RIVAROXABAN OR ASPIRIN FOR PATENT FORAMEN OVALE AND EMBOLIC STROKE OF UNDETERMINED SOURCE: PRESPECIFIED SUBGROUP ANALYSIS FROM THE NAVIGATE ESUS RANDOMISED TRIAL

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Abstract

Background: Patent foramen ovale (PFO) is a contributor to embolic stroke of undetermined source (ESUS). Subgroup analyses from prior studies suggest that anticoagulation could reduce recurrent stroke compared with antiplatelet therapy. We hypothesized that anticoagulant treatment with rivaroxaban, an oral factor-Xa inhibitor, would reduce the risk of recurrent stroke compared with aspirin among patients with PFO enrolled in the NAVIGATE-ESUS trial.

Methods: The NAVIGATE-ESUS double-blind, randomised trial assessed the efficacy and safety of rivaroxaban 15mg versus aspirin 100mg once daily for secondary stroke prevention in patients with ESUS. For this prespecified subgroup analysis, cohorts with and without PFO were defined based on transthoracic(TTE) and transesophageal echocardiography(TEE). The primary efficacy outcome was time-to-recurrent ischemic stroke between treatment groups. In addition, a systematic review of the literature incorporated prior studies in which patients with cryptogenic stroke and PFO were randomly assigned to anticoagulant or antiplatelet therapy.

Findings: 7213 participants were enrolled and followed for a mean of 11 months due to early trial termination. PFO was reported as present in 534 (7.4%) patients based on either TTE or TEE. Aspirin-assigned patients with PFO had a recurrent stroke rate of 4.8% per year. Among patients with known PFO, there was insufficient evidence to support a difference in hazards between rivaroxaban and aspirin (HR 0.54; 95%CI:0.22-1.36), while hazards were high similar for those without known PFO (HR 1.06; 95%CI:0.84-1.33); the interaction was not statistically significant (p=0.18). Major bleeding was likely increased with rivaroxaban compared with aspirin (HR 2.05; 95%CI:0.51-8.2) in patients with PFO. Systematic review that included 2 prior trials yielded a summary odds ratio of 0.48 (95%CI:0.24-0.96; p=0.04) in favour of anticoagulation, without evidence of heterogeneity.

Interpretation: Among patients with ESUS who have PFO, anticoagulation may reduce the risk of recurrent stroke by about half, though substantial imprecision remains. Dedicated trials of anticoagulation vs. antiplatelet therapy and/or PFO closure are warranted.

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Patent foramen ovale (PFO) is a potential cause of cryptogenic stroke. Device closure of PFO in patients with ischemic stroke has been tested in 6 randomised trials,[1-6] with 3 demonstrating significant reductions in the intention-to-treat analyses for recurrent stroke,[4-6] and meta-analyses supporting efficacy of closure compared with medical therapy.[7, 8] Notably, all but one of these trials allowed anticoagulation as an option for medical therapy, and the benefit of closure was observed predominantly in comparison to antiplatelet therapy, not to anticoagulants.[9, 10] Stroke related to PFO is primarily thought to be consequent to paradoxical embolism originating as venous thrombus and there are ample data indicating that anticoagulation is superior to antiplatelet agents for prevention and treatment of venous thromboembolism (VTE). [11]

Importantly, the PFO closure randomised trials only included subjects under 60 years of age.[1-6] The role of PFO in older patients is less clear.[12] Older patients are generally at increased risk of thrombosis, and some studies have suggested that PFO confers an increased risk of stroke in this group,[13] while others have suggested that PFO is more likely to be unrelated to stroke in older patients and therefore an innocent bystander.[14]

We aimed to compare antithrombotic strategies in a large cohort of subjects with PFO and cryptogenic ischemic stroke. The NAVIGATE ESUS trial compared rivaroxaban to aspirin in 7213 patients with embolic strokes of undetermined source (ESUS).[15] All patients were required to have echocardiography prior to enrollment, thereby providing an opportunity to explore the risk of recurrent stroke in a large cohort of patients with PFO. We hypothesized that those with PFO would have a lower risk of subsequent stroke if randomised to rivaroxaban rather than to aspirin. The NAVIGATE ESUS trial enrolled an older population than the closure trials, thereby allowing an analysis of the relationships among age, PFO, and stroke risk, in addition to the effects of antithrombotic treatment.

Methods

Study design: NAVIGATE ESUS (ClinicalTrials.gov: NCT02313909) was an international, double-blinded, randomised phase III trial conducted at 459 centers in 31 countries. The main hypothesis was that rivaroxaban would be superior to aspirin in reducing the risk of recurrent stroke and systemic embolism (the primary efficacy outcome) for patients with recent ESUS. The study rationale, additional design details, and participant features have been previously published.[15, 16] Patients were randomly allocated to either rivaroxaban or aspirin in a 1:1 ratio, stratified by country and by age <60 or ≥ 60 years. Each patient was given either rivaroxaban at a dose of 15 mg (immediate-release, film-coated tablets) plus placebo-aspirin or aspirin at a dose of 100 mg (enteric coated tablets) plus placebo-rivaroxaban; in each group, the two tablets (active drug and placebo) were to be taken orally once daily with food. Participants returned for study visits at 1, 6, and 12 months and then every 6 months during which there was assessment for the occurrence of safety and efficacy events, adherence, and adverse events. The protocol was approved by appropriate health authorities and institutional review boards at all study sites and all patients provided written informed consent prior to participation.

Study population: Patients with recent (between 7 days and 6 months) ischemic stroke confirmed by neuroimaging were eligible who met criteria for ESUS as proposed by the Cryptogenic Stroke / ESUS

International Working group,[17] with minor modifications. [15] In brief, participants were required to have an ischemic stroke visualized by neuroimaging that was not lacunar, documented absence of extracranial atherosclerosis causing >50% luminal stenosis in arteries supplying the area of ischemia (intracranial imaging was optional, but if done, >50% stenosis excluded participation), no major-risk cardioembolic source of embolism, and no other specific cause of stroke identified. Participants had to be >50 years-old at the time of qualifying stroke and, if between ages 50 to 59, were required to have at least one additional vascular risk factor. After the qualifying stroke, at least 20 hours of cardiac rhythm monitoring was required to exclude atrial fibrillation lasting >6 minutes, although investigators could choose to monitor for longer periods per local clinical practice standards. However, all cardiac rhythm monitoring must have been completed prior to randomisation (i.e. implantable loop recorders excluded participation). Patients diagnosed with PFO were eligible unless there were plans for closure. Notably, trials demonstrating efficacy of PFO closure were published only 1 week prior to the completion of enrollment in NAVIGATE ESUS, and therefore unlikely to have a relevant impact on recruitment into this trial.[2, 4, 5] Exclusion criteria included a history of atrial fibrillation, severely disabling stroke (modified Rankin score ≥4 at screening), the presence of, or plan to insert, an implantable ECG loop recorder, specific indication for chronic anticoagulation or for chronic antiplatelet therapy, or previous non-traumatic intracranial hemorrhage (see protocol[15] for complete list of exclusion criteria). Patients were enrolled from December 2014 to September 2017 and followed until trial termination in October 2017.

Assessment of PFO: Echocardiography was required for all patients prior to enrollment to assess for intracardiac thrombus (an exclusion criterion), but the protocol did not specify transthoracic (TTE) or transesophageal (TEE) echocardiography, nor did it require the performance or documentation of a "bubble" (agitated saline or echocardiographic contrast media) study. For either TTE or TEE, PFO was described as present, absent, or not reported. For these analyses, we dichotomized exposure as PFO present or not present. If TEE was performed and PFO was present, it was further characterized as small, large, or of uncertain size, and the presence or absence of atrial septal aneurysm was also recorded, both based on local interpretation. We therefore defined three partially-overlapping analytic cohorts: (1) patients with TTE, (2) patients with TEE, and (3) patients with TTE and/or TEE, with the latter being used for the primary analyses. Other diagnostic testing for PFO such as transcranial Doppler ultrasound with bubble study was not recorded.

Outcomes: The primary efficacy outcome of NAVIGATE ESUS was time to recurrent stroke (including ischemic, hemorrhagic or undefined strokes) or systemic embolism.[15] For this analysis, the primary efficacy outcome was time to recurrent ischemic stroke, to be consistent with other PFO trials. The primary safety outcome was major bleeding according to the criteria of the International Society of Thrombosis and Haemostasis.[18] Potential efficacy and safety outcome events were verified by a blinded adjudication process.

Statistical analysis: The NAVIGATE ESUS trial was terminated early at the recommendation of the data monitoring committee due to absence of efficacy for stroke prevention coupled with an increase in major bleeding associated with rivaroxaban.[15] A pre-specified subgroup analysis of the effect of antithrombotic treatments among patients with PFO was planned prior to completion of the trial. We expected that PFO would be detected in about 40% of subjects who were equally randomised into both

arms, and assumed a 4% annual stroke rate on aspirin over an average of 2 years of follow-up, which would provide 80% power with α of 0.05 to detect at least 34% lower hazard of stroke with rivaroxaban. Due to early termination of the trial, fewer events were observed than anticipated.

The primary analyses were based on the intent-to-treat population. Sensitivity analysis was also performed using an on-treatment analysis.[15] Time-to-recurrent ischemic stroke between treatment groups was compared with a log-rank test, and Kaplan-Meier estimates were used to plot the cumulative incidence risk over time. Risk reduction was estimated with the Cox proportional hazards model. Comparisons by randomized treatment assignment were not adjusted for any covariates. The comparison of event rates in the PFO group vs. the no PFO group were presented both unadjusted and adjusted for age and vascular risk factors. All reported P values are two-sided. We did not adjust for multiplicity in these exploratory analyses.

In addition, a systematic review of the literature was undertaken to identify prior studies in which patients with cryptogenic stroke and PFO confirmed by TEE were randomly assigned to treatment with an anticoagulant or antiplatelet therapy, and reported the risk of recurrent stroke. We employed the following search strategy in MEDLINE on May 17, 2018: ("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND (PFO[All Fields] OR ("foramen ovale"[MeSH Terms] OR ("foramen"[All Fields] AND "ovale"[All Fields]) OR "foramen ovale"[All Fields])) AND (anticoagulation[All Fields] OR ("warfarin"[MeSH Terms] OR "warfarin"[All Fields])) AND (("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields]) OR ("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "randomised"[All Fields])). We also reviewed references lists and asked experts in the field to identify any additional studies. We then performed a random-effects meta-analysis of these studies along with the data from our TEE cohort.

Role of the funding source: The study sponsors participated in the design of the parent NAVIGATE ESUS trial along with the investigators. Two of the coauthors are employed by the sponsors. The sponsors were not otherwise involved in the design, analysis, or interpretation of this PFO cohort subgroup analysis. The sponsors had the opportunity to review the manuscript and to provide optional suggestions, but sponsor approval was not required. The sponsor had no other role in the writing of this report nor in the decision to submit it for publication.

Results

Among 7213 patients enrolled in NAVIGATE ESUS, TTE was performed in 6884, TEE in 1382, and either TTE or TEE in 7210 (including both in 1056) (Supplemental Figure F1). Echocardiographic information was missing for 3 patients. PFO was reported as present in 534 (7.4%) patients based on either TTE or TEE. Notably, PFO was detected in 313 (4.6%) based on TTE but 379 (27.4%) based on TEE. Baseline characteristics based on TTE and/or TEE are summarized in Table 1 (with the separate TTE and TEE cohorts in Supplemental Tables S1 and S2). Patients with PFO were younger, had a lower burden of traditional vascular risk factors, and had less severe strokes than those without PFO. There were also global regional differences in the detection of PFO, with higher rates of detection in the USA, Canada, and Western Europe compared with elsewhere (Supplemental Table S3).

Recurrent ischemic stroke occurred at a rate of 3.7 events per 100 person-years among patients with PFO on TTE and/or TEE, compared with 4.8 events per 100 person-years in those without evidence of PFO (unadjusted HR=0.80, 95%CI: 0.51-1.26; p=0.33, after adjustment for age, hypertension, diabetes, coronary disease, and heart failure HR=0.84, 95%CI: 0.53-1.32; p=0.44). In the PFO group, 70% of the recurrent ischemic strokes were classified as recurrent ESUS and involved cerebral and/or cerebellar cortex (Table 3). About 20% of recurrent ischemic strokes were potentially disabling with a modified Rankin score >2 at 7 days or discharge.

In the overall NAVIGATE ESUS study, there was no difference in the risk of recurrent ischemic stroke with rivaroxaban compared to aspirin (hazard ratio [HR] 1.07; 95% confidence interval [CI]: 0.87-1.33, p=0.52). Due to early termination of the trial, the anticipated statistical power required for our analyses was not achieved, and a post hoc calculation based on the observed effects indicated only 45% power. With this caveat, there appeared to be effect modification in relation to PFO (Table 2 and Figure 1). Among patients with PFO detected by either TTE or TEE, there was insufficient evidence to support a difference in the risk of recurrent ischemic stroke with rivaroxaban compared with aspirin (HR 0.54; 95%CI: 0.22-1.36). There was no difference between treatments for those without known PFO (HR 1.06; 95%CI: 0.84-1.33). The interaction between PFO and treatment was not statistically significant (p=0.18). We observed consistent effect sizes of rivaroxaban versus aspirin for the outcome of recurrent ESUS (Supplemental Table S4). We also performed an on-treatment analysis with no difference in results (Supplemental Table S5).

Given the modest number of recurrent events, we were limited in the assessment of potential prognostic factors for stroke related to PFO such as size, atrial septal aneurysm, and risk of paradoxical embolism (RoPE) score, which are summarized in Table 2. However, there was an apparent divergent treatment effect of age among those with PFO, with a benefit of rivaroxaban suggested mainly among those over the age of 60 years.

When these analyses were repeated based on TTE alone or TEE alone, or for the outcome of recurrent ESUS, the results were consistent (Supplemental Tables S6 and S7).

Atrial fibrillation was detected during follow-up at a rate of 2.4 events per 100 person-years among patients with PFO detected by either TTE or TEE compared to 3.7 per 100 person-years in those without PFO (HR 0.65; 95%CI:0.37-1.13, see Supplemental Table S8), with similar rates of AF detection in all three cohorts. The risks of major bleeding with rivaroxaban compared to aspirin were similar in patients with PFO (HR 2.05; 95%CI:0.51-8.2) and without PFO (HR 2.82; 95%CI: 1.69-4.7) (interaction p=0.68, Supplemental Table S9).

Systematic review and meta-analysis

Systematic review of the literature identified 62 published studies. Only 2 prior trials enrolled patients with cryptogenic stroke who had PFO confirmed by TEE, performed a randomised comparison of anticoagulation vs. antiplatelet therapy, and reported the outcome of ischemic stroke. The PFO in Cryptogenic Stroke Study (PICSS) trial included a cohort of 98 cryptogenic stroke patients who were randomly assigned to warfarin vs. aspirin.[19] The Patent Foramen Ovale Closure or Anticoagulants versus

Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) included a cohort of 361 patients who were randomly allocated to anticoagulation or antiplatelet therapy, with the choice of medication within each category left to the treating physician (93% on anticoagulation were given vitamin K antagonists).[5] These two studies, along with 379 patients with PFO in the TEE cohort from NAVIGATE ESUS, yielded highly concordant results and were combined in a random-effects meta-analysis. The summary OR was 0.48 (95%CI: 0.24-0.96; p=0.04) in favour of anticoagulation among patients with PFO, without evidence of heterogeneity (I^2=0%) (Figure 2 and Supplemental Table S10).

Discussion

Patients with embolic stroke of undetermined source with PFO who were enrolled in the NAVIGATE ESUS trial were younger and had fewer vascular risk factors than those without an identified PFO, suggesting that they are a specific subset of the larger ESUS population that may be pathophysiologically distinct.[14] Nevertheless, these patients had a high risk of recurrent stroke, similar to the overall ESUS population, and greater than that in younger patients (< 60 years) enrolled in the PFO closure trials. The rate of recurrent stroke was not significantly lower in PFO patients receiving rivaroxaban, nor was there a significant interaction in treatment effect according to PFO status. Because the NAVIGATE ESUS trial was terminated early at the recommendation of the data monitoring committee, the power of this study was limited. Combined with data from prior randomised trials, although each also had limited power, our meta-analysis estimates that anticoagulation may reduce recurrent stroke in patients with PFO and ESUS by about half, though substantial imprecision remains. This result was also similar to meta-analyses based on non-randomised comparisons.[10]

Age may be a pertinent factor in the role of anticoagulants for PFO.[13, 20] We did not find significant treatment interaction by age, again possibly owing to limited power, but point estimates suggested a benefit in the older group. Notably, while there has been a possible association reported between the risk of atrial fibrillation and PFO,[21] we did not find any such relationship in this cohort, suggesting that this is not the mechanism by which PFO patients might benefit from anticoagulation. Older patients may be exposed to higher risk of venous thromboembolism due to reduced physical activity and comorbidities, and therefore may be more likely to benefit from an anticoagulation strategy.[22] The efficacy and safety of PFO closure has been demonstrated in younger patients, and may not necessarily apply to this older group.[23] A recent meta-analysis of randomised trials of percutaneous closure of PFO indicated that percutaneous closure was superior to aspirin therapy, but not clearly superior to anticoagulation.[9] Further, some patients with paradoxical embolism might be at risk of future venous thromboembolism or pulmonary embolism, which would not be prevented with closure.

In the NAVIGATE ESUS trial, PFO was underdetected, particularly when TTE was used alone, because the use of a bubble study was not mandated by protocol or recorded. Among those who underwent TEE, PFO was identified in 27%, a prevalence slightly greater than that observed in the general population[24, 25] and similar to older populations with cryptogenic stroke.[12, 20, 26] There were notable regional differences in PFO detection by echocardiography, suggesting variations in practice in the evaluation of cryptogenic stroke. These differences could be related to the availability of resources for diagnostic testing or

variability in opinion about the importance of detecting PFO in this population, especially prior to the results of the recent closure trials.

Our study has strengths and limitations. The major strength is the randomised comparison of anticoagulation vs. antiplatelet therapy in a pre-specified subgroup of interest. Results of subgroup analyses of negative trials, even those that are pre-specified, must be interpreted with caution.[27, 28] The NAVIGATE ESUS trial required echocardiography for all subjects, but did not require a standardized approach to the diagnosis of PFO, and therefore we very likely underestimated the prevalence of PFO. We may also have been more likely to detect larger PFOs. Some sites may have used transcranial Doppler to detect PFO, but this information was not collected. This type of misclassification likely biases our results toward the null, though the effect size is comparable to prior research in which PFO was specifically evaluated. [5, 19] The early termination of the trial dramatically truncated our planned period of follow-up and yielded a lower number of events than anticipated, reducing power to only 51%. Statistical tests for interactions typically offer limited power as well. Moreover, our meta-analysis included only 3 trials over a 20-year span with relatively few events, and there were likely changes in diagnosis and treatment during this period that may limit the validity of data pooling, though the lack of heterogeneity is reassuring.

We conclude that patients meeting criteria for ESUS and who have PFO represent an identifiable group of patients for whom further trials of anticoagulation vs. antiplatelet therapy and/or PFO closure are warranted.

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Table 1. Baseline characteristics by patent foramen ovale Identified by either transthoracic or transesophageal echocardiography

Characteristic	PFO detected (N=534)	PFO not detected (N=6675)*
Age, years (mean ± s.d.)	64.6 ± 9.2	67.1 ± 9.8
Age<60 years	30 %	23 %
Male sex	63 %	61 %
Race:		
White only	69 %	73 %
Black only	1 %	2 %
East Asian only	19 %	20 %
Others (includes not reported/multiracial)	11 %	6 %
BMI, kg/m^2 (mean ± s.d.)	26.9 ± 5.0	27.3 ± 5.0
Weight, kg (mean ± s.d.)	77.0 ± 16.4	76.1 ± 16.5
Estimated glomerular filtration rate (eGFR), mL/min per 1.73 m^2	78.4 ± 19.3	78.6 ± 20.6
Medical history:		
Hypertension	67 %	78 %
Diabetes mellitus	18 %	26 %
Current tobacco use	20 %	21 %
Coronary artery disease	4 %	7 %
Heart failure	1 %	3 %
Cancer	6 %	9 %
Prior stroke or TIA	17 %	17 %
Global region:		

Characteristic	PFO detected (N=534)	PFO not detected (N=6675)*
U.S.A. and Canada	18 %	12 %
Latin America	6 %	11 %
Western Europe	51 %	42 %
Eastern Europe	7 %	16 %
East Asia	19 %	19 %
Qualifying stroke:		
Clinical TIA with imaging-confirmed infarction as qualifying event:	13 %	7 %
Arterial territory of qualifying stroke:		
Anterior circulation	71 %	72 %
Posterior circulation	33 %	31 %
Location of qualifying stroke:		
Single Location:		
Cerebral hemisphere with cortical involvement	60 %	56 %
Cerebral hemisphere, subcortical only	15 %	22 %
Brainstem only	4 %	5 %
Cerebellum only	9 %	8 %
Multiple Locations:	13 %	10 %
Chronic infarct on imaging (in addition to index stroke)	26 %	33 %
Aspirin use prior to qualifying stroke	15 %	18 %
Statin use prior to randomisation	61 %	62 %
Treated with intravenous tPA for qualifying stroke	23 %	17 %
Treated with endovascular intervention for qualifying stroke	5 %	4 %

Characteristic	PFO detected (N=534)	PFO not detected (N=6675)*
NIHSS score at randomisation (median, IQR)	0.0 (0.0, 1.0)	1.0 (0.0, 2.0)
NIHSS score ≤5	98 %	96 %
Modified Rankin Scale (mRS) at randomisation:		
mRS 0 or 1	73 %	64 %
mRS 2	20 %	23 %
mRS ≥3	7 %	12 %
MoCA score at randomisation (median, IQR)	26.0 (23.0, 28.0)	24.0 (21.0, 27.0)
Time from qualifying stroke to randomisation, days (median, IQR)	39.5 (15.0, 98.0)	36.0 (14.0, 87.0)
Extracranial vascular imaging completed:		
CTA	43 %	38 %
MRA	46 %	32 %
Carotid ultrasound	57 %	64 %
Conventional angiography	2 %	2 %
Intracranial vascular imaging completed:	90%	77%
Duration of cardiac rhythm monitoring ≥48 hours	48 %	33 %

Table 2. Recurrent strokes in cohort evaluated with transthoracic and/or transesophageal echocardiography

	Rivaroxaban-assigned (N=3609)		Aspirin-assigned (N=3604)			
Subgroup	**No. Rand**	**No. Events (Event Rate*)**	**No. Rand**	**No. Events (Event Rate*)**	**Hazard Ratio (95% CI)****	**P value (interaction)****
Overall[+]	3607	159 (4.7)	3602	156 (4.7)	1.02 (0.82, 1.27)	0.86
Presence of PFO(TTE or TEE)						
- Present[1]	259	7 (2.6)	275	13 (4.8)	0.54 (0.22, 1.36)	
- Absent/Not reported[2]	3348	152 (4.9)	3327	143 (4.6)	1.06 (0.84, 1.33)	0.18
Size of PFO[1]						
- Large	23	0 (0.0)	25	2 (9.4)	N/A	
- Small	112	6 (4.5)	112	8 (6.6)	0.68 (0.24, 1.97)	N/A
Arterial septal aneurysm reported[1]						
- Yes	31	0 (0.0)	40	3 (6.7)	N/A	
- No	151	7 (4.4)	157	9 (6.0)	0.75 (0.28, 2.02)	N/A
ROPE score[2]						
- 0-4	118	5 (4.1)	135	4 (2.9)	1.32 (0.35, 4.94)	
- 5-10	141	2 (1.4)	140	9 (6.8)	0.21 (0.05, 0.98)	0.07
Age (years)[3]						
- <60	77	4 (5.1)	85	3 (3.8)	1.42 (0.32, 6.34)	
- 60 - <70	103	2 (1.9)	108	7 (6.9)	0.29 (0.06, 1.39)	
- ≥70	79	1 (1.2)	82	3 (3.5)	0.34 (0.03, 3.25)	0.30

* Event rates reported per 100 person-years

** Hazard Ratio, 95% CI, and p for interaction not reported if Hazard Ratio is ≥10 or cannot be computed

+ Among participants who reported information (presence/absence) on PFO using either TTE or TEE. Excludes those not reported (n=4).

1 Information available only when PFO is identified using TEE

2 ROPE score calculated only if PFO present

3 Observed only among PFO (+) participants using the diagnostic test mentioned in the table title.

Table 3. Features of recurrent strokes in cohort evaluated with transthoracic and/or transesophageal echocardiography

	PFO detected (n=20)	PFO not detected (n=295)	P value
Recurrent strokes	20	295	0.46
Topography:			
Deep only[1]	6 (30%)	100 (34%)	0.44
All others	14 (70%)	158 (54%)	
Subtype:			
ESUS	14 (70%)	144 (49%)	0.07
Non-ESUS	6 (30%)	151 (51%)	
Outcome at 7 days or discharge:			
mRS≤2	16 (80%)	182 (65%)	0.16
mRS>2	4 (20%)[2]	100 (35%)	

[1] Deep only = subcortical only or brainstem only, All others = any cortical, any cerebellum, multiple, etc.

[2] Of the 4 disabling strokes, 3 occurred on rivaroxaban and 1 on aspirin

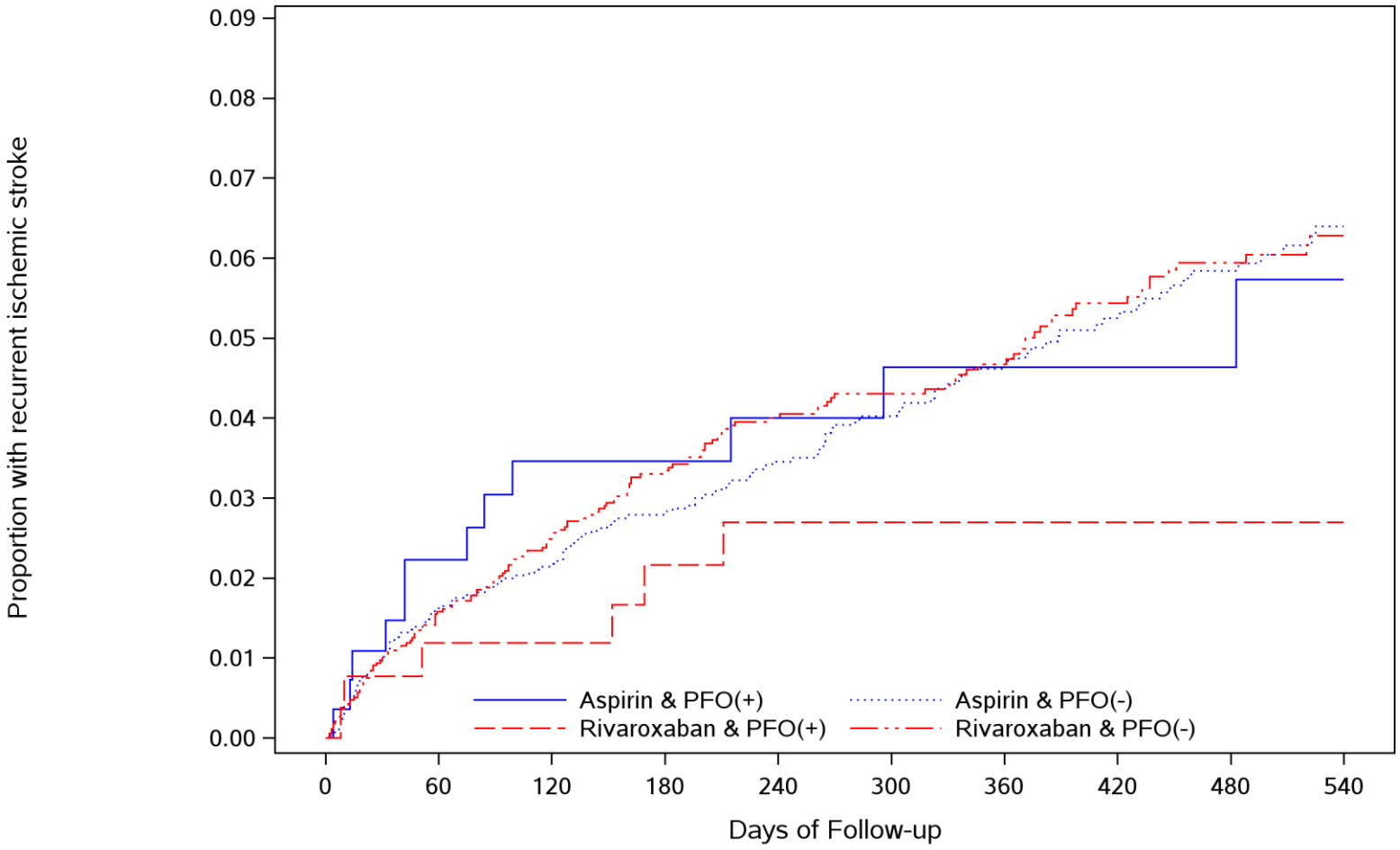
Figure Legends

Figure 1. Cumulative incidence of recurrent ischemic stroke according to treatment assignment

Figure 2. Meta-analysis of randomised comparisons of anticoagulation or antiplatelet therapy for patent foramen ovale

Figure 1. Kaplan-Meier curve for time to recurrent ischemic stroke

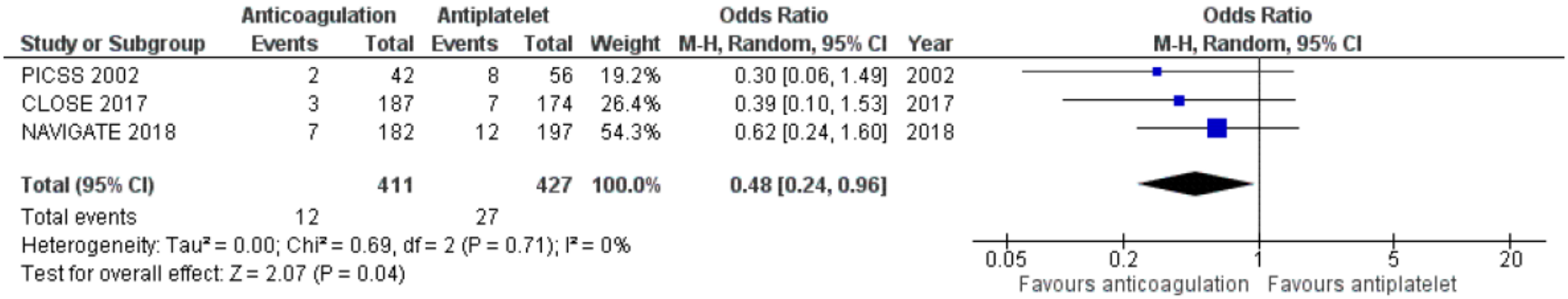
Figure 1. Kaplan-Meier curves for time to recurrent ischemic stroke by treatment and PFO status



No. at risk:

Aspirin & PFO(+)	275	248	223	194	169	150	132	110	87	65
Aspirin & PFO(-)	3327	2957	2637	2340	1999	1732	1449	1211	950	715
Rivaroxaban & PFO(+)	259	234	213	194	171	150	131	112	92	75
Rivaroxaban & PFO(-)	3348	2978	2642	2334	1989	1729	1456	1194	955	711

Figure 2. Meta-analysis of randomised comparisons of anticoagulation or antiplatelet therapy for patent foramen ovale



Research in context

Evidence before this study:

We searched MEDLINE up to May 2018 for randomised controlled trials comparing anticoagulant to antiplatelet therapy for secondary stroke prevention in patients with cryptogenic ischemic stroke and patent foramen ovale (PFO). Several showed that PFO closure was superior to medical therapy for the prevention of stroke in patients under 60 years of age, but only two included direct randomised comparisons of anticoagulation vs. antiplatelet therapy.

Added value of this study

The NAVIGATE ESUS trial was a large randomised clinical trial that compared anticoagulation using rivaroxaban with antiplatelet therapy using aspirin in patients with embolic stroke of undetermined source (ESUS). It was terminated early due to lack of efficacy in the overall study population. This prespecified subgroup analysis evaluated the treatment effect in patients with PFO, and found a strong suggestion that rivaroxaban lowered the risk of recurrent stroke compared to aspirin, though the result in this study alone did not reach statistical significance. When combined with prior randomised trial data, the strategy of anticoagulation significantly reduced the risk of recurrent stroke by about half.

Implications of all the available evidence

The efficacy of anticoagulation for stroke prevention in patients with cryptogenic stroke and PFO has not been established, but existing data suggest that this strategy should be further evaluated in dedicated randomised trials. Anticoagulation may be a preferred option for older patients who were not studied in prior trials or for patients who are averse to device implantation.

Authors' contributions

Scott E. Kasner, MD--steering committee member, data interpretation, drafted manuscript, literature search
Balakumar Swaminathan, MSc--data analysis
Pablo Lavados, MD MPH--steering committee member, data collection, critical review
Mukul Sharma, MD MSc--steering committee member, data collection, critical review
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Ashkan Shoamanesh, MD--data collection, critical review
Scott D. Berkowitz, MD—sponsor, critical review
Hardi Mundl, MD—sponsor, critical review
Stuart J. Connolly, MD—NAVIGATE ESUS trial PI, critical review
Robert G. Hart, MD—NAVIGATE ESUS trial PI, critical review

Declarations of interests

Dr. Ameriso reports grants from Bayer and Janssen during the conduct of the study.
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Dr. Berkowitz reports employment by Bayer during the conduct of the study.
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Mr. Swaminathan has nothing to disclose.
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