

Age As a Determinant of Adverse Events in Medically Treated Cryptogenic Stroke Patients With Patent Foramen Ovale

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Background and Purpose—Patent foramen ovale (PFO) is associated with cryptogenic stroke. There is no study that assessed the effect of age on adverse event rates in cryptogenic stroke patients with PFO. The purpose of this retrospective analysis from PFO in Cryptogenic Stroke Study (PICSS) database was to assess the effect of age on the risk of adverse events in medically treated cryptogenic stroke patients with PFO.

Methods—250 cryptogenic stroke patients from PICSS were followed-up for 24 months, with death and recurrent ischemic stroke as primary endpoints. Hazard ratios were calculated for determination of relative risk in cryptogenic stroke patients with and without PFO in 3 age groups (younger than 55, 55 to 64, and 65 years or older).

Results—Among the 2 younger age groups, the presence of PFO did not significantly affect the risk of adverse events ($P=0.15$; hazard ratio=0.21; 95% CI, 0.02 to 1.78; 2-year event rates, 2.0% versus 9.3%; and $P=0.70$; hazard ratio=0.72; 95% CI, 0.14 to 3.73; 2-year event rates, 10.0% versus 13.9%). However, in those aged 65 years or older, the risk of adverse events was significantly higher in the patients with PFO ($P=0.01$; hazard ratio=3.21; 95% CI, 1.33 to 7.75; 2-year event rates 37.9% versus 14.5%).

Conclusions—In this exploratory analysis, the presence of PFO in the younger cryptogenic stroke patients did not increase the risk of adverse events. However, in the older patients, PFO significantly increased the risk of adverse events. (*Stroke*. 2004;35:2145-2149.)

Key Words: aspirin ■ echocardiography ■ stroke ■ warfarin

Patent foramen ovale (PFO) has been associated with stroke, particularly in young patients with cryptogenic stroke.^{1,2} For medically treated cryptogenic stroke patients with PFO, data on recurrent event rates are available for the younger patients,³⁻⁵ but there is no information on the event rates among older patients. We have recently shown in PFO in Cryptogenic Stroke Study (PICSS) that in the overall group of ischemic stroke patients receiving medical therapy, adverse event rates are similar between those with and without PFO.⁶ The patient population in PICSS was unique because, unlike previous studies, both younger and older cryptogenic stroke patients were included. In this retrospective study using PICSS data, we tested the hypothesis that the effect of the presence of PFO on the risk of adverse events differs by age.

Materials and Methods

Patient Recruitment

PICSS collaborated with Warfarin–Aspirin Recurrent Stroke Study (WARSS) for patient recruitment and follow-up.⁷ WARSS was a 48-center double-blind study that randomized 2206 stroke patients to

either warfarin or aspirin, with follow-up for stroke recurrence or death over a 24-month period. At each center, cryptogenic stroke patients in WARSS were solicited to undergo transesophageal echocardiography (TE). PICSS also included all WARSS patients that underwent TE for clinical purposes. All protocols for WARSS and PICSS were approved by the Institutional Review Board at each participating center.

Eligibility

Patients aged 30 to 85 deemed safe to undergo warfarin therapy were eligible. Eligible patients experienced ischemic stroke within the previous 30 days and rated ≥ 3 on the Glasgow Outcome Scale (severe disability, moderate disability, no or minimal disability).⁸ Ineligible patients had baseline international normalized ratio (INR) above the normal range (>1.4), stroke related to a procedure, attributable to cardioembolic source, or planned to undergo surgery for high-grade carotid stenosis. Patients with contraindication to TE were excluded from consideration for participation in PICSS.

Stroke Subtyping

All baseline strokes were subtyped by a local neurology primary investigator based on a predefined criteria set in the WARSS protocol, modeled after the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank and Trial of Org 10172 in Acute Stroke Therapy (TOAST).⁹ Subtypes were lacunar,

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large vessel, cryptogenic, other determined cause, and conflicting mechanisms. Cryptogenic strokes typically have no definite source of the stroke despite an adequate diagnostic evaluation.

Medications and Blinding

Medications used were aspirin (Sterling-Winthrop [now Bayer]) 325-mg tablets taken once daily and warfarin (duPont) in 2-mg scored tablets taken daily, adjusted to achieve and maintain INR 1.4 to 2.8. Patients were double-blindly randomized to active aspirin or warfarin, and to an identical placebo.

Follow-Up

All patients were followed-up for 2 years, operationalized as 24±1 months. Follow-up was made on a monthly basis by phone or in person to assess compliance and to regulate INRs. Quarterly and annual in-person follow-ups for detailed examination were also made.

TE Protocol

All patients underwent TE guided by a predefined PICSS protocol using either a biplane or a multiplane probe. The TE protocol emphasized delineation of TE-associated embolic sources, including extensive characterization of PFO. Saline contrast injection was performed at rest as well as with and without Valsalva maneuver or cough. Ongoing quality control was maintained with feedback to the site regarding TE study quality.

Analysis of Tapes

All TE tapes were analyzed by a single observer blinded to treatment assignment, stroke subtype, or outcome. PFO was determined to be present if on saline contrast injection there was appearance of at least 1 microbubble in left atrium within 3 cardiac cycles after opacification of right atrium.^{6,10,11} PFOs with either ≥2-mm separation of septum secundum and primum or ≥10 microbubbles appearing in the left atrium were classified as large. All other PFOs were classified as small.⁶

Assessment of Endpoints

The primary endpoint was recurrent ischemic stroke or death from any cause. Secondary endpoints included stroke, death or transient ischemic attack (TIA), stroke or TIA, and stroke. Clinical evidence of a recurrent ischemic stroke was a new lesion on CT or MRI, or when new lesions were absent or clinical syndrome consistent with stroke of >24 hours' duration. All clinical and radiological events were adjudicated independently by a panel blinded to treatment assignment.⁷

Statistical Analysis

Patients were divided into 3 age groups and categorized as to the presence or absence of PFO. Within each age group, differences between those with and without PFO for sociodemographic variables, stroke risk factors, and stroke characteristics were assessed by unpaired *t* test for continuous variables and by Fisher exact test for categorical variables. Kaplan–Meier curves were constructed and a Cox proportional hazards model was used to determine the relative hazard ratio and associated 95% confidence interval for PFO with patients stratified into different age groups. Differences in hazard ratios between age strata were assessed using indicator variables. Multivariate analyses were performed that included stroke risk factors that were differentially distributed between subjects with and without the exposure variable of interest within any of the age groups. Analyses were performed for the primary endpoint and each of the secondary endpoints. Reported 2-year event rates are point estimates derived from the Kaplan–Meier curves. *P*<0.05 was considered significant for all analyses.

Results

In PICSS, 630 patients were enrolled. After the planned 2 years of follow-up, endpoint status was known for 620

TABLE 1. Demographic and Stroke Risk Factors in Patients Aged Younger Than 55 Years With and Without PFO

Variable	PFO (N=49)	No PFO (N=54)	<i>P</i> *
Sociodemographic			
Age	42.9±7.0	44.5±6.6	0.24
Male (%)	28/49 (57.1)	28/54 (51.9)	0.69
Stroke characteristics (%)			
Glasgow score <5	7/49 (14.3)	19/54 (35.2)	0.02
Barthel score <95	7/49 (14.3)	11/54 (20.4)	0.45
Risk factors (%)			
Hypertension	13/49 (26.5)	21/54 (38.9)	0.21
Diabetes	4/49 (8.2)	9/54 (16.7)	0.24
Heart disease	6/49 (12.2)	8/54 (14.8)	0.78
Previous stroke	1/47 (2.1)	6/52 (11.5)	0.12
Current smoker	16/49 (32.7)	25/54 (46.3)	0.17
Sedentary	5/48 (10.4)	16/54 (29.6)	0.03
Obese	23/49 (46.9)	30/54 (55.6)	0.43
Heavy alcohol consumption	6/49 (12.2)	6/54 (11.1)	1.0
Moderate alcohol consumption	28/49 (57.1)	24/54 (44.4)	0.24
Treatment assignment: warfarin (%)	22/49 (44.9)	30/54 (55.6)	0.33

*PFO vs no PFO.

(98.4%). The remaining 10 (1.6%) withdrew consent or were lost to follow-up at a mean 13.2±10.5 months after randomization. There were 223 patients aged <55 years, 177 aged 55 or older to younger than 65 years, and 230 aged 65 years or older. When the strokes among the 630 PICSS patients were subtyped, 265 (42.1%) were cryptogenic and 365 (47.9%) were other subtypes (244 lacunar, 68 large vessel, 27 other determined cause, and 26 conflicting mechanism). Of 265 cryptogenic stroke patients, TE tapes for 15 were inadequate for analysis, leaving 250 patients for analysis in this study. There were 103 cryptogenic stroke patients aged younger than 55 years, 56 who were aged 55 to 64 years, and 91 aged 65 years or older. The mean INR in the warfarin-treated patients was 1.98±0.40 (median 2.0).

Endpoints

The analyses were adjusted for the 4 patients lost to follow-up using a prespecified imputation procedure.⁷ Using this model, the overall primary event rate was 12.8%. Among the 265 cryptogenic stroke patients, there were a total of 34 endpoints, including 24 strokes and 10 deaths. Additionally, 16 TIAs occurred, including 3 that occurred before the primary event.

Events According to Age and PFO Status

Sociodemographic factors for cryptogenic stroke patients in different age groups are shown in Tables 1, 2, and 3. As shown in Tables 4 and 5, the presence of PFO did not increase the risk of adverse events in the 2 younger age groups. This was the case with and without inclusion of TIA as an additional endpoint and when stroke and TIA, as well as stroke alone, were considered as separate endpoints. After adjusting for unevenly distributed variables that affect out-

TABLE 2. Demographic and Stroke Risk Factors in Patients Aged 55 to 64 Years With and Without PFO

Variable	PFO (N=20)	No PFO (N=36)	P*
Sociodemographic			
Age	60.0±3.2	60.2±3.1	0.78
Male (%)	15/20 (75.0)	24/36 (66.7)	0.56
Stroke characteristics (%)			
Glasgow score <5	6/20 (30.0)	12/36 (33.3)	1.0
Barthel score <95	3/20 (15.0)	12/36 (33.3)	0.21
Risk factors (%)			
Hypertension	8/20 (40.0)	22/33 (66.7)	0.09
Diabetes	3/19 (15.8)	11/36 (30.6)	0.33
Heart disease	4/20 (20.0)	6/36 (16.7)	0.73
Previous stroke	1/18 (5.6)	5/32 (15.6)	0.40
Current smoker	3/20 (15.0)	16/36 (44.4)	0.04
Sedentary	4/20 (20.0)	17/35 (48.6)	0.05
Obese	10/20 (50.0)	15/36 (41.7)	0.59
Heavy alcohol consumption	1/20 (5.0)	7/36 (19.4)	0.24
Moderate alcohol consumption	12/20 (60.0)	10/36 (27.8)	0.02
Treatment assignment: warfarin (%)	9/20 (45.0)	16/36 (44.4)	1.0

*PFO vs no PFO.

come (Glasgow score, moderate alcohol consumption, current smoking, and sedentary lifestyle), there were no significant differences in the findings.

However, as shown in Table 6, when the cryptogenic stroke patients with and without PFO were compared in those aged 65 years or older, there was a significantly increased risk of an adverse event in those with PFO. This was the case

TABLE 3. Demographic and Stroke Risk Factors in Patients Aged 65 Years or Older With and Without PFO

Variable	PFO (N=29)	No PFO (N=62)	P*
Sociodemographic			
Age	72.4±4.4	72.1±5.2	0.73
Male (%)	19/29 (65.5)	29/62 (46.7)	0.12
Stroke characteristics (%)			
Glasgow score <5	8/29 (27.6)	20/62 (32.3)	0.81
Barthel score <95	6/29 (20.7)	17/62 (27.4)	0.61
Risk factors (%)			
Hypertension	14/29 (48.3)	24/62 (38.7)	0.49
Diabetes	5/29 (17.2)	16/62 (25.8)	0.43
Heart disease	8/29 (27.6)	13/62 (21.0)	0.59
Previous stroke	4/28 (14.3)	7/56 (12.5)	1.0
Current smoker	5/29 (17.2)	8/62 (12.9)	0.75
Sedentary	14/28 (50.0)	26/62 (41.9)	0.50
Obese	11/29 (37.9)	25/62 (40.3)	1.0
Heavy alcohol consumption	2/29 (6.9)	5/62 (8.1)	1.0
Moderate alcohol consumption	14/29 (48.2)	24/62 (38.7)	0.49
Treatment assignment: warfarin (%)	11/29 (37.9)	26/62 (41.9)	0.82

*PFO vs no PFO.

TABLE 4. Hazard Ratios and 2-Year Adverse Event Rates in Patients Aged Younger Than 55 Years With and Without PFO

	PFO, % (N=49)	No PFO, % (N=54)	Hazard Ratio (95% CI)	P*
Death/stroke	2.0	9.3	0.21 (0.02–1.78)	0.15
			0.25 (0.03–2.14)	0.20
Death/stroke/TIA	12.2	16.7	0.68 (0.20–1.35)	0.47
			0.79 (0.28–2.26)	0.66
Stroke/TIA	12.2	16.7	0.68 (0.20–1.35)	0.47
			0.77 (0.26–2.13)	0.58
Stroke	2.0	9.3	0.21 (0.02–1.78)	0.15
			0.23 (0.03–1.96)	0.18

Values in **bold** are from multivariate model adjusting for sedentary lifestyle, moderate alcohol use, current smoking, and Glasgow score <5.

*PFO vs no PFO.

when TIA was included as an endpoint and when stroke and TIA, as well as stroke alone, were considered as separate endpoints. We also repeated the multivariate analyses including hypertension, diabetes, and previous stroke, along with the other risk factors already included. These analyses yielded similar results.

To assess if difference in PFO size played a role in these findings, we compared the prevalence of large PFO in the oldest age group to that in the younger groups; the prevalence of large PFOs was lower in the oldest group (63% in those younger than 55 years, 45% in those 55 to 64 years, and 34% in those 65 years or older; $P=0.01$ for trend). Thus the event rates in patients with PFO in the oldest age group was high despite the presence of smaller PFO. We also assessed INR in warfarin-treated patients in those with and without PFO in different age groups to determine if the variation in INR may have played a part in the outcome variation; there was no difference in INR achieved among different age groups.

Discussion

Although PFO has been associated with cryptogenic stroke in young patients, only a few studies have assessed the association of PFO with cryptogenic stroke in older patients. Several studies noted an association of PFO with cryptogenic

TABLE 5. Hazard Ratios and 2-Year Adverse Event Rates in Patients Aged 55 to 64 Years With and Without PFO

	PFO, % (N=20)	No PFO, % (N=36)	Hazard Ratio (95% CI)	P*
Death/stroke	10.0	13.9	0.72 (0.14–3.73)	0.70
			0.78 (0.14–4.28)	0.77
Death/stroke/TIA	10.0	16.7	0.59 (0.03–1.92)	0.52
			0.77 (0.15–4.01)	0.76
Stroke/TIA	5.0	13.9	0.36 (0.04–3.08)	0.35
			0.46 (0.05–4.13)	0.49
Stroke	5.0	11.1	0.46 (0.05–4.08)	0.48
			0.48 (0.05–4.57)	0.52

Values in **bold** are from multivariate model adjusting for sedentary lifestyle, moderate alcohol use, current smoking, and Glasgow score <5.

*PFO vs no PFO.

TABLE 6. Hazard Ratios and 2-Year Adverse Event Rates in Patients Aged 65 Years or Older With and Without PFO

	PFO, % (N=29)	No PFO, % (N=62)	Hazard Ratio (95% CI)	P*
Death/stroke	37.9	14.5	3.21 (1.33–7.75)†	0.01
			3.32 (1.36–8.10)†	0.01
Death/stroke/TIA	41.4	17.7	2.96 (1.30–6.72)†	0.01
			2.92 (1.28–6.68)	0.01
Stroke/TIA	31.0	11.3	3.43 (1.27–9.22)†	0.01
			3.32 (1.22–8.98)†	0.02
Stroke	27.6	8.1	4.14 (1.35–12.67)†	0.01
			4.21 (1.36–13.02)†	0.01

Values in **bold** are from multivariate model adjusting for sedentary lifestyle, moderate alcohol use, current smoking, and Glasgow score <5.

*PFO vs no PFO.

†P<0.05 vs patients younger than 55 years old.

stroke,^{2,12} whereas another did not.¹³ The effect of medical therapy in younger cryptogenic stroke patients with PFO has previously been reported.^{4,5} However, there are no studies that assessed the efficacy of medical therapy in older cryptogenic stroke patients with PFO. Thus we sought to determine if differences in age affected the risk of adverse events in medically treated cryptogenic stroke patients with PFO. PICSS presented a unique opportunity to assess the adverse event rates in older cryptogenic stroke patients with PFO because a large proportion of the enrolled patients were older patients. We chose to analyze the PFO effect in the 3 different age groups, including a group aged younger than 55 years, which is the age range of patients in recent studies evaluating the efficacy of medical therapy in patients with PFO.

When the effect of the presence of PFO was assessed in the cryptogenic stroke patients, we found that in younger patients, PFO did not increase the risk of adverse events. Our event rate of 2.0% over 2 years or 1.0% per year in those younger than 55 years is similar to the rates from the previously published reports. Mas et al report 13 deaths or strokes in 277 patients with PFO aged 55 or younger followed-up for an average of 38 months, or an annual event rate of 1.6%.⁵ Bogousslavsky et al report an annual rate of 2.4% for death or stroke in 140 patients younger than 60.⁴ These relatively low event rates in the younger patients may be caused by several factors; in younger patients, medical therapy with aspirin or warfarin may be effective or the event rate may be low even without the use of medication.

However, among the older patients compared with those without PFO, although demonstrating similar stroke risk factor profile, we find that older patients with PFO have a particularly high adverse event rate. In the older patients, the prevalence of factors contributing to paradoxical embolization may increase. Some studies have noted higher prevalence of thrombophilic disorders in cryptogenic stroke patients with PFO, hinting that the propensity for venous thrombosis may increase the chance of paradoxical embolization.^{14,15} Higher prevalence of deep venous thrombosis has been reported in some cryptogenic stroke patients with PFO.¹⁶ Older patients in general, and especially those who have had a stroke, have an increased propensity for venous thrombus formation be-

cause of the decreased physical activity level.^{17,18} Additionally, there are changes in the endothelial and platelet function, which may increase the chance for venous thrombus formation.^{19,20} As one ages, there is also an increase in right ventricular pressure that may predispose to right-to-left shunting in the presence of PFO.^{21,22} Thus the increased availability of potentially embolic material and hemodynamics favoring right-to-left shunt may contribute to the increased chance of paradoxical embolization in older patients.

The present study found that older cryptogenic stroke patients with PFO are at greater risk, whereas younger cryptogenic stroke patients with PFO are not. This finding implies that the effect of age on risk of stroke recurrence differs between patients with and without PFO. It is possible to demonstrate a significantly greater hazard ratio ($P=0.02$) per decade of age in cryptogenic stroke patients with PFO (hazard ratio=3.00; 95% CI, 1.66 to 5.37) compared with cryptogenic stroke patients without PFO (hazard ratio=1.34; 95% CI, 0.92 to 1.95).

Catheter or surgical closure of PFO has been used for potentially reducing recurrent event rates in cryptogenic stroke patients with PFO.^{23–25} Because of relative simplicity, the use of catheter closure has supplanted surgical closure.²⁶ Catheter closure studies without control groups have reported low recurrent event rates.^{24,25} However, it is important to note that patients enrolled in catheter closure studies are young patients and therefore are expected to have low event rates, as shown in our and other studies. Therefore, compared with medical therapy, efficacy of PFO closure to prevent recurrent events in the young cryptogenic stroke patients remains undefined and will require a large number of patients to compare their effectiveness. Additionally, because device placement may have an enhanced placebo effect, this factor needs to be carefully considered in the design of such a study.²⁷ However, in the older medically treated cryptogenic stroke patients with PFO, there appears to be a substantial risk deriving from the presence of PFO. As such, a trial to address the efficacy of PFO closure may need to focus on this particular group of patients.

This is the first study to our knowledge that attempts to compare the effect of age on the risk of adverse events in medically treated cryptogenic stroke patients with PFO. Patients were prospectively enrolled and treatment assignment was double-blindly. All patients were followed-up systematically and the echocardiograms were centrally blindly analyzed. In addition, we adjusted our analyses for any unevenly distributed variables that affect outcome. Also, we assessed a combination of different endpoints to exclude the possibility that non-neurological events accounted for the high event rates in older population. Furthermore, to exclude the possibility that large PFOs in an older population may have contributed to increased event rates, we compared the prevalence of large PFOs in different age groups. We also confirmed that INR were similar among all groups treated with warfarin.

However, there are inherent limitations in this study. First, the study group was chosen from patients enrolled in PICSS, which represented a subgroup of WARSS patients. Then, the analysis was not prespecified and the number of patients in

some of the groups was small. Additionally, we did not compare the efficacy of aspirin with warfarin in each age group because the number of patients became too small in each comparison group.

Conclusions

The effect of age on adverse event rates in cryptogenic stroke patients with PFO was assessed from patients enrolled in PICSS. Although the number of patients is small and the analysis is retrospective, we find that the presence of PFO in the younger cryptogenic stroke patients did not increase the risk of adverse events; however, in the older patients, PFO significantly increased the risk while medical therapy was being used.

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