Effect of Clopidogrel and Aspirin vs Aspirin Alone on Migraine Headaches After Transcatheter Atrial Septal Closure: The CANOA Randomized Trial

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On behalf of the CANOA Investigators

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CANOA Trial

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CANOA Trial - Background

- **The occurrence of new-onset migraine headaches is a well known complication of transcatheter atrial septal defect (ASD) closure**
- **In patients with ASD and no history of migraine, the rate of new-onset migraine headaches following transcatheter ASD closure is ~15%[1-5]**
- **The choice of antithrombotic treatment following ASD closure has evolved empirically, with aspirin for 6 months being the most common therapy**
- **Preliminary retrospective studies have suggested that the addition of clopidogrel on top of aspirin is associated with a reduction in the occurrence of migraine headaches following ASD closure[1,3,5,6]**

1) Sharifi M et al. J Interv Cardiol 2005; 2) Fernandez-Mayorales DM et al. Cephalalgia 2007; 3) Mortelmans et al. Eur Heart J 2005; 4) Yew et al. Catheter Cardiovasc Interv 2005; 5) Rodés-Cabau et al. Am J Cardiol 2008; 6) Wilmshurst T et al. Heart 2005

CANOA Trial - Objective

Objective

To evaluate the incidence and severity of new-onset migraine headache episodes following transcatheter ASD closure in patients treated with aspirin alone compared to those on aspirin and clopidogrel therapy as antithrombotic treatment after the procedure.

CANOA Trial – Inclusion/Exclusion Criteria

■ Inclusion criteria

- Patients ≥ 18 year old undergoing transcatheter ASD closure with the Amplatzer Septal Occluder device (AGA medical Corp., MN, USA).
- Female subjects must be post-menopausal, surgically sterile, or using an effective method of birth control.
- Signed an informed consent document.

■ Exclusion criteria

- History of migraine headaches (based on migraine headache questionnaire).
- Previous stroke.
- Need for anticoagulation therapy.
- Allergy or intolerance to any of the antithrombotic drugs (aspirin, clopidogrel) used in the study.
- Use of ASD closure devices other than the Amplatzer Septal Occluder device.
- Refusal to sign the informed consent.
- Pregnancy or breast-feeding or planning to become pregnant during the study.

CANOA Trial – Efficacy Outcomes

■ Primary endpoint

- Monthly number of migraine days within the 3 months following transcatheter ASD closure.

■ Secondary endpoints

- Incidence of new-onset migraine attacks

- Total number of migraine days during the first month and 3-month period following ASD closure (the entire study population and patients with migraine attacks only).

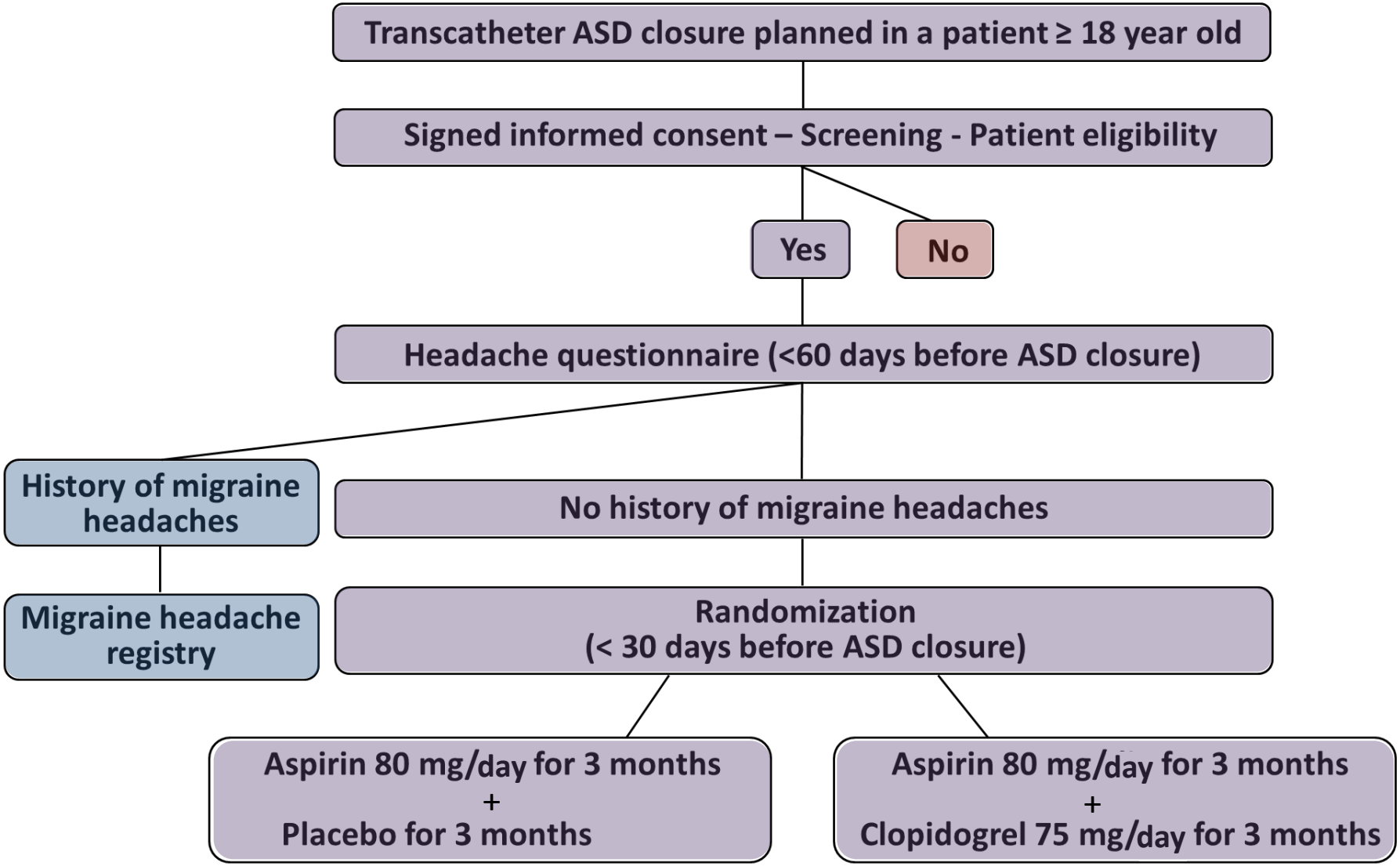
- Monthly number of new-onset migraine days within 3 months following ASD closure in patients with migraine attacks only

- Severity of migraine attacks following ASD closure as evaluated by the Migraine Disability Assessment (MIDAS) questionnaire at 3-month follow-up

- Incidence of adverse events at 3-month follow-up including death, stroke, TIA, bleeding complications, and adverse drug reactions (*safety endpoint*).

CANOA Trial - Study Design

Multicenter, prospective, double blind randomized trial – Clinicaltrials.gov: NCT00799045



CANOA Trial
Evaluation of Migraine Headaches

- **Evaluation of the occurrence, characteristics and severity of headaches:**

  -Structured headache questionnaire (including Migraine Disability Assessment [MIDAS])

  -Headache diary

- **Headache questionnaire timing: within 60 days before ASD closure, and at 30 and 90 days after ASD closure**

- **Evaluation by 2 neurologists blinded to group assignment**

- **Definition of migraine according to the International Headache Society criteria (Cephalalgia 2004;24[Suppl 1]: 9-160)**

CANOA Trial
Sample Size Calculation

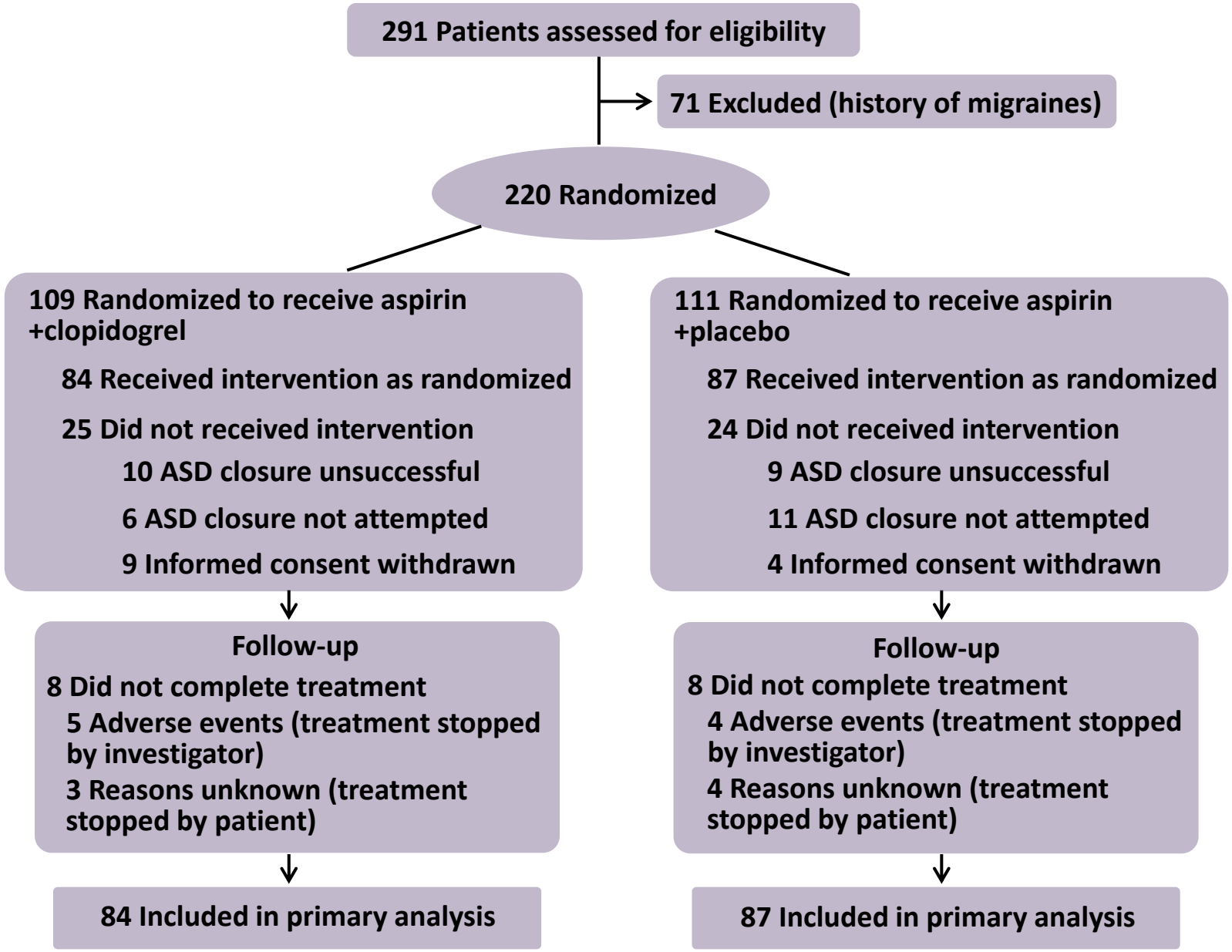
- **Anticipated rate of new-onset migraine attacks following ASD closure: 15%[3-5]**

- **Expected reduction in the occurrence and number of new-onset migraine attacks by adding clopidogrel on top of aspirin: 50%[1,3]**

- **Based on a mixture of zero-truncated Poisson distribution and zero-constant distribution (logistic model), and considering a drop out rate of 10%, a total of 80 patients per group was estimated to provide 80% power to detect differences between groups with a P value <0.05**

1) Sharifi M et al. J Interv Cardiol 2005; 2) Fernandez-Mayorales DM et al. Cephalalgia 2007; 3) Mortelmans et al. Eur Heart J 2005; 4) Yew et al. Catheter Cardiovasc Interv 2005; 5) Rodés-Cabau et al. Am J Cardiol 2008

CANOA Trial – Flow Chart



Baseline and Procedural Characteristics

	Treatment	
	Aspirin	Aspirin+ Clopidogrel
	n=87	n=84
Age, mean (SD)	48 (15)	49 (16)
Male sex, (n, %)	29 (33.3)	36 (42.9)
NYHA class, n (%)		
≥II	22 (26.5)	14 (17)
Pulmonary pressure, mean (SD), mmHg	22.4 (6.3)	20.4 (5.6)
Qp/Qs, mean (SD)	1.89 (0.81)	1.93 (0.84)
Atrial septal aneurysm, n (%)	11 (16.4)	11 (15.5)
ASD size, mean(SD), mm, TEE	16.9 (5.7)	15.7 (5.7)
ASD size, mean(SD), mm, balloon	21.7 (5.3)	20.3 (6.3)
Device size, median (IQR), mm	22 (19-28)	22 (18-26)
Hospitalization length, mean (SD), days	1 (1-1)	1 (1-1)
Residual shunt* (hospital discharge), n (%)	26 (29.8)	27 (32.1)
Mild	25 (28.7)	26 (30.1)
Moderate-severe	1 (1.1)	1 (1.2)
Residual shunt (3-month follow-up), n (%)	9 (10.3)	8 (12.7)
Mild	8 (9.2)	8 (12.7)
Moderate-severe	1 (1.1)	0

*Mild if color jet width (Doppler echocardiography) ≤2 mm, moderate-severe if >2 mm

Incidence and Number of New-Onset Migraine Attacks (Intention-to-Treat)

	Treatment					
	Aspirin n=87	Aspirin+ Clopidogrel n=84	IRR (95%CI) **	P value	OR (95%CI) *	P value
New-onset migraine attacks n (%)	19 (21.8)	8 (9.5)			0.38 (0.15-0.89)	0.031
With aura	11 (57.9)	3 (37.5)				0.33
Without aura	8 (42.1)	5 (62.5)				
Migraine days per month mean (SD) (primary outcome)	1.4 (4.1)	0.4 (1.4)	0.61 (0.41-0.91)	0.035	0.39 (0.16-0.95)	0.015
Migraine days (1st month) mean (SD)	1.5 (4.5)	0.5 (2.2)	0.84 (0.59-1.20)	0.34	0.33 (0.13-0.83)	0.018
Total migraine days at 3 months mean (SD)	3.8 (10.6)	1.0 (4.1)	0.61 (0.48-0.77)	<0.001	0.38 (0.16-0.92)	0.031

*OR: odds ratio; Zero-inflated Poisson regression model (probability of migraine attacks)

**IRR: incidence risk ratio; Zero-inflated Poisson regression model (number of migraine attacks)

Incidence and Number of New-Onset Migraine Attacks (As Treated; n=155)

	Treatment					
	Aspirin n=79	Aspirin+ Clopidogrel n=76	IRR (95%CI) **	P value	OR (95%CI) *	P value
New-onset migraine attacks n (%)	19 (24.1)	7 (9.2)			0.32 (0.13-0.81)	0.017
With aura	11 (57.9)	3 (42.9)				0.495
Without aura	8 (42.1)	4 (57.1)				
Migraine days per month mean (SD)	1.6 (4.3)	0.4 (1.4)	0.58 (0.38-0.90)	0.020	0.33 (0.13-0.83)	0.015
Migraine days (1st month) mean (SD)	1.7 (4.7)	0.4 (1.7)	0.61 (0.41-0.91)	0.040	0.39 (0.16-0.95)	0.010
Total migraine days at 3 months mean (SD)	4.2 (11.1)	0.9 (4.0)	0.58 (0.45-0.75)	<0.001	0.32 (0.13-0.81)	0.020

*OR: odds ratio; Zero-inflated Poisson regression model (probability of migraine attacks)

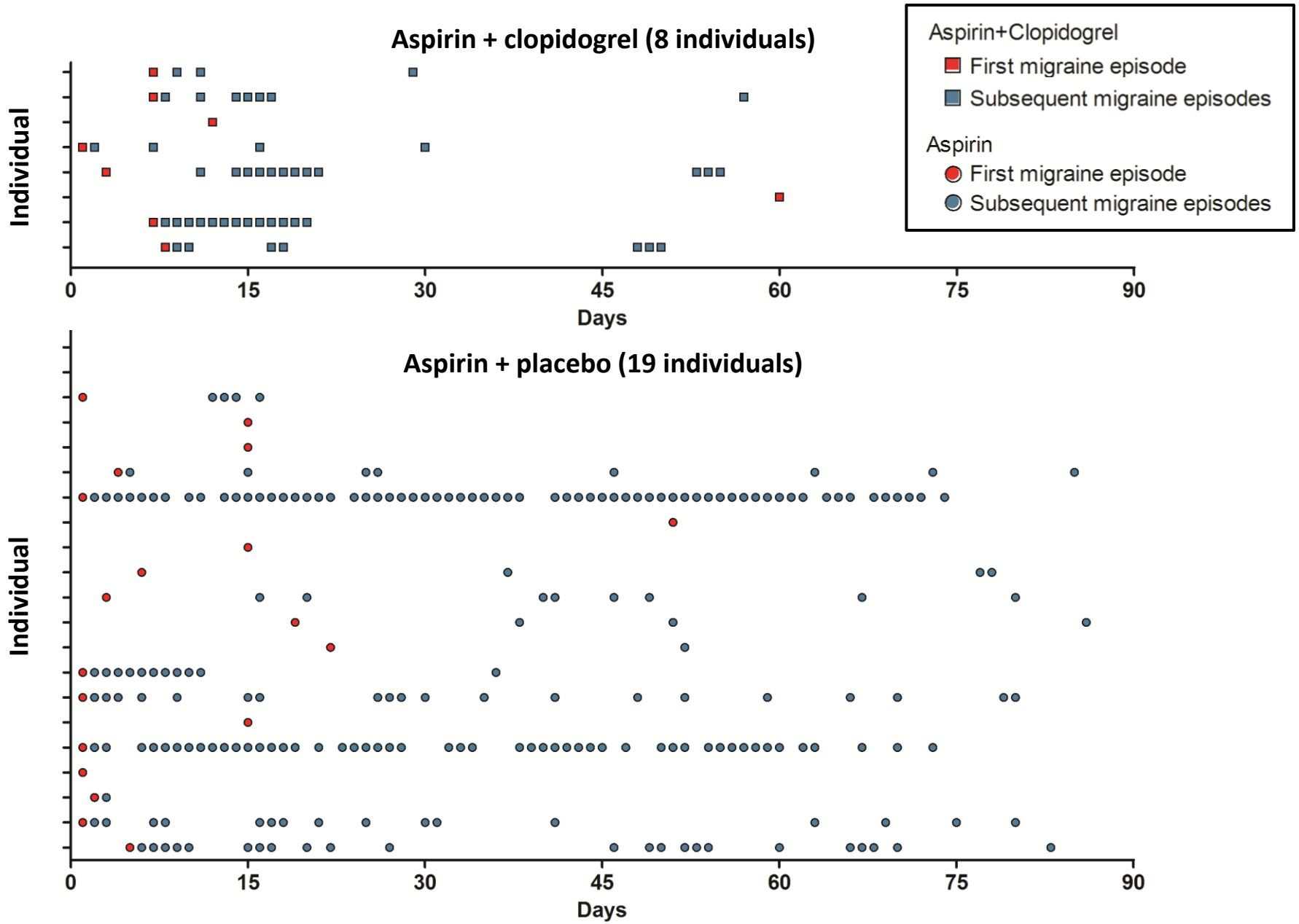
**IRR: incidence risk ratio; Zero-inflated Poisson regression model (number of migraine attacks)

Migraine Headache Characteristics

	Treatment		
	Aspirin n=19	Aspirin+ Clopidogrel n=8	P value
Migraine days per month, median (IQR)	5 (2-8)	3.5 (2-5)	0.39
Migraine days (1st month), median (IQR)	4 (2-9)	3.5 (1-9)	0.31
Migraine days (3 months), median (IQR)	13 (6-20)	7 (5-14.5)	0.30
Migraine duration, median (IQR), hours, per attack	4 (3-6)	4 (3.5-5.5)	0.94
Aura	11 (57.9)	3 (37.5)	0.33
Time to first migraine attack, median (IQR), days from the procedure	4 (2-15)	7 (5.15)	0.42
MIDAS (n, %)			
I-II	12 (63.2)	8 (100)	0.046
III-IV*	7 (36.8)	0	

*Moderate or severe disabling migraine attacks

Timing of the First and Subsequent Migraine Attacks



Adverse Events at 3-Month Follow-Up

	Treatment		
	Aspirin n=87	Aspirin+ Clopidogrel n=84	P value
Death	0	0	
Pericardial effusion	0	0	
Device embolization	0	0	
Need for cardiac surgery	0	0	
Device thrombosis	0	0	
Stroke	0	0	
Transient ischemic attack	1 (1.2)	0	>.99
Major bleeding	0	0	
Minor bleeding*	1 (1.2)	5 (5.9)	0.11
Access site complications	1 (1.2)	0	>.99
Atrial fibrillation	5 (5.8)	2 (2.4)	0.44
Cutaneous rash	2 (2.3)	3 (3.6)	0.68

*Epistaxis (n=4), gingival bleeding (n=1), minor hematuria (n=1)

Data are presented as n (%)

Conclusions

- Clopidogrel on top of aspirin following transcatheter ASD closure was associated with a significant reduction in the occurrence and number of new-onset migraine headaches within the 3 months following the procedure
- In those patients with migraine attacks, dual antiplatelet therapy reduced the severity of migraine episodes
- These results have an important clinical impact on the management of patients undergoing transcatheter ASD closure and may be considered when analyzing the results of studies assessing the efficacy of interatrial shunt closure for the treatment of migraines
- This study provides further insight into the mechanisms of migraine, suggesting a potential role of prothrombotic status on the pathogenesis of migraine in certain groups of patients

Research

Original Investigation

Effect of Clopidogrel and Aspirin vs Aspirin Alone on Migraine Headaches After Transcatheter Atrial Septal Defect Closure

The CANOA Randomized Clinical Trial

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IMPORTANCE The occurrence of new-onset migraine attacks is a complication of transcatheter atrial septal defect (ASD) closure. It has been suggested that clopidogrel may reduce migraine attacks after ASD closure.

OBJECTIVE To assess the efficacy of clopidogrel, used in addition to taking aspirin, for the prevention of migraine attacks following ASD closure.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind clinical trial performed in 6 university hospitals in Canada. Participants were 171 patients with an indication for ASD closure and no history of migraine.

INTERVENTIONS Patients were randomized (1:1) to receive dual antiplatelet therapy (aspirin + clopidogrel [the clopidogrel group], n = 84) vs single antiplatelet therapy (aspirin + placebo [the placebo group], n = 87) for 3 months following transcatheter ASD closure. The first patient was enrolled in December 2008, and the last follow-up was completed in February 2015.

MAIN OUTCOMES AND MEASURES The primary efficacy outcome was the monthly number of migraine days within the 3 months following ASD closure in the entire study population. The incidence and severity of new-onset migraine attacks, as evaluated by the Migraine Disability Assessment questionnaire, were prespecified secondary end points. A zero-inflated Poisson regression model was used for data analysis.

RESULTS The mean (SD) age of the participants was 49 (15) years and 62% (106) were women. Patients in the clopidogrel group had a reduced mean (SD) number of monthly migraine days within the 3 months following the procedure (0.4 [95% CI, 0.07 to 0.69] days) vs the placebo group (1.4 [95% CI, 0.54 to 2.26] days; difference, −1.02 days [95% CI, −1.94 to −0.10 days]; incident risk ratio [IRR], 0.61 [95% CI, 0.41 to 0.91]; $P = .04$) and a lower incidence of migraine attacks following ASD closure (9.5% for the clopidogrel group vs 21.8% for the placebo group; difference, −12.3% [95% CI, −23% to −1.6%]; odds ratio [OR], 0.38 [95% CI, 0.15 to 0.89]; $P = .03$). Among patients with migraines, those in the clopidogrel group had less-severe migraine attacks (zero patients with moderately or severely disabling migraine attacks vs 37% [7 patients] in the placebo group; difference, −36.8% [95% CI, −58.5% to −15.2%]; $P = .046$). There were no between-group differences in the rate of patients with at least 1 adverse event (16.7% [14 patients] in the clopidogrel group vs 21.8% [19 patients] in the placebo group; difference, −5.2% [95% CI, −17% to 6.6%]; $P = .44$).

CONCLUSIONS AND RELEVANCE Among patients who underwent transcatheter ASD closure, the use of clopidogrel and aspirin, compared with aspirin alone, resulted in a lower monthly frequency of migraine attacks over 3 months. Further studies are needed to assess generalizability and durability of this effect.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00799045

Supplemental content at jama.com

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