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Research paper

Sex differences in baseline profiles and short-term outcomes in patients undergoing closure of patent foramen ovale☆

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ABSTRACT

Objectives: Although sex differences have been emphasized in stroke and congenital heart disease, there has been limited investigation into their role in patent foramen ovale (PFO) closure for secondary prevention of stroke. We aimed to explore differences by sex in baseline profiles, procedural characteristics, and short-term outcomes of patients undergoing transcatheter PFO closure.

Methods: Data of adult patients undergoing transcatheter PFO closure at the Toronto General Hospital from 1997 to 2017 was retrospectively analyzed. Baseline information included demographic characteristics, medical history, diagnostic, and procedural information, and periprocedural complications. Post-closure outcomes were captured at index hospitalization and during the first follow-up.

Results: From 1031 patients in the cohort sample, 80.7 % underwent closure for cryptogenic stroke and 44.7 % (n = 461) were females. We observed significant sex-related differences in baseline characteristics; females were younger, less likely to have a history of smoking, and less likely to have several cardiovascular risk factors at baseline ($p < 0.05$). The median time to first follow-up was 89 days for both groups. Recurrent stroke was observed in 0.1 % and TIA observed in 0.4 % of in the 'cryptogenic stroke/TIA' group; in the 'other indications' group, 1.4 % stroke and no TIA were reported. No significant differences were present between sexes.

Conclusions: There were no differences in procedural and short-term outcomes between males and females undergoing transcatheter PFO closure, but significant baseline differences in risk factors were identified. There is a critical need for long-term, systematic studies to understand sex and gender differences in the PFO population.

1. Introduction

In 2014, the American Heart Association and the American Stroke Association released a joint statement to emphasize differences in stroke risk profiles between sexes, highlighting the need for sex-specific research to reduce the gap in care between males and females [1]. There has been increasing evidence suggesting sex and gender differences in disease severity, management, and mortality of patients with congenital heart disease [2–4]. Very few studies, however, have investigated the role of sex in patent foramen ovale (PFO) closure for the secondary prevention of stroke. In fact, key guidelines on the management of PFO do not comment on sex specific considerations in characteristics or outcomes of patients [5–8].

The foramen ovale is a flap-like opening that allows fetal blood to bypass pulmonary circulation; it closes naturally upon birth. A PFO is the remnant of this opening into adulthood, occurring in approximately 20–34 % of the population [9]. A majority of individuals in this population are asymptomatic, but some may present with cryptogenic stroke (i.e. stroke of unknown origin) or transient ischemic attack (TIA), with 40 % of cryptogenic stroke patients under the age of 55 years found to

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have a PFO [10]. Gupta et al. reported that the prevalence of PFO did not differ significantly among males and females with cryptogenic stroke or TIA (32.4 % vs 28.15 %; p = 0.15) [11]. In contrast, Nedeltechev et al. reported that among patients with cryptogenic stroke or TIA, males had a higher prevalence of PFO than females (38 % versus 28 %, p < 0.05) [12].

Recent randomized controlled trials (RCTs) have demonstrated that in cryptogenic stroke patients, transcatheter PFO closure significantly reduces the risk of recurrent stroke in comparison to medical therapy alone [13]. As such, current US, Canadian, and European guidelines on PFO management recommend closure for patients between the ages of 18 to 60 who have a confirmed diagnosis of non-lacunar embolic ischemic stroke or TIA attributable to their PFO [5–7]. Recent meta-analyses, evaluating pooled results from RCTs however, report that PFO closure is superior to medical therapy in reducing the risk of recurrent stroke in males but not in females [14–16]. This further emphasizes the need for investigating sex-specific outcomes after PFO closure. The aim of this study was to assess differences in baseline profiles, procedural characteristics, and short-term outcomes by sex in patients undergoing transcatheter PFO closure in a large academic centre in Canada.

2. Methods

2.1. Study design and population

We performed a retrospective cohort study including adult patients (>18 years old) undergoing transcatheter PFO closure at the Toronto General Hospital (Toronto, Ontario, Canada) between 1997 and 2017. All patients included in a clinical registry, created using a detailed chart abstraction, were included in the current analysis. The study protocol was reviewed and approved by the ethics board of the University Health Network.

2.2. Data sources and data elements

A structured data form and data dictionary were used to abstract data from paper and electronic medical records by trained research personnel. Patient baseline characteristics included demographics, medical history (e.g., symptoms, comorbidities), current medications, and diagnostic testing data. Any abnormalities in Protein C, Protein S, antithrombin III, anticardiolipin ab (antibodies), lupus anticoagulant, Factor V Leiden, and prothrombin mutation testing were used to establish thrombophilia diagnosis. We also extracted information on procedural characteristics and periprocedural complications like major vascular complications, arrythmia, pericardial effusion, device embolization, stroke, sepsis, cardiac reinterventions, and acute kidney infections Procedural success was defined as successful device implantation and discharge with device in place. Post-closure outcomes included recurrent stroke, atrial fibrillation, and other complications such as migraines, chest pain, and palpitations at the first follow-up visit.

2.3. Procedural information

Patients underwent a transesophageal echocardiogram (TEE) as part of a source of embolism study at the discretion of the referring physician to confirm the presence of the PFO prior to the procedure. Transcatheter PFO closure was performed under conscious sedation with local anaesthesia, and under fluoroscopic guidance as needed, and has been described in detail in previous literature [17].

2.4. Statistical analysis

R software version 4.0.2 was used to conduct all statistical analyses [18]. Considering the inherent differences in patients referred for PFO closure for prevention of recurrent cryptogenic stroke or TIA from those referred for other reasons (e.g., decompression sickness, platypnea–orthodeoxia syndrome), all outcomes were presented separately for each subgroup. Continuous data were described using means and standard deviations (SD) and categorical data were described using frequencies and percentages. Baseline characteristics, procedural characteristics, and follow-up outcomes were compared between sexes using the Student's *t*-test for continuous data and χ^2 or Fischer's exact test for categorical data. Among patients with available data on symptoms at baseline and at follow-up, changes in symptoms (i.e., resolved, newly developed, remained non-symptomatic or remained symptomatic) were assessed using χ^2 or Fischer's exact test. A p-value less than or equal to 0.05 was considered significant.

3. Results

3.1. Baseline characteristics

The study sample included 1031 patients, 570 of whom were males (55.3 %). The number of procedures through the study period did not differ significantly by sex (p = 0.168, Fig. 1). Indication for closure was cryptogenic stroke/TIA in 833 (80.8 %) patients and other reasons in 198 (19.2 %) patients. The mean age of patients within this sample was 46.8 years (SD = 12.4), with a mean age of 45.7 years (SD = 13.1) in females and 47.7 (SD = 11.7) years in males (p = 0.023). On presentation, females had a higher prevalence of migraines (39.2 vs 24.4 %, p < 0.001), and palpitations (17.3 vs 9.7 %, p < 0.05). Males were more likely to present with a history of past and current smoking (39.0 vs. 26.3 %, *p* < 0.001). Right ventricular dilation was also more common among males than females (11.6 % vs. 6.3 %, p = 0.020). Table 1 presents baseline characteristics in the 'stroke/TIA indication' sample.

Table A (in Supplemental Material) present baseline characteristics in the 'other indication' group. The mean age of this sample was 55.8 (SD = 17.8) and the most common indication for closure included platypnea-orthodeoxia syndrome (POS) or desaturation in 23.7 % followed by permanent pacemaker in 19.2 % of patients. Vascular risk factors were not significantly different between sexes with the exception of CAD, which was present in 33.6 % of males in comparison to 19.8 % of females (p = 0.043).

Parameters from right heart catheterization are reported in the Supplemental material, Table B. In the 'stroke/TIA indication' group, males had a higher cardiac output than females (p < 0.001). In patients with PFO closure for other indications, females had lower pulmonary artery, pulmonary capillary wedge, mean left atrial pressures and lower cardiac output than males (p < 0.05). Males were significantly more likely to be on statins than females (Table C, Supplemental material).

3.2. Procedural characteristics and outcomes

The procedure was successful in 99.9 % of 'stroke/TIA indication' patients. In a 64-year-old female patient, the PFO closure device embolized right after deployment; it was surgically retrieved, and the PFO was closed with a patch in the operation room. Procedural success was 100 % in the 'other indications' group. Procedural characteristics and outcomes are summarized in Table 2.

3.3. In-hospital outcomes

No differences were observed in in-hospital outcomes by sex (Table 3). In the 'Stroke/TIA indication' group, 10.1 % of patients had a hospital stay greater than one day. There were no in-hospital deaths or stroke events reported in this indication group; one instance of in-hospital complication was reported. The patient had major access bleeding, which was resolved, and the patient attended the first follow-up visit.

One in-hospital death was reported in the 'other indications' group. A 56-year-old male was transferred from another centre with multiple

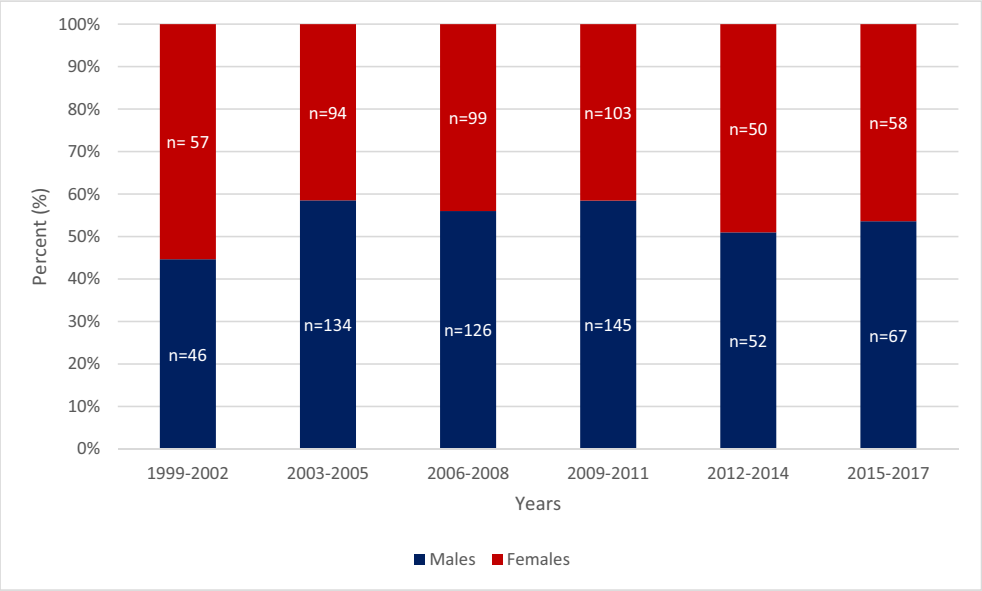

Fig. 1. PFO closure over the years by sex (all patients, n = 1031).

comorbidities, had successful closure of his PFO, but passed away five days later due to his severe health conditions. There were also 2 cases (1.0 %) of other in-hospital complications, including myocardial infarction and shock (Table 3).

3.4. Follow-up data

From 1031 patients, 910 (88.3 %) had their first follow-up visit at the hospital outpatient clinic (Table 4). The median time to follow-up for the 'stroke/TIA indication' group was 89 days [interquartile range (IQR) = 62.0–126.0]. Among these patients, 1 (0.1 %) was reported to have a recurrent stroke and 3 (0.4 %) reported to have a recurrent TIA; no differences by sex were observed. One instance of device thrombosis was reported in a female patient who received the Cardioseal closure device. After closure, migraines remained at a higher proportion in females ($p < 0.05$). Reports of newly developed palpitations were higher than resolved cases after the procedure (7.1 % resolved vs 17.1 % newly developed) whereas migraine was reported as resolved in a higher proportion of patients (22.0 % resolved vs 4.5 % newly developed); there were no differences by sex in changes of symptoms. Supplemental Table D1 reports changes in the presence of symptoms from baseline to follow-up in both sexes.

The median time to follow-up for the 'other indications' group was 88.5 days [IQR = 58.3–124.0]. There were 2 (1.4 %) instances of post-closure stroke and no reported TIA. Within this group, 3 (2.2 %) instances of device thrombosis were reported where 2 patients received the Amplatzer PFO device and 1 patient received STARflex, with no difference by sex. Although there was a higher prevalence of migraine in females after closure (24.6 % versus 5.4 %, $p < 0.05$), there were no sex differences in change in symptoms from baseline to follow-up (Table D2, Supplemental material). Again, reports of newly developed palpitations were more frequent than palpitation resolution (9.7 % resolved vs. 10.4 % newly developed). As expected, the symptom profiles were quite different between indication criteria.

4. Discussion

In this large retrospective study of 1031 patients who underwent PFO closure at a single centre, we found significant differences in several baseline characteristics between males and females, but no differences in procedural and short-term follow-up outcomes. Our study population was similar to other large PFO closure populations in age and sex distribution. The percent of females in our sample was 45 %, a proportion that falls within the range of 38–54 % reported in PFO RCTs that compared transcatheter closure against medical therapy [19–24].

The stark absence of literature commenting on sex differences in patients undergoing PFO closure is surprising, especially considering that significant sex differences in stroke and congenital heart disease have been well-established. To our knowledge, this is the first study to assess sex differences in baseline profiles and outcomes of PFO patients who underwent transcatheter closure.

4.1. Patient profiles

In our cohort, the mean age of males undergoing transcatheter PFO closure was significantly higher than females. Additionally, atherosclerotic risk factors, including diabetes, dyslipidemia and history of smoking were reported more frequently in males. A higher proportion of male smokers was also consistent with the 2021 Canadian National Tobacco and Nicotine Survey [25].

At baseline, a significantly higher proportion of males in our 'Stroke/TIA indication' sample were prescribed angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers which aligns with our finding of significantly increased hypertension in males within this population. Statins were also prescribed more frequently to males, both at baseline and at the first follow-up, in line with the significantly higher proportion of dyslipidemia in males. Our findings differ from those reported by Nedeltechev et al., the only study to our knowledge that compared PFO patient population by sex. The authors reported no sex difference in baseline comorbidities, including hypertension, diabetes, smoking and coronary artery disease. The population of their study, however, may not be representative of the general closure population; among 167 included patients with PFO and cryptogenic stroke, only 35.9 % were females and only 23 % received PFO closure [12].

4.2. Periprocedural outcomes

Rates of periprocedural and in-hospital adverse events were low overall and comparable among males and females, indicating similar effectiveness (i.e., successful closure) and safety outcomes by sex. In a retrospective cohort study of 1887 patients with transcatheter PFO closure for cryptogenic stroke, Merkler et al. also did not observe

Table 1
Patient baseline characteristics by sex – closure for 'stroke/TIA indication'.

Characteristics	All Patients	Males	Females	p-value
	n = 833	n = 463	n = 370	
Age (years), mean (SD)	46.8 (12.4)	47.7 (11.7)	45.7 (13.1)	0.023
BMI[a] (kg/m^2), mean (SD)	27.1 (5.4)	27.4 (4.8)	26.8 (6.0)	0.122
Hypertension, n (%)	191 (22.9)	117 (25.3)	74 (20.0)	0.086
Diabetes, n (%)	44 (5.3)	32 (6.9)	12 (3.2)	0.028
Smoking history, n (%)				
Current	101 (12.1)	59 (12.7)	42 (11.4)	<0.001
Prior	177 (21.2)	122 (26.3)	55 (14.9)	
Never	555 (66.6)	282 (60.9)	273 (73.8)	
Dyslipidemia, n (%)	295 (35.4)	184 (39.7)	111 (30.0)	0.004
CAD, n (%)	41 (4.9)	29 (6.3)	12 (3.2)	0.066
Atrial fibrillation, n (%)	5 (0.6)	4 (0.9)	1 (0.3)	0.515
Atrial septal aneurysm[a], n (%)	248 (38.2)	136 (37.9)	112 (38.5)	0.939
COPD/other lung disease, n (%)	22 (2.6)	13 (2.8)	9 (2.4)	0.906
Malignancy, n (%)	43 (5.2)	19 (4.1)	24 (6.5)	0.166
Thrombophilia[a], n (%)	176 (25.6)	89 (23.3)	87 (28.4)	0.148
Migraine, n (%)	258 (31.0)	113 (24.4)	145 (39.2)	<0.001
Migraine w/aura, n (%)	141 (16.9)	62 (13.4)	79 (21.4)	0.003
Symptoms at time of closure				
Chest pain, n (%)	77 (9.2)	36 (7.8)	41 (11.1)	0.129
Shortness of breath, n (%)	63 (7.6)	29 (6.3)	34 (9.2)	0.146
Palpitation, n (%)	109 (13.1)	45 (9.7)	64 (17.3)	0.002
Echocardiographic (TEE/TTE) parameters				
LV dilation, n (%)[a]	8 (1.2)	6 (1.7)	2 (0.7)	0.455
LV systolic dysfunction, n (%)[a]	17 (2.5)	11 (2.9)	6 (2.0)	0.626
RV dilation, n (%)[a]	30 (5.2)	24 (7.5)	6 (2.3)	0.009
RV systolic dysfunction, n (%)[a]	8 (1.4)	7 (2.2)	1 (0.4)	0.140

BMI = body mass index; CAD = coronary artery disease; COPD = coronary obstructive pulmonary disease; LV = left ventricle; RV = right ventricle; TIA = transient ischemic attack; TEE = Transesophageal echocardiogram; TTE = transthoracic echocardiogram.

[a] BMI data missing in 77 (9 %), atrial septal aneurysm in 183(22.0 %), thrombophilia in 145 (17.4), LV dilation in 185 (22.2 %), LV systolic dysfunction in 147 (17.6 %), RV dilation in 256 (30.7 %), and RV systolic dysfunction in 249 (29.9 %) patients. Calculations in these characteristics were performed after excluding missing values.

differences in their composite outcome of adverse in-hospital events by sex, with adverse events reported in 7.9 % of females and 6.2 % of males (p = 0.15) [26]. Adverse outcomes included the occurrence of atrial fibrillation, pneumothorax or haemothorax, cardiac tamponade, major vascular access complications, or death; recurrent stroke and/or TIA events were not included.

4.3. Follow-up outcomes

Some meta-analyses, based on past RCTs with variable follow-up lengths, evaluated the effectiveness of PFO closure in males and females through subgroup analyses. In the meta-analysis by Agasthi et al., the pooled odds ratio (OR) for stroke recurrence after PFO closure was 0.32 (95 % CI = 0.14–0.73) in males but 0.84 (95 % CI = 0.47–1.51) in females [14]. Hakeem et al. and Akobeng et al. reported similar results [15,16]. Therefore, while RCTs showed that PFO closure is superior to

Table 2
Procedural characteristics and outcomes.

Characteristics	All patients	Males	Females	p-value
Stroke/TIA indication	n = 833	n = 463	n = 370	
Device type, n (%)				
Amplatzer PFO				0.301
25 mm	240 (28.8)	134 (28.9)	106 (28.6)	
30 mm	7 (0.8)	3 (0.6)	4 (1.1)	
35 mm	266 (31.9)	143 (30.9)	123 (33.2)	
STARFlex				
28 mm	176 (21.1)	91 (19.7)	85 (23.0)	
33 mm	69 (8.3)	43 (9.3)	26 (7.0)	
Other devices	75 (9.0)	49 (10.6)	26 (7.0)	
Intracardiac echo used, n (%)	163 (19.6)	86 (18.6)	77 (20.8)	0.481
Procedural success, n (%)	832 (99.9)	463 (100.0)	369 (99.7)	0.910
Procedural complications				
Arrhythmia requiring treatment, n (%)	17 (2.0)	9 (1.9)	8 (2.2)	1.000
Device embolization	1 (0.1)	0 (0.0)	1 (0.3)	0.910

Characteristics	All patients	Males	Females	p-value
Other indications	n = 198	n = 107	n = 91	
Device type, n (%)				0.131
Amplatzer PFO				
25 mm	64 (32.5)	40 (37.4)	24 (26.7)	
30 mm	5 (2.5)	2 (1.9)	3 (3.3)	
35 mm	92 (46.7)	49 (45.8)	43 (47.8)	
STARFlex				
28 mm	14 (7.1)	3 (2.8)	11 (12.2)	
33 mm	7 (3.6)	4 (3.7)	3 (3.3)	
Other devices	15 (7.6)	9 (8.4)	6 (6.7)	
Procedural success, n (%)	198 (100)	107 (100.0)	91 (100.0)	1.000
Intracardiac echo used, n (%)	80 (40.4)	46 (43.0)	33 (36.7)	0.450
Procedural complications				
Arrhythmia requiring treatment, n (%)	6 (3.0)	2 (1.9)	4 (4.5)	0.518
Device embolization	0 (0.0)	0 (0.0)	0 (0.0)	NA

IQR = interquartile range; PFO = patent foramen ovale; TIA = transient ischemic attack.

Table 3
In-hospital outcomes.

Outcomes	All patients	Males	Females	p-value
Stroke/TIA indication	n = 833	n = 463	n = 370	
Hospital stay >1 day, n (%)	84 (10.1)	49 (10.6)	35 (9.5)	0.675
In-hospital death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Stroke, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
TIA, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Other in-hospital complications, n (%)	1 (0.1)	0 (0.0)	1 (0.3)	0.910
Other indications	n = 198	n = 107	n = 91	
Hospital stay >1 day, n (%)	60 (30.3)	34 (31.8)	26 (28.6)	0.739
In-hospital death, n (%)	1 (0.5)	1 (0.9)	0 (0.0)	1.000
Stroke, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
TIA, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Other in-hospital complications, n (%)	2 (1.0)	1 (0.9)	1 (1.1)	1.000

TIA = transient ischemic attack.

Table 4
Outcomes at first follow-up.

Outcomes	Sample size	All patients	Males	Females	p-value
Stroke/TIA Indication		n = 833	n = 463	n = 370	
Time to follow-up (days), median [IQR]	752	89.0 [62.0, 126.3]	87.0 [61.0, 123.5]	92.0 [66.0, 131.0]	0.132
Complications					
Stroke, n (%)	757	1 (0.1)	0 (0.0)	1 (0.3)	0.903
TIA, n (%)	757	3 (0.4)	2 (0.4)	1 (0.3)	1.000
Atrial fibrillation, n (%)	679	34 (5.0)	24 (6.4)	10 (3.3)	0.091
New onset of atrial fibrillation	679	32 (4.7)	22 (5.9)	10 (3.3)	0.158
Device-related thrombosis, n (%)	702	1 (0.1)	0 (0.0)	1 (0.3)	0.911
Symptoms at follow-up					
Chest pain, n (%)	631	73 (11.6)	40 (11.1)	33 (12.2)	0.773
Shortness of breath, n (%)	585	33 (5.6)	18 (5.4)	15 (6.0)	0.918
Palpitation, n (%)	665	161 (24.2)	80 (21.3)	81 (27.9)	0.060
Migraine, n (%)	558	85 (15.2)	38 (12.1)	47 (19.2)	0.029
Other indication		n = 198	n = 107	n = 91	
Time to follow-up (days), median (IQR)	158	88.5 [58.6, 124.0]	88.0 [61.0, 108.5]	90.0 [55.5, 134.0]	0.709
Complications					
Stroke, n (%)	158	2 (1.4)	1 (1.4)	1 (1.5)	1.000
TIA, n (%)	158	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Atrial fibrillation, n (%)	133	15 (11.3)	10 (14.7)	5 (7.7)	0.315
New onset of atrial fibrillation	133	8 (6.0)	5 (7.4)	3 (4.6)	0.853
Device-related thrombosis, n (%)	139	3 (2.2)	2 (2.8)	1 (1.5)	1.000
Symptoms at follow-up					
Chest pain, n (%)	127	15 (11.8)	6 (9.4)	9 (14.3)	0.560
Shortness of breath, n (%)	127	27 (21.3)	12 (18.8)	15 (23.8)	0.631
Palpitation, n (%)	134	27 (20.1)	9 (13.2)	18 (27.3)	0.070
Migraine, n (%)	113	17 (15.0)	3 (5.4)	14 (24.6)	0.010

IQR = interquartile range; TIA = transient ischemic attack.

medical therapy in males, they failed to prove superiority in females. In our large sample of PFO patients, all patients underwent transcatheter closure and only 3-month follow-up outcomes were available. In patients undergoing PFO closure for cryptogenic stroke, at 3 months, recurrent stroke was reported in 0.1 % of the sample or in 0 % of males and 0.3 % of females ($p > 0.05$); TIA was reported in 0.4 % males and 0.3 % females ($p > 0.05$). Similar to our study, Nedeltechev et al. did not report sex-related differences in 3-month outcomes; however, outcomes were not separated by treatment type (medical therapy only versus PFO closure and medical therapy) and a direct comparison with our study cannot be made [12].

4.4. Symptoms before and after closure

The observed differences in symptoms at baseline and at follow-up are worth discussing. Although patient-reported symptoms can be considered subjective, they can drive health-seeking behaviour and, subsequently, an early or a delayed diagnosis. In our cohort, females were more likely to report migraine at baseline and after closure, a finding that is consistent with migraine prevalence in the general population [27]. We also observed an overall trend in resolution of migraine symptoms in all patients after PFO closure, with 22 % of patients reporting resolution. A recently published meta-analysis, pooling individual patient data from two independent RCTs assessing migraine improvement after PFO closure, reported similar findings [28]. Mojadidi et al. reported that there was a significant difference in the number of patients reporting migraine resolution after PFO closure vs medical therapy ($p < 0.001$), as well as a significant reduction in average monthly migraine days and monthly migraine attacks ($p < 0.05$) [28]. In our results, females were also significantly more likely to report palpitations at baseline in comparison to males, but this difference did not reach statistical significance at follow-up. Overall, a high proportion of patients reported new development of palpitations after the procedure (17.6 %) although new onset of atrial fibrillation was reported only in 4.7 % of patients. However, symptom evaluation was not conducted systematically in our study, and further research is required to support our findings.

4.5. Implication for research

Currently, guidelines and criteria on closure do not address sex-related differences in profiles or outcomes of PFO patients [5–7]. Although the differences in characteristics that we observed in our cohort did not translate into differences in adverse events in immediate and short-term outcomes, the effect on long-term outcomes is currently unknown. Therefore, prospective cohort studies with long-term outcomes are needed to generate more evidence on sex-related outcomes after PFO closure. Future studies should also explore associations between different hemodynamic data and adverse outcomes after PFO closure.

4.6. Limitations

This study has limitations that are inherent to a retrospective design; information was abstracted from charts and missing values were present for several variables. In addition, symptoms were not evaluated using a standardized approach. Our study was not able to comment on gender differences and could only capture short-term outcomes. Significant differences between the indications for closure groups compelled us to separate our analyses by 'Stroke/TIA indication' and 'other indications'. As expected, rates of adverse events differed by indication due to the inherent differences in patient comorbidity profiles; thus, we reported results by indication group. As literature reporting outcomes on 'other indications' for PFO closure is scarce, inclusion of this sample in our study sheds light on the characteristics and outcomes of patients in this group.

5. Conclusions

There is limited literature on sex specific PFO outcomes even though significant differences in stroke and congenital heart disease have consistently been reported between sexes. In our study, we observed significant differences in baseline patient profiles by sex but no differences in periprocedural and short-term outcomes. There is a pressing need for prospective and long-term outcome studies to continue this line of investigation. Future studies should also address how gender influences short and long-term clinical and patient-reported outcomes of PFO patients undergoing closure.

CRediT authorship contribution statement

Areeba Asghar: Conceptualization, Formal Analysis, Writing- Original Draft, Writing- Review & Editing, Visualization; Ada C. Stefanescu Schmidt: Writing- Review and Editing; Yeva Sahakyan: Formal Analysis; Eric M. Horlick: Conceptualization, Writing- Review & Editing,

Methodology; Lusine Abrahamyan: Conceptualization, Supervision, Writing- Original Draft, Writing- Review & Editing, Methodology.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Eric Horlick reports a relationship with Abbott that includes: consulting or advisory and funding grants. Abbott was not involved in planning or execution of this analysis and has not seen or reviewed this manuscript. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2022.100199.

References

[1] C. Bushnell, L.D. McCullough, I.A. Awad, M.V. Chireau, W.N. Fedder, K.L. Furie, et al., Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 45 (5) (2014) 1545–1588.

[2] P. Engelfriet, B.J. Mulder, Gender differences in adult congenital heart disease, Neth. Hear. J. 17 (11) (2009) 414–417.

[3] C.L. Verheugt, C.S. Uiterwaal, E.T. van der Velde, F.J. Meijboom, P.G. Pieper, H. W. Vliegen, et al., Gender and outcome in adult congenital heart disease, Circulation 118 (1) (2008) 26–32.

[4] A.C. Zomer, R. Ionescu-Ittu, I. Vaartjes, L. Pilote, A.S. Mackie, J. Therrien, et al., Sex differences in hospital mortality in adults with congenital heart disease: the impact of reproductive health, J. Am. Coll. Cardiol. 62 (1) (2013) 58–67.

[5] T. Wein, M.P. Lindsay, R. Cote, N. Foley, J. Berlingieri, S. Bhogal, Canadian stroke best practice recommendations: secondary prevention of stroke, sixth edition practice guidelines, update 2017, Int. J. Stroke 13 (4) (2018) 420–443.

[6] C. Pristipino, H. Sievert, F. D'Ascenzo, J. Louis Mas, B. Meier, P. Scacciatella, et al., European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism, Eur. Heart J. 40 (38) (2019) 3182–3195.

[7] S.R. Messe, G.S. Gronseth, D.M. Kent, J.R. Kizer, S. Homma, L. Rosterman, et al., Practice advisory update summary: patent foramen ovale and secondary stroke prevention: report of the guideline Subcommittee of the American Academy of neurology, Neurology 94 (20) (2020) 876–885.

[8] E. Horlick, C.J. Kavinsky, Z. Amin, K.D. Boudoulas, J.D. Carroll, Z.M. Hijazi, et al., SCAI expert consensus statement on operator and institutional requirements for PFO closure for secondary prevention of paradoxical embolic stroke: the American Academy of Neurology affirms the value of this statement as an educational tool for neurologists, Catheter. Cardiovasc. Interv. 93 (5) (2019) 859–874.

[9] I. Koutroulou, G. Tsivgoulis, D. Tsalikakis, D. Karacostas, N. Grigoriadis, T. Karapanayiotides, Epidemiology of patent foramen ovale in general population and in stroke patients: a narrative review, Front. Neurol. 11 (2020) 281.

[10] M. Handke, A. Harloff, M. Olschewski, A. Hetzel, A. Geibel, Patent foramen ovale and cryptogenic stroke in older patients, N. Engl. J. Med. 357 (22) (2007) 2262–2268.

[11] V. Gupta, D. Yesilbursa, W.Y. Huang, K. Aggarwal, V. Gupta, C. Gomez, et al., Patent foramen ovale in a large population of ischemic stroke patients: diagnosis, age distribution, gender, and race, Echocardiography 25 (2) (2008) 217–227.

[12] K. Nedeltchev, S. Wiedmer, M. Schwerzmann, S. Windecker, T. Haefeli, B. Meier, et al., Sex differences in cryptogenic stroke with patent foramen ovale, Am. Heart J. 156 (3) (2008) 461–465.

[13] P. Sitwala, M.F. Khalid, F. Khattak, J. Bagai, S. Bhogal, V. Ladia, et al., Percutaneous closure of patent foramen ovale in patients with cryptogenic stroke - an updated comprehensive meta-analysis, Cardiovasc. Revasc. Med. 20 (8) (2019) 687–694.

[14] P. Agasthi, K.R. Kolla, C. Yerasi, S. Tullah, V.S. Pulivarthi, B. Louka, et al., Are we there yet with patent foramen ovale closure for secondary prevention in cryptogenic stroke? A systematic review and meta-analysis of randomized trials, SAGE Open Med. 7 (2019), 2050312119828261.

[15] A. Hakeem, M. Cilingiroglu, A. Katramados, K.D. Boudoulas, C. Iliescu, B. Gundogdu, et al., Transcatheter closure of patent foramen ovale for secondary prevention of ischemic stroke: quantitative synthesis of pooled randomized trial data, Catheter. Cardiovasc. Interv. 92 (6) (2018) 1153–1160.

[16] A.K. Akobeng, I. Abdelgadir, Y. Boudjemline, Z.M. Hijazi, Patent foramen ovale (PFO) closure versus medical therapy for prevention of recurrent stroke in patients with prior cryptogenic stroke: a systematic review and meta-analysis of randomized controlled trials, Catheter. Cardiovasc. Interv. 92 (1) (2018) 165–173.

[17] M. Barker, A.M. Muthuppalaniappan, L. Abrahamyan, M.D. Osten, L.N. Benson, Y. Bach, et al., Periprocedural outcomes of fluoroscopy-guided patent foramen ovale closure with selective use of intracardiac echocardiography, Can. J. Cardiol. 36 (10) (2020) 1608–1615.

[18] R Development Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2020.

[19] A.J. Furlan, M. Reisman, J. Massaro, L. Mauri, H. Adams, G.W. Albers, et al., Closure or medical therapy for cryptogenic stroke with patent foramen ovale, N. Engl. J. Med. 366 (11) (2012) 991–999.

[20] B. Meier, B. Kalesan, H.P. Mattle, A.A. Khattab, D. Hildick-Smith, D. Dudek, et al., Percutaneous closure of patent foramen ovale in cryptogenic embolism, N. Engl. J. Med. 368 (12) (2013) 1083–1091.

[21] J.L. Mas, G. Derumeaux, B. Guillon, E. Massardier, H. Hosseini, L. Mechtouff, et al., Patent foramen ovale closure or anticoagulation vs. Antiplatelets after stroke, N. Engl. J. Med. 377 (11) (2017) 1011–1021.

[22] L. Sondergaard, S.E. Kasner, J.F. Rhodes, G. Andersen, H.K. Iversen, J.E. Nielsen-Kudsk, et al., Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke, N. Engl. J. Med. 377 (11) (2017) 1033–1042.

[23] J.L. Saver, J.D. Carroll, D.E. Thaler, R.W. Smalling, L.A. MacDonald, D.S. Marks, et al., Long-term outcomes of patent foramen ovale closure or medical therapy after stroke, N. Engl. J. Med. 377 (11) (2017) 1022–1032.

[24] P.H. Lee, J.K. Song, J.S. Kim, R. Heo, S. Lee, D.H. Kim, et al., Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial, J. Am. Coll. Cardiol. 71 (20) (2018) 2335–2342.

[25] Statistics Canada, Canadian Tobacco and Nicotine Survey (CTNS) 2021; 2022 May 5, 2021.

[26] A.E. Merkler, G. Gialdini, S. Yaghi, P.M. Okin, C. Iadecola, B.B. Navi, et al., Safety outcomes after percutaneous transcatheter closure of patent foramen ovale, Stroke 48 (11) (2017) 3073–3077.

[27] K.G. Vetvik, E.A. MacGregor, Sex differences in the epidemiology, clinical features, and pathophysiology of migraine, Lancet Neurol. 16 (1) (2017) 76–87.

[28] M.K. Mojadidi, P. Kumar, A.N. Mahmoud, I.Y. Elgendy, H. Shapiro, B. West, et al., Pooled analysis of PFO occluder device trials in patients with PFO and migraine, J. Am. Coll. Cardiol. 77 (6) (2021) 667–676.