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Artificial intelligence-enabled electrocardiogram (AI-ECG) does not predict atrial fibrillation following patent foramen ovale closure

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ABSTRACT

Background: Atrial fibrillation (AF) is a known complication following patent foramen ovale (PFO) closure. AI-enabled ECG (AI-ECG) acquired during normal sinus rhythm has been shown to identify individuals with AF by noting high-risk ECG features invisible to the human eye. We sought to characterize the value of AI-ECG in predicting AF development following PFO closure and investigate key clinical and procedural characteristics possibly associated with post-procedural AF.

Methods: We performed a retrospective analysis of patients who underwent PFO closure at our hospital from January 2011 to December 2022. We recorded the probability (%) of AF using the Mayo Clinic AI-ECG dashboard from pre- and post-procedure ECGs. The cut-off point of $\geq$ 11 %, which was found to optimally balance sensitivity and specificity in the original derivation paper (the Youden index) was used to label an AI-ECG "positive" for AF. Pre-procedural transesophageal echocardiography (TEE) and pre- and post-procedure transcranial doppler (TCD) data was also recorded.

Results: Out of 93 patients, 49 (53 %) were male, mean age was 55 $\pm$ 15 years with mean post-procedure follow up of 29 $\pm$ 3 months. Indication for PFO closure in 69 (74 %) patients was for secondary prevention of transient ischemic attack (TIA) and/or stroke. Twenty patients (22 %) developed paroxysmal AF post-procedure, with the majority within the first month post-procedure (15 patients, 75 %). Patients who developed AF were not significantly more likely to have a positive post-procedure AI-ECG than those who did not develop AF (30 % AF vs 27 % no AF, $p = 0.8$).

Based on the PFO-Associated Stroke Causal Likelihood (PASCAL) classification, patients who had PFO closure for secondary prevention of TIA and/or stroke in the "possible" group were significantly more likely to develop AF than patients in "probable" and "unlikely" groups ($p = 0.034$). AF-developing patients were more likely to have post-procedure implantable loop recorder (ILR) (55 % vs 9.6 %, $p < 0.001$), and longer duration of ILR monitoring (121 vs 92.5 weeks, $p = 0.035$). There were no significant differences in TCD and TEE characteristics, device type, or device size between those who developed AF vs those who did not.

Conclusions: In this small, retrospective study, AI-ECG did not accurately distinguish patients who developed AF post-PFO closure from those who did not. Although AI-ECG has emerged as a valuable tool for risk prediction of AF, extrapolation of its performance to procedural settings such as PFO closure requires further investigation.

1. Introduction

Artificial intelligence (AI) interpretation of ECG (AI-ECG) can be used to determine the probabilities for the presence of various clinical entities including left ventricular (LV) systolic dysfunction, silent atrial fibrillation (AF), hypertrophic cardiomyopathy, cardiac amyloidosis, and aortic stenosis [1–3]. An AI-ECG system that was developed at Mayo Clinic using convolutional neural network and standard 12-lead ECGs

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performed well in detecting atrial fibrillation present during normal sinus rhythm (AUC 0·87 for a single ECG and 0·90 for multiple) [1]. To demonstrate its value, a case was reported of a patient with recurrent cryptogenic stroke in whom AI-ECG analysis had reported a high AF risk 12 years prior to the first thromboembolic event [4]. The patient was found to have AF shortly following a recurrent stroke, 17 years after the first time the AI-ECG analysis had reported a high AF risk [4].

AF is a complication of patent foramen ovale (PFO) closure with an incidence ranging from 0.7 %−19 % [5–11]. A recent systematic review and *meta*-analysis including over 3,000 patients noted that the risk of AF development was significantly higher in PFO patients who had percutaneous closure than those who were medically treated (odds ratio, 5.3 [95 % CI, 2.5–11.41]; P < 0.001) [12]. The risk of AF development was also found to be concentrated in the first 45 days post-closure, with studies containing older patients reporting a higher AF rate [12]. A possible mechanism of this observation is the atrial irritation caused by the procedure, with the device inducing an inflammatory response or acting as a mechanical barrier increasing arrhythmogenicity [12]. Although initially thought to be a transient post-procedure complication, postprocedural ECG changes, such as an increase in P-wave duration and QT interval have been shown to persist on intermediate and longer-term follow-up [13]. It remains a challenge to identify patients who would benefit from closer post-procedure cardiac rhythm monitoring and the impact of post procedure AF on the long-term risk of arrhythmias and stroke is unclear.

To the best of our knowledge, no studies have been previously conducted focused on AI-ECG-predicted AF risk in the context of PFO closure. Through this study, we retrospectively review AI-powered ECG analysis in patients before and after PFO closure, and investigate differences in AI-reported AF probability, patient risk factors, and associated clinical outcomes between patients who developed AF post-procedure and those who did not.

2. Methods

We performed a retrospective analysis of patients who underwent PFO closure at Mayo Clinic, Arizona from January 2011 to December 2022. The study proposal was reviewed by the Mayo Clinic Institutional Review Board (IRB) and determined to be exempt from the requirement for IRB approval. Study participants included all adult patients (age ≥ 18 years) who underwent PFO closure between January 2011 and December 2022 at our hospital. Inclusion criteria included patients who underwent PFO closure and had both pre-procedure (within 6 months of PFO closure) and post-procedure ECG and AI-ECG data (in most cases within one day post-procedure). Patients with a prior history of AF, pre-procedure ECG older than 6 months, missing AI-ECG data, or no post-procedure follow up were excluded from the study.

Through retrospective chart review, we collected baseline patient data and PFO closure procedural details. We recorded the probability of AF using the Mayo Clinic AI-ECG dashboard from pre- and post-procedure ECGs [1]. The binary classification cut-off point of probability of AF ≥ 11 %, which was found to optimally balance sensitivity and specificity in the original derivation paper (the Youden index) was used to label an AI-ECG "positive" for AF.

Descriptive statistics for data were presented as mean ± (SD; standard deviation) or median (IQR; interquartile range) for continuous variables and percentages for categorical variables. Participants were categorized into two groups according to the development of AF. Independent *t*-test, Wilcoxon rank sum test, Pearson's Chi-squared test, and Fisher's exact test were used to find associated factors with development of AF. Wilcoxon signed rank test was used to find if there was a difference between pre and post AI-ECG AF risk. Data were analyzed using SPSS version 28 and R software version 4.0.2.

3. Results

3.1. Clinical and patient characteristics

One hundred and seventeen patients underwent PFO closure, out of which 24 were excluded from the study due to missing AI-ECG data. Out of 93 included patients, 49 (53 %) were male, mean age was 55 ± 15 years with mean post-procedure follow up of 29 ± 3 months (Table 1**).** There were no significant differences in demographics and clinical characteristics between patients who developed AF and those who did not; this was also true when only patients who developed AF within 3 months post-procedure were considered (n = 17). For patients who underwent PFO closure for secondary prevention of transient ischemic attack (TIA) and/or stroke, overall mean Risk of Paradoxical Embolism (RoPE) score was 5.2 ± 1.7, with no significant difference in mean RoPE score between AF and non-AF developing patients.

Table 1
Patient demographics and clinical characteristics.

Variables	N	Overall, N = 93[1]	AF following PFO closure		p-value[2]
			No, N = 73[1]	Yes, N = 20[1]	
Age at time of closure, years	93				
Mean ± SD		55 ± 15	54 ± 15	57 ± 13	0.5
Median (IQR)		55 (44, 63)	53 (42, 65)	57 (52, 61)	
Gender	93				
Female		44 (47 %)	38 (52 %)	6 (30 %)	0.08
Male		49 (53 %)	35 (48 %)	14 (70 %)	
Past medical history	93				
Hypertension		38 (41 %)	30 (41 %)	8 (40 %)	>0.9
Diabetes mellitus		7 (7.5 %)	5 (6.8 %)	2 (10 %)	0.6
Coronary artery disease		15 (16 %)	14 (19 %)	1 (5.0 %)	0.2
Dyslipidemia		40 (43 %)	33 (45 %)	7 (35 %)	0.4
Obstructive sleep apnea		19 (20 %)	14 (19 %)	5 (25 %)	0.5
Deep venous thrombosis		5 (5.4 %)	3 (4.1 %)	2 (10 %)	0.3
Pulmonary embolism		7 (7.5 %)	4 (5.5 %)	3 (15 %)	0.2
Transient ischemia attack		20 (22 %)	18 (25 %)	2 (10 %)	0.2
Stroke		61 (66 %)	48 (66 %)	13 (65 %)	>0.9
Chronic kidney disease		2 (2.2 %)	1 (1.4 %)	1 (5.0 %)	0.4
Cancer diagnosis		7 (7.5 %)	6 (8.2 %)	1 (5.0 %)	>0.9
Alcohol intake					
Non-drinker	89	27 (30 %)	22 (31 %)	5 (26 %)	0.7
Former	93	2 (2.2 %)	1 (1.4 %)	1 (5.0 %)	0.4
Current – Moderate *	93	57 (61 %)	45 (62 %)	12 (60 %)	0.9
Current > Moderate	93	1 (1.1 %)	0 (0.0 %)	1 (5.0 %)	0.2
Current – Heavy **	93	1 (1.1 %)	1 (1.4 %)	0 (0.0 %)	>0.9
Tobacco usage					
Non-smoker	91	64 (70 %)	48 (68 %)	16 (80 %)	0.3
Former smoker	93	22 (24 %)	19 (26 %)	3 (15 %)	0.4
Current Smoker	93	4 (4.3 %)	3 (4.1 %)	1 (5.0 %)	1

[1] Mean ± SD; Median (IQR): n (%).
[2] Independent *t*-test; Pearson's Chi-squared test; Fisher's exact test.
* Moderate intake – 1 drink a day for women, up to 2 drinks a day for men.
** Heavy intake – 3 drinks on any day for women, 4 drinks on any day for men.

Patients were noted to be on aspirin (n = 70, 75 %), clopidogrel (n = 17, 18 %), ticagrelor (n = 1, 1 %), warfarin (n = 3, 3 %), apixaban (n = 9, 10 %), beta blockers (n = 20, 22 %), calcium channel blockers (n = 7, 8 %), ACE-inhibitors (n = 16, 17 %), angiotensin receptor blockers (ARBs) (n = 16, 17 %), and statins (n = 55, 59 %). We found no significant differences in medications between patients who developed AF and those who did not.

3.2. Procedural characteristics

The indication for PFO closure in 69 (74 %) patients was for secondary prevention of TIA and/or stroke (Table 2). Amplatzer Cribriform Occluder, Amplatzer PFO Occluder, GORE CARDIOFORM Septal Occluder and GORE HELEX Septal Occluder were used in 10 (11 %), 3 (3.2 %), 71 (76 %) and 9 (10 %) patients, respectively. The difference in development of AF between devices was not statistically significant (p = 0.089).

3.3. Post-procedure AF

The mean length of follow up following PFO closure was 29 ± 3.2 months. Twenty (22 %) patients developed paroxysmal AF post-procedure (Table 3). Two patients developed AF on the day of the procedure, 13 within the first month, 2 within the second month, 1 between 6 and 12 months, and 2 after one year post-procedure. Rate control therapy was used in 13 patients, with metoprolol used in 10 patients, digoxin used in 2 patients, and atenolol, diltiazem, and labetalol used in one patient each. Based on the PFO-Associated Stroke Causal Likelihood (PASCAL) Classification, patients in the "possible" group were significantly more likely to develop AF than patients in "probable" and "unlikely" groups (p = 0.034). As PASCAL classification is only applicable to patients undergoing PFO closure for secondary stroke prevention, only patients with a prior stroke/TIA with data available to determine PASCAL classification were included in this specific analysis (n = 54).

Table 2
Procedural details.

Variables	N	Overall, N = 93[1]	AF following PFO closure		p-value[2]
			No, N = 731	Yes, N = 201	
Indication	93				
Stroke/TIA		69 (74 %)	55 (75 %)	14 (70 %)	0.6
Hypoxia		23 (25 %)	16 (22 %)	7 (35 %)	0.3
Suspected coronary embolism		2 (2.2 %)	2 (2.7 %)	0 (0.0 %)	>0.9
Iatrogenic ASD		1 (1.1 %)	1 (1.4 %)	0 (0.0 %)	>0.9
Decompression illness	93	1 (1.1 %)	1 (1.4 %)	0 (0.0 %)	>0.9
Residual shunt following previous PFO closure	93	1 (1.1 %)	1 (1.4 %)	0 (0.0 %)	>0.9
Device Type	93				0.089
Amplatzer Cribriform Occluder		10 (11 %)	10 (14 %)	0 (0.0 %)	
Amplatzer PFO Occluder		3 (3.2 %)	1 (1.4 %)	2 (10 %)	
GORE CARDIOFORM Septal Occluder		71 (76 %)	55 (75 %)	16 (80 %)	
GORE HELEX septal occluder		9 (9.7 %)	7 (9.6 %)	2 (10 %)	
Size	92				0.6
20 mm		1 (1.1 %)	1 (1.4 %)	0 (0.0 %)	
25 mm		38 (41 %)	32 (44 %)	6 (30 %)	
30 mm		49 (53 %)	35 (49 %)	14 (70 %)	
35 mm		1 (1.1 %)	1 (1.4 %)	0 (0.0 %)	
44 mm		3 (3.3 %)	3 (4.2 %)	0 (0.0 %)	

ASD: Atrial septal defect, PFO: Patient foramen ovale.
[1] n (%)
[2] Pearson's Chi-squared test; Fisher's exact test.

3.4. AI-ECG AF prediction

Among those who developed AF (20 patients), 15 patients had a higher post-procedure than pre-procedure AI-ECG AF probability (Fig. 1 and Table 4). Twenty-six patients had a positive post-procedure AI-ECG for AF (probability of AF per AI-ECG ≥ 11 %), out of which six patients developed AF, and 20 did not (30 % AF vs 27 % no AF, p = 0.8). In an exploratory analysis, we applied the same cut-off point to pre-procedure AI-ECG yielding 17 patients with a positive AI-ECG for AF, out of which three developed AF and 14 did not (15 % AF vs 19 % no AF, p > 0.9).

The mean pre-procedure AF probability was 7.1 ± 17 % for those who developed AF, and 9.7 ± 20 % for those who did not. The mean post-procedure AF probability was 14 ± 24 % for those who developed AF, and 12 ± 21 % for those who did not. Mean difference between pre-procedure and post-procedure AI-ECG AF probability was 16 ± 44 % for those who developed AF, and 2.3 ± 4.1 % for those who did not (p = 0.5) (Table 5).

3.5. Pre- and post-procedural cardiac rhythm monitoring

Pre-procedure AF monitoring included ambulatory ECG in 39 (42 %) patients with mean duration of 1.5 ± 1.5 weeks, implantable loop recorder (ILR) in 18 (19 %) patients, with mean duration of 34 ± 43 weeks. Five patients (5.4 %) had a pacemaker. Post procedure AF monitoring was done with ambulatory ECG in 30 patients (32 %) with mean duration of 1.3 ± 1.4 weeks and ILR in 18 patients (19 %) with mean duration of 110 ± 116 weeks. Patients who developed AF were more likely to have post-procedure implantable loop recorder (ILR) (55 % vs 9.6 %, p < 0.001), and longer duration of ILR monitoring (121 vs 93 weeks, p = 0.035) (Table 6).

3.6. Imaging characteristics

Transesophageal echocardiography (TEE) characteristics including shunt size, LV ejection fraction, LA size, E/E' (lateral), Biplane Volume Index, and E-A ratio were not significantly different between those who developed AF versus those who did not (Table 7). There were no significant differences in pre- and post-procedure TCD characteristics between those who developed AF versus those who did not.

4. Discussion

This study aimed to evaluate the utility of AI-ECG in the prediction of AF development following PFO closure. Baseline characteristics, as outlined in Table 1, did not show any statistically significant differences between patients that developed AF following the procedure and those that did not. A systematic review and *meta*-analysis published in 2021 by Chen et al [12] suggested that studies with older patients reported a higher rate of AF. Although this is consistent with the well-established, age-related risk of AF in the general population, we did not appreciate this pattern in our study group. Reasons for this may include a smaller study sample and variability in the type of device used.

Nearly 22 % of our patients developed paroxysmal AF post-procedure. The incidence of paroxysmal AF post PFO closure is highly variable in the literature, ranging from 6.6 % [14] to 76 % [15]. However, most cases were transient and had no documented recurrence. The extent of monitoring for AF post procedure impacts the reported incidence of AF. Indeed, one-third and nearly 20 % of our patients were

Table 3
Detailed information for patients who developed AF post-procedure.

Patient number	Age (years)	Gender	Time to develop AF from procedure	PFO size	Indication for PFO closure	Device placed	LA size on echo (cm^2)	RoPe score	PASCAL classification
1	57	Female	Within first month	30 mm	Hypoxia	GORE CARDIOFORM Septal Occluder	39	6	Possible
2	74	Male	Within first month	30 mm	Hypoxia	GORE CARDIOFORM Septal Occluder	60	2	Possible
3	63	Male	Within first month	25 mm	Hypoxia	GORE CARDIOFORM Septal Occluder	–	4	Unlikely
4	58	Male	Between 6 and –12 months	30 mm	Stroke/TIA	GORE CARDIOFORM Septal Occluder	46	5	Possible
5	52	Male	Within first month	30 mm	Stroke/TIA	GORE CARDIOFORM Septal Occluder	–	5	Possible
6	58	Male	Within first month	30 mm	Stroke/TIA	GORE CARDIOFORM Septal Occluder	61	6	Possible
7	82	Male	Within first month	30 mm	Hypoxia	GORE CARDIOFORM Septal Occluder	56	3	Possible
8	65	Male	Within first month	30 mm	Stroke/TIA	GORE CARDIOFORM Septal Occluder	34	4	Possible
9	27	Male	Within first month	30 mm	Stroke/TIA	GORE CARDIOFORM Septal Occluder	53	9	Possible
10	81	Female	Within second month	30 mm	Stroke/TIA	GORE CARDIOFORM Septal Occluder	65	3	Possible
11	55	Male	After one year	30 mm	Stroke/TIA	GORE CARDIOFORM Septal Occluder	60	6	Possible
12	39	Male	Within first month	25 mm	Stroke/TIA	GORE CARDIOFORM Septal Occluder	–	8	Possible
13	59	Male	Within first month	30 mm	Stroke/TIA	GORE CARDIOFORM Septal Occluder	65	6	Possible
14	56	Female	On the day of procedure	25 mm	Hypoxia	Amplatzer PFO Occluder	45	4	Possible
15	42	Female	Within first month	25 mm	Stroke/TIA	GORE CARDIOFORM Septal Occluder	55	6	Possible
16	52	Male	Within first month	25 mm	Stroke/TIA	Amplatzer PFO Occluder	–	6	–
17	52	Female	Within first month	30 mm	Stroke/TIA	GORE CARDIOFORM Septal Occluder	37	6	Possible
18	57	Female	Within second month	25 mm	Stroke/TIA	GORE HELEX septal occluder	44	6	Unlikely
19	49	Male	On the day of procedure	30 mm	Stroke/TIA	GORE CARDIOFORM Septal Occluder	70	5	–
20	60	Male	After one year	30 mm	Hypoxia	GORE HELEX septal occluder	–	5	Possible

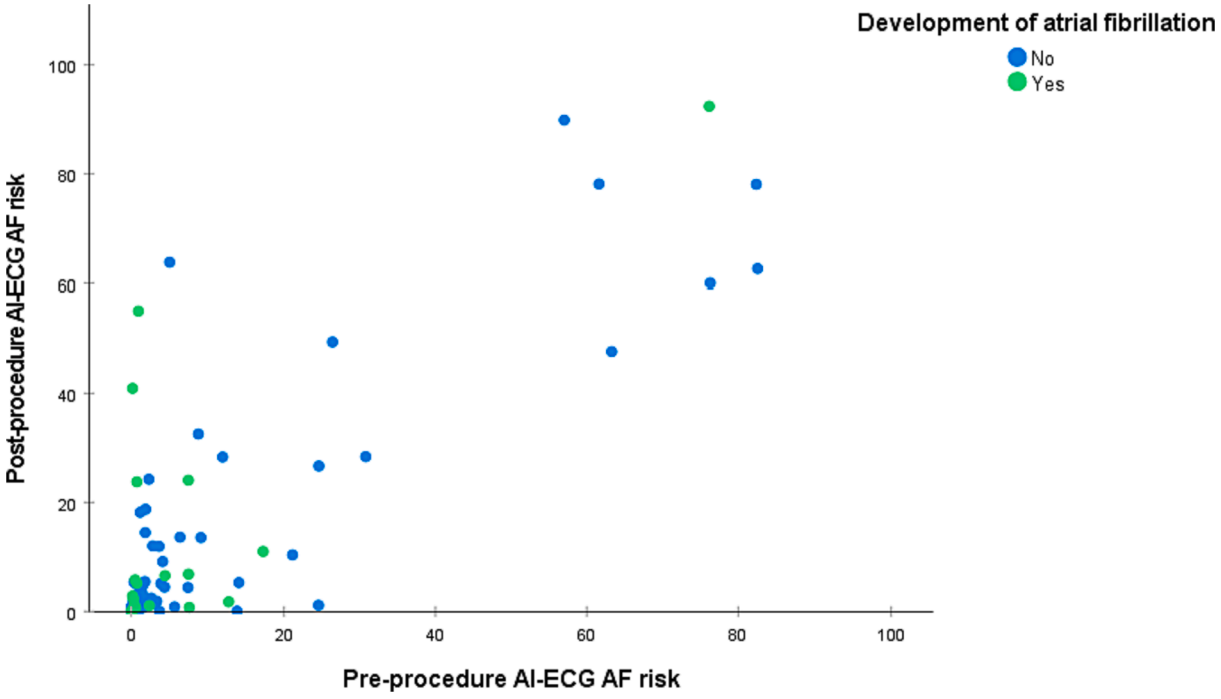

Fig. 1. Pre-procedural and post-procedural AI-ECG AF risk.

Table 4
Pre and post-procedure AI-ECG AF probability.

Variables	N	Overall, N = 93[1]	AF following PFO closure		p-value[2]
			No, N = 73[1]	Yes, N = 20[1]	
Post-procedure AI-ECG AF probability ≥ 11 %	93				0.8
Yes (positive)		26 (28 %)	20 (27 %)	6 (30 %)	
No (negative)		67 (72 %)	53 (72.6 %)	14 (70 %)	
Pre-procedure AI-ECG AF probability ≥ 11 %	93				>0.9
Yes (positive)		17 (18 %)	14 (19 %)	3 (15 %)	
No (negative)		76 (82 %)	59 (81 %)	17 (85 %)	

[1] n (%).
[2] Fisher's exact test; Pearson's Chi-squared test.

Table 5
Pre- and post-procedure AI-ECG prediction based on dashboard reported %.

Variables	N	Overall, N = 93[1]	AF following PFO closure		p-value[2]
			No, N = 73[1]	Yes, N = 20[1]	
Pre-procedure AI-ECG AF risk	93				
Mean ± SD		9.1 ± 19	9.7 ± 20	7.1 ± 17	0.3
Median (IQR)		1.3 (0.5, 6.5)	1.5 (0.7, 5.8)	0.8 (0.4, 7.6)	
Post-procedure AI-ECG AF risk	93				
Mean ± SD		13 ± 21	12.3 ± 21	14.2 ± 24	0.7
Median (IQR)		2.6 (0.9, 12.1)	2.6 (0.9, 12.1)	4.0 (1.0, 14.2)	
Change in AI-ECG AF risk	93				
Mean ± SD		5.3 ± 21	2.3 ± 4.1	16 ± 44	0.5
Median (IQR)		0.9 (-0.2, 4.3)	0.9 (-0.2, 3.2)	1.3 (-0.1, 8.0)	

[1] Mean ± SD; Median (IQR): n (%).
[2] Wilcoxon rank sum test.

monitored using ambulatory ECG and ILR, respectively, after PFO closure, with patients who developed AF significantly more likely to have ILR and longer ILR monitoring duration. Patients with relevant risk factors who were suspected to have higher risk of AF development were monitored more extensively. It has been suggested that trial-reported AF incidence post-PFO closure of 2–6.6 % is likely a gross underestimation, with asymptomatic and paroxysmal AF likely to be missed. This was elucidated in a study that noted AF incidence of 37 % post-PFO closure in patients on ILR monitoring [16]. In essence, the closer you look, the more you will find. Furthermore, it is well established that PFO closure is associated with a higher incidence of early-onset AF (less than or equal to 45 days following PFO closure) compared to late-onset AF, with no substantial long-term increased risk of developing AF [15,17]. Age > 60 years (hazard ratio [HR] 2.82; 95 % confidence interval [CI] 1.76–4.51; P < 0.001) and diabetes (HR 2.49; 95 % CI 1.48–4.18; P < 0.001) have been previously identified as statistically significant independent predictors of AF [18]. Although the AI-ECG model performed well in predicting AF in the original study, it did not accurately predict post-procedure AF in our patient group, neither early nor late, suggesting different mechanisms of AF development than non-procedural patients included in the AI-ECG model development.

To better determine which patients with a stroke could benefit from

Table 6
Pre and post closure AF monitoring.

Variables	N	Overall, N = 93[1]	AF following PFO closure		p-value[2]
			No, N = 73[1]	Yes, N = 20[1]	
Pre-closure AF monitoring					
Ambulatory EKG (Yes)	93	39 (42 %)	35 (48 %)	4 (20 %)	**0.025**
Duration of ambulatory EKG (weeks)	34				
Mean ± SD		1.5 ± 1.5	1.5 ± 1.5	1.3 ± 1.6	0.9
Median (IQR)		0.7 (0.2, 3.2)	0.9 (0.2, 3.2)	0.7 (0.5, 1.4)	
Range (Min - Max)		(0.13–4.3)	(0.13–4.3)	(0.14–3.6)	
ILR (Yes)	93	18 (19.4 %)	9 (12.3 %)	9 (45.0 %)	**0.003**
Duration of ILR (weeks)	18				
Mean ± SD		34 ± 43	26 ± 31	43 ± 54	0.7
Median (IQR)		16 (8.5, 37)	16 (11, 23)	16 (7.7, 56)	
Range (Min - Max)		(1.9–172)	(1.9–104)	(6.1–172)	
PPM (Pacemaker) (Yes)	93	5 (5.4 %)	4 (5.5 %)	1 (5.0 %)	>0.9
Post-closure AF monitoring					
Ambulatory EKG (Yes)	93	30 (32 %)	20 (27 %)	10 (50 %)	0.055
Duration of ambulatory EKG (weeks)	21				
Mean ± SD		1.3 ± 1.4	1.5 ± 1.4	1.0 ± 1.3	0.2
Median (IQR)		1.0 (0.3, 1.7)	1.1 (0.3, 2.0)	0.3 (0.1, 1.6)	
Range (Min - Max)		(0.13–4.3)	(0.13–4.3)	(0.14–4)	
ILR (Yes)	93	18 (19 %)	7 (9.6 %)	11 (55 %)	**<0.001**
Duration of ILR (weeks)	18				
Mean ± SD		110 ± 116.0	93 ± 152	121 ± 93	**0.035**
Median (IQR)		76 (46, 127)	44 (23, 55)	87 (76, 136)	
Range (Min - Max)		(14–435)	(14–435)	(25–370)	

ILR: implantable loop recorder.
[1] Mean ± SD; Median (IQR): n (%).
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

PFO closure, the PFO-Associated Stroke Causal Likelihood (PASCAL) classification system was proposed, which combines RoPE score with presence or absence of high risk PFO features including large shunt and atrial septal aneurysm, to determine likelihood of the stroke being PFO-associated ("unlikely", "possible", or "probable") [19]. The "possible" group includes patients with either a high RoPE score (≥7) or high-risk PFO characteristics, while "probable" includes patients with both. In our study, based on the PASCAL classification, patients with a prior stroke/TIA in the "possible" group were significantly more likely to develop AF than patients in "probable" and "unlikely" groups (p = 0.034). This is a notable finding, and perhaps a closer investigation of patient demographics, as well as clinical and procedural characteristics in context of PASCAL classification could shed further light on this. The PASCAL classification identifies patients where PFO is causal for stroke. If PFO is not considered to be likely causal, then other causes, such as subclinical atrial fibrillation should be considered. AF detection rates approach 30 % with prolonged cardiac rhythm monitoring among patients with prior cryptogenic stroke [20,21].

Despite the utility of the Mayo Clinic AI-ECG dashboard to predict

Table 7
Pre-procedure TEE, and pre and post procedure TCD characteristics.

Variables	N	Overall, N = 93[1]	AF following PFO closure		p-value[2]
			No, N = 73[1]	Yes, N = 20[1]	
Pre-procedure					
Size by TEE * [3,4]	65				0.084
Small		18 (28 %)	16 (33 %)	2 (13 %)	
Small to moderate		3 (4.6 %)	3 (6.1 %)	0 (0.0 %)	
Moderate		14 (22 %)	12 (25 %)	2 (13 %)	
Large		30 (46 %)	18 (37 %)	12 (75 %)	
Shunt by color? Yes/No	92				0.5
No		29 (32 %)	24 (33 %)	5 (25 %)	
Yes		63 (69 %)	48 (67 %)	15 (75 %)	
Shunt by agitated saline? Yes/No	91				
Yes		91 (100 %)	71 (100 %)	20 (100 %)	
ASA (atrial septal aneurysm)?	91				0.5
No		60 (66 %)	48 (68 %)	12 (60 %)	
Yes		31 (34 %)	23 (32 %)	8 (40 %)	
Tunnel? Yes/ No	31				0.3
No		24 (77 %)	19 (83 %)	5 (63 %)	
Yes		7 (23 %)	4 (17 %)	3 (38 %)	
Ejection fraction	92				
Mean ± SD		62 ± 4.9	61 ± 5.1	62 ± 4.2	>0.9
Median (IQR)		62 (60, 65)	62 (60, 65)	63 (59, 65)	
Left atrial size (Biplane cc)	63				
Mean ± SD		52 ± 13	51 ± 14	53 ± 11	0.7
Median (IQR)		53 (43, 61)	52 (42, 61)	55 (45, 61)	
E/E(Lateral)	77				
Mean ± SD		7.3 ± 2.7	7.3 ± 2.6	7.0 ± 3.0	0.7
Median (IQR)		7.1 (5.0, 8.8)	7.3 (5.5, 8.8)	6.3 (4.4, 8.1)	
Biplane volume index	70				
Mean ± SD		26 ± 5.7	27 ± 5.8	26 ± 5.2	0.5
Median (IQR)		26 (23, 30)	25 (23, 31)	26 (21, 28)	
E-A ratio	76				
Mean ± SD		1.2 ± 0.6	1.2 ± 0.6	1.1 ± 0.5	0.5
Median (IQR)		1.1 (0.8, 1.5)	1.1 (0.8, 1.5)	1.0 (0.8, 1.3)	
TCD- Pre closure					
Spenser grade shunt Valsalva [5]	55				0.2
Grade 0		1 (1.8 %)	0 (0.0 %)	1 (9.1 %)	
Grade 1		1 (1.8 %)	1 (2.3 %)	0 (0.0 %)	
Grade 2		5 (9.1 %)	4 (9.1 %)	1 (9.1 %)	
Grade 3		12 (22 %)	9 (21 %)	3 (27 %)	
Grade 4		20 (36 %)	15 (34 %)	5 (46 %)	
Grade 5		16 (29 %)	15 (34 %)	1 (9.1 %)	
TCD- post closure					
Spenser grade shunt Valsalva	50				>0.9
Grade 0		33 (66 %)	23 (62 %)	10 (77 %)	
Grade 1		11 (22 %)	9 (24 %)	2 (15 %)	
Grade 2		1 (2.0 %)	1 (2.7 %)	0 (0.0 %)	
Grade 3		4 (8.0 %)	3 (8.1 %)	1 (7.7 %)	
Grade 4		1 (2.0 %)	1 (2.7 %)	0 (0.0 %)	

TEE – transesophageal echocardiography. TCD- transcranial doppler.

[1] Mean ± SD; Median (IQR): n (%).
[2] Wilcoxon rank sum test; Independent *t*-test; Pearson's Chi-squared test; Fisher's exact test.
[*] Size by TEE - Small: Grade I (fewer than 5 bubbles), Moderate: Grade 2 (6–25 bubbles), Large: Grade 3 (25 or more).
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AF, we were not able to demonstrate a significant difference in positivity of AI-ECG for AF between patients who developed AF and those who did not. To our knowledge, there have been no studies that evaluated the risk of AF development following PFO closure using AI-ECG technology. Although the relatively small number of patients may have limited our statistical significance, we believe that further trials involving a larger number of patients may have sufficient power to more definitively test the hypothesis that AI-ECG can predict AF post percutaneous closure of PFO. Two recent studies done by Han et al and Rabinstein et al evaluated the role of AI-ECG in predicting the risk of AF in stroke patients. Both studies concluded that among patients with non-cardioembolic ischemic strokes and embolic strokes of unknown source, respectively, the probability of AF detected by AI-ECG was associated with a higher likelihood of AF detection compared to the control groups [22–24]. These studies support the role of AI-ECG as a cost-effective screening tool to identify patients with paroxysmal AF at an increased risk of cardioembolic disease, paving the way for implementation of protocols for prolonged cardiac monitoring or initiation of anticoagulation as primary prevention in select patients, an area where our understanding continues to evolve [25,26].

While AI models such as AI-ECG may appear to have a wide range of applications and perform quite well, experts have advised caution when extrapolating model performance from one setting or population to another [27]. This was demonstrated by a study assessing the performance of the original AI-ECG algorithm, one that was developed based on a general, unselected population, in predicting postoperative AF (POAF) in patients undergoing non-cardiac surgery and patients undergoing coronary artery bypass graft (CABG) surgery. The AI-ECG model resulted in a sensitivity of 75 % and a specificity of 49 % in the non-cardiac surgery cohort (AUC of 0.66 (95 % CI 0.62–0.71), and a sensitivity of 50 % and specificity of 61 % in the CABG cohort (AUC of 0.58 (95 % CI 0.57–0.60) [27]. These results contrasted with the significantly better performance of the AF-detecting model in the derivation study [AUC 0.87 (95 % CI 0.86–0.88) with sensitivity and specificity of 79 % and 80 %, respectively] [1].

The value of AI-guided AF screening was demonstrated in the Batch Enrollment for an AI Guided Intervention to Lower Neurologic Events in Patients with Undiagnosed Atrial Fibrillation (BEAGLE) trial, a recently published pragmatic, prospective, non-randomized interventional study which noted that AI-guided screening was associated with increased AF detection (high-risk group: 3.6 % [95 % CI 2.3–5.4] with usual care vs 10.6 % [8.3–13.2] with AI-guided screening, $p < 0.0001$; low-risk group: 0·9% vs 2·4%, $p = 0·12$) [28]. The ECG AI-Guided Screening for Low Ejection Fraction (EAGLE) trial conducted across the Mayo Clinic Health System found that access to AI-ECG increased the diagnosis of low ejection fraction (EF) within 90 days of the ECG when compared to usual care (no access to AI features) (1.6 % in the control arm vs 2.1 % in the intervention arm, odds ratio (OR) 1.32 (1.01–1.61), $P = 0.007$) [29]. Another study exploring the use of an AI-supported smart wristband device to detect AF reported the sensitivity, specificity, and accuracy of wristband ECG to be 87.33 %, 99.20 %, and

94.76 %, respectively [30].

Another variable that was identified in some studies to increase the risk of AF development was the type of device used. Some closure devices have been associated with a higher incidence of AF due to local stretch or septal irritation that occur during and/or after device deployment [31]. A network *meta*-analysis of 2,963 patients with cryptogenic stroke showed that development of AF was more pronounced with the STARFlex device compared to the AMPLATZER PFO Occluder or the HELEX device [31]. It is worth noting that this *meta*-analysis identified an increased risk of AF across different closure devices even after the STARFlex device was excluded, but this risk was not identified when analysis was limited to trials using the AMPLATZER PFO Occluder. Another study showed that occluder size was a significant predictor of post-procedural AF especially after PFO closure [24]. The difference in the incidence of AF between the different devices used in our study did not meet clinical significance ($p = 0.089$). The GORE CARDIOFORM Septal Occluder device was used in 16 of the 20 patients who developed AF. Of note, this device was used in 71 (76 %) of the 93 patients. There were no differences between different occluder sizes and rate of development of AF. Finally, our study did not identify any significant differences in TEE or TCD characteristics between both groups of patients.

Limitations of our study include its retrospective design and associated impact on data analysis due to missing data, and a relatively small sample size. Only a proportion of patients were placed on long-term rhythm monitoring. Although this approach may impact post-procedure AF detection and influence study results, it more closely aligns with real-life clinical practice, where select patients at highest risk for AF development are placed on long term rhythm monitoring. We believe that the study highlighted certain trends that may reach statistical significance in the future if a larger sample size is utilized to achieve sufficient power to detect differences, in this instance considering an enterprise-wide Mayo Clinic study.

5. Conclusions

PFO closure is associated with a higher rate of AF when compared to the general population, with incidence concentrated in the early post-procedural period and it remains a challenge to identify patients who would benefit from closer post-procedure cardiac rhythm monitoring. AI-ECG has emerged as a valuable, inexpensive and a rapid clinical tool for risk stratification and prognostication that can assist with day-to-day clinical decisions.

Although our pilot study did not observe a significant difference in AF prediction based on AI-ECG analysis between those who developed AF and those who did not, AI-guided clinical decision-making has the potential to facilitate our understanding and care of patients undergoing structural cardiac interventions. Further larger studies are needed to better evaluate application of AI-powered ECG predictions in procedural settings including PFO closure. Ongoing development of new AI models as well as external validation of existing models will facilitate application of AI tools in diverse clinical settings across various patient populations. Meanwhile, extrapolation of AI model performance to unfamiliar settings or populations must be approached with caution.

CRediT authorship contribution statement

Omar Baqal: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Eiad A. Habib:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Elfatih A. Hasabo:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Francesca Galasso:** Investigation, Data curation. **Timothy Barry:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Reza Arsanjani:** Writing – review & editing, Data curation, Conceptualization. **John P. Sweeney:** Writing – review & editing, Project administration, Investigation, Data curation. **Peter Noseworthy:** Writing – review & editing, Validation, Supervision, Investigation, Data curation, Conceptualization. **F. David Fortuin:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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