Usefulness of a Combination of Interatrial Block and a High CHADS₂ Score to Predict New Onset Atrial Fibrillation

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SUMMARY

Interatrial block (IAB) is associated with an increased risk of atrial fibrillation (AF). The aim of this retrospective study was to investigate the association of a combination of IAB and the CHADS₂ score, an AF-related risk score for ischemic stroke, with new onset AF in patients in sinus rhythm. A total of 1,571 patients (803 males, 768 females; mean age: 58 ± 16 years) were included in this study. IAB was defined as a P-wave duration > 120 ms in the 12-lead electrocardiogram, and a high CHADS₂ score as ≥ 2 points. During the mean follow-up period of 4.8 ± 0.7 years, new onset AF occurred in 122 patients (16.1 per 1,000 patient-years). The incidence of new onset AF was 4.0 per 1,000 patient-years in patients with no IAB and a low CHADS₂ score, and 44.0 per 1,000 patient-years in patients with IAB and a high CHADS₂ score. In multivariate Cox regression analysis, the hazard ratio for IAB and a high CHADS₂ score compared with no IAB and a low CHADS₂ score was 12.18 (95% confidence interval: 6.22–23.87, *P* < 0.001), after adjustment for age, sex, coronary artery disease, valvular heart disease, smoking, medications, and echocardiographic parameters. In conclusion, IAB and a high CHADS₂ score independently and synergistically predict new onset AF in patients in sinus rhythm, indicating an approximately 12-fold higher risk in patients with both IAB and a high CHADS₂ score. Patients meeting these criteria should have more aggressive early intervention to prevent AF. (Int Heart J 2016; 57: 580-585)

Key words: Electrocardiogram, Prognosis

Atrial fibrillation (AF) is a common cardiac arrhythmia in the general population¹⁾ and is associated with an increased risk of death, hospitalization, stroke, and heart failure.²⁻⁵⁾ Therefore, it is crucial to identify patients who are at increased risk of developing new onset AF. Interatrial block (IAB) is manifested in the 12-lead electrocardiogram (ECG) by a P-wave duration > 120 ms,⁶⁾ and has been associated with increased risk of AF.⁷⁻¹¹⁾ Currently, the CHADS₂ score is widely used for predicting future ischemic stroke in patients with AF.¹²⁾ Although AF is more prevalent in subjects with high CHADS₂ scores than in those with low CHADS₂ scores,^{13,14)} the combined role of IAB and the CHADS₂ score in new onset AF in patients in sinus rhythm remains unclear. Therefore, in the present study, we investigated the association of a combination of IAB and high CHADS₂ score on new onset AF in patients in sinus rhythm.

METHODS

Study population: Our database of ECG recordings of patients who were hospitalized in Henan Provincial People's

Hospital for any therapy between March 1, 2010 and March 15, 2010 was retrospectively reviewed. If patients had more than one ECG recording during the index hospitalization, only the first recording was analyzed to measure P-wave duration, and all of the ECG recordings were analyzed to detect AF. P-wave duration was measured using a resting 12-lead ECG (high-pass filter 0.05 Hz, low-pass filter 150 Hz, 25 mm/s, 10 mm/mv) in all patients in sinus rhythm. The ECGs were scanned at 300 DPI, and the images were amplified × 10. P-waves were measured manually using a caliper in all 12 ECG leads to identify the wave with the longest duration. At least 3 beats were measured on each ECG lead. The onset of the P-wave was identified as the point of initial upward or downward deflection from the baseline, and the P-wave endpoint was defined as the point where the waveform returned to the baseline. IAB was defined as a P-wave duration > 120 ms in the 12-lead ECG.⁶⁾ The ECG analyses were performed by two blinded independent observers, and any differences between the observers were resolved by consensus. The clinical records of all patients were then reviewed. The CHADS₂ score was calculated for each patient by assigning 1 point each for age > 75 years, hypertension, diabetes mellitus, and congestive heart failure

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Table I. Baseline Clinical Characteristics

	Mean $\pm$ SD or %
Age (years)	58 $\pm$ 16
Age $\geq$ 75	264 (16.8%)
Male, <i>n</i> (%)	803 (51.1%)
Valvular heart disease, <i>n</i> (%)	127 (8.1%)
Coronary artery disease, <i>n</i> (%)	450 (28.6%)
Diabetes mellitus, <i>n</i> (%)	453 (28.8%)
Hypertension, <i>n</i> (%)	590 (37.6%)
Heart failure, <i>n</i> (%)	121 (7.7%)
Smoker, <i>n</i> (%)	437 (27.8%)
Stroke or TIA, <i>n</i> (%)	166 (10.6%)
CHADS ₂ score	
Mean	1.1 $\pm$ 1.3
0	685 (43.6%)
1	424 (27.0%)
2	213 (13.6%)
3	139 (8.8%)
4	72 (4.6%)
5	34 (2.2%)
6	4 (0.3%)
$\geq$ 2	462 (29.4%)
Left atrial diameter (mm)	35.7 $\pm$ 4.4
LVEF, %	63.4 $\pm$ 8.2
Calcium channel blockers, <i>n</i> (%)	351 (22.3%)
β -blockers, <i>n</i> (%)	178 (11.3%)
ACEI/ARB, <i>n</i> (%)	205 (13.0%)
Statins, <i>n</i> (%)	398 (25.3%)
Anticoagulants, <i>n</i> (%)	26 (1.7%)
Antiplatelet medications, <i>n</i> (%)	554 (35.3%)

TIA indicates transient ischemic attack; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitors; and ARB, angiotensin receptor blockers.

and 2 points for a prior stroke or transient ischemic attack (TIA).¹²⁾ The main exclusion criteria were patients with known AF, missing data for calculation of the CHADS₂ score, and inadequate follow-up. If the data of patients could not be obtained for any reason within 1 month after the time point of follow-up or patients died from causes unrelated to AF during follow-up, patients were identified as those with inadequate follow-up. The study protocol was approved by the local institutional review board. The requirement for informed consent was waived because of the anonymous nature of the data.

Patient follow-up: All patients included in the study were followed up until occurrence of new onset AF or until March 1, 2015 if no new onset AF occurred. All study subjects were contacted by telephone every 6 months. Follow-up interviews with participants or their proxies were conducted to inquire about death or hospitalization during the intervening time. For any reported event, medical records were retrieved and reviewed. New onset AF was defined as a subsequent hospital discharge diagnosis of AF.

Statistical analysis: All analyses were performed with SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous data are presented as the mean $\pm$ standard deviation. Univariate analysis to assess the predictive value of clinical variables on AF recurrence was performed using the unpaired independent samples *t*-test for continuous variables and the χ^2 test or Fisher's exact test as necessary for categorical variables. We calculated the cumulative incidence stratified by IAB and CHADS₂ score. The study population was classified into dichotomous categories: 1) IAB and no IAB; and 2) high

Figure 1. Incidence of new onset AF per 1,000 patient-years according to IAB or not (A) and CHADS₂ score (B). AF indicates atrial fibrillation; and IAB, interatrial block.

CHADS₂ score ($\geq$ 2 points) and low CHADS₂ score ($<$ 2 points). Differences in the cumulative incidence of new onset AF were then estimated using the Kaplan-Meier method and tested using the log-rank test. Finally, Cox regression analysis was performed by testing the adjusted models for the independent and synergistic effects of IAB and a high CHADS₂ score. In the adjusted model, the effect of IAB and a high CHADS₂ score was adjusted by age, sex, coronary artery disease, valvular heart disease, smoking, medications, and echocardiographic parameters, including left atrial dimension and left ventricular ejection fraction (LVEF). All probability values were 2-sided, and $P < 0.05$ was considered significant.

RESULTS

A total of 1571 patients (803 males, 768 females; mean age: 58 $\pm$ 16 years) were included in this study. IAB was detected in 548 (34.9%), and 462 patients (29.4%) had a CHADS₂ score $\geq$ 2, which was considered a high score in this study. Table I lists the baseline clinical characteristics of the study population.

Over a median follow-up of 4.8 $\pm$ 0.7 years (range, 0–5 years), new onset AF occurred in 122 patients (16.1 per 1,000 patient-years). Figure 1 shows the incidence of new onset AF in relation to IAB or not and to CHADS₂ score. The incidence of new onset AF was 4.3 per 1,000 patient-years for patients without IAB and 39.5 per 1,000 patient-years for patients with IAB. Similarly, the incidence of new onset AF increased from

Table II. Clinical Characteristics of Patients With IAB and Without IAB

	IAB (<i>n</i> = 548)	No IAB (<i>n</i> = 1023)	<i>P</i>
Age (years)	65 ± 11	54 ± 17	< 0.001
Age ≥ 75	171 (31.2%)	93 (9.1%)	< 0.001
Male, <i>n</i> (%)	311 (56.8%)	492 (48.1%)	0.001
Valvular heart disease, <i>n</i> (%)	59 (10.8%)	68 (6.6%)	0.004
Coronary artery disease, <i>n</i> (%)	227 (41.4%)	223 (21.8%)	< 0.001
Diabetes mellitus, <i>n</i> (%)	243 (44.3%)	210 (20.5%)	< 0.001
Hypertension, <i>n</i> (%)	319 (58.2%)	271 (26.5%)	< 0.001
Heart failure, <i>n</i> (%)	45 (8.2%)	76 (7.4%)	0.579
Smoker, <i>n</i> (%)	161 (29.4%)	276 (27.0%)	0.312
Prior stroke or TIA, <i>n</i> (%)	111 (20.2%)	56 (5.5%)	< 0.001
CHADS ₂ score			
Mean	1.8 ± 1.3	0.7 ± 1.2	< 0.001
0	82	603	
1	170	254	
2	143	70	
3	94	45	
4	37	35	
5	18	16	
6	4	0	
≥ 2	296 (54.0%)	166 (16.2%)	< 0.001
Left atrial diameter (mm)	36.6 ± 4.4	35.2 ± 4.4	< 0.001
LVEF, %	62.6 ± 9.7	63.8 ± 7.3	0.007
Calcium channel blockers, <i>n</i> (%)	154 (28.1%)	197 (19.3%)	< 0.001
β-blockers, <i>n</i> (%)	73 (13.5%)	105 (10.3%)	0.068
ACEI/ARB, <i>n</i> (%)	107 (19.5%)	98 (9.6%)	< 0.001
Statins, <i>n</i> (%)	205 (37.4%)	193 (18.9%)	< 0.001
Anticoagulants, <i>n</i> (%)	15 (2.7%)	11 (1.1%)	0.014
Antiplatelet, <i>n</i> (%)	236 (43.1%)	319 (31.2%)	< 0.001

IAB indicates interatrial block. For other abbreviations, see Table I.

Table III. Clinical Characteristics of Patients With High and Low CHADS₂ Scores

	CHADS ₂ ≥ 2 (<i>n</i> = 462)	CHADS ₂ < 2 (<i>n</i> = 1109)	<i>P</i>
Age (years)	70 ± 10	53 ± 16	< 0.001
Age ≥ 75	234 (50.6%)	58 (5.2%)	< 0.001
Male, <i>n</i> (%)	257 (55.6%)	546 (49.2%)	0.014
Valvular heart disease, <i>n</i> (%)	39 (8.4%)	88 (7.9%)	0.737
Coronary artery disease, <i>n</i> (%)	222 (48.1%)	228 (20.6%)	< 0.001
Diabetes mellitus, <i>n</i> (%)	309 (66.9%)	144 (13.0%)	< 0.001
Hypertension, <i>n</i> (%)	363 (78.6%)	227 (20.5%)	< 0.001
Heart failure, <i>n</i> (%)	88 (19.0%)	33 (3.0%)	< 0.001
Smoker, <i>n</i> (%)	166 (35.9%)	271 (24.4%)	0.109
Prior stroke or TIA, <i>n</i> (%)	166 (35.9%)	0 (0.0%)	< 0.001
IAB, <i>n</i> (%)	296 (64.1%)	252 (22.7%)	< 0.001
No IAB, <i>n</i> (%)	166 (35.9%)	857 (77.3%)	< 0.001
Left atrial diameter (mm)	37.1 ± 4.5	35.1 ± 4.3	< 0.001
LVEF, %	62.8 ± 9.7	63.6 ± 7.7	0.085
Calcium channel blockers, <i>n</i> (%)	165 (35.7%)	186 (16.8%)	< 0.001
β-blockers, <i>n</i> (%)	87 (18.8%)	91 (8.2%)	< 0.001
ACEI/ARB, <i>n</i> (%)	103 (22.3%)	102 (9.2%)	< 0.001
Statins, <i>n</i> (%)	219 (47.4%)	179 (16.1%)	< 0.001
Anticoagulants, <i>n</i> (%)	18 (3.9%)	8 (0.7%)	< 0.001
Antiplatelet, <i>n</i> (%)	320 (69.3%)	234 (21.1%)	< 0.001

For abbreviations, see Table I and Table II.

8.6 per 1,000 person-years in patients with a CHADS₂ score of 0 to 13.9 and 29.7 per 1,000 person-years in patients with CHADS₂ scores of 1 and ≥ 2, respectively.

The clinical characteristics of patients with and without IAB and with high and low CHADS₂ scores are listed in Ta-

bles II and III. The prevalences of male sex, valvular heart disease, coronary artery disease, diabetes mellitus, hypertension, and prior stroke or TIA were significantly higher in patients with IAB than in those without IAB. Left atrial diameter was significantly greater in patients with IAB than in those without

IAB. Patients with IAB had higher CHADS₂ scores and lower LVEF than those without IAB. In patients with high CHADS₂ scores, the prevalences of male sex, coronary artery disease, diabetes mellitus, hypertension, heart failure, and prior stroke or TIA were significantly higher than in patients with low CHADS₂ scores. Patients with high CHADS₂ had a greater left atrial diameter and lower LVEF.

Kaplan-Meier curves showed that IAB was associated with a higher incidence of new onset AF than no IAB ($P < 0.001$) (Figure 2A). Similarly, a high CHADS₂ score was associated with a higher incidence of new onset AF than a low CHADS₂ score ($P < 0.001$) (Figure 2B).

Cox regression analysis with adjustment for age, sex, cor-

onary artery disease, valvular heart disease, smoking, medications, left atrial dimension, and LVEF identified IAB (hazard ratio, 8.66; 95% confidence interval, 5.27–14.23; $P < 0.001$) and a high CHADS₂ score (hazard ratio, 2.61; 95% confidence interval, 1.61–4.25; $P < 0.001$) separately as an independent predictor of new onset AF. Even after adjusting for high CHADS₂ score, IAB was still identified as an independent predictor of new onset AF (hazard ratio, 8.11; 95% confidence interval, 4.88–13.46; $P < 0.001$). The incidence of new onset AF according to combinations of IAB and no IAB and high and low CHADS₂ scores are shown in Table IV. The combination of IAB and a high CHADS₂ score was associated with a higher incidence of new onset AF compared with a combination of no IAB and a low CHADS₂ score, with an adjusted hazard ratio of 12.18 (95% confidence interval: 6.22–23.87; $P < 0.001$). Additionally, the combination of IAB and a low CHADS₂ score was also associated with a higher incidence of new onset AF compared with a combination of no IAB and a low CHADS₂ score, with an adjusted hazard ratio of 7.79 (95% confidence interval: 4.20–14.42; $P < 0.001$).

DISCUSSION

The main findings of this study are as follows: 1) in patients with sinus rhythm, IAB and a high CHADS₂ score independently and synergistically predicted new onset AF; and 2) a combination of IAB and a high CHADS₂ score was associated with approximately a 12-fold higher risk of new onset AF compared with a combination of no IAB and a low CHADS₂ score, after adjustment for various clinical factors.

Previous studies have indicated that IAB is associated with the development of AF.^{7–11} A study by Bayes, *et al* found that, during a 30-month follow-up of 16 patients with IAB, half developed AF.⁷ In an investigation by Agarwal, *et al*, 308 patients developed AF during a mean of 16 months, and 52% had IAB.⁸ In contrast, in a group of patients who remained in sinus rhythm, the prevalence of IAB was 18%.⁸ In the present study, we confirmed the association between IAB and AF in a larger cohort of 1571 in-hospital patients. The exact mechanism for this is unknown. IAB possibly has a role in initiating and maintaining reentry circuits by promoting the occurrence of unidirectional block,¹⁵ which is an important mechanism in the development of AF. In addition, IAB probably reflects underlying atrial disease such as atrial fibrosis,¹⁶ which may be a major factor in AF development. Although IAB is a separate entity from atrial enlargement, both are frequently associated with left atrial enlargement,¹⁷ which has been shown to be associated with AF.^{18,19}

Figure 2. Kaplan-Meier curves showing incidence of new onset AF stratified by IAB or not and CHADS₂ score. **A:** Patients with IAB had a higher incidence of new onset AF than patients without IAB ($P < 0.001$). **B:** Patients with a high CHADS₂ score had a higher incidence of new onset AF than patients with a low CHADS₂ score ($P < 0.001$).

Table IV. Incidence Rates and Hazard Ratios for New Onset AF

Variables	No IAB, CHADS ₂ score < 2	No IAB, CHADS ₂ score ≥ 2	IAB, CHADS ₂ score < 2	IAB, CHADS ₂ score ≥ 2
Patient-years	4254	814	1190	1341
Number of new onset AF	17	5	41	59
Incidence rate (per 1,000 patient-years)	4.0	6.1	34.5	44.0
Adjusted HR* (95% CI), P	1.00	1.42 (0.47–4.27), 0.535	7.79 (4.20–14.42), < 0.001	12.18 (6.22–23.87), < 0.001

AF indicates atrial fibrillation; HR, hazard ratio and CI, confidence interval. For other abbreviations, see Table II. *Adjusted for age, sex, coronary artery disease, valvular heart disease, smoking, medications, and left atrial dimension and left ventricular ejection fraction.

The CHADS₂ score has emerged as the main predictive tool to estimate the risk of stroke or systemic thromboembolism in patients with non-valvular AF.¹²⁾ Recently, the CHADS₂ score was found to be associated with an increased risk of AF.^{13,14,20-23)} The present study also showed that the CHADS₂ score was an independent predictive factor for new onset AF in an in-hospital population with sinus rhythm. This finding is not surprising because most of the risk factors for AF are, at the same time, the constituents of the CHADS₂ score.^{24,25)} Moreover, a high CHADS₂ score was demonstrated to be associated with an arrhythmogenic substrate and larger size of the left atrium,²⁶⁾ which was associated with the development of AF.

In this study, we found that a combination of IAB and a high CHADS₂ score synergistically predicted new onset AF, with an approximately 12-fold greater risk than no IAB and a low CHADS₂ score in patients in sinus rhythm. These results indicate that for patients in sinus rhythm who had IAB and a high CHADS₂ score, more aggressive intervention for prevention of AF is necessary. In addition, this study also showed patients with a low CHADS₂ score who have IAB had approximately 7.8-fold higher risk of new onset AF than the patients who have no IAB. This finding supports the findings of previous studies that IAB was associated with an increased risk of AF.⁷⁻¹¹⁾ Patients meeting these criteria should also be followed for new onset AF.

In the present study, patients with IAB had a higher incidence of prior stroke or TIA than patients without IAB. These results are in accordance with the findings of previous studies²⁷⁻²⁹⁾ in which IAB was associated with an increased risk of ischemic stroke. However, the underlying mechanism has not been fully explained. In this study, we found that among patients with IAB in sinus rhythm, those who also had a high CHADS₂ score (≥ 2 points) had a higher incidence of new onset AF than those with a low CHADS₂ score. These results might partially explain the previously observed association between IAB and the incidence of ischemic stroke, assuming that patients with IAB who develop AF are more likely to have a high CHADS₂ score and consequently have a greater risk of stroke.

This study had several limitations. First, because our criterion for exclusion of subjects with AF was the baseline ECG and medical history, it is possible that individuals with asymptomatic paroxysmal AF who were in sinus rhythm at the time of the baseline ECG could have been misclassified as non-AF participants and included in the analysis. Second, ascertainment of new onset AF is also incomplete because it was identified using hospital discharge data. However, because AF is asymptomatic in some patients, only continuous ECG monitoring would have correctly classified all patients. Third, with regard to the degree of IAB, IAB was classified into partial (P-wave duration > 120 ms) or advanced IAB (P-wave duration > 120 ms with biphasic ($\pm$) morphology in inferior leads).⁶⁾ However, IAB was analyzed in this study in a global manner and no distinction was made between the degree of this condition. In addition, previous studies have indicated that frequent premature atrial complexes (PACs) are associated with new onset AF.^{21,30,31)} However, because the data of PACs were unavailable in the present study, it was difficult to determine whether IAB or the combination of IAB and high CHADS₂ score is independently associated with AF after adjusting for frequent PACs. Finally, this was a retrospective study from a

single center.

In conclusion, IAB and a high CHADS₂ score independently and synergistically predicted new onset AF in patients in sinus rhythm, indicating an approximately 12-fold higher risk in patients with both IAB and a high CHADS₂ score. Patients meeting these criteria should have more aggressive early intervention to prevent AF.

REFERENCES

- Guo Y, Tian Y, Wang H, Si Q, Wang Y, Lip GY. Prevalence, incidence, and lifetime risk of atrial fibrillation in China: new insights into the global burden of atrial fibrillation. *Chest* 2015; 147: 109-19.
- Wändell P, Carlsson AC, Gasevic D, Sundquist J, Sundquist K. Neighbourhood socio-economic status and all-cause mortality in adults with atrial fibrillation: A cohort study of patients treated in primary care in Sweden. *Int J Cardiol* 2016; 202: 776-81.
- Patel NJ, Deshmukh A, Pant S, *et al.* Contemporary trends of hospitalization for atrial fibrillation in the United States, 2000 through 2010: implications for healthcare planning. *Circulation* 2014; 129: 2371-9.
- Hamatani Y, Yamashita Y, Esato M, *et al.* Predictors for stroke and death in non-anticoagulated Asian patients with atrial fibrillation: The Fushimi AF Registry. *PLoS One* 2015; 10: e0142394.
- Vermond RA, Geelhoed B, Verweij N, *et al.* Incidence of atrial fibrillation and relationship with cardiovascular events, heart failure, and mortality: A community-based study from the Netherlands. *J Am Coll Cardiol* 2015; 66: 1000-7.
- Bayés de Luna A, Platonov P, Cosio FG, *et al.* Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. *J Electrocardiol* 2012; 45: 445-51.
- Bayés de Luna A, Cladellas M, Oter R, *et al.* Interatrial conduction block and retrograde activation of the left atrium and paroxysmal supraventricular tachyarrhythmia. *Eur Heart J* 1988; 9: 1112-8.
- Agarwal YK, Aronow WS, Levy JA, Spodick DH. Association of interatrial block with development of atrial fibrillation. *Am J Cardiol* 2003; 91: 882.
- Conde D, Baranchuk A. Interatrial block as anatomical-electrical substrate for supraventricular arrhythmias: Bayés syndrome. *Arch Cardiol Mex* 2014; 84: 32-40. (Review, Spanish)
- Abe Y, Fukunami M, Yamada T, *et al.* Prediction of transition to chronic atrial fibrillation in patients with paroxysmal atrial fibrillation by signal-averaged electrocardiography: a prospective study. *Circulation* 1997; 96: 2612-6.
- Dixen U, Larsen MV, Ravn L, Parner J, Jensen GB. Signal-averaged P wave duration and the long-term risk of permanent atrial fibrillation. *Scand Cardiovasc J* 2008; 42: 31-7.
- 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.
- Sciacqua A, Perticone M, Tripepi G, *et al.* CHADS₂ and CHA₂DS₂-VASc scores are independently associated with incident atrial fibrillation: the Catanzaro Atrial Fibrillation Project. *Intern Emerg Med* 2015; 10: 815-21.
- Yang Y, Zhang Z, Ng CY, Li G, Liu T. Meta-analysis of CHADS₂ Score in Predicting Atrial Fibrillation. *Am J Cardiol* 2015; 116: 554-62.
- Daubert JC, Pavin D, Jauvert G, Mabo P. Intra and interatrial conduction delay: Implications for cardiac pacing. *Pacing Clin Electrophysiol* 2004; 27: 507-25. (Review)
- Legato MJ, Bull MB, Ferrer MI. Atrial ultrastructure in patients with fixed intra-atrial block. *Chest* 1974; 65: 252-61.
- Bayés de Luna A, Platonov P, Cosio FG, *et al.* Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. *J*

- Electrocardiol 2012; 45: 445-51.
18. Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implication. *Circ Arrhythm Electrophysiol* 2008; 1: 62-73. (Review)
 19. Khan A, Moe GW, Nili N, *et al.* The cardiac atria are chambers of active remodeling and dynamic collagen turnover during evolving heart failure. *J Am Coll Cardiol* 2004; 43: 68-76.
 20. Zhang X, Li G, Zhao Z, Xu Y, Liu T. The value of CHADS₂ score in predicting new-onset atrial fibrillation in Chinese patients with acute myocardial infarction. *Int J Cardiol* 2014; 176: 1235-7.
 21. Suzuki S, Sagara K, Otsuka T, *et al.* Usefulness of frequent supraventricular extrasystoles and a high CHADS₂ score to predict first-time appearance of atrial fibrillation. *Am J Cardiol* 2013; 111: 1602-7.
 22. Yin L, Ling X, Zhang Y, *et al.* CHADS₂ and CHA₂DS₂-VASc scoring systems for predicting atrial fibrillation following cardiac valve surgery. *PLoS One* 2015; 10: e0123858.
 23. Sareh S, Toppen W, Mukdad L, *et al.* CHADS₂ score predicts atrial fibrillation following cardiac surgery. *J Surg Res* 2014; 190: 407-12.
 24. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population based cohort. The Framingham Heart Study. *JAMA* 1994; 271: 840-4.
 25. Psaty BM, Manolio TA, Kuller LH, *et al.* Incidence of and risk factors for atrial fibrillation in older adults. *Circulation* 1997; 96: 2455-61.
 26. Chao TF, Cheng CC, Lin WS, *et al.* Associations among the CHADS₂ score, atrial substrate properties, and outcome of catheter ablation in patients with paroxysmal atrial fibrillation. *Heart Rhythm* 2011; 8: 1155-9.
 27. Lorbar M, Levraut R, Phadke JG, Spodick DH. Interatrial block as a predictor of embolic stroke. *Am J Cardiol* 2005; 95: 667-8.
 28. Ariyaratna V, Apiyasawat S, Najjar H, Mercado K, Puri P, Spodick DH. Frequency of interatrial block in patients with sinus rhythm hospitalized for stroke and comparison to those without interatrial block. *Am J Cardiol* 2007; 99: 49-52.
 29. Ariyaratna V, Puri P, Apiyasawat S, Spodick DH. Interatrial block: a novel risk factor for embolic stroke? *Ann Noninvasive Electrocardiol* 2007; 12: 15-20.
 30. 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.
 31. Chong BH, Pong V, Lam KF, *et al.* Frequent premature atrial complexes predict new occurrence of atrial fibrillation and adverse cardiovascular events. *Europace* 2012; 14: 942-7.