European Heart Journal (2016) **37**, 2029–2036
doi:10.1093/eurheartj/ehw027

Percutaneous closure of patent foramen ovale in migraine with aura, a randomized controlled trial

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Received 28 December 2015; revised 10 January 2016; accepted 20 January 2016; online publish-ahead-of-print 22 February 2016

See page 2037 for the editorial comment on this article (doi:10.1093/eurheartj/ehw088)

Aims Migraine with aura and patent foramen ovale (PFO) are associated. The Percutaneous Closure of PFO in Migraine with Aura (PRIMA) trial is a multicentre, randomized trial to investigate the effect of percutaneous PFO closure in patients refractory to medical treatment.

Methods Migraine with aura patients and PFO who were unresponsive to preventive medications were randomized to PFO closure or medical treatment. Both groups were given acetylsalicylic acid 75–100 mg/day for 6 months and clopidogrel 75 mg/day for 3 months. The primary endpoint was reduction in monthly migraine days during months 9–12 after randomization compared with a 3-month baseline phase before randomization. The committee reviewing the headache diaries were blinded to treatment assignment.

Results One hundred and seven patients were randomly allocated to treatment with an Amplatzer PFO Occluder ($N = 53$) or control with medical management ($N = 54$). The trial was terminated prematurely because of slow enrolment. Eighty-three patients (40 occluder, 43 control) completed 12-month follow-up. Mean migraine days at baseline were 8 (± 4.7 SD) in the closure group and 8.3 (± 2.4) in controls. The primary endpoint was negative with -2.9 days after PFO closure vs. -1.7 days in control group ($P = 0.17$). Patent foramen ovale closure caused five adverse events without permanent sequelae.

Conclusion In patients with refractory migraine with aura and PFO, PFO closure did not reduce overall monthly migraine days.

Keywords Migraine • Migraine with aura • Patent foramen ovale • Patent foramen ovale closure

Introduction

Migraine is a complex disease and has an estimated prevalence of 8–13% in the western population.[1,2] Hence, >55 million Europeans and Americans suffer from migraine. One in three subjects with migraine has at least occasional migraine attacks with aura. The neurological symptoms of a migraine aura are likely related to a self-propagating wave of cortical excitation followed by temporary depression of neuronal activity, a phenomenon called cortical spreading depression (CSD).[3]

Several studies have indicated an increased prevalence of patent foramen ovale (PFO) in migraine patients with aura, and vice versa, an increased prevalence of migraine with or without aura in subjects with PFO.[4,5] Percutaneous closure of a PFO or a secundum atrial septal defect for secondary prevention of paradoxical embolism has been reported to reduce migraine frequency more often than to increase it

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in subjects with concomitant migraine with aura or to induce new onset migraine.[6–10] This argues in favour of a causal link. Observational studies also showed a reduction of migraine frequency with oral anticoagulation and low-dose acetylsalicylic acid.[11–13] In the experimental setting, CSD can be initiated by focal hypoxia.[3] These observations gave rise to the hypothesis of paradoxical microembolism as a potential trigger mechanism for migraine attacks. Serotonin release in the venous circulation with shunt-induced arterial peaks was also considered as a potential mechanism.[14]

On average, migraine patients are unable to function properly due to headache for 3 days in any 3-month period.[15] Migraine affects quality of life and impairs work, social activities, and family life. This calls for effective treatment.[16] On that basis, we embarked on the Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura (PRIMA) trial to test percutaneous PFO closure as a means of migraine prophylaxis.

Methods

Study design, purpose, and oversight

The PRIMA trial is a multicentre, prospective, randomized, open label, international trial with blinded endpoint evaluation (PROBE design) performed at 20 centres in Canada, Germany, Switzerland, and the UK. The purpose was to evaluate whether percutaneous PFO closure is effective in reducing migraine headaches in patients diagnosed with migraine with aura who are refractory to medical treatment.

The steering committee members (Supplementary material online, *Appendix*) designed the trial based on a preliminary protocol of the Bern University Hospital, Bern, Switzerland. The trial was funded by St. Jude Medical, Plymouth, MN, USA, the manufacturer of the Amplatzer PFO Occluder used as closure device. All trial administrative functions were the responsibility of the sponsor which also provided clinical trial supplies. In addition to the steering committee, an independent data and safety monitoring board, an endpoint review committee, and an echocardiography core laboratory met periodically to ensure the overall integrity of the trial conduct and evaluation of trial results (Supplementary material online, *Appendix*). The headache specialists assessing the headache diary in the endpoint review committee were blinded to the treatment assignment and had no contact with patients. Additionally, external vendors were used to announce the trial and screen potential participants.

The members of the steering committee had access to the data as adjudicated by the other committees and as compiled by the sponsor. The manuscript was drafted by HPM and co-edited and approved by all authors. The study was conducted in accordance with the Declaration of Helsinki and each site obtained approval by the responsible ethics committee. All patients provided written informed consent.

Patients and randomization

Patients with migraine with aura diagnosed by a neurologist according to the criteria of the International Headache Society (2nd edition) were eligible if their migraine appeared before 50 years of age, if they experienced in a 3-month baseline phase either a minimum of three migraine attacks or five migraine headache days per month and <15 headache days per month, and if they were unresponsive to two commonly applied preventive medications.[17] In addition, they had to be willing to accept randomization to PFO closure, if applicable, and comply with a headache diary and follow-up visits (*Figure 1*). For a full list of inclusion and exclusion criteria, see Supplementary material online, *Table S1* or the trial protocol (http://www.neurologie.insel.ch/de/forschung/neuro-clinical-trial-unit-nctu/).

At a second visit, transcranial Doppler sonography or echocardiography with intravenous saline/air or other contrast medium injection at the end of a sustained Valsalva manoeuvre was used to screen for a right-to-left shunt. If positive, a PFO had to be documented using contrast transoesophageal echocardiography with Valsalva manoeuvre (TOE) as previously described.[18]

At a third visit, the neurologist reviewed the headache diary and the medication history of at least 3 months. In addition, disability due to migraine, quality of life, and depression were assessed using the Migraine Disability Assessment Questionnaire (MIDAS),[19] Quality of Life Questionnaire SF12v2,[20] and the Beck Depression Inventory (BDI).[21]

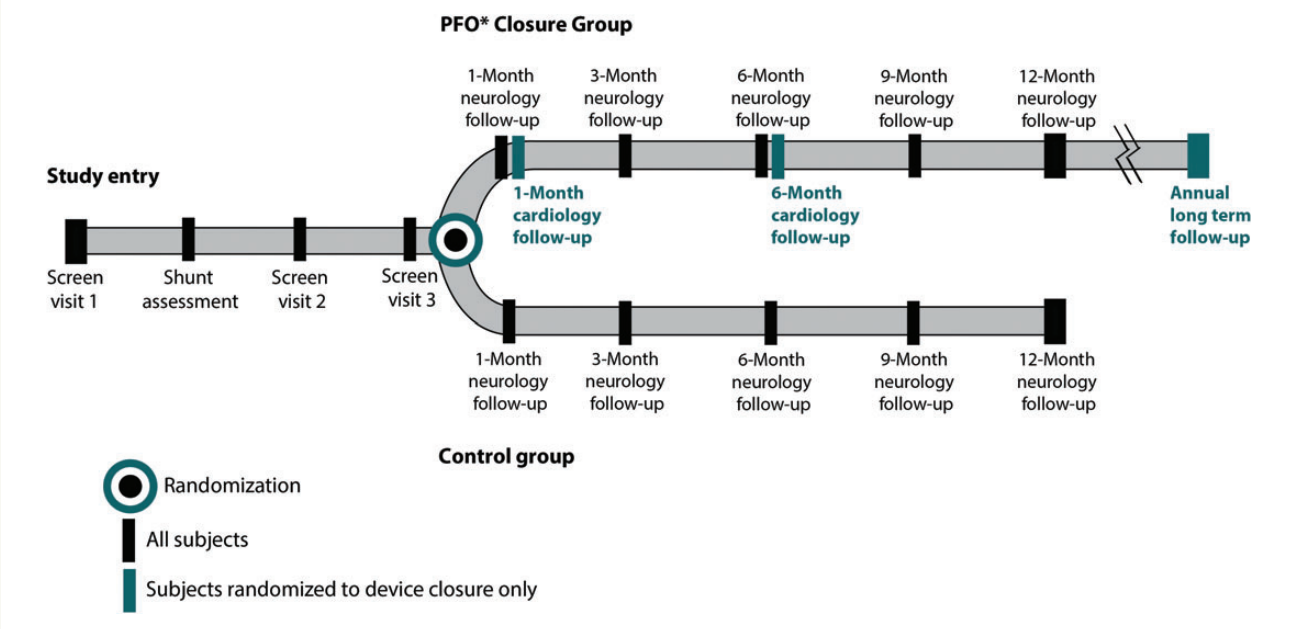

Figure 1 PRIMA trial design. *Patent foramen ovale.

Enrolled patients were randomized 1:1 to percutaneous PFO closure or medical management with stratification by sex and age (<30, 30–40, or >40 years) after the 90-day screening phase headache diary had been completed and all inclusion criteria were met. Index cards printed with the stratification subgroup and randomization assignment were kept in sealed envelopes. At randomization, a member of the trial team opened the first envelope for the appropriate group to obtain the randomized assignment and informed the requesting physician. Persons adjudicating the endpoints were blinded as to the intervention in contrast to the patients.

Study procedures and treatment

Within 14 days of randomization patients of both treatment groups were given acetylsalicylic acid 75–100 mg/day for 6 months and clopidogrel 75 mg/day for 3 months. Patients in the PFO closure group were then generally admitted on the day of the device implantation and discharged the same or the following day. Device implantation was guided by fluoroscopy with or without transoesophageal or intracardiac echocardiography. Prophylactic antibiotic therapy during the periprocedural period and endocarditis prophylaxis for 6 months were recommended. Changes in preventive migraine medication type, dose, or frequency were discouraged throughout the course of the trial. Follow-up visits occurred at 1, 3, 6, 9, and 12 months. Additionally, PFO closure group patients underwent TOE after 6 months and if the PFO was not completely closed TOE was repeated at the 12-month visit. Patent foramen ovale closure group patients continued follow-up visits annually until all patients had completed the 12-month follow-up.

Study endpoints

The primary endpoint was reduction in monthly migraine days during months 9–12 after randomization compared with a 3-month baseline phase before randomization. This and pre-specified secondary endpoints for intention-to-treat analysis are listed in Supplementary material online, *Table S2*. In an additional *post hoc* analysis, we also compared the change in the monthly number of migraine with aura days in months 10–12 of the treatment phase to the mean monthly number in the 3-month baseline phase. In addition, we report the number of patients free of migraine attacks with aura and the number of patients completely free of migraine. The adverse event classification encompassed type, relatedness, and seriousness of adverse events.

Statistical analysis

We calculated that a sample size of 60 patients per group would yield a power of 80% at a two-sided significance level of 0.05 assuming a 50% reduction in the number of migraine days after PFO closure and a 25% reduction in the control group. The calculation was based on the assumption of similar frequencies and migraine days as in a recent trial with topiramate.[22] In order to account for a 20% loss-to-follow-up rate, 72 patients were to be randomized into each group.

Baseline characteristics were summarized using descriptive statistics. Continuous variables are reported as mean, standard deviation, N, and the minimum and maximum values. Categorical variables were summarized with the number of subjects exhibiting the characteristic of interest, *N*, and the percentage of patients exhibiting the characteristic. For primary and secondary endpoint analyses, each endpoint was summarized by treatment group using means, standard deviations, and the minimum and maximum values. The comparison of treatment group means was accomplished using a Student's *T*-test assuming unequal variances. Significance was claimed if the *P*-value associated with the test was ≤ 0.05.

The comparison of the percentage of improved patients (responders) in the treatment group to that in the control group was accomplished using a standard Pearson χ^2 statistic. Significance was declared if the *P*-value associated with the χ^2 test was ≤ 0.05. No adjustment to the alpha level was made to compensate for multiple tests. For comparison of patients with complete cessation of migraine or migraine with aura attacks, we used Fisher's exact test.

Results

Study patients

Screening of a total of 705 patients started in April 2006 (*Figure 2*). Three hundred and seventy-six patients (53%) failed screening because of an absence of right-to-left shunt or because PFO was not confirmed. Reasons for screening failure and non-randomization are given in Supplementary material online, *Table S3*. In August 2006, the first patient was enrolled in the treatment phase. By February 2012, 107 patients from 20 centres in Canada, Germany, Switzerland, and the UK had been randomly assigned to the device group (53 patients) or to the medical management group (54 patients). Because of slow enrolment the sponsor decided in January 2012 to stop the trial prematurely. Baseline characteristics are given in *Table 1*. They were similar in both groups.

Study treatments and follow-up

Of the 53 patients assigned to PFO closure, 45 agreed to have device implantation. In four of them, no device was implanted. The mean time from randomization to procedure was 9.9 $\pm$ 5.3 days or a median of 9.0 (minimum 2, maximum 28) days. Forty patients of this group and 43 of the 54 patients assigned to medical management completed 12-month follow-up. The attrition rate was 24 patients (22%). Nineteen of the 107 patients did not complete the trial because of withdrawal of consent (11 patients), adverse events (2 patients), or other reasons (6 patients), and 5 patients were lost to follow-up. There were no crossovers from medical management to device implantation.

Efficacy results

The primary endpoint, i.e. reduction in monthly migraine days at 1 year after randomization was not reached according to the intention-to-treat analysis (*Table 2*, *Figure 3A*). The mean reduction of migraine days per month was 1.2 days greater in the PFO closure group when compared with the control group, but this was not significant (−2.9 vs. −1.7 days; $P = 0.17$).

Most secondary endpoints were not reached either. The average reduction in migraine attacks was numerically greater in the PFO closure group than in the control group, but this was not significant (−2.1 vs. −1.3; $P = 0.097$; *Table 2*). However, there were more responders in the PFO closure group than in the control group ($P = 0.0189$) (*Figure 3B*). In the PFO closure group 15 of 40 patients (38%) experienced a 50% or greater reduction in number of migraine days relative to baseline compared with 6 of 41 in the control group (15%; $P = 0.0189$).

Migraine medication use was similar in both groups (*Table 2*). There was no significant influence of antiplatelet agents on headache days. The improvement in BDI, MIDAS, and SF12 Mental and Physical Component scores from baseline to 12 months was not significantly different between the two groups (*Table 3*).

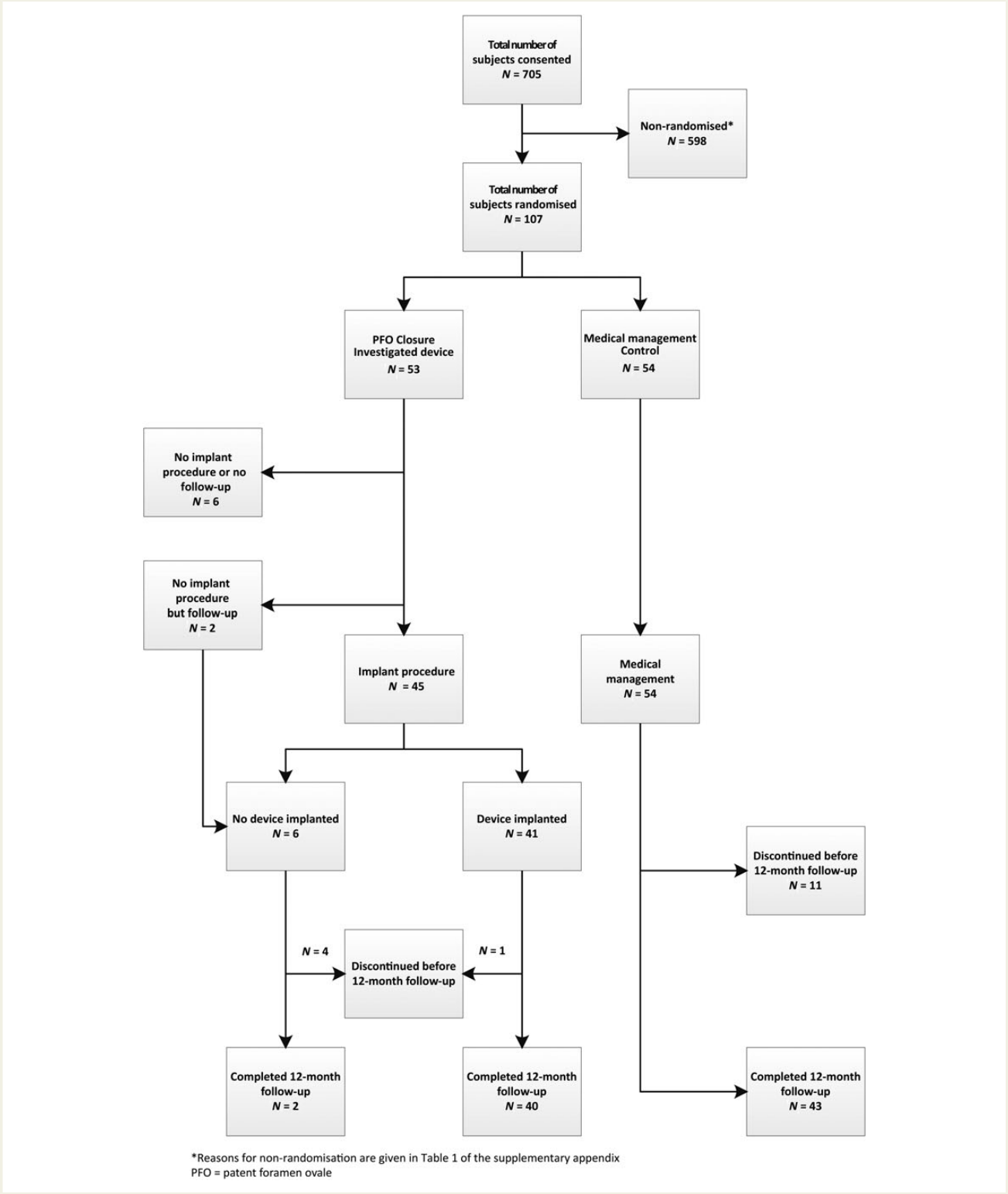

Figure 2 Subject disposition.

Patent foramen ovale closure after Valsalva manoeuvre as adjudicated by the echocardiographic core laboratory was completed in 35 of 40 patients (88%) who underwent control TOE at 6 months.

Post hoc analyses showed a greater mean reduction in migraine with aura days per month (−2.4 vs. −0.6 days; $P = 0.0141$, *Table 4*, *Figure 3A*, Supplementary material online, *Figure S1B*) and the number of migraine attacks with aura in the PFO closure group

compared with the control group (−2.0 vs. −0.5; $P = 0.0003$; *Table 4*, *Figure 3A*). In addition, 4 of 40 patients (10%) in the PFO closure group were free of migraine attacks during months 10–12 compared with none among 41 controls ($P = 0.055$), and 16 of 40 (40%) were free of migraine attacks with aura compared with 4 of 40 (10%; $P = 0.004$) (*Figure 3B*). In approximately half of the patients, >50% of migraine attacks at baseline included an aura. The mean reduction of migraine attacks with aura per month in these patients was greater in the PFO closure group ($N = 22$) than among controls ($N = 20$; −3.2 vs. −0.8; $P = 0.0001$) (*Table 4*).

Table 1 Baseline characteristics

Variable	PFO closure	Control
Age (years, mean ± SD), (*N*), [min, max]	44.1 ± 10.7 (53) [21–61]	42.7 ± 11.0 (54) [20–62]
Sex		
Male	8/53 (15%)	9/54 (17%)
Female	45/53 (85%)	45/54 (83%)
Head trauma/serious injury	1/53 (2%)	2/53 (4%)
Mood disorder	1/51 (2%)	5/52 (10%)
Indication for ongoing acetylsalicylic acid therapy	0/52	1/54 (2%)
Steroid use	2/53 (4%)	0/53
Snoring	17/51 (34%)	10/52 (19%)
Palpitations	1/53 (2%)	4/53 (8%)
Hypertension	4/53 (8%)	3/53 (6%)
Arrhythmia	1/53 (2%)	1/53 (2%)
Heart block	0/52	1/52 (2%)
Other arrhythmia	1/52 (2%)	0/52
Diabetes	0/53	1/53 (2%)
TIA	1/53 (2%)	0/53
Unresponsive to two medications	52/53 (98%)	53/54 (98%)
IHS headache classification		
Migraine with aura	53/53 (100.0%)	53/54 (98%)
Additional migraine without aura[a]	28/53 (53%)	30/54 (56%)
Other headache history	12/51 (24%)	7/52 (14%)
Majority of migraine attacks with aura	28/51 (55%)	30/52 (58%)

IHS, International Headache Society; PFO, patent foramen ovale; TIA, transient ischaemic attack.
[a]Some patients had both migraine with aura and migraine without aura attacks.

Safety and adverse events

There were six serious adverse events in the PFO closure group, three device related (one transient atrial fibrillation, one general fatigue, one syncope), two related to the implant procedure (one access site bleeding, one retroperitoneal haematoma), and one unrelated (muscle wasting). All adverse events resolved without sequelae. During follow-up, available from 40 device patients for 1 year or longer there was no device-related side effect. The total treatment exposure time in the PFO closure group was 119 years.

Discussion

The PRIMA randomized trial used blinded endpoint evaluation to test the efficacy of PFO closure using the Amplatzer device in patients with migraine with aura. Patients were aware of their treatment assignment. Recruitment was slow and the study was stopped before reaching the power calculation-based target number of patients. The significance level for the primary endpoint, reduction in migraine days at 1 year after randomization, was not met.

Migraine Intervention with STARFlex Technology, the only published randomized controlled trial on PFO closure, did not meet its primary endpoint.[23] Migraine Intervention With STARFlex Technology used the rate of headache-free responders as primary endpoint. PREMIUM, presented but not published yet, used responder rate as the primary endpoint and was also negative.[24] Secondary predefined endpoints in PREMIUM such as reduction of headache days or responder rate in patients whose attacks mostly included an aura were positive.

Pre-defined secondary endpoints in the PRIMA trial such as BDI, MIDAS, and SF12 Mental and Physical Component scores were negative and contribute to the overall negative result. Responder

Table 2 Primary endpoint, change in migraine with and without aura days, and secondary endpoints, change in migraine attacks with aura or without aura, and change of days with acute migraine medication use

Type of endpoint	Randomization assignment	Number	Mean at baseline	Mean at months 10–12	Mean reduction, [95% CI][a]	SD (min., max.)	*P*-Value
Migraine with and without aura days (= primary endpoint)	PFO closure	40	8.0	5.1	−2.9 [−4.4, −1.4]	4.7 (−11.7, 9)	0.1682
	Control	41	8.3	6.5	−1.7 [−2.5, −1.0]	2.4 (−6.3, 3.5)	
Migraine attacks with or without aura[b]	PFO closure	40	5.2	3.1	−2.1 [−2.8, −1.3]	2.4 (−7.8, 2.00)	0.0970
	Control	41	5.3	4.0	−1.3 [−1.8, −0.8]	1.7 (−5.0, 1.7)	
Days with acute migraine medication use	PFO closure	50	29.4	15.6	−13.9 [−19.1, −8.7]	18.3 (−70.0, 24.0)	0.1232
	Control	52	28.1	19.8	−8.3 ± [−13.3, −3.4]	17.8 (−51.0, 42)	

PFO, patent foramen ovale; Max, maximum; Min, minimum; CI, confidence interval; SD, standard deviation.
[a]Average treatment phase (months 10–12 post-randomization) minus baseline phase (3 months before randomization). Includes patients who completed 12-month visit with >80% diary compliance.
[b]Individual migraine attacks are separated by at least 24 h of headache symptom free time.

rate was the only positive secondary endpoint. There were 23% more responders in the PFO closure group than in the control group ($P = 0.0189$).

Post hoc analyses provide some interesting results. Migraine attacks preceded by an aura and migraine with aura days were markedly reduced in the PFO closure group compared with controls ($P = 0.0003$ and 0.0141, respectively). Patients with complete cessation of migraine were 10% in the PFO closure group and none among controls ($P = 0.055$). However, looking only at patients free of migraine attacks with aura the difference was pronounced with 40% in the PFO closure group and 10% in the control group ($P = 0.004$).The findings of more responders and greater reduction of migraine attacks preceded by aura and migraine with aura days in the PFO closure group compared with controls might give rise to the hypothesis that PFOs differ in pathogenicity for migraine. In stroke, the Risk of Paradoxical Embolism Study (ROPE) has identified clinical characteristics and constructed a probability score that a discovered PFO is likely to be stroke related vs. incidental.[25] Identifying similar characteristics for migraine might help to resolve the question of incidental vs. pathogenic PFO when PFO is detected in migraine patients. One of those characteristics might be migraine that is preceded by an aura in the majority of attacks.

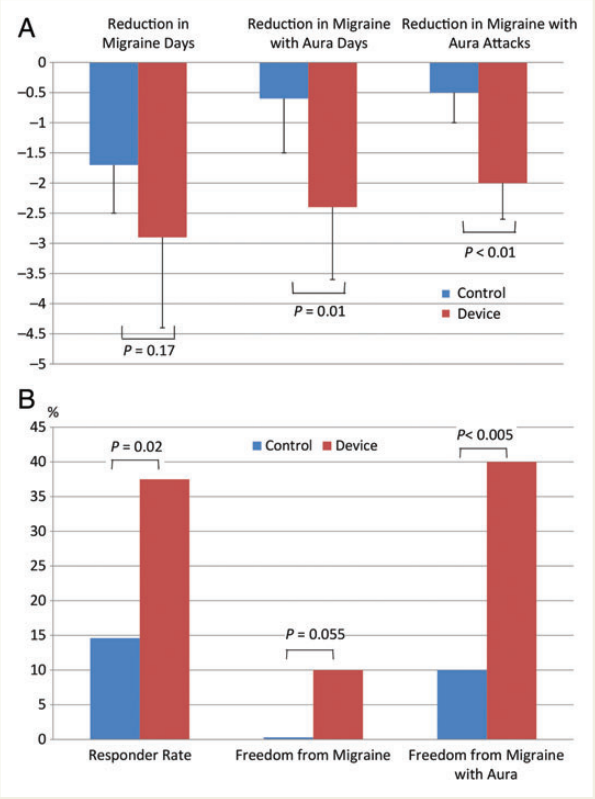

Figure 3 (*A*) Reduction in migraine days (primary endpoint) and reduction of migraine with aura days and migraine with aura attacks (bar graph with 95% confidence intervals). (*B*) Responder rate and number of patients free of migraine and free of migraine with aura.

When planning the PRIMA trial, a sham intervention for controls was considered but dismissed. This would have needed deep sedation or general anaesthesia while PFO closure is frequently performed under local anaesthesia within a few minutes. In this dilemma, the steering committee felt that a sham intervention would not be acceptable, and a sham intervention in local anaesthesia would not have provided adequate blinding. The lack of a sham intervention is a limitation of PRIMA, because only adjudicators of endpoints were blinded to the intervention, but the patients themselves were not.

The lack of blinding of our PRIMA patients might have introduced a placebo effect and biased the results. However, a placebo effect would likely influence all types of migraine headaches equally. In PRIMA, the reduction of migraine attacks with aura and migraine days with aura was greater than the reduction of all types of migraine attacks and days. Therefore, this unequal and greater effect on migraine with aura is likely a true effect of PFO closure.

Our trial has additional limitations. First, patient enrolment was terminated prematurely and therefore the planned sample size to provide a significant result was not reached. Second, the inclusion criterion that accepted only migraine patients who had failed two

Table 3 Improvement in Beck Depression Inventory Score, Migraine Disability Assessment Questionnaire score, SF12 mental, and physical component scores from baseline to 12 months

Endpoint	Randomization assignment	*N*	Mean at baseline	Mean months 10–12	Mean improvement [95% CI]*	Std deviation (min, max)	*P*-Value
BDI score	PFO closure	42	7.0	4.5	−2.5 [−4.9, −0.1]	7.8 (−24.0, 24.0)	0.0821
	Control	43	6.1	6.4	0.3 [−1.8, 2.5]	6.9 (−16.0, 19.0)	
MIDAS score	PFO closure	41	35.4	17.0	−18.3 [−29.2, −7.4]	34.6 (−187.0, 39.0)	0.5299
	Control	43	37.1	23.2	−13.9 [−22.9, −5.0]	29.1 (−110.0, 60.0)	
SF12 Mental Component score	PFO closure	42	50.2	50.7	0.6 [−2.8, 3.9]	10.9 (−37.9, 23.7)	0.9880
	Control	43	49.8	50.4	0.5 [−2.6, 3.6]	10.1 (−23.1, 19.3)	
SF12 Physical Component score	PFO closure	42	43.1	47.3	4.2 [1.3, 7.2]	9.4 (−21.1, 29.3)	0.0953
	Control	43	44.8	46.0	1.2 [−0.9, 3.4]	6.9 (−15.4, 18.3)	

BDI, Beck Depression Inventory; MIDAS, Migraine Disability Assessment Questionnaire; SF, short form; improvement represented by a lower score in BDI and MDAS and by a higher score in SF12.

Table 4 Reduction in migraine with aura days and migraine attacks with aura

Type of endpoint	Randomization assignment	Number	Mean at baseline	Mean at months 10–12	Mean reduction, [95% CI][a]	SD (min., max.)	*P*-Value
Migraine with aura days[a]	PFO closure	40	4.1	1.7	−2.4 [−3.6, −1.3]	3.6 (−9.7, 7.3)	0.0141
	Control	40	4.0	3.4	−0.6 [−1.5, 0.3]	2.7 (−9.1, 5.5)	
Migraine attacks with aura[b]	PFO closure	40	3.0	1.0	−2.0 [−2.0, −1.3]	2.0 (−7.16, 1.00)	0.0003
	Control	40	2.8	2.28	−0.5 [−1.0, −0.0]	1.5 (−3.3, 3.4)	
Migraine attacks with aura in patients who experienced >50% of migraine attacks with aura at baseline	PFO closure	22	4.6	1.4	−3.2 [−4.1, −2.3]	2.0 (−7.2, 0.3)	0.0001
	Control	20	4.1	3.3	−0.8 [−1.5, −0.1]	1.6 (−3.3, 3.4)	

PFO, patent foramen ovale; Max, maximum; Min, minimum; CI, confidence interval; SD, standard deviation.
[a]Average treatment phase (months 10–12 post-randomization) − baseline phase (3 months before randomization). Includes patients who completed 12-month visit with >80% diary compliance.
[b]Individual migraine attacks are separated by at least 24 h of headache symptom free time.

commonly used preventive medications turned out to be highly selective. Thus, we had difficulty to recruit patients leading to an unusually long enrolment period. Third, the failure to completely abolish the right-to-left shunt in 12% is a limitation that would have favoured the control group. Furthermore, patient retention was slightly lower than anticipated, which might bias the results in either direction.

In conclusion, PFO device closure with the Amplatzer Occluder was safe in the long term. There were no adverse events with permanent sequelae. The primary endpoint to reduce migraine days at 1 year after randomization was missed and the trial was negative . However, device closure enhanced responder rates and *post hoc* analyses raise the hypothesis, that PFO closure might decrease migraine attacks with aura in patients with predominantly migraine with aura attacks at baseline. However, such a hypothesis derived from PRIMA will have to be confirmed in another trial. At present, PFO closure cannot be recommended for prevention of migraine in patients with PFO.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

St. Jude Medical statisticians performed statistical analysis. H.P.M., S.E., W.B., D.H-S., B.M. handled funding and supervision. H.P.M., S.E., D.H-S., W.J.B., H.B., J.C., M.G., H.G., A.H., E.H., I.M., S.R., A.Z., O.F., S.W., B.M. acquired the data. H.P.M., S.W., B.M. conceived and designed the research. H.P.M. drafted the manuscript. S.E., D.H.-S., W.J.B., H.B., J.C., M.G., H.G., A.H., E.H., I.M., S.R., A.Z., O.F., S.W., B.M. made critical revision of the manuscript for key intellectual content.

Acknowledgements

We thank Theresa K. Thomas, MS, St. Jude Medical, for her invaluable support with the PRIMA Trial.

Funding

Funded by St. Jude Medical; ClinicalTrials.gov Identifier NCT00505570.

Conflict of interest: B.M. speaker and proctor honoraria and research support to the institution from St. Jude Medical. D.H.: proctor or Advisory Board or Honoraria from St Jude, Gore, and Occlutech. E.H.: research support and proctor honoraria from St. Jude Medical. H.P.M.: research support to the institution from St. Jude Medical. I.M.: honoraria from St Jude and honoraria and proctoring for Occlutech. S.E.: research grants and honoraria from the following companies in the last 2 years: Allergan, Ipsen, Menarini, MSD, Neurocore, Pfizer, St. Jude, UCB. S.W.: research support to the institution from St. Jude Medical. W.B.: research support to the institution from St. Jude Medical.

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CARDIOVASCULAR FLASHLIGHT

doi:10.1093/eurheartj/ehv168
Online publish-ahead-of-print 20 May 2015

Foetal and maternal cardiac rhabdomyomas associated with tuberous sclerosis

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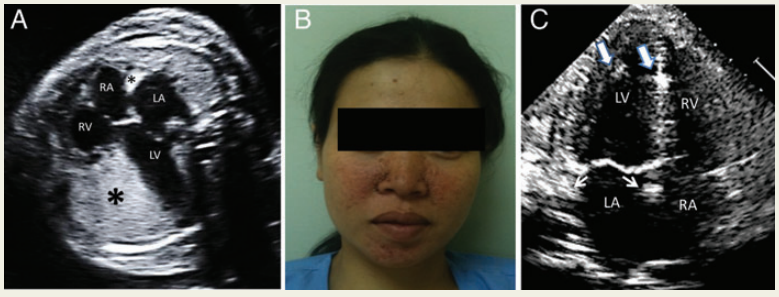

A 29-year-old pregnant lady at 32 weeks of gestation presented with haematuria and flank pain caused by a concealed rupture of left renal mass. A foetal ultrasound revealed polyhydramnios and multiple intramural cardiac masses (*Panel A*, asterisks; see Supplementary material online, *Video S1*) consistent with cardiac rhabdomyomas involving right and left ventricles, interventricular septum, and interatrial septum. On examination, she had facial angiofibromas on bilateral malar eminences and nasolabial folds (*Panel B*). Her echocardiogram revealed multiple echo-densities suggestive of cardiac rhabdomyomas (*Panel C*, arrows; see Supplementary material online, *Video S2*) involving the interventricular septum, left ventricular wall, interatrial septum, and left atrial free wall. Postpartum, she underwent left radical nephrectomy. The histopathological examination revealed renal angiomyolipoma. The diagnosis of tuberous sclerosis (TSC) was established, presence of facial angiofibromas, renal angiomyolipoma, and cardiac rhabdomyomas. As clinical diagnostic criteria for tuberous sclerosis complex were met in this case, genetic testing was not performed. The baby was delivered at 36-week gestation and was dead due to cardiac failure 12 h after delivery.

Cardiac rhabdomyoma is the most common cardiac tumour in infancy and childhood. Most tumours regress spontaneously and rarely present in adults. About 40% of patients with pathologically confirmed cardiac rhabdomyomas are diagnosed as TSC. About 50–70% of patients with TSC have cardiac rhabdomyomas. Tuberous sclerosis complex is an autosomal-dominant disorder, mutations in tumour suppressor gene TSC1 or TSC2, with variable expression. Dermatological identification may aid in diagnosis of TSC and help for prenatal genetic counselling.

Supplementary material is available at *European Heart Journal* online.