Prevalence and Significance of Interatrial Block in Takotsubo Syndrome (from the RETAKO Registry)

Irene Martín-Demiguel, MD[a], Iván J. Núñez-Gil, MD, PhD[b], Alberto Pérez-Castellanos, MD[c], Oscar Vedia, MD[b], Aitor Uribarri, MD[d], Albert Durán-Cambra, MD[e], Agustín Martín-García, MD, PhD[f], Miguel Corbí-Pascual, MD[g], Marta Guillén Marzo, MD[h], and Manuel Martínez-Sellés, MD, PhD[a,i,*]

Interatrial block (IAB) represents a conduction delay between right and left atria and is associated with an increased risk of atrial fibrillation and stroke. IAB has not been previously assessed in patients with Takotsubo syndrome (TS). Our aim was to describe the prevalence and prognostic significance of IAB in patients with TS. Data come from the Spanish National prospective registry of patients with definitive TS diagnosis. IAB was defined as a P-wave ≥120 ms and was considered partial when the P-wave was positive in inferior leads and advanced when it was biphasic (+/−). A total of 246 patients were included, normal P-wave was found in 151 (61%), partial IAB in 58 (24%), atrial fibrillation in 18 (7%), advanced IAB in 13 (5%), and 6 (2%) were pacemaker dependent. During a mean follow up of 12 months the composite of all-cause mortality and hospital readmission was significantly higher in patients with advanced IAB (31%) or atrial fibrillation (33%) than in the rest of the cohort (pacemaker stimulation 17%, normal P-wave 13%, partial IAB 12%), p < 0.01. The data regarding P wave characteristics were an independent predictor of the composite end point all-cause death and hospital readmission. IAB has a high prevalence in patients with TS. Advanced IAB and atrial fibrillation are associated with a poor prognosis. © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;123:2039−2043)

Interatrial block (IAB) is a conduction delay between the right and left atria over the Bachmann's bundle, resulting in a more prolonged left atrial depolarization.[1] It is defined as a P-wave duration ≥120 ms and is considered partial when de P-wave is positive in inferior leads and advanced when it has a biphasic (+/−) morphology.[2−7] IAB increases the risk of atrial fibrillation (AF) and/or thromboembolic events,[8−11] and even all-cause mortality.[3,12−14] IAB is more prevalent in patients with advanced age, frailty, arterial hypertension, left atrial enlargement or mitral regurgitation, and has been associated with more coronary artery disease.[7,12,15,16] Patients with Takotsubo syndrome (TS) present with characteristic electrocardiographic features, which include repolarization alterations mimicking myocardial infarction, and typically develop profound T-wave inversion and prolonged corrected QT interval.[17−21] IAB has not been assessed previously in patients with TS. The present study aims to determine the prevalence and prognostic significance of IAB in an unselected real-life cohort of patients with TS.

Methods

Our data come from The Spanish Multicenter REgistry of TAKOtsubo syndrome (RETAKO).[22] RETAKO includes data from TS based in the modified Mayo Clinic criteria, that is: (1) transient wall motion abnormalities extending beyond a single epicardial vascular territory, stressful trigger may be present, (2) absence of obstructive coronary disease, (3) new electrocardiographic abnormalities and modest elevation in cardiac troponin, and (4) absence of pheochromocytoma and myocarditis. Data from January 1, 2003 until December 31, 2017 from patients with a definitive TS diagnosis and an available 12-lead surface electrocardiogram (ECG) at admission were included. Baseline characteristics, ECG measurements and arrhythmia development, in-hospital adverse events, pharmacological and device requirement, short- and long-term outcome, hospital readmission, and TS recurrence were collected through an electronic case report form. Follow-up was performed by review of medical records, telephone contact with the patient or family or the patient's referring physician. Total follow-up time was calculated as the time between home discharge and last available contact. The study protocol fulfilled the Declaration of Helsinki, and was approved by the Institutional Ethics Committee of Clinico San Carlos Hospital, Madrid, Spain. All patients provided written informed consent.

Twelve-lead admission surface ECG using 25 ms and 10 mm/mV standardization were analyzed for this study. ECG measurements were carried out by an investigator (IM) blinded to patient data. P wave duration was simultaneously measured in the 3 inferior leads (II, III, aVF) and in additional leads in case of needed confirmation of the

[a]Servicio de Cardiología, Hospital General Universitario Gregorio Marañón, CIBERCV, Madrid, Spain; [b]Instituto Cardiovascular, Hospital Clínico San Carlos, Madrid, Spain; [c]Servicio de Cardiología, Hospital de Manacor, Baleares, Spain; [d]Complejo Hospitalario de Navarra, Navarra, Spain; [e]Hospital de Sant Pau, Barcelona, Spain; [f]Hospital Universitario de Salamanca, Salamanca, Spain; [g]Complejo Hospitalario de Albacete, Albacete, Spain; [h]Hospital Joan XXIII, Tarragona, Spain; and [i]Universidad Europea, Universidad Complutense, Madrid, Spain. Manuscript received November 17, 2018; revised manuscript received and accepted March 7, 2019.

See page 2042 for disclosure information.

*Corresponding author: Tel: 915868286; fax: 915868276.

E-mail address: mmselles@secardiologia.es (M. Martínez-Sellés).

Table 1
Baseline characteristics according to rhythm at admission

Variable	Normal P-wave (n = 151)	Partial IAB (n = 58)	AF (n = 18)	Advanced IAB (n = 13)	Pacemaker (n = 6)	p
Age (years)	70 (12)	70 (12)	79 (8)	78 (5)	74 (9)	<0.01
Men	18 (12%)	10 (17%)	0	1 (8%)	2 (33%)	0.04
Hypertension*	97 (64%)	31 (53%)	13 (72%)	10 (77%)	5 (83%)	0.38
Diabetes mellitus	22 (15%)	9 (16%)	6 (33%)	0	2 (33%)	0.06
Dyslipidemia†	68 (45%)	31 (53%)	11 (61%)	10 (77%)	4 (67%)	0.67
Smokers	44 (30%)	19 (33%)	2 (11%)	1 (8%)	3 (50%)	0.28
Stroke/ Transient ischemic attack	10 (7%)	2 (3%)	0	2 (15%)	0	0.21
Cancer	25 (17%)	7 (12%)	1 (6%)	1 (8%)	3 (50%)	0.37
Chronic obstructive pulmonary disease/Asthma	36 (24%)	11 (19%)	3 (17%)	1 (8%)	2 (33%)	0.51
Stressful trigger						0.63
None	40 (27%)	15 (26%)	3 (17%)	3 (23%)	2 (33%)	
Emotional	61 (40%)	20 (35%)	10 (56%)	9 (69%)	3 (50%)	
Physical	43 (29%)	22 (38%)	5 (28%)	1 (8%)	1 (17%)	
Both	7 (5%)	1 (2%)	0	0	0	
Medication on admission						
Beta-blocker	13 (9%)	9 (16%)	4 (22%)	2 (15%)	0	0.34
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.	72 (48%)	21 (36%)	8 (44%)	6 (46%)	6 (100%)	0.86
Statin	46 (31%)	17 (29%)	8 (44%)	6 (46%)	1 (17%)	0.45
Antidepressant/Anxiolytic	49 (33%)	21 (36%)	5 (28%)	6 (46%)	2 (33%)	0.28

* Blood pressure ≥140/90 mm Hg.

† Total cholesterol ≥200 mg/dl.

Values are mean ± SD, median (interquartile range [IQR]) or absolute frequency and percentage (%).

values. P-wave measurement began at the joint of the iso-electric line with the beginning of the P deflection and ended at the joint between the end of the P deflection and the PR segment. The longest P-wave was chosen for the record.

The primary end point of this study was the composite of all-cause mortality and hospital readmission. Secondary end points included all-cause mortality and the composite of all-cause mortality and TS recurrence. Recurrence was defined as a new nonfatal episode of TS according to the previously explained diagnostic criteria. Consensus of 2 local investigators was required for primary or secondary event adjudication and electronic medical records were reviewed if available. Subjects with incomplete data registration or lack of correct follow-up were excluded for the statistical analysis.

Continuous variables are shown as mean ± SD or median (interquartile range) and are compared by the Student's *t* Test or the Mann-Whitney U test. Categorical variables are reported as number (percentage) and compared with the chi-square test or Fisher's exact test. The association between IAB status and mortality or mortality plus hospital readmission or TS recurrence was assessed by the Cox regression method. The degree of IAB was codified by a polinomial distribution in order to assess its linear association with mortality and hospitalization. Mortality rates were plotted according to the Kaplan-Meier product limit method. All statistical analyses were performed with SPSS software (version 21, SPSS, Chicago, Illinois).

Results

From the total cohort of 946 patients, 246 (26%) had a 12-lead ECG at admission and complete data record. Mean follow-up time was 12 months. A total of 151 patients

(61%) had normal P-wave, 58 (24%) partial IAB, 18 (7%) AF, 13 (5%) advanced IAB, and 6 (2%) were pacemaker dependent. Patients with advanced IAB or AF had a more advanced age (Table 1). Female sex was more frequent in all groups but this was more marked in patients with AF (no males) than in those with advanced IAB (only 1 male). Patients with AF and with advanced IAB needed more frequently noninvasive mechanical ventilation than those in the other groups (Table 2). The primary end point of the composite of all-cause mortality and hospital readmission was significantly higher in patients with AF or advanced IAB (33% and 31%, respectively) than in patients with normal P-wave, partial IAB or pacemaker rhythm (13%, 12%, and 17%, respectively). All-cause mortality and the composite end point of all-cause death and TS recurrence were also higher in patients with AF or advanced IAB (Table 3). Survival free from the individual end points (mortality, TS recurrence, and hospitalization) was significantly lower in the cohorts of AF and advance IAB (Figure 1). P wave characteristics were an independent predictor of the composite end point all-cause death and/or hospital readmission. Compared with patients with normal p-wave those with AF had a higher risk (hazard ratio [HR] 2.2, 95% confidence interval [CI] 0.8 to 5.8) and this was also the case with advanced IAB (HR 6.1, 95% CI 1.9 to 19.7). We found no significant association in patients with partial IAB (HR 0.8, 95% CI 0.3 to 2.0) and in patients with pacemaker rhythm (HR 4.6, 95% CI 0.5 to 37.0).

Discussion

The results from our study can be summarized as follows: (1) The prevalence of IAB in a nonselected TS population is about 30%; (2) advanced IAB and AF are associated with a poor prognosis.

Table 2
In-hospital course according to rhythm at admission

Variable	Normal P-wave (n = 151)	Partial IAB (n = 58)	AF (n = 18)	Advanced IAB (n = 13)	Pacemaker (n = 6)	p
Intensive care stay (days)	4 (5)	3 (3)	4 (3)	2 (1)	2 (1)	0.63
Hospitalization duration (days)	10 (11)	8 (9)	16 (23)	5 (2)	6 (2)	0.07
Clinical presentation						
Takostubo syndrome pattern						0.91
Apical	133 (88%)	52 (90%)	17 (94%)	12 (92%)	100 (100%)	
Mid-ventricular	10 (7%)	4 (7%)	0	0	0	
Basal	5 (3%)	1 (2%)	0	0	0	
Other	3 (2%)	1 (2%)	1 (6%)	1 (8%)	0	
Left ventricular ejection fraction (%)	41 (13)	41 (14)	33 (13)	38 (8)	41 (6)	0.78
Pulmonary artery systolic pressure ≥40 mm Hg	17 (12%)	11 (19%)	9 (50%)	2 (15%)	1 (17%)	0.08
Maximal Killip Kimbal class						0.13
I	87 (58%)	37 (64%)	4 (22%)	7 (54%)	3 (50%)	
II	31 (21%)	13 (22%)	5 (28%)	2 (15%)	1 (17%)	
III	12 (8%)	2 (3%)	5 (28%)	1 (8%)	1 (17%)	
IV	20 (13%)	6 (10%)	4 (22%)	3 (23%)	1 (17%)	
Left ventricular outflow tract obstruction	18 (12%)	6 (10%)	0 (0%)	1 (8%)	0 (0%)	0.21
Mitral regurgitation III−IV	16 (11%)	5 (9%)	3 (17%)	2 (15%)	0	0.18
Acute renal failure	14 (9%)	5 (9%)	3 (16%)	3 (23%)	1 (17%)	0.09
Infection	24 (16%)	2 (4%)	3 (17%)	0 (0%)	1 (17%)	0.12
Use of vasoactive drugs	21 (14%)	7 (12%)	5 (28%)	2 (15%)	1 (17%)	0.19
Noninvasive ventilation	12 (8%)	4 (7%)	4 (22%)	2 (15%)	0 (0%)	0.02
Invasive mechanical ventilation	9 (6%)	4 (7%)	1 (6%)	1 (8%)	1 (17%)	0.54

Values are mean ± SD, median (interquartile range [IQR]) or absolute frequency and percentage (%).

TS is typically associated with characteristic electrocardiographic features and some of them have shown prognostic implications. At admission, there are usually ST-segment and T-wave alterations that resemble those of acute coronary syndromes.[20] Approximately 48 hours afterwards, generalized profound T-wave inversion and prolonged corrected QT interval develop, the latter being associated with a more adverse outcome.[19,21,23] Ours is the first study that assesses IAB in these patients. IAB has been proposed as part of the aging process of the heart, and fibrosis is one pathophysiological mechanism underlying this conduction delay.[9,24,25] Hence, advanced IAB may represent a higher ageing velocity in the atrial tissue.[12,16] Patients with TS are usually advanced age women,[22,23] so a relatively high prevalence of IAB might be expected. Previous works suggest that IAB is associated with worse prognosis in the general population, particularly in the case of advanced IAB.[3,12] Our study extrapolates those findings in the specific group of TS patients, highlighting the importance of paying attention to this disturbance, as it may identify patients at a higher risk. Patients with TS may suffer from thromboembolic complications because of the intraventricular thrombi that can develop in the akinetic apex. Taking into account the high prevalence of IAB and the increased risk of AF in this subgroup of patients with TS, thromboembolic complications may not only derive from intraventricular thrombi, as AF can be detected in approximately 25% of unexplained strokes.[26−30]

The present study has the inherent limitations of an observational nonrandomized work. The sample size of this substudy is relatively small, despite the large number of patients included in the registry, as few subjects had complete ECG documentation. This together with the low number of adverse events, reduces the statistical power of the work. Nevertheless, significant differences between groups have been found for clinically relevant end points such as all-cause death, hospital readmission or TS recurrence. Echocardiography measurements to assess the previously established relation between IAB and left atrial enlargement were not available.[3] Finally, we had no data regarding AF or stroke development.

Table 3
Primary and secondary end points

	Normal P-wave (n = 151)	Partial IAB (n = 58)	AF (n = 18)	Advanced IAB (n = 13)	Pacemaker (n = 6)	p
All-cause death	7 (5%)	3 (5%)	2 (11%)	2 (15%)	0 (0%)	0.02
All-cause death or Takotsubo syndrome recurrence	8 (5%)	3 (5%)	4 (22%)	2 (15%)	0 (0%)	0.01
All-cause death or rehospitalization	20 (13%)	7 (12%)	6 (33%)	4 (31%)	1 (17%)	<0.01

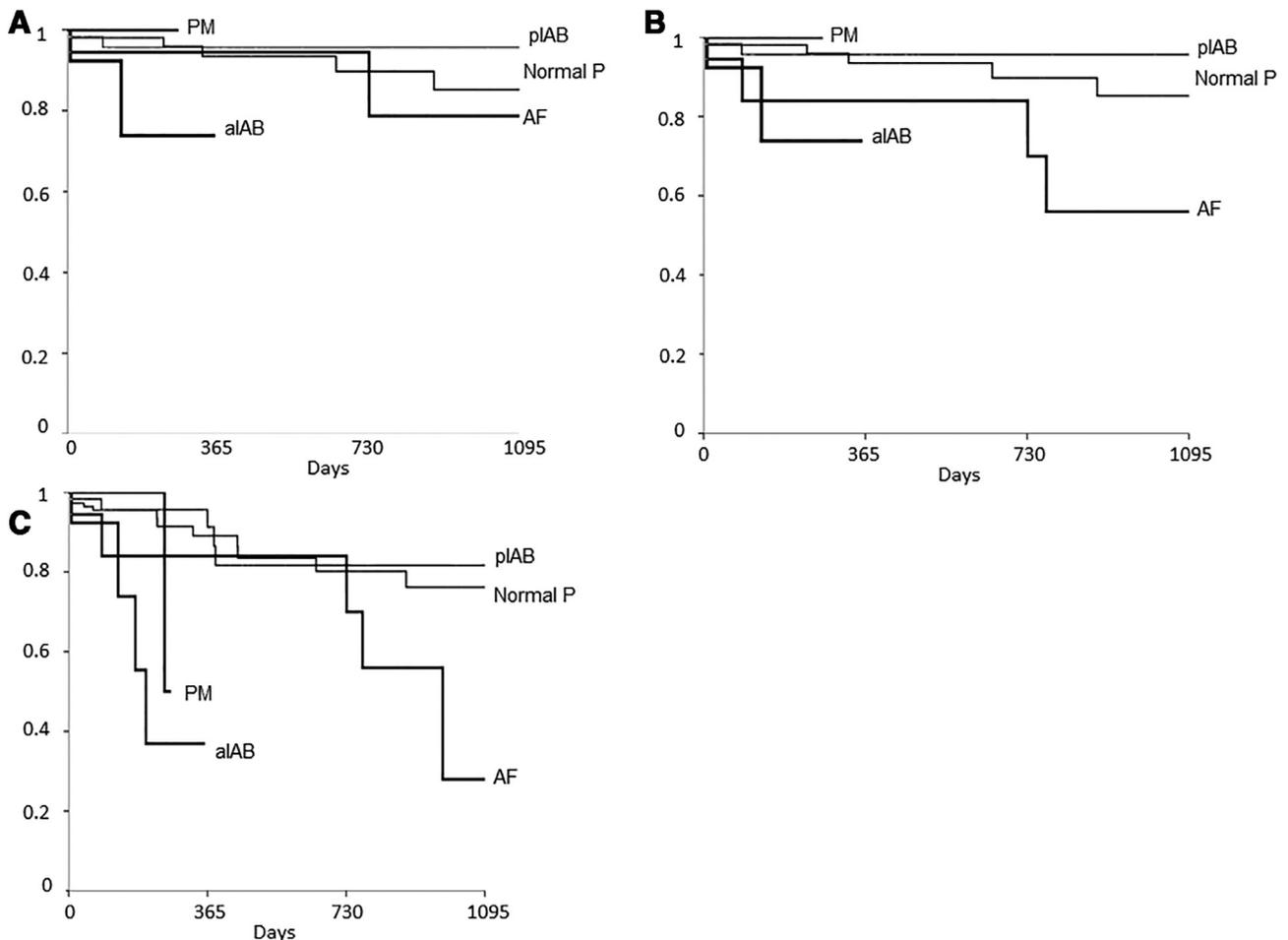Values in absolute frequency and percentage (%).

Figure 1. Adjusted Cumulative Kaplan-Meier Curves showing survival free from all-cause mortality (*A*), Takotsubo syndrome recurrence (*B*), and hospitalization (*C*). Total follow-up was calculated as the time between home discharge and last available contact.
AF = atrial fibrillation; aIAB = advanced interatrial block; normal P = normal P wave; pIAB = partial interatrial block; PM = pacemaker.
PM and aIAB curves are shorter than the total duration of follow-up as they reflect the largest follow-up available in those groups.

In conclusion, IAB has a high prevalence in patients with TS. Advanced IAB and AF are associated with a poor prognosis.

Acknowledgment

Disclosures

The authors have no conflicts of interest to disclose.

1. Bayes de Luna A, Fort de Ribot R, Trilla E, Julia J, Garcia J, Sadurni J, Riba J, Sagues F. Electrocardiographic and vectorcardiographic study of interatrial conduction disturbances with left atrial retrograde activation. *J Electrocardiol* 1985;18:1–13.
2. Bayes de Luna A, Oter MC, Guindo J. Interatrial conduction block with retrograde activation of the left atrium and paroxysmal supraventricular tachyarrhythmias: influence of preventive antiarrhythmic treatment. *Int J Cardiol* 1989;22:147–150.
3. Bayes de Luna A, Platonov P, Cosio FG, Cygankiewicz I, Pastore C, Baranowski R, Bayes-Genis A, Guindo J, Vinolas X, Garcia-Niebla J, Barbosa R, Stern S, Spodick D. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. *J Electrocardiol* 2012;45:445–451.
4. Bacharova L, Wagner GS. The time for naming the Interatrial Block Syndrome: Bayes Syndrome. *J Electrocardiol* 2015;48:133–134.
5. Martinez-Selles M, Baranchuk A, Elosua R, de Luna AB. Rationale and design of the BAYES (Interatrial Block and Yearly Events) registry. *Clin Cardiol* 2017;40:196–199.
6. Bayes de Luna A, Baranchuk A, Nino Pulido C, Martinez-Selles M, Bayes-Genis A, Elosua R, Elizari MV. Second-degree interatrial block: brief review and concept. *Ann Noninvasive Electrocardiol* 2018:e12583.
7. Alexander B, MacHaalany J, Lam B, van Rooy H, Haseeb S, Kuchtaruk A, Glover B, Bayes de Luna A, Baranchuk A. Comparison of the extent of coronary artery disease in patients with versus without interatrial block and implications for new-onset atrial fibrillation. *Am J Cardiol* 2017;119:1162–1165.
8. Cinier G, Tekkesin AI, Turkkan C, Alper AT. Interatrial block predicts silent atrial fibrillation episodes detected by cardiac implantable electronic devices. *Pacing Clin Electrophysiol* 2018;41:435.
9. Vicent L, Martinez-Selles M. Electrocardiogeriatrics: ECG in advanced age. *J Electrocardiol* 2017;50:698–700.
10. Alexander B, Haseeb S, van Rooy H, Tse G, Hopman W, Martinez-Selles M, de Luna AB, Cinier G, Baranchuk A. Reduced P-wave voltage in lead i is associated with development of atrial fibrillation in patients with coronary artery disease. *J Atr Fibrillation* 2017;10:1657.
11. Skov MW, Ghouse J, Kuhl JT, Platonov PG, Graff C, Fuchs A, Rasmussen PV, Pietersen A, Nordestgaard BG, Torp-Pedersen C, Hansen

SM, Olesen MS, Haunso S, Kober L, Gerds TA, Kofoed KF, Svendsen JH, Holst AG, Nielsen JB. Risk prediction of atrial fibrillation based on electrocardiographic interatrial block. *J Am Heart Assoc* 2018;7 (11):pii:e008247.

12. Bernal E, Bayes-Genis A, Ariza-Sole A, Formiga F, Vidan MT, Escobar-Robledo LA, Aboal J, Alcoberro L, Guerrero C, Ariza-Segovia I, Hernandez de Benito A, Vilardell P, Sanchez-Salado JC, Lorente V, Bayes de Luna A, Martinez-Selles M. Interatrial block, frailty and prognosis in elderly patients with myocardial infarction. *J Electrocardiol* 2018;51:1–7.

13. Martinez-Selles M, Robledo LA, Baranchuk A. Interatrial block and the risk of ischemic stroke. *J Atheroscler Thromb* 2017;24:185–186.

14. Maheshwari A, Norby FL, Soliman EZ, Alraies MC, Adabag S, O'Neal WT, Alonso A, Chen LY. Relation of prolonged P-wave duration to risk of sudden cardiac death in the general population (from the Atherosclerosis Risk in Communities Study). *Am J Cardiol* 2017;119:1302–1306.

15. O'Neal WT, Zhang ZM, Loehr LR, Chen LY, Alonso A, Soliman EZ. Electrocardiographic advanced interatrial block and atrial fibrillation risk in the general population. *Am J Cardiol* 2016;117:1755–1759.

16. Martinez-Selles M, Masso-van Roessel A, Alvarez-Garcia J, Garcia de la Villa B, Cruz-Jentoft AJ, Vidan MT, Lopez Diaz J, Felix Redondo FJ, Duran Guerrero JM, Bayes-Genis A, Bayes de Luna A. Interatrial block and atrial arrhythmias in centenarians: prevalence, associations, and clinical implications. *Heart rhythm* 2016;13:645–651.

17. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, S YH, Migliore F, Horowitz JD, Shimokawa H, Luscher TF, Templin C. International expert consensus document on Takotsubo syndrome (Part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J* 2018;39:2032–2046.

18. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, S YH, Migliore F, Horowitz JD, Shimokawa H, Luscher TF, Templin C. International expert consensus document on Takotsubo syndrome (Part II): diagnostic workup, outcome, and management. *Eur Heart J* 2018;39:2047–2062.

19. Kosuge M, Ebina T, Hibi K, Iwahashi N, Tsukahara K, Endo M, Maejima N, Nagashima Z, Suzuki H, Morita S, Umemura S, Kimura K. Differences in negative T waves between Takotsubo cardiomyopathy and reperfused anterior acute myocardial infarction. *Circ J* 2012;76:462–468.

20. Weihs V, Szucs D, Fellner B, Eber B, Weihs W, Lambert T, Metzler B, Titscher G, Hochmayer B, Dechant C, Eder V, Siostrzonek P, Leisch F, Pichler M, Pachinger O, Gaul G, Weber H, Podczeck-Schweighofer A, Nesser HJ, Huber K. Electrocardiogram changes and wall motion abnormalities in the acute phase of Tako-Tsubo syndrome. *Eur Heart J Acute Cardiovasc Care* 2016;5:481–488.

21. Imran TF, Rahman I, Dikdan S, Shah R, Niazi OT, Thirunahari N, Alhaj E, Klapholz M, Gaziano JM, Djousse L. QT prolongation and clinical outcomes in patients with Takotsubo cardiomyopathy. *Pacing Clin Electrophysiol* 2016;39:607–611.

22. Pérez-Castellanos A, Martínez-Sellés M, Mejía-Rentería H, Andrés M, Sionis A, Almendro-Delia M, Martín-García A, Aguilera MC, Pereyra E, Linares Vicente JA, García de la Villa B, Núñez-Gil IJ. Tako-tsubo syndrome in men: rare, but with poor prognosis. *Revista Española de Cardiología (English Edition)* 2018;71:703–708.

23. Almendro-Delia M, Nunez-Gil IJ, Lobo M, Andres M, Vedia O, Sionis A, Martin-Garcia A, Cruz Aguilera M, Pereyra E, Martin de Miguel I, Linares Vicente JA, Corbi-Pascual M, Bosch X, Fabregat Andres O, Sanchez Grande Flecha A, Perez-Castellanos A, Pais JL, De Mora Martin M, Escudier Villa JM, Martin Asenjo R, Guillen Marzo M, Rueda Sobella F, Acena A, Garcia Acuna JM, Garcia-Rubira JC. Short- and long-term prognostic relevance of cardiogenic shock in Takotsubo syndrome: results from the RETAKO registry. *JACC Heart Fail* 2018;6:928–936.

24. Martinez-Selles M, Bayes de Luna A. Atrial fibrillation in the elderly. *J Geriatr Cardiol* 2017;14:155–157.

25. Martinez-Selles M. Prevalence and incidence of interatrial block in global population and in different clinical situations. *J Geriatr Cardiol* 2017;14:158–160.

26. Bayes de Luna A, Martinez-Selles M, Bayes-Genis A, Elosua R, Baranchuk A. Surface ECG interatrial block-guided treatment for stroke prevention: rationale for an attractive hypothesis. *BMC Cardiovasc Disord* 2017;17:211.

27. Martinez-Selles M, Garcia-Izquierdo Jaen E, Fernandez Lozano I. Anticoagulation in elderly patients at high risk of atrial fibrillation without documented arrhythmias. *J Geriatr Cardiol* 2017;14:166–168.

28. Escobar-Robledo LA, Bayes-de-Luna A, Lupon J, Baranchuk A, Moliner P, Martinez-Selles M, Zamora E, de Antonio M, Domingo M, Cediel G, Nunez J, Santiago-Vacas E, Bayes-Genis A. Advanced interatrial block predicts new-onset atrial fibrillation and ischemic stroke in patients with heart failure: the "Bayes' Syndrome-HF" study. *Int J Cardiol* 2018;271:174–180.

29. Martinez-Selles M, Baranchuk A, Elosua R, Bayes de Luna A, O'Neal WT, Kamel H, Zhang ZM, Chen LY, Alonso A, Soliman EZ. Advanced interatrial block and ischemic stroke: the atherosclerosis risk in communities study. *Neurology* 2016;87:2499.

30. Arboix A, Marti L, Dorison S, Sanchez MJ. Bayes syndrome and acute cardioembolic ischemic stroke. *World J Clin Cases* 2017;5:93–101.