


Atrial fibrillation trial to evaluate real-world procedures for their utility in helping to lower stroke events: A randomized clinical trial

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Abstract

Background: Enhancing detection of unrecognized atrial fibrillation among acute ischemic stroke patients is crucial for secondary stroke prevention.

Aim: To evaluate whether the detection rate of new atrial fibrillation in acute ischemic stroke patients without known atrial fibrillation could be improved by doing serial 12-lead electrocardiograms once daily for five days, compared with conventional 24-h Holter monitoring (24-h Holter).

Methods: We conducted a randomized clinical trial to compare the detection rates of paroxysmal atrial fibrillation between serial electrocardiograms versus 24-h Holter from October 2015 to October 2018 at six hospitals. Eligible participants were acute ischemic stroke patients with aged ≥ 65 years, with neither atrial fibrillation history nor any presence of atrial fibrillation on baseline electrocardiogram at admission. The primary outcome was newly detected electrocardiogram in the serial electrocardiograms and 24-h Holter group.

Results: Among 826 patients, baseline characteristics were similar between both groups. In the intention-to-treat analysis, there was no statistical difference between serial electrocardiograms versus 24-Holter to detect atrial fibrillation (8.4% vs. 6.9%; adjusted odds ratio 1.17, 95% confidence interval 0.69–2.01). Stepwise multivariate logistic regression revealed age ≥ 80 years and history of heart failure were associated with detection of paroxysmal atrial fibrillation whereas patients with lacunar infarction had lower odds for detection of paroxysmal atrial fibrillation.

Conclusions: Serial electrocardiograms had comparable detection rate of paroxysmal atrial fibrillation compared with 24-h Holter and might be a viable alternative to 24-h Holter as a first-line approach to survey for potential paroxysmal atrial fibrillation among elderly patients with acute ischemic stroke.

Clinical Trial Registration: URL <https://clinicaltrials.gov/ct2/show/NCT02578979>

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Keywords

Atrial fibrillation, stroke, electrocardiography, 24-h Holter, randomized controlled trial

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Introduction

Atrial fibrillation (AF) is the most common chronic cardiac arrhythmia in the elderly and is known to be associated with fivefold risk of future ischemic stroke in general population.^{1,2} A new diagnosis of AF after discharge for stroke is associated with an increased risk of recurrent stroke, compared with patients without AF and with known AF.³ Even when an index stroke is presumed to be caused by another pathophysiologic mechanism, such as lacunar infarct or large artery atherosclerosis, AF may still exist. Once AF is found, oral anticoagulant therapy, rather than antiplatelet therapy, is recommended for secondary stroke prevention because the initiation of oral anticoagulation is the most effective strategy for secondary stroke prevention in stroke patients with AF.⁴

While approaches for detecting AF vary,⁵ doing a conventional 12-lead electrocardiogram (ECG) or 24-h Holter monitoring are typically seen as the standard and cost-effective methods for detecting occult AF.⁶ Prolonged ECG monitoring may improve the detection rate of AF, but it is relatively expensive and inconvenient, thereby limiting its widespread use in clinical practice.^{7,8} A standard 12-lead ECG is a basic and mandatory device in all hospitals, and remains a gold standard modality for the diagnosis of AF.⁹ A retrospective study suggested that serial ECGs could improve the detection rate of paroxysmal AF when compared to a single ECG in patients with acute ischemic stroke, and the sensitivity of AF detection was not different between serial ECGs and 24-h Holter monitoring.¹⁰

The objective of the Atrial Fibrillation Trial to Evaluate Real-world Procedures for their Utility in helping to Lower Stroke Events (AFTER-PULSE) was to compare the detection rate of AF with serial 12-lead ECGs once daily for five days versus 24-h Holter monitoring in elderly patients with acute ischemic stroke and no known AF at the time of admission.

Methodology

Trial design

Details of the study design and methods have been published previously.¹¹ In brief, we conducted a multicenter, randomized clinical trial at six hospitals in Taiwan to compare the detection rates of paroxysmal AF between serial 12-lead ECGs once daily for five days vs. 24-h Holter monitoring in acute ischemic stroke patients, without known AF, from 1 October 2015 to 31 October 2018. This trial followed CONSORT guidelines for reporting clinical trial protocols¹² and was approved by the local Institutional Review Board of

Chang Gung Memorial Hospital, Chiayi Branch, Taiwan (103-7597B and 104-9611C).

Trial participants

Eligible participants were patients admitted to a hospital for an ischemic stroke within two days of stroke symptom onset, and aged ≥ 65 years, with neither a history of AF nor any presence of AF on baseline ECG at the time of hospital admission. Patients were excluded if they had an indication for oral anticoagulation at randomization, intracerebral hemorrhage by medical history, pacemaker or implantable cardioverter-defibrillator device, or end-stage renal disease.

Trial procedure

We randomly allocated eligible patients in a 1:1 ratio to receive 12-lead ECGs once daily for five days (intervention group) or 24-h Holter monitoring (comparator group). Allocation occurred when a study participant met the inclusion criteria and did not meet any exclusion criterion and signed the informed consent forms. Randomization was done in blocks of random sizes of 4 and 6 at each site by using of a web-based randomization service. One investigator (YLW) conducted computer-generated site-specific randomization lists, wrote an assigned-group on a small paper, put it in an envelope in sequence, and then sent it to a research assistant at each participated hospital in advance. Once an eligible patient agreed to participate in this trial, an investigator would then open up an envelope to discover to which group the patient was randomly assigned. Investigators and patients were aware of study group allocation. The interpretations of findings for both the 12-lead ECG and 24-h Holter groups were made by attending cardiologists who were unaware of the objectives of this study.

Trial intervention

If participants were randomly assigned to the serial ECG group, they first received 12-lead ECG within two days of stroke onset and then a 12-lead ECG was repeated once daily for five days during hospitalization. If five exams of 12-lead ECGs could not be completed during hospitalization, the remaining 12-lead ECGs would be done when the patient returned to an outpatient clinic and all 12-lead ECG exams were supposed to be done within three months after index stroke. Participants who were randomly assigned to the 24-h Holter group received Holter monitoring at each hospital site during their hospitalization. Participants in both randomized groups did not receive any specific additional medical treatment.

All secondary stroke prevention therapies and rehabilitation treatments were determined at the discretion of the patients treating physicians.

Sample size calculation

We calculated sample size based on our preliminary data preceding the actual conduct of this trial. We evaluated 193 patients comprising 96 patients in a serial 12-lead ECG group and 97 patients a Holter monitoring group. AF was detected in five patients in the serial ECG group and in two patients in the Holter monitoring group. For a two-tailed *t*-test at the 5% level and with 80% power, 576 patients would be required per group. To allow for dropouts, 600 patients would be recruited in each group. Sample size calculation was performed using G Power software by one investigator (YLW)

Statistical analysis

Primary outcome was newly detected AF on a 12-lead ECG in the serial ECG group and 24-h Holter group after randomization based on intention-to-treat analysis. We also conducted additional analyses based on per-protocol. For the intention-to-treat analysis, all newly detected AF was counted regardless of the modality (e.g., stroke patients assigned to the 24-h Holter monitoring group may not have AF detected by 24-h Holter monitoring, but have AF detected by transthoracic echocardiogram, and in such a situation, AF would not be counted in the per-protocol analysis, but would be counted in the intention-to-treat analysis). For the per-protocol analysis, newly detected AF was counted only when AF was detected by the modality to which the patient was randomly assigned. Subgroup analyses to explore whether certain baseline characteristics (e.g., age, sex, National Institutes of Health Stroke Scale (NIHSS) score, stroke type (lacunar infarction vs. non-lacunar infarction) hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease, heart failure, and previous stroke or transient ischemic attack) would influence overall results were conducted. Oral anticoagulants therapy, including warfarin or non-vitamin K oral anticoagulant (NOAC), in each group was recorded at discharge and at 90 days among stroke patients with newly detected AF. Baseline characteristics were compared using chi-square (categorical variables), Mann-Whitney U (continuous variables which were not normally distributed) or Student *t*-test (continuous variables which were normally distributed). Detection rates for paroxysmal AF between the two groups were compared using chi-square test with adjustment of age, sex, NIHSS score, lacunar stroke, hypertension, diabetes mellitus, chronic

kidney disease, coronary artery disease, heart failure, and previous stroke or transient ischemic attack. Stepwise multivariate logistic regression was conducted to explore the association between baseline factors and newly detected AF using the entire trial data. All statistical analyses were performed with IBM SPSS statistics 19 for Windows.

Results

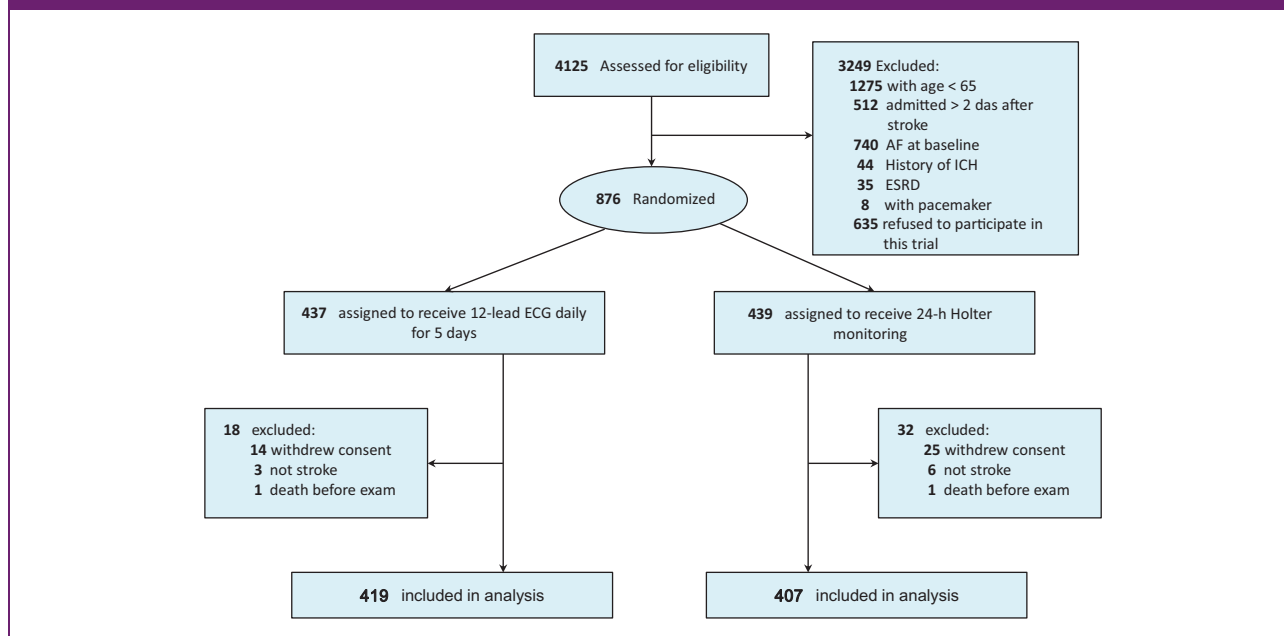
Between 1 October 2015 and 31 July 2018, 874 patients were randomized and 826 patients were included for analysis with 419 patients received 12-lead ECGs once daily for five days and 407 patients received 24-h Holter monitoring at six study hospitals (Figure 1). Baseline characteristics of both groups are summarized in Table 1 and there were no significant differences between the groups in terms of age, sex, NIHSS score, length of hospitalization, stroke type (lacunar infarction vs. non-lacunar infarction), comorbidity, and laboratory data. The duration of each 12-lead ECG recording was ~5 min and the formal result was reported by a cardiologist within one day after examination. The median duration of 24-h Holter report was three days after examination (interquartile range two to five days). Overall, a higher frequency of newly detected paroxysmal AF was found in ischemic stroke patients ≥ 80 years vs. 65–79 years (12.6% vs. 5.3%).

In the intention-to-treat analysis, of the 419 patients whom received serial 12-lead ECGs once daily for 5 days, 35 (8.4%) patients were identified as having newly detected AF, whereas of the 407 patients who received 24-h Holter monitoring, 28 (6.9%) patients were identified as having newly detected AF. There was no statistical difference between serial 12-lead ECG and 24-Holter to detect AF (adjusted odds ratio (OR) 1.17, 95% confidence interval (CI) 0.69–2.01). In subgroup analysis, all baseline characteristics did not influence new AF detection between these two modalities (Table 2).

In the per-protocol analysis, of the 419 patients who received serial 12-lead ECGs once daily for five days, 30 (7.2%) patients were identified as having newly detected AF, whereas of the 407 patients who received 24-h Holter monitoring, 22 (5.4%) patients were identified as having newly detected AF. There was no statistical difference between serial 12-lead ECG and 24-Holter to detect AF (adjusted OR 1.29, 95% CI 0.71–2.32). Most baseline characteristics did not influence new AF detection between these two modalities (Table 3).

Of the patients who had newly detected AF, 37.1% of patients in serial ECG group versus 39.3% of patients in 24-Holter group were on an oral anticoagulant at discharge, while 51.4% of patients in serial ECG

Figure 1. Study flowchart of patient selection.



group versus 64.3% of patients in 24-Holter group were on an oral anticoagulant at three months after their index ischemic stroke (Table 4).

Stepwise multivariate logistic regression revealed age ≥ 80 years (adjusted OR 2.14, 95% CI 1.24–3.69) and history of heart failure (adjusted OR 8.10, 95% CI 2.21–29.74) were associated with detection of paroxysmal AF, whereas patients with lacunar infarction had lower odds for detection of paroxysmal AF (adjusted OR 0.48, 95% CI 0.26–0.91) (Table 5).

Discussion

To our knowledge, this is the first randomized clinical trial to evaluate the detection rate of paroxysmal AF by serial 12-lead ECGs versus 24-h Holter monitoring in elderly ischemic stroke patients without known AF at baseline. The results suggested serial 12-lead ECGs once daily for five days compared with 24-h Holter monitoring, had comparable detection rate of paroxysmal AF among hospitalized elderly ischemic stroke patients without baseline known AF. The new AF detection rate for serial 12-lead ECGs in the current study among Taiwanese patients was similar to a previously published observational study among Canadian patients¹⁰ and provides some external validation for our findings. Since it is not uncommon for paroxysmal AF to be undetected in a single ECG on admission among ischemic stroke patients,¹³ additional cardiac rhythm workup is usually necessary. Our results imply that serial 12-lead ECGs might be a viable

alternative to 24-h Holter monitoring as a first-line approach to survey for potential paroxysmal AF in acute ischemic stroke patients.

Two recent large clinical trials showed that NOACs, rivaroxaban,¹⁴ and dabigatran¹⁵ failed to show superiority over aspirin to prevent recurrent stroke after embolic stroke of undetermined source, which further highlights the importance of identifying AF before use of NOACs. Since 25–40% of AF is paroxysmal and clinically silent,¹⁶ it can be a major challenge to detect paroxysmal AF in ischemic stroke patients and a comprehensive scrutiny is often necessary. A recent study indicated that among ischemic stroke patients without AF diagnosed at discharge, 4% actually had an unrecognized history of transient AF and these patients had higher risk of recurrent strokes at one-year follow-up compared to ischemic stroke patients without AF.¹⁷ Therefore, a careful history review to uncover a paroxysmal AF history is important for ischemic stroke patients. Since the 12-lead ECG is an inexpensive, readily available, diagnostic modality and the current study showed that serial 12-lead ECGs had comparable AF detection rate compared with 24-h Holter monitoring, it may not be unreasonable to do serial 12-lead ECGs in all elder ischemic stroke patients without known AF by history or baseline ECG at admission. For ischemic stroke patients without AF identified by careful AF history review and serial 12-lead ECGs, but in whom paroxysmal AF is still suspected, prolonged ECG monitoring may be necessary to identify potential paroxysmal AF.^{7,8} Also, we found that ischemic stroke

Table 1. Baseline demographics and clinical characteristics of patients with acute ischemic stroke, divided by the strategies for detection of atrial fibrillation

	ECG once daily for five days (n = 419)	24-h Holter monitoring (n = 407)
Age (years)	76 (69–82)	75 (69–81)
Male	242 (57.8%)	256 (62.9%)
Height (cm)	160 (153–165)	160 (153–165)
Weight (kg)	62 (54–70)	62 (55–70)
Body mass index (kg/m ²)	24.5 (22.3–27.2)	24.5 (22.3–27.0)
NIHSS score at admission	4 (3–7)	4 (2–7)
Length of hospitalization	9 (6–16)	9 (7–16)
Stroke type		
Lacunar infarction	253 (60.4%)	236 (58.0%)
Non-lacunar infarction	166 (39.6%)	171 (42.0%)
Comorbidity		
Hypertension	318 (75.9%)	316 (77.6%)
Diabetes mellitus	171 (40.8%)	153 (37.6%)
Hypercholesterolemia	127 (30.3%)	121 (29.7%)
Valvular heart disease	4 (1.0%)	5 (1.2%)
Chronic kidney disease	39 (9.3%)	29 (7.1%)
Coronary artery disease	46 (11.0%)	30 (7.4%)
Heart failure	8 (1.9%)	4 (1.0%)
Previous ischemic stroke or TIA	89 (21.2%)	98 (24.1%)
Cancer	24 (5.7%)	23 (5.7%)
Lab data		
Glycohemoglobin (%)	6.2 (5.8–7.3)	6.0 (5.7–7.0)
Creatinine (mg/dL)	1.0 (0.8–1.2)	1.0 (0.8–1.2)
Total cholesterol (mg/dL)	180 (152–205)	175 (151–200)
Triglyceride (mg/dL)	120 (77–150)	107 (79–144)
LDL cholesterol (mg/dL)	110 (76–162)	111 (89–131)
HDL cholesterol (mg/dL)	42 (35–49)	41 (34–48)

ECG: electrocardiogram; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NIHSS: National Institutes of Health Stroke Scale; TIA: transient ischemic attack.

Data are presented as median (interquartile range) or n (%).

*p < 0.05, Chi-square or Mann–Whitney U test.

Table 2. Intention-to-treat analysis for the detection rate of atrial fibrillation, ECG once daily for five days versus 24-h Holter monitoring

	ECG once daily for five days, event/total (%)	24-h Holter, event/total (%)	OR (95% CI)	Adjusted OR (95% CI) ^a	P for interaction
Overall	35/419 (8.4%)	28/407 (6.9%)	1.23 (0.74–2.07)	1.17 (0.69–2.01)	
Age					
≥80 years	16/141 (11.3%)	17/120 (14.2%)	0.78 (0.37–1.61)	0.74 (0.34–1.60)	0.14
65–79 years	19/278 (6.8%)	11/287 (3.8%)	1.84 (0.86–3.94)	2.03 (0.92–4.49)	
Sex					
Men	19/242 (7.9%)	18/256 (7.0%)	1.13 (0.58–2.20)	1.07 (0.53–2.15)	0.67
Women	16/177 (9.0%)	10/151 (6.6%)	1.40 (0.62–3.19)	1.81 (0.72–4.55)	
NIHSS					
0–4	11/221 (5.0%)	14/209 (6.7%)	0.73 (0.32–1.65)	0.76 (0.33–1.77)	0.07
≥5	24/198 (12.1%)	14/198 (7.1%)	1.81 (0.91–3.62)	1.61 (0.77–3.35)	
Stroke type					
Lacunar infarction	11/253 (4.3%)	13/236 (5.5%)	0.78 (0.34–1.78)	0.92 (0.39–2.16)	0.07
Non-lacunar infarction	24/166 (14.5%)	15/171 (8.8%)	1.76 (0.89–3.48)	1.64 (0.80–3.36)	
Hypertension					
Yes	28/318 (8.8%)	21/316 (6.6%)	0.89 (0.30–2.65)	1.30 (0.70–2.43)	0.51
No	7/101 (6.9%)	7/91 (7.7%)	0.89 (0.30–2.65)	1.04 (0.33–3.31)	
Diabetes mellitus					
Yes	10/171 (5.8%)	6/153 (3.9%)	1.52 (0.54–4.29)	1.61 (0.51–5.09)	0.89
No	25/248 (10.1%)	22/254 (8.7%)	1.18 (0.65–2.16)	1.15 (0.61–2.15)	
Chronic kidney disease					
Yes	4/39 (10.3%)	5/29 (17.2%)	0.55 (0.13–2.26)	0.17 (0.01–2.83)	0.18
No	31/380 (8.2%)	23/378 (6.1%)	1.37 (0.78–2.40)	1.40 (0.79–2.48)	
Coronary artery disease					
Yes	3/46 (6.5%)	3/30 (10%)	0.63 (0.12–3.34)	– ^b	0.41
No	32/373 (8.6%)	25/377 (6.6%)	1.32 (0.77–2.28)	1.29 (0.73–2.25)	
Heart failure					
Yes	4/8 (50%)	1/4 (25%)	3.00 (0.21–42.62)	– ^b	0.14
No	31/411 (7.5%)	27/403 (6.7%)	1.14 (0.67–1.94)	1.16 (0.67–2.00)	
Previous stroke or TIA					
Yes	6/89 (6.7%)	5/98 (5.1%)	1.35 (0.40–4.57)	1.28 (0.33–4.92)	0.95

(continued)

Table 2. Continued

	ECG once daily for five days, event/total (%)	24-h Holter, event/total (%)	OR (95% CI)	Adjusted OR (95% CI) ^a	P for interaction
No	29/330 (8.8%)	23/309 (7.4%)	1.20 (0.68–2.12)	1.17 (0.64–2.11)	

CI: confidence interval; ECG: electrocardiogram; OR: odds ratio; TIA: transient ischemic attack.

Data are presented as *n* (%).

^aAdjustment of age, sex, National Institutes of Health Stroke Scale (NIHSS) score, lacunar stroke, hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease, heart failure, and previous stroke or transient ischemic attack.

^bUnable to obtain results due to small sample size.

Table 3. Per-protocol analysis for the detection rate of atrial fibrillation, ECG once daily for five days versus 24-h Holter monitoring

	ECG once daily for five days, event/total (%)	24-h Holter, event/total (%)	OR (95% CI)	Adjusted (OR 95% CI) ^a	P for interaction
Overall	30/419 (7.2%)	22/407 (5.4%)	1.35 (0.77–2.38)	1.29 (0.71–2.32)	
Age					
≥80 years	15/141 (10.6%)	15/120 (12.5%)	0.83 (0.39–1.78)	0.80 (0.36–1.79)	0.18
65–79 years	15/278 (5.4%)	7/287 (2.4%)	2.28 (0.92–5.68)	2.59 (1.01–6.66)	
Sex					
Men	16/242 (6.6%)	13/256 (5.1%)	1.32 (0.62–2.81)	1.21 (0.55–2.64)	0.91
Women	14/177 (7.9%)	9/151 (6.0%)	1.36 (0.57–3.23)	1.70 (0.64–4.50)	
NIHSS					
0–4	9/221 (4.1%)	11/209 (5.3%)	0.76 (0.31–1.88)	0.87 (0.34–2.20)	0.07
≥5	21/198 (10.6%)	11/198 (5.6%)	2.02 (0.95–4.30)	1.76 (0.78–3.99)	
Stroke type					
Lacunar infarction	8/253 (3.2%)	10/236 (4.2%)	0.74 (0.29–1.90)	0.81 (0.31–2.15)	0.03
Non-lacunar infarction	22/166 (13.3%)	12/171 (7.0%)	2.02 (0.97–4.24)	1.86 (0.85–4.05)	
Hypertension					
Yes	23/318 (7.2%)	18/316 (5.7%)	1.29 (0.68–2.44)	1.24 (0.63–2.43)	0.80
No	7/101 (6.9%)	4/91 (4.4%)	1.62 (0.46–5.73)	1.79 (0.48–6.72)	
Diabetes mellitus					
Yes	8/171 (4.7%)	4/153 (2.6%)	1.83 (0.54–6.20)	2.09 (0.51–8.52)	0.94
No	22/248 (8.9%)	18/254 (7.1%)	1.28 (0.67–2.44)	1.23 (0.62–2.43)	
Chronic kidney disease					
Yes	4/39 (10.3%)	5/29 (17.2%)	0.55 (0.13–2.26)	0.17 (0.01–2.83)	0.13

(continued)

Table 3. Continued

	ECG once daily for five days, event/total (%)	24-h Holter, event/total (%)	OR (95% CI)	Adjusted (OR 95% CI) ^a	P for interaction
No	26/380 (6.8%)	17/378 (4.5%)	1.56 (0.83–2.91)	1.62 (0.85–3.09)	
Coronary artery disease					
Yes	2/46 (4.3%)	3/30 (10%)	0.41 (0.06–2.61)	– ^b	0.17
No	28/373 (7.5%)	19/377 (5.0%)	1.53 (0.84–2.79)	1.53 (0.82–2.85)	
Heart failure					
Yes	3/8 (37.5%)	1/4 (25%)	1.80 0.12–26.20)	– ^b	0.45
No	27/411 (6.6%)	21/403 (5.2%)	1.28 (0.71–2.30)	1.33 (0.73–2.45)	
Previous stroke or TIA					
Yes	6/89 (6.7%)	4/98 (4.1%)	1.70 (0.46–6.23)	1.73 (0.41–7.27)	0.77
No	24/330 (7.3%)	18/309 (5.8%)	1.27 (0.67–2.39)	1.23 (0.64–2.38)	

CI: confidence interval; ECG: electrocardiogram; OR: odds ratio; TIA: transient ischemic attack.

Data are presented as *n* (%).

^aAdjustment of age, sex, National Institutes of Health Stroke Scale (NIHSS) score, lacunar stroke, hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease, heart failure, and previous stroke or transient ischemic attack.

^bUnable to obtain results due to small sample size.

Table 4. Oral anticoagulation in patients with atrial fibrillation detected in serial ECGs and 24-h Holter monitoring groups, respectively, at discharge and at three months

Oral anticoagulation	ECG once daily for five days (n/N)	24-h Holter (n/N)
At discharge	13/35 (37.1%)	11/28 (39.3%)
Three months	18/35 (51.4%)	18/28 (64.3%)

N: number of patients that paroxysmal atrial fibrillation was detected, n: number of patients that an oral anticoagulant was used.

patients with age ≥ 80 years, non-lacunar stroke, or heart failure were significantly more likely have paroxysmal AF, and these patients in particular, may benefit from more intensive AF surveillance.

We found 37.1% and 39.3% of patients with newly detected AF took oral anticoagulants in serial ECG and 24-h Holter groups, respectively, at discharge. There were several reasons that may explain the relatively low rate of oral anticoagulation use in these people who were supposed to take oral anticoagulants for secondary stroke prevention. First, the ratio of hemorrhagic stroke to ischemic stroke is higher in Asian than non-Asian populations¹⁸ and there is a higher risk for anticoagulation-related intracranial hemorrhage among Asian patients with AF.¹⁹ Second, Taiwan National Health Bureau only reimburses NOACs after two weeks of ischemic stroke in AF

patients. Therefore many attending neurologists hesitate to use oral anticoagulants during acute stage of ischemic stroke even AF exists. Furthermore, it was possible that in certain cases, research assistants did not relay the information of newly detected AF to attending neurologists in time and therefore an oral anticoagulant would not be used at discharge.

AF is the main underlying heart disease of cardioembolic stroke^{20,21} and is associated with a higher in-hospital rate among ischemic stroke patients generally as well as among cardioembolic stroke subtype patients specifically.²² Among patients with cardioembolic stroke, in-hospital mortality was 32% for those with AF versus 15% for those without AF, while among patients with atherothrombotic stroke, in-hospital mortality was 29% in those with AF versus 19% in those without AF.²³ Presence of AF is associated with a poor

Table 5. Logistic regression for predictors of new-onset atrial fibrillation in patients with acute ischemic stroke using the whole trial cohort

Variables	Univariate logistic regression, odds ratio (95% CI)	Stepwise multivariate logistic regression, odds ratio (95% CI)
Age \geq 80 years	2.58 (1.54–4.33)	2.14 (1.24–3.69)
Male	0.93 (0.55–1.57)	
Height	1.00 (0.97–1.03)	
Weight	1.00 (0.98–1.02)	
Body mass index	0.99 (0.92–1.06)	
NIHSS score \geq 5	1.72 (1.02–2.91)	
Length of stay	1.01 (0.99–1.03)	
Lacunar infarction	0.39 (0.23–0.67)	0.48 (0.26–0.91)
Hypertension	1.07 (0.57–1.97)	
Diabetes mellitus	0.50 (0.28–0.90)	
Hypercholesterolemia	0.78 (0.43–1.40)	
Valvular heart disease	0.00 (0.00–)	
Chronic kidney disease	1.99 (0.94–4.23)	
Coronary artery disease	1.04 (0.43–2.50)	
Heart failure	9.31 (2.87–30.25)	8.10 (2.21–29.74)
Previous stroke or TIA	0.71 (0.36–1.38)	
Cancer	0.25 (0.03–1.85)	
Glycohemoglobin	0.72 (0.57–0.93)	
Creatinine	1.07(0.78–1.46)	
Total cholesterol	0.99 (0.98–1.00)	
Triglyceride	1.00 (0.99–1.00)	
LDL cholesterol	0.99 (0.98–1.00)	
HDL cholesterol	1.01 (0.99–1.04)	

CI: confidence interval; TIA: transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale; LDL: low density lipoprotein; HDL: high density lipoprotein.

clinical outcome in both cardioembolic and atherothrombotic infarction, which may be due to a higher frequency of heart failure in the group of cardioembolic stroke with AF, and a higher frequency of ischemic heart disease in the group of atherothrombotic stroke with AF.²²

Lacunar infarcts are the ischemic stroke subtype with a better functional prognosis and a cardiac

source of embolism or AF is not typical with this ischemic stroke subtype.²⁴ In this study, we found that patients with lacunar infarction had lower odds for detection of paroxysmal AF. Although autopsy-based evidence shows that cardioembolic occlusion can be an unusual cause of lacunar infarction,²⁵ in patients aged \geq 85 years vs. under 85 years, the higher occurrence of AF and the lower prevalence of hypertension

and diabetes mellitus, suggest that the cardioembolic pathogenic mechanism may be more frequent than lacunar syndromes in very elderly stroke patients.²⁶ Furthermore, a large clinical trial involving patients with recent symptomatic lacunar infarcts showed that about 9% of the recurrent ischemic strokes were caused by cardioembolism²⁷ and therefore survey of potential abnormality of heart, rhythm, and structure, is still crucial in patients with lacunar infarction.

This study has several limitations. First, some patients with paroxysmal AF may remain undetected by doing serial 12-lead ECGs once daily or 24-h Holter monitoring. However, since neither serial 12-lead ECGs nor 24-h Holter monitoring is the most powerful modality for identifying new AF, our study purpose was actually to establish the best first-line tool that can be applied universally to acute ischemic stroke patients without baseline known AF. Second, different underlying stroke mechanisms might influence the detection rate of paroxysmal AF, these varied among our enrolled patients. Since we did not collect detailed data on precise stroke mechanisms among the enrolled stroke patients, further analysis could not be conducted. Nonetheless, underlying stroke mechanisms were not likely to be different between the two groups because we randomly assigned patients to each group. Finally, lack of trial blinding on the part of investigators and patients may have introduced some bias, but the final results were interpreted by cardiologists unaware of the objectives of the study, which likely minimized this issue.

Conclusions

In conclusion, this randomized clinical trial showed that serial 12-lead ECGs once daily for five days compared with 24-h Holter monitoring had comparable detection rate of paroxysmal AF among elder patients with acute ischemic stroke and without known baseline AF, which suggests that serial 12-lead ECGs once daily for five days could be a viable alternative as a first-line approach to detect paroxysmal AF in these patients. Further studies may be warranted to assess whether detection of paroxysmal AF is eventually associated with a lower risk of stroke recurrence, due to an increased timely initiation of oral anticoagulants.

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