Hirosaki Med. J. 72 : 43—50, 2022

ORIGINAL ARTICLE

Frequent supraventricular premature contractions are an independent predictor for detection of atrial fibrillation in patients with embolic stroke undetermined source

Kazutaka Kitayama[1, 2], Shin Saito[2], Misato Hamadate[2], Naotake Miura[2], Natsumi Yamada[2], Hiroshi Shiroto[2], Norifumi Metoki[2], Joji Hagii[2], Takaatsu Kamada[2], Shingo Takanashi[2], and Hirofumi Tomita[1, 3]

Abstract

Background: Implantable cardiac monitor (ICM) is an effective tool to detect atrial fibrillation (AF) in patients with embolic stroke undetermined sources (ESUS). We investigated predictive factors for AF detection in ESUS patients with ICM implantation.

Methods: A total of 29 ESUS patients who underwent ICM implantation (median 71 [66-84] years and 18 males) were followed-up for a median of 253 [44-570] days.

Results: AF was detected in 10 patients (34.5%). The median time from ICM implantation to AF detection was 41.5 [33.25-59.25] days and that from stroke onset to AF detection was 62.5 [52.25-71.75] days. AF was detected within 90 days after ICM implantation in 90% (9/10) of the study patients. Plasma brain natriuretic peptide level was significantly higher in patients with AF detection than in those without it (125 [49.8-550.8] versus 18.2 [14.1-60.0] pg/mL, p=0.007). More frequent supraventricular premature contraction (SVPC) on Holter electrocardiogram (ECG) was observed in patients with AF detection than in those without it (1.81 [0.40-4.80] versus 0.04 [0.02-0.13] %/day, p<0.001). Cox proportional hazards model showed that the frequent SVPCs was a significant factor for AF detection.

Conclusions: The frequent SVPCs on Holter ECG is an independent predictor for covert AF in ESUS patients.

Hirosaki Med. J. 72 : 43—50, 2022

Key words: Embolic stroke undetermined source; Implantable cardiac monitor; Supraventricular premature contraction; Atrial fibrillation.

Introduction

Stroke subtype in patients with ischemic stroke is generally determined according to the Trial of Org 10172 (TOAST) classification[1], which comprises five subtypes of ischemic stroke: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology (cryptogenic stroke). Among them, cryptogenic stroke is diagnosed when the diagnostic evaluation is incomplete, no cause can be found despite the adequate evaluation, or there are two or more probable causes. Since many cases of cryptogenic stroke show embolic patterns, Hart et al. introduced the concept of embolic stroke undetermined source (ESUS) to determine new therapeutic options[2].

Atrial fibrillation (AF) was assumed to be a potential cause of ESUS, and therefore anticoagulation therapy using direct oral anticoagulant (DOAC) was expected to be useful for secondary prevention in patients with ESUS. However, dabigatran and rivaroxaban, both of which are

[1] Department of Cardiology and Nephrology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan
[2] Hirosaki Stroke and Rehabilitation Center, Hirosaki, Japan
[3] Department of Stroke and Cerebrovascular Medicine, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

Correspondence: H. Tomita, MD, PhD
Received for publication, November 22, 2021
Accepted for publication, December 22, 2021

DOAC, failed to demonstrate their benefit compared to aspirin, but rather resulted in more adverse events associated with bleeding[3, 4]. These findings indicate that AF is not a common source of thrombus in patients with ESUS. The left atrium, left ventricle, or atherosclerotic plaques in the aorta or carotid artery are considered to be a potential source of thrombus in ESUS patients[5].

Implantable cardiac monitor (ICM) was first introduced in 1990 and has been gradually miniaturized[6]. The detection rate of AF using this device in patients with cryptogenic stroke was reported to be 12.4% at 12 months after ICM implantation[7], making it possible to identify patients who require anticoagulation therapy. Furthermore, covert AF should be found as soon as possible in patients with ESUS, because the functional prognosis of cardioembolism caused by AF is known to be worst[8]. In the present study, we assessed predictive factors for AF detection using ICM in patients with ESUS.

Methods

Study patients and ESUS diagnosis

This is an observational study of 1,675 consecutive ischemic stroke patients admitted to the Hirosaki Stroke and Rehabilitation Center (HSRC) between September 1, 2018 and February 28, 2021. The diagnosis of cerebral infarction was made by at least two stroke specialists certified by the Japanese Stroke Association based on the TOAST classification[1]. ESUS was diagnosed by the diagnostic criteria of Hart et al.[2], and examinations including transthoracic echocardiography, transesophageal echocardiography (TEE), standard 12-lead electrocardiogram (ECG), and 24-hour Holter ECG were performed. Atherosclerotic lesions were evaluated by carotid echocardiography, computed tomography angiography, and magnetic resonance angiography. When a right-left shunt (atrial septal defect, and patent foramen ovale, etc.) was found on TEE, a lower extremity venous ultrasonography was additionally performed to determine the presence of deep vein thrombosis (DVT) in order to diagnose paradoxical cerebral embolism. As a result, 90 (5.4%) patients were diagnosed with ESUS. Of them, 60 patients in whom ICM was not proposed based on the overall judgment of the attending physician or consent was not obtained were excluded. ICM implantation was performed in 30 patients who finally gave consent, but one patient in whom ICM implantation was performed more than 1 year after onset was excluded from the study. Finally, 29 patients were followed-up until March 31, 2021.

Stroke severity was assessed based on the National Institutes of Health Stroke Scale (NIHSS) score on admission. The $CHADS_2$ and CHA_2DS_2-VASc scores for risk stratification of thromboembolism before stroke onset were determined in each patient, as described previously[9, 10]. The percentage of supraventricular premature contraction (SVPC) on Holter ECG was calculated.

This study was approved by the ethics committees of the HSRC (20B005, 20B005-1).

Blood sampling and ICM implantation procedure

Blood sampling was performed in all patients before ICM implantation. Reveal LINQ (Medtronic, Minneapolis, MN, USA) was used as a monitoring device. It was inserted under local anesthesia in a 45-degree direction over the left lateral margin of the fourth intercostal space. Adequate R-wave height of more than 0.2 mV, the recommended value, was observed in all cases. When AF was suspected by the RR irregularity detection program, automatic data transmission was performed through the Medtronic's Care Link network. The transmitted data were reviewed by a cardiologist for the final diagnosis of AF. Data sent by March 31, 2021 were used for analysis.

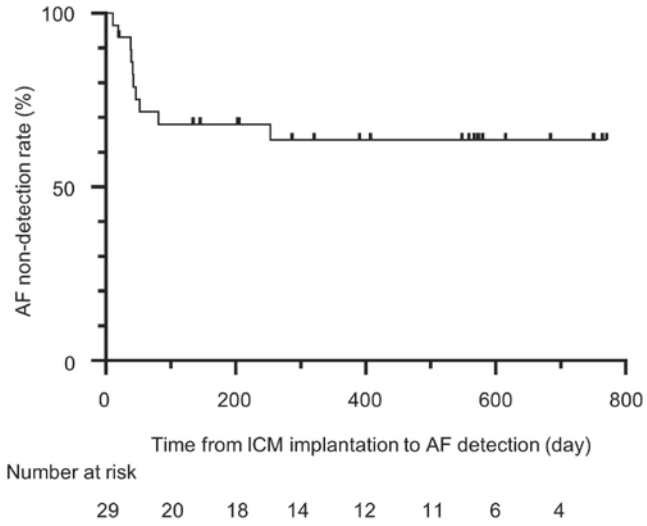

Figure 1 Kaplan-Meier estimates for AF non-detection rate.

Statistical analysis

Continuous and ordinal variables were presented as median and quartile range (25-75th percentiles). Nominal variables were presented as number and percentage. Continuous variables were statistically examined using the Mann-Whitney U test, and nominal variables were using the Fisher's exact test. The Kaplan–Meier estimate was performed to assess AF non-detection rate. Cox proportional hazards model was used to calculate hazard ratio (HR) and 95% confidence interval (CI) for AF detection rate. Receiver operating characteristic curve analysis was performed to evaluate cutoff value, sensitivity, and specificity for AF detection. JMP® 16 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Results

Characteristics of the study patients who underwent ICM implantation are shown in Table 1. The median age was 71 [66-84] years and 18 patients were male. The NIHSS score was 2 [1-14], and the $CHADS_2$ score and the CHA_2DS_2-VASc score was 3 [3-4] and 5 [3-6], respectively. The left atrial diameter was 34.0 [30.9-39.0] mm, and the percentage of SVPC detected by the Holter ECG was 0.13 [0.03-0.74] %.

The median time from admission to ICM implantation was 19 [14.0-31.5] days, and the median observation period was 253 [44-570] days. AF was detected in 10 patients (10/29, 34.5%). The Kaplan-Meier curve for AF non-detection rate is shown in Figure 1. The median time from ICM implantation to AF detection was 41.5 [33.25-59.25] days, and the median time from stroke onset to AF detection was 62.5 [52.25-71.75] days. AF was detected within 60 days in 80% (8/10) of the patients and within 90 days in 90% (9/10) of the patients after ICM implantation. All AF was detected within 1 year.

Characteristics between patients with AF detection (n=10) and those without it (n=19) were compared (Table 1). There were no differences in age, sex, the $CHADS_2$ score, the CHA_2DS_2-VASc score, and the left atrial diameter between the two groups. Brain natriuretic peptide (BNP) level and the frequency of SVPC were significantly higher in patients with AF detection than in those without it (125 [49.8-550.8] versus 18.2 [14.1-60.0] pg/mL, p=0.007, and 1.81 [0.40-4.80] versus 0.04 [0.02-0.13] %, p<0.001, respectively). Cox proportional hazards

Table 1. Clinical characteristics of the study patients

Variables	Total n=29	Patients with AF detection n=10	Patients without AF detection n=19	p-value
Basic characteristics				
Age (years)	71 [66-84]	80.5 [65.5-87]	71 [66-83]	0.206
Male	18 (62)	5 (50)	13 (68)	0.432
BMI (kg/m^2)	22.4 [20.5-25.8]	21.9 [16.9-24.1]	22.6 [21.2-25.3]	0.302
NIHSS	2 [1-14]	13 [1-16]	2 [1-9]	0.102
Risk factors				
Congestive heart failure	1 (3)	1 (10)	0 (0)	0.345
Hypertension	20 (69)	7 (70)	13 (68)	1.000
Diabetes mellitus	9 (31)	4 (40)	5 (26)	0.675
Previous stroke or TIA	4 (14)	1 (10)	3 (16)	1.000
$CHADS_2$ score	3 [3-4]	4 [3-4]	3 [2-4]	0.205
CHA_2DS_2-VASc score	5 [3-6]	5 [4-6]	4 [3-5]	0.181
Blood chemistry				
LDL (mg/dL)	117 [89.5-148.5]	120 [85.5-140.5]	112 [89-150]	0.795
CCr (mL/min)	63 [51.5-84.5]	57.5 [47-80.3]	64 [58-88]	0.435
CRP (mg/dL)	0.12 [0.055-1.032]	0.216 [0.099-1.652]	0.097 [0.049-0.946]	0.169
D-dimer (μg/mL)	1.2 [0.60-3.17]	2.09 [0.69-4.66]	1.11 [0.45-1.90]	0.162
BNP (pg/mL)	46.3 [15.0-136.7]	125 [49.8-550.8]	18.2 [14.1-60.0]	0.007
Plt ($10^4/\mu L$)	22.2 [19.9-27.1]	21.8 [17.8-27.0]	22.6 [20.7-27.8]	0.291
Fibrinogen (mg/dL)	395 [290-464]	400 [283.7-486.8]	392 [296.5-470.5]	0.934
HbA1c (%)	5.9 [5.5-6.3]	6.0 [5.6-6.9]	5.9 [5.5-6.3]	0.180
Echocardiography				
Left atrial diameter (mm)	34.0 [30.9-39.0]	37.3 [32.4-41.0]	33.6 [30.4-37.1]	0.119
Holter electrocardiogram				
SVPC (%)	0.13 [0.03-0.74]	1.81 [0.40-4.80]	0.04 [0.02-0.13]	< 0.001

Data are shown as median [25-75th percentiles], or n (%). Creatinine clearance was estimated by the Cockcroft-Gault equation. BMI indicates body mass index, TIA; transient ischemic attack, NIHSS; National Institutes of Health Stroke Scale, CCr; creatinine clearance, CRP; C-reactive protein, LDL-C; low-density lipoprotein cholesterol, HbA1c; hemoglobin A1c, BNP; brain natriuretic peptide, SVPC; supraventricular premature contraction.

Table 2. Cox proportional hazards model for AF detection in the study patients

	Hazard ratio	95% CI	p-value
Age	1.02	0.95-1.10	0.625
Male sex	0.43	0.11-1.72	0.235
BNP (pg/mL) per 10 pg/mL increase	1.02	0.98-1.05	0.327
SVPC (%) per 1% increase	1.68	1.20-2.46	0.003

Analysis was performed after adjusting for age, sex, and included significant factors shown in univariate analysis. CI indicates confidence interval, BNP; brain natriuretic peptide, SVPC; supraventricular premature contraction.

Table 3. Cutoff value, area under the curve, sensitivity, and specificity of SVPC for AF detection

	Cutoff value	AUC	Sensitivity	Specificity
SVPC	0.204%	0.94	100%	84%

SVPC indicates supraventricular premature contraction, AUC; area under the curve.

model showed that only the frequency of SVPC per 1% increase was a significant factor for AF detection (HR 1.68, 95% CI; 1.20-2.46, p=0.003) (Table 2). Using a cutoff value of 0.204% for SVPC in ESUS patients, the sensitivity and specificity for detecting AF were 100% and 84% (Table 3).

Among 10 patients with AF detection by ICM, antiplatelet therapy was switched to anticoagulation therapy in 7 patients (70%) within a median

of 1 [1-10] days, 2 patients already received anticoagulation therapy before ICM implantation, and the remaining 1 patient did not receive anticoagulation therapy because of severe pneumonia. All 19 patients without AF detection by ICM continued antiplatelet therapy. On the other hand, among 60 patients without ICM implantation, 47 patients (78%) continued antiplatelet therapy, 8 patients received anticoagulant therapy due to DVT, suspected thrombus detected by TEE in the left atrial appendage, and so on. The remaining 5 patients did not receive antithrombotic therapy due to severe pneumonia or terminal stage of the disease.

Discussion

In recent years, there have been several reports on predictors of AF detection in ESUS patients, including those related to SVPC, biomarkers of the coagulation system, P-wave findings on ECG, and left atrial enlargement[11-16]. In the present study, we found that the frequency of SVPC detected by the Holter ECG and BNP values were different between patients with AF detection and without it, and the frequency of SVPC was an independent predictor for AF detection in multivariate analysis.

AF detection rate in ESUS patients

In the present study, AF was captured at a relatively high rate of 34.5% (10/29 patients) in a median observation period of 253 days. A recent report in the Japanese cryptogenic stroke patients showed that AF detection rate was 28.8% (19/66 patients) in a median observation period of approximately 8 months, which was a similar AF detection rate to the present study[17]. Sanna T et al. reported that AF detection rate in patients with cryptogenic stroke (median 61.6 years old) was 8.9% at 6 months, 12.4% at 12 months, and 30.0% at 36 months after ICM implantation[7]. As previous reports have shown that age is a predictor for AF detection after ESUS[16], the relatively large number of elderly patients (median 71 years) in the present study may have contributed to the high detection rate of AF. In addition, in our hospital, ICM was implanted in patients with undetected AF after monitoring ECG for 2-3 weeks after stroke onset and during acute care. Different time point at which ICM was implanted may be related to the difference in AF detection rate between the previous reports and the present study.

Another important finding in the present study was that the median time to AF detection was 41.5 days, which was a relatively early detection after ICM implantation. The Kaplan-Meier curve of the previous Japanese study also showed a high AF detection rate between 2 and 3 months[17], similar to the result of the present study. This suggests that it may be possible to detect AF not only by ICM implantation but also by adequate observation period with a wearable or patch-type Holter ECG for 2 to 3 months after the onset of ischemic stroke. This benefit may be particularly applicable to the severely ill patients who were excluded in the present study, and future studies with focus on these patients are awaited.

Association between AF and BNP

In the present study, BNP value was significantly higher in the AF detection patients than in AF non-detection patients. There have been numerous reports on the possibility that high BNP value may predict the incidence of AF in general inhabitants excluding those with heart failure[18], and that high preoperative BNP value was associated with AF detection and recurrence after cardiac surgery and ablation therapy[19, 20]. Furthermore, BNP value was reported to be significantly higher in hospitalized ischemic stroke patients with newly captured AF on 7-day Holter ECG[21]. Furthermore, we previously reported that in 222 hospitalized ischemic stroke

patients within 48 hours of onset, BNP value on admission is significantly higher in patients with paroxysmal AF than in those with sinus rhythm[22]. Importantly, BNP value is a significant factor for predicting paroxysmal AF after hospitalization, indicating that BNP may be clinically useful for detecting paroxysmal AF in ischemic stroke patients. These findings support our results of the present study showing that BNP value was significantly higher in patients with AF detection than in those without it. However, multivariate analysis did not show the significance of BNP value for AF detection, maybe due to a small number of study patients in the present study and the difference in the patients' characteristics among these studies. Further large-scale studies regarding this point are required.

Association between AF and SVPC

In the present study, the frequency of SVPC on Holter ECG was significantly higher in patients with AF detection and the frequent SVPCs was a significant predictor for AF detection in ESUS patients. The Framingham score is known to be a predictive score for detection of AF in the general population[23], and the addition of SVPC into this scoring system is shown to predict AF detection more accurately during an observation of 15 years. It is reported that the specificity for the development of AF exceeds 90% when cut off value of SVPC is 32 beats/h[24]. If we have a daily heart rate of 100,000 beats/day, 32 beats/h corresponds to 0.768%/day. In addition, patients with ≥30 SVPCs per hour or any episode of runs of ≥ 20 SVPCs had a higher incidence of hospitalization for newly AF detection than those without them, with a hazard ratio of 2.78 for up to 7 years of follow-up[25]. These studies suggest that the frequent SVPCs may be a predictor of AF detection in a general population.

Recent study reported that AF was detected by ICM in cryptogenic stroke patients with SVPCs > 222 beats/day during a median observation of 228 days[17]. This frequency of SVPC corresponds to 0.222%/day under a daily heart rate of 100,000 beats/day. Victor et al. also reported that AF in ESUS patients was detected with a sensitivity of 89% and specificity of 90%, when SVPC on Holter ECG was set at 0.15% as a cutoff value[26]. The cutoff value of 0.204% in the present study is also a similar value to the previous reports. All these findings indicate that the frequent SVPCs may be related to the incidence of AF, and approximately 0.2%/day of SVPC may be a significant predictor for AF detection in ESUS patients.

Limitations

There are several limitations in the present study. First, this is a single-center and small size retrospective study, and therefore, generalization of results may be limited. Second, since the main purpose of ICM implantation was to detect AF and to prevent recurrent stroke, ICM was not implanted in all patients diagnosed with ESUS. Patients with relatively mild severity were included, but severely ill patients were not included in the present study. Therefore, there may be a possibility of bias in patients' selection. Finally, the follow-up period ranged from 2 months to 2.5 years. It is possible that the number of AF events may have been underestimated because the follow-up period was not long enough.

Conclusion

The frequent SVPCs on Holter ECG is an independent predictor for covert AF in ESUS patients. Careful monitoring including a long-term Holter ECG or ICM implantation may be useful for detecting AF in ESUS patients to receive appropriate secondary prevention,

especially in those with frequent SVPCs.

Conflicts of Interest

Dr. Tomita received research funding from Boehringer Ingelheim, Bayer, Daiichi-Sankyo, and Pfizer, and Speakers' Bureau/Honorarium from Boehringer Ingelheim, Bayer, Daiichi-Sankyo, and Bristol-Myers Squibb. The rest of the authors have no relevant disclosures.

Acknowledgment

We are grateful to Ms. Haruka Tonosaki for her excellent technical support.

References

1) Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35-41.

2) Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, Sacco RL, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13:429-38.

3) Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, Swaminathan B, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. N Engl J Med. 2018;378:2191-201.

4) Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, Kreuzer J, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. N Engl J Med. 2019;380:1906-17.

5) Ntaios G. Embolic Stroke of Undetermined Source: JACC review topic of the week. J Am Coll Cardiol. 2020;75:333-40.

6) Bisignani A, De Bonis S, Mancuso L, Ceravolo G, Bisignani G. Implantable loop recorder in clinical practice. J Arrhythm. 2019;35:25-32.

7) Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014;370:2478-86.

8) Tomita H, Sasaki S, Hagii J, Metoki N. Covert atrial fibrillation and atrial high-rate episodes as a potential cause of embolic strokes of undetermined source: Their detection and possible management strategy. J Cardiol. 2018;72:1-9.

9) Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the national registry of atrial fibrillation. JAMA. 2001;285:2864-70.

10) Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, et al. Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;31:2369-429.

11) Li TYW, Yeo LLL, Ho JSY, Leow AS, Chan MY, Dalakoti M, Chan BPL, et al. Association of electrocardiographic P-Wave markers and atrial fibrillation in embolic stroke of undetermined source. Cerebrovasc Dis. 2021;50:46-53.

12) Sade LE, Keskin S, Can U, Çolak A, Yüce D, Çiftçi O, Özin B, et al. Left atrial mechanics for secondary prevention from embolic stroke of undetermined source. Eur Heart J Cardiovasc Imaging. 2020. https://doi.org/10.1093/ehjci/jeaa311

13) Sieweke JT, Biber S, Weissenborn K, Heuschmann PU, Akin M, Zauner F, Gabrie MM, et al. Septal total atrial conduction time for prediction of atrial fibrillation in embolic stroke of unknown source: a pilot study. Clin Res Cardiol. 2020;109:205-14.

14) Ellis D, Rangaraju S, Duncan A, Hoskins M, Raza SA, Rahman H, Winningham M, et al. Coagulation markers and echocardiography predict atrial fibrillation, malignancy or recurrent stroke after cryptogenic stroke. Medicine (Baltimore). 2018;97: e13830.

15) Kusunose K, Takahashi H, Nishio S, Hirata Y, Zheng R, Ise T, Yamaguchi K, et al. Predictive value of left atrial function for latent paroxysmal atrial fibrillation as the cause of embolic stroke of

undetermined source. J Cardiol. 2021;5:355-361.

16) Israel C, Kitsiou A, Kalyani M, Deelawar S, Ejangue LE, Rogalewski A, Hagemeister C, et al. Detection of atrial fibrillation in patients with embolic stroke of undetermined source by prolonged monitoring with implantable loop recorders. Thromb Haemost. 2017;117:1962-9.

17) Todo K, Iwata T, Doijiri R, Yamagami H, Morimoto M, Hashimoto T, Sonoda K, et al. Frequent premature atrial contractions in cryptogenic stroke predict atrial fibrillation detection with insertable cardiac monitoring. Cerebrovasc Dis. 2020;49:144-50.

18) Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, Wolf PA, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med. 2004;350:655-63.

19) Hernández-Leiva E, Dennis R, Isaza D, Umaña JP. Hemoglobin and B-type natriuretic peptide preoperative values but not inflammatory markers, are associated with postoperative morbidity in cardiac surgery: a prospective cohort analytic study. J Cardiothorac Surg. 2013;8:170.

20) Xu M, Liu F, Ge ZX, Li JM, Xie X, Yang JH. Functional studies of left atrium and BNP in patients with paroxysmal atrial fibrillation and the prediction of recurrence after CPVA. Eur Rev Med Pharmacol Sci. 2020;24:4997-5007.

21) Wachter R, Lahno R, Haase B, Weber-Krüger M, Seegers J, Edelmann F, Wohlfahrt J, et al. Natriuretic peptides for the detection of paroxysmal atrial fibrillation in patients with cerebral ischemia-the Find-AF study. PLoS One. 2012;7:e34351.

22) Shiroto H, Tomita H, Hagii J, Metoki N, Fujita A, Kamada T, Takahashi K, et al. Impact of atrial natriuretic peptide value for predicting paroxysmal atrial fibrillation in ischemic stroke patients. J Stroke Cerebrovasc Dis. 2017;26:772-8.

23) Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, Sr., Newton-Cheh C, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet. 2009;373:739-45.

24) Dewland TA, Vittinghoff E, Mandyam MC, Heckbert SR, Siscovick DS, Stein PK, Psaty BM, et al. Atrial ectopy as a predictor of incident atrial fibrillation: a cohort study. Ann Intern Med. 2013;159:721-8.

25) Binici Z, Intzilakis T, Nielsen OW, Køber L, Sajadieh A. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. Circulation. 2010;121:1904-11.

26) Víctor CU, Carolina PE, Jorge TR, Joaquín CR, Manuel SG, Marta CM, María FVJ, et al. Incidence and predictive factors of hidden atrial fibrillation detected by implantable loop recorder after an embolic stroke of undetermined source. J Atr Fibrillation. 2018;11:2078.