79 [11.37]), including the 3 randomized clinical trials of antithrombotic treatment.^{9,25,28} Excluding these 3 trials, the pooled risk was 2.04 per 100 patient-

Figure 2. Meta-Regression Analysis Between Recurrent Ischemic Stroke Risk and Mean Study Age

Dotted circles represent the medical arm of patent foramen ovale closure trials.

years (95% CI, 1.55-2.69) for the observational cohorts only.^{17,22-24,29-38}

In 7 of the above-mentioned studies, ischemic stroke risk was reported in patients with cryptogenic TIA/stroke with PFO vs those without PFO.^{9,17,23,24,28-30} When pooling the subgroup of studies reporting this association stratified by age^{9,23,24} with the OxVasc Study data, we found that the association between PFO and stroke risk increased with age (<65 years: OR,

Figure 3. Risk of Ischemic Stroke Recurrence After Cryptogenic Transient Ischemic Attack/Stroke in Patients With Patent Foramen Ovale (PFO) vs Patients Without PFO

0.8; 95% CI, 0.4-1.5; ≥65 years: OR, 2.5; 95% CI, 1.4-4.2; $P = .001$ for difference; $P = .39$ for heterogeneity) (Figure 3).

Although the pooled ischemic stroke risk per 100 patient-years at age 60 years or older was 3.27 per 100 patient-years (95% CI, 2.59-4.13), for the purpose of sample-size calculation, we assumed a more conservative estimate for the non-closure arms of future trial cohorts of 2.0 per 100 patient-years. The PFO closure trials showed 66% risk reductions in the interventional arm compared with medical treatment only; however, we ran the main analysis based on a hypothetical 33% risk reduction, which would take into consideration increased background risk of stroke due to other causes in the population aged 60 years or older, or a comparison with anticoagulation. For trials of PFO closure vs medical treatment, projected total trial sample size was 2160 (1080 per arm) with 33% risk reduction and 432 (216 per arm) with 66% risk reduction for trials of PFO closure vs medical treatment (eTable 3 in the Supplement).

Discussion

Our data suggest that age is a determinant of prognosis after cryptogenic TIA/stroke in patients with PFO who are receiving medical treatment alone. Reasons for this age-related increase in risk of recurrent stroke associated with PFO might include the increasing prevalence of venous thrombosis with age,⁵⁹ increasing pulmonary pathologic changes and right-ventricular pressure potentially uncovering latent or previously nonsignificant right-to-left shunts,¹¹ and increase in PFO size with age, albeit that PFO prevalence appears to decrease.⁶⁰ However, it cannot necessarily be assumed that the proportion of strokes that are causally related to PFO is maintained at older ages, as the prevalence of other causes of stroke will tend to increase with age. Nevertheless, we also found that the

relative risk of ischemic stroke in patients with cryptogenic TIA/stroke with vs without PFO was greatest at older ages.

Our systematic review included cohorts from both randomized and nonrandomized studies that included patients with cryptogenic TIA/stroke with PFO who were receiving only medical treatment. We found significant heterogeneity between studies in terms of absolute risk of recurrent stroke, which was mainly explained by the age of the patients. In addition, PFO closure trials^{2-5,26,27} suggested a lower absolute risk of stroke recurrence during medical treatment only (1.26 per 100 patient-years in our meta-analysis), while observational cohorts and nonclosure trials suggested a higher risk of 2.37. However, this difference was also mainly associated with the difference in the nature of the study, with mean age being significantly lower among closure trials (46.51 vs 51.79 years). Studies in which the mean age of the patients was 60 years or older included large randomized clinical trials, such as NAVIGATE ESUS²⁸ and RE-SPECT ESUS,²⁵ with overall mean ischemic stroke risk per 100 patient-years as high as 3.27—almost 3 times higher than the risk in PFO closure trials.

By comparing the risk of stroke recurrence in patients with vs without PFO stratified by age, we noted an apparent age-related excess risk of recurrent stroke conferred by PFO, with stroke risk associated with PFO being greater only in patients with PFO who were 65 years or older. This finding suggests that the increase in stroke risk with age in our main analysis of PFO cohorts is not simply due to the increase in the background vascular risk burden with age.²¹ The choice of a different age threshold of 65 years (as opposed to 60 years used in PFO trials) for our analysis of risk for PFO vs no PFO was related to the age thresholds reported in the studies included in the analysis.^{9,23,24}

Although randomized clinical trials of PFO closure showed benefit in younger patients, we did not find an increased risk

of stroke recurrence in younger patients with PFO. However, these findings are not inconsistent, but instead suggest that PFO-associated cryptogenic stroke in younger patients has a relatively low risk of recurrence, albeit lowered further by closure. It is also possible that increasingly effective medical treatment in more recent studies might be associated with reduced risks. Given the small numbers of studies and outcome events in this analysis, it is also possible that our study lacked statistical power to detect potentially clinically important associations reliably.

Older patients account for most strokes, and a previous study suggested that cryptogenic TIA/stroke associated with PFO at older ages is common,⁶ with an estimated number of 6000 cryptogenic TIA/nondisabling strokes every year in the UK in patients older than 60 years with large PFOs, suggesting that recruitment into future randomized clinical trials of PFO closure in the older population might be easier than it was for trials in the younger population. However, in our sample size calculation for possible future trials of PFO closure in the older population, we included a scenario in which the relative reduction in stroke risk with closure was smaller than reported in the previous trials in younger patients (33% risk reduction vs 66% reported for the younger population). In the older population, the increased background risk of stroke due to other causes, such as atrial fibrillation, could attenuate the benefit of PFO closure, as might preexisting anticoagulation for other conditions. Moreover, trials in the older population might show that PFO closure is higher risk than in younger patients,⁶¹ for example, owing to the potentially higher risk of procedure-related atrial fibrillation. However, similar concerns about the outcomes of other procedures at older ages have proved to be unfounded in the past.^{62,63} Either way, off-label closure outside clinical trials should not be routinely advocated for older patients.

Strengths and Limitations

Our study has a number of strengths. It included a large, population-based evaluation of the prognosis of patients with cryptogenic TIA/stroke and PFO who were receiving only medical treatment and a meta-analysis of all available data from trial and nontrial cohorts. However, our study has some limitations. First, we cannot rule out a bias in some of the studies included in the analysis, which could produce an artificially low risk of recurrent stroke in medically treated patients. It is clear in some of the observational studies^{22,31-33,37,38} that patients considered at high risk of recurrent stroke (presence of atrial septal aneurysm, large shunt, multiple index events) underwent percutaneous closure of PFO and were not therefore

included in the study of prognosis while receiving only medical treatment. This bias might be true even for PFO closure trials, which had slow enrollment owing to the wide offer of off-label PFO closure to patients.⁶⁴ It is therefore possible that our meta-analysis for patients receiving medical treatment underestimated the absolute risk of stroke. Moreover, because such inclusion bias might be greater in younger patients, it is possible that we may have overestimated the association between stroke risk and age. Second, we found a limited number of studies including older patients, so our meta-regression was based on fewer studies at older ages. However, some of these studies were large and contributed a significant number of patients and events.^{25,28} Third, assuming a 10% risk of recurrence over 5 years based on a rate of 2 per 100 patient-years could lead to an underestimated sample size calculation, as most of the included studies for the risk calculation did not reach 5 years of follow-up. Fourth, OxVasc Study participants with right-to-left shunt on bubble-TCD did not systematically undergo transesophageal echocardiography because of the absence of evidence on the benefit of PFO closure at the time of our study. Potentially, a small proportion of the right-to-left shunts found could be due to non-PFO sources, usually pulmonary shunts; however, most TCD-detected right-to-left shunts are shown to be due to PFO on transesophageal echocardiography.⁶⁵ Fifth, owing to the small number of recurrent events, the OxVasc Study did not have sufficient power to reliably determine whether the recurrence risk was greater after stroke than after TIA. Sixth, the data from the OxVasc Study may not be fully generalizable to routine clinical practice in all centers. In the OxVasc Study, patients are extensively investigated through prolonged 5-day ECG monitoring to detect occult paroxysmal atrial fibrillation, transthoracic echocardiography, and home telemetric blood pressure monitoring, and are treated equally aggressively with dual antiplatelet therapy at least for 1 month, followed by single antiplatelet therapy thereafter, and intensive therapy to lower blood pressure and cholesterol levels.

Conclusions

Increasing age is associated with a higher risk of ischemic stroke after cryptogenic TIA/stroke in patients with PFO. The findings of this study suggest that trials of PFO closure in secondary prevention of cryptogenic TIA/stroke at older ages are justified, although sample sizes would need to be large if the relative reduction in risk of recurrent stroke with closure is smaller than in previous trials of younger patients.

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Author Contributions: Drs Mazzucco and Rothwell had full access to all of the data in the study and

take responsibility for the integrity of the data and the accuracy of the data analysis.

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