Circulation Reports
Circ Rep 2021; 3: 273–278
doi:10.1253/circrep.CR-20-0101

ORIGINAL ARTICLE
Myocardial Disease

Importance of Paroxysmal Atrial Fibrillation and Sex Differences in the Prevention of Embolic Stroke in Hypertrophic Cardiomyopathy

Junya Komatsu, MD; Ryu-ichiro Imai, MD; Yoko Nakaoka, MD; Koji Nishida, MD; Shu-ichi Seki, MD; Toru Kubo, MD; Naohito Yamasaki, MD; Hiroaki Kitaoka, MD; Sho-ichi Kubokawa, MD; Kazuya Kawai, MD; Naohisa Hamashige, MD; Yoshinori L Doi, MD

Background: Although atrial fibrillation (AF) is a well-known risk factor for embolic stroke in hypertrophic cardiomyopathy (HCM), there is a paucity of information derived from HCM patients who have experienced embolic stroke.

Methods and Results: From 141 consecutive HCM patients who had been hospitalized between 2000 and 2018, the clinical characteristics and management of 86 patients with AF were analyzed retrospectively. The incidence of embolic stroke was 36% (n=31 patients). The median (interquartile range) age of embolic stroke was younger in male than female HCM patients (71 [64–80] vs. 83 [77–87] years, respectively; P=0.009). The prevalence of paroxysmal AF (74%) was significantly higher than that of chronic AF (26%) in 31 patients with embolic stroke (P=0.007). The $CHADS_2$ score in patients with embolic stroke was not particularly useful in predicting the occurrence of embolic stroke.

Conclusions: One-third of HCM patients with AF developed embolic stroke, and male HCM patients were younger at the time of the embolic stroke than female HCM patients. The prevalence of paroxysmal AF was significantly higher than that of chronic AF in patients with AF and embolic stroke. Early introduction of anticoagulation therapy is recommended at the first documentation of paroxysmal AF.

Key Words: Embolic stroke; Hypertrophic cardiomyopathy; Paroxysmal atrial fibrillation; Sex difference

Atrial fibrillation (AF) is the most common sustained arrhythmia in the general population and is associated with a significantly increased risk of stroke and heart failure.[1–3] AF is also common in patients with hypertrophic cardiomyopathy (HCM),[4–8] with a prevalence reportedly between 9% and 28%.[4,7–13] The presence of AF can denote a turning point in the progression of HCM, with a marked increased risk of embolic stroke, heart failure, and overall mortality.[4,7,8,14] Compared with patients with HCM in sinus rhythm, those in AF were shown to have an eightfold increase in embolic stroke risk.[4] However, although the risk of embolic stroke in HCM patients with AF is well recognized, there is a paucity of information derived from HCM patients who have experienced an embolic stroke.

Several independent risk factors for the development of embolic stroke have been reported in the general population,[3] as well as in patients with HCM and AF.[4,5,14,15] Advancing age, increased left atrial size, impaired left atrial function, and the presence of heart failure symptoms are suggested risk factors,[4,5,15,16] although there are conflicting reports in the HCM population.[8,17–19] Therefore, a consensus as to what constitutes an increased risk of embolic stroke in the HCM population has yet to be reached. To further investigate ways to prevent embolic stroke, we assessed the clinical characteristics of HCM patients with AF who experienced an embolic stroke.

Methods

Patient Selection

This study consecutively enrolled 141 patients with HCM who presented to an emergency department and were hospitalized at Chikamori Hospital between 2000 and 2018.

Received September 7, 2020; revised manuscript received February 12, 2021; accepted March 7, 2021; J-STAGE Advance Publication released online April 6, 2021 Time for primary review: 27 days
Department of Cardiology (J.K., R.I., Y.N., K.N., S.S., S.K., K.K., N.H., Y.L.D.), Cardiomyopathy Institute (Y.L.D.), Chikamori Hospital, Kochi; Department of Cardiology and Aging Science, Kochi Medial School, Kochi (T.K., N.Y., H.K.), Japan
H.K. is a member of *Circulation Reports*' Editorial Team.
Mailing address: Yoshinori L Doi, MD, PhD, Cardiomyopathy Institute, Chikamori Hospital, Kochi 780-8522, Japan. E-mail: ydoi@chikamori.com

ISSN-2434-0790

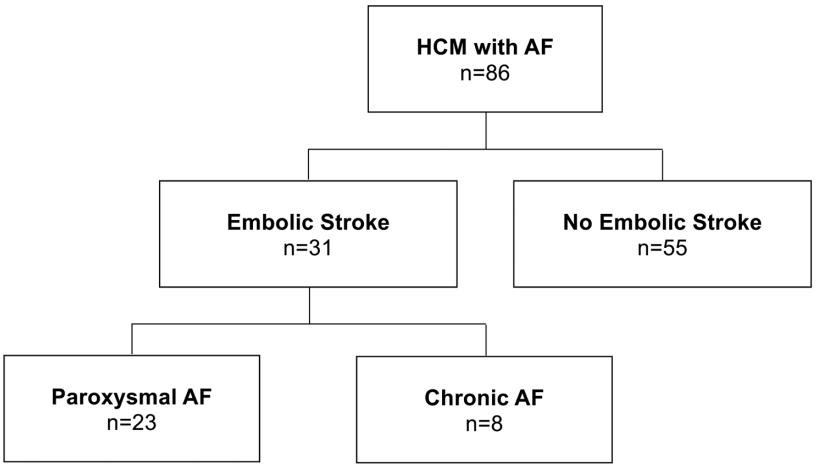

Figure 1. Baseline information at the time of admission. AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy.

The initial evaluation in the present cross-sectional study was regarded as the first clinical assessment during which an echocardiographic diagnosis of HCM was made at Chikamori Hospital. Of the 141 patients with HCM, 55 without AF were excluded from this study, leaving 86 HCM patients with AF enrolled in the study (**Figure 1**). The AF patients underwent clinical evaluation at the time of admission, which included determining the incidence of concomitant embolic stroke, age at embolic stroke, the type of AF, anticoagulation therapy, and the significance of the $CHADS_2$ score.

Definitions

HCM The diagnosis of HCM was based on echocardiographic identification of a hypertrophied, non-dilated left ventricle (LV) with maximum LV wall thickness ≥15 mm,[20] in the absence of any other cardiac or systemic disease capable of producing similar hypertrophy. The diagnosis of HCM was made at the time of admission.

AF The presence of AF was documented by a 12-lead resting electrocardiogram (ECG) at the time of admission or an ambulatory ECG performed after the acute onset of symptoms. AF was defined as paroxysmal when it was self-terminating and considered chronic when it became established.

Embolic Stroke Embolic stroke was defined as permanent neurological disability and impairment caused by ischemic stroke with radiological evidence (computed tomography [CT] images) that had been diagnosed as embolic stroke by a radiologist. Embolic stroke events were also classified by 2 experienced physicians (a neurologist and cardiologist) at the time of admission. These events were ascertained by the study investigators by reviewing CT images and patients' medical records.

Echocardiographic Evaluation

Echocardiographic studies were performed at the time of admission using commercially available ultrasound systems. The dimensions of the LV and left atrium were measured according to previously published criteria.[21] The magnitude and distribution of LV hypertrophy were assessed using 2-dimensional images and indices, as described previously.[21] The peak instantaneous LV outflow tract gradient was estimated using continuous-wave Doppler ultrasound under basal conditions. An LV outflow tract gradient ≥30 mmHg was considered significant.

Statistical Analysis

Categorical variables are reported as frequencies and percentages. Continuous variables are reported as the median and interquartile range (IQR) for non-normally distributed values or as the mean±SD for normally distributed values. Data were analyzed using the 2-sample Student's t-test and Chi-squared test, as appropriate. Two-tailed $P<0.05$ was considered significant.

Results

Characteristics of Patients With and Without Embolic Stroke

The baseline characteristics of the 86 HCM patients with AF, with and without concomitant embolic stroke, are presented in the **Table**. Paroxysmal AF was found more frequently than chronic AF in both groups. The rate of occurrence of paroxysmal AF did not differ between patients with and without embolic stroke (74% vs. 62%; NS). Regarding echocardiographic findings, the median LV ejection fraction was significantly lower in patients with than without embolic stroke (62% vs. 67%; P=0.0086). Maximum LV wall thickness was ≥15 mm in both groups as diagnostically defined. The median maximum LV wall thickness was slightly thicker in patients with than without embolic stroke, but the difference was not statistically significant (18 mm vs. 16 mm, respectively; P=0.052). Anticoagulation either with warfarin or non-vitamin K anticoagulants (NOACs) was less often used in patients with than without embolic stroke (64% vs. 84%; P=0.044). The administration of NOACs was slightly less frequent in patients with than without embolic stroke (19% vs. 42%; P=0.034). There were no significant differences between the 2 groups in terms of sex and laboratory findings, including B-type natriuretic peptide (BNP).

Three patients with embolic stroke also had embolic events to organs other than the brain. These embolic events involved the limbs (n=2) or heart (n=1). None of the patients who did not have embolic stroke experienced arte-

Table. Baseline Characteristics on Admission

	ES (n=31)	No ES (n=55)	P value
Age on admission (years)	77 [69–85]	79 [70–85]	0.815
Male sex	17 (55)	34 (62)	0.527
ECG findings			
Paroxysmal AF	23 (74)	34 (62)	0.243
Chronic AF	8 (26)	21 (38)	
Echocardiographic findings			
Maximum wall thickness (mm)	18 [17–19]	16 [15–19]	0.052
IVS (mm)	13 [11–15]	12 [11–15]	0.392
PW (mm)	12 [10–13]	11 [10–12]	0.452
LVDd (mm)	48 [43–52]	46 [42–51]	0.394
LVDs (mm)	32 [26–36]	29 [26–3]	0.072
LA (mm)	46 [41–51]	44 [38–48]	0.117
LVEF (%)	62 [52–68]	67 [63–72]	0.0086
Laboratory findings			
Peak BNP (pg/mL; n=76)	627 [437–1,014]	607 [329–1,486]	0.929
Hb (g/dL; n=76)	14.2 [12.3–14.9]	12.9 [11.2–14.9]	0.187
Cr (mg/dL; n=76)	0.9 [0.6–1.1]	1.0 [0.7–1.4]	0.101
GOT (IU/L; n=76)	27 [23–32]	27 [22–32]	0.597
GPT (IU/L; n=76)	18 [12–26]	22 [14–30]	0.261
Anticoagulation			
Yes	20 (64)	46 (84)	0.044
Warfarin	14 (45)	23 (42)	0.764
NOAC	6 (19)	23 (42)	0.034
No	9 (30)	9 (16)	0.166
Undetermined	2 (6)	0 (0)	–

Unless indicated otherwise, data are presented as the median [interquartile range] or n (%). Laboratory examinations were performed in the number of patients indicated. AF, atrial fibrillation; BNP, B-type natriuretic peptide; Cr, creatinine; ECG, electrocardiography; ES, embolic stroke; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvate transaminase; Hb, hemoglobin; IVS, interventricular septum; LA, left atrium; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; NOAC, non-vitamin K oral anticoagulant; PW, posterior wall.

rial embolization to the non-central nervous system.

Characteristics of HCM Patients With AF and Embolic Stroke

Incidence of Embolic Stroke Of the 86 HCM patients with AF, 31 had a concomitant embolic stroke at the time of admission (**Figure 1**). The rate of embolic stroke was estimated to be 36% (**Figure 2**). At the time of the embolic stroke, 14 patients (45%) were on warfarin, 6 (19%) were on NOACs, and 9 (29 %) were not receiving anticoagulation treatment.

Age at Embolic Stroke The median age at the event was 77 years (IQR 69–85 years). A significant difference in age at the time of embolic stroke was noted between male and female HCM patients (**Figure 3**). The median (IQR) age at the onset of embolic stroke was significantly younger in male than female HCM patients (71 [64–80] vs. 83 [77–87 years] years, respectively; P=0.009).

Type of AF The prevalence of paroxysmal AF was significantly higher than that of chronic AF in the 31 HCM patients with embolic stroke; 23 (74%) patients had paroxysmal AF and 8 (26%) had chronic AF (P=0.007). Comparing the clinical characteristics of the 31 HCM patients with embolic stroke between the 2 AF types, there were no significant differences with respect to age at embolic stroke, echocardiographic findings, features of blood tests, and anticoagulation treatment.

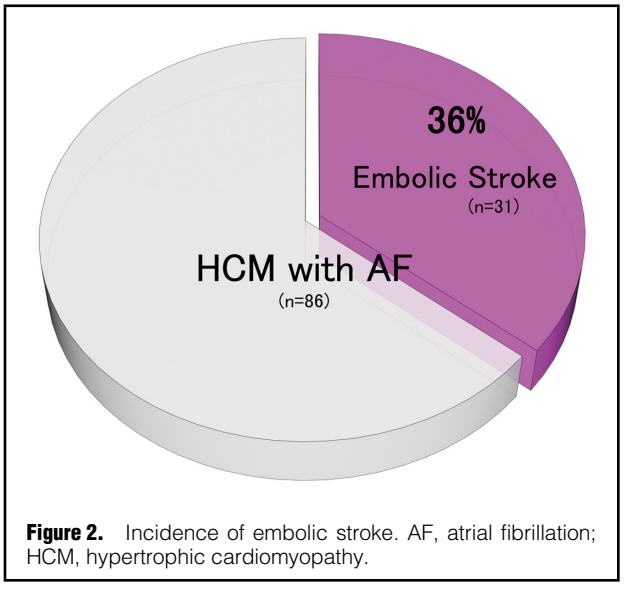

Figure 2. Incidence of embolic stroke. AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy.

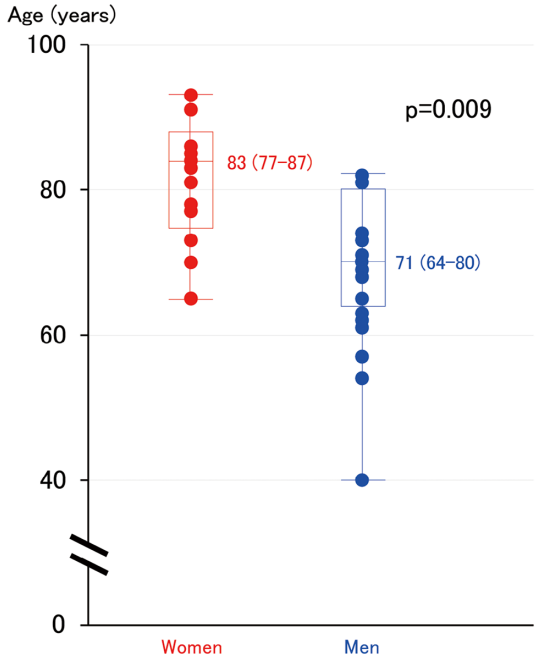

Figure 3. Age at the onset of embolic stroke in male and female patients with hypertrophic cardiomyopathy. The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range.

Severity and Outcomes of Embolic Stroke Of the 31 patients with embolic stroke, 3 died and 3 became bedridden as a direct consequence of their events. Of the remaining 25 patients who survived, 21 had varying degrees of permanent neurologic impairment.

Anticoagulation Therapy

Of the 86 HCM patients with AF, 66 (77%) were anticoagulated with either warfarin (n=37 patients) or approved doses of NOACs (n=29 patients). Eighteen patients (21%) were not on anticoagulation treatment. There were slight differences in the rate of anticoagulation treatment between patients with and without embolic stroke (64.5% vs. 83.6%, respectively; P=0.044). The control of prothrombin time-international normalized ratio (PT-INR) was not sufficient in patients with embolic stroke who were treated with warfarin; the PT-INR was significantly lower in patients with than without embolic stroke (1.19±0.10 vs. 2.01±0.20, respectively; P<0.0001).

$CHADS_2$ Score in Patients With Embolic Stroke

Twelve patients (39%) had a $CHADS_2$ score of 0–1, 6 (19%) had a $CHADS_2$ score of 2, and 10 (32%) had a $CHADS_2$ score of 3–5. The $CHADS_2$ score was not determined in 3 patients (10%). There was no significant difference in $CHADS_2$ scores between patients with and without embolic stroke.

Discussion

Limited Information Derived From HCM Patients With AF and Embolic Stroke

Risk stratification and the prevention of sudden cardiac death have been the primary focus of investigations in the HCM population, despite the fact that heart failure and stroke are also known complications of HCM.[22] AF represents the most common sustained arrhythmia in the HCM population,[4–8] and is a well-known risk factor for embolic stroke in HCM.[4,7,8,13] However, there is limited information derived from HCM patients who actually experience embolic stroke. The present study provides important information concerning the occurrence and profile of embolic stroke in the HCM population that has significant clinical implications.

Incidence of Embolic Stroke

The combination of HCM and AF is associated with a significantly increased risk of embolic stroke.[4,7,8,13] The rate of embolic stroke in HCM patients with AF varies among studies, ranging from 7% to 53%.[6,15,23–25] The results of the present study are consistent with previous reports, demonstrating that a significant number (36%) of HCM patients with AF experienced embolic stroke.

Because of retrospective nature of the present study, it may be possible that the incidence of embolic stroke in HCM patients with AF had been affected by the use of anticoagulation therapy. The prevalence of anticoagulation therapy either with warfarin or NOACs was lower in HCM patients with AF who experienced embolic stroke than in patients with AF and no embolic stroke. It should also be noted that the PT-INR was significantly lower at the time of the event, well below the treatment threshold, in HCM patients with AF and embolic stroke compared with patients with AF and no embolic stroke. These results may have contributed to the somewhat higher incidence of embolic stroke in the present study compared with that in previous large-scale studies (20–27%).[4,6,11]

Type of AF in HCM Patients With Embolic Stroke

The importance of paroxysmal AF in the prevention of embolic stroke needs to be emphasized. To date, the significance of the type of AF has not been extensively evaluated in HCM patients who experienced embolic stroke, although a study by Olivotto et al indicated that patients with chronic AF had a higher combined probability of HCM-related death, functional impairment, and stroke.[4] These authors also suggested that the prevalence of stroke was independent of whether AF was paroxysmal or chronic. However, in the present study, we found that the prevalence of paroxysmal AF was significantly higher than that of chronic AF in HCM patients who experienced embolic stroke. In the retrospective analysis of 1,558 HCM patients by Rowin et al, 226 patients (74%) had paroxysmal AF and 78 (26%) had persistent AF.[26] These findings support those of the present study. It is also conceivable that this high prevalence of paroxysmal AF is probably related to the fact that all our HCM patients with AF had been hospitalized through an emergency department because of acute and/or a sudden onset of symptoms. Given the strong burden of evidence supporting a high risk of embolic stroke in HCM patients who develop AF, such patients should be identified early and treated early. The results of the present study suggest the importance of starting anticoagulation treatment at the first documentation of AF, even if only paroxysmal, particularly in patients aged >50 years. Our findings, together with those of a previous report showing that fatal stroke occurred in patients developing AF at >50 years of age, indicate that this suggestion

is particularly important and useful in clinical practice.

Sex Differences in the Age of Development of Embolic Stroke

In the general population, in addition to age, with which the prevalence of AF increases progressively,[3] male sex has been suggested as a risk factors for the development of AF.[3] However, to date, no data are available on sex differences in the development of embolic stroke in the HCM population. In the present study, embolic stroke occurred over a wide age range, from 40 to 91 years of age, and a significantly earlier development of embolic stroke was demonstrated in male than female HCM patients. Because HCM patients with earlier AF occurrence were previously shown to be at greater risk of stroke, it can be postulated that male HCM patients developing AF at a younger age may have an increased risk of embolic stroke events. In any case, because HCM itself may be considered an important risk factor for embolic stroke, early introduction of anticoagulation therapy is recommended in all HCM patients who develop AF.

Anticoagulation Therapy: Warfarin vs. NOACs

Systemic anticoagulation with warfarin has been associated with a lower risk of stroke in HCM.[4,6,25] For example, a relative risk reduction of 54.8% for thromboembolic events with warfarin was shown in 4,821 HCM patients with AF.[25] Therefore, current consensus guidelines advise that all HCM patients with AF receive anticoagulation with warfarin.[27,28] Concerning NOACs, although there are some small-scale studies suggesting no significant difference between warfarin and NOACs in the rate of stroke,[29,30] large-scale analyses of NOAC therapy have failed to provide any specific discussion of HCM patients.[31,32] In addition, because no data are available from randomized trials of NOACs in reducing embolic stroke risk in this population, NOACs have been recommended as second-line agents in HCM patients with AF.[27,28]

The use of traditional scores, such as the $CHADS_2$ and CHA_2DS_2-VASc scores, for the risk stratification for embolic stroke in HCM patients is not proposed in current guidelines[26,33] because of a poor correlation between these traditional scores and the development of thromboembolism in the population of un-anticoagulated HCM patients with AF.[25] Despite the fact that traditional scores such as the $CHADS_2$ and CHA_2DS_2-VASc scores are commonly used for stroke risk stratification,[34] it is important to recognize once again that these scores are not validated in the HCM population, as demonstrated in the present study.

Risk Stratification and Prevention of Embolic Stroke in HCM Patients Without AF

Acute embolic stroke can be the first presentation in HCM patients together with the first AF occurrence. It is therefore desirable to risk-stratify HCM patients and start prophylactic anticoagulation treatment before AF is found, even if only paroxysmal, to prevent the often catastrophic event of embolic stroke.[35] Although AF occurrence was previously suggested to be predicted by advancing age, increased left atrial size, and impaired left atrial function, there is the need for prospective efforts to further precisely define the risk factors that can predict AF occurrence in HCM patients who are at risk of developing embolic stroke. Further to left atrial size and function, a recent study using cardiac magnetic resonance imaging demonstrated that HCM patients with paroxysmal AF have a greater extent of left atrial wall fibrosis on late gadolinium enhancement, together with a number of other functional and morphological features.[36] This association between AF and left atrial late gadolinium enhancement indicates the importance of assessing not only LV fibrosis,[37] but also left atrial fibrosis as an important adverse marker in HCM patients. In this context, the recently proposed concept of atrial failure[38] may also be relevant to the HCM population, because the presence of atrial failure may predispose a patient to new-onset AF. The risk stratification and prevention of embolic stroke with anticoagulation in HCM patients who have not yet developed AF therefore remains an extremely important challenge in clinical practice, as well as in future research.

Study Limitations

The limitations of the present study may include its retrospective nature with a relatively small sample size. It was not possible to collect echocardiographic information reportedly predictive of embolic events, such as left atrial appendage dysfunction and Doppler flow patterns, in this study. Second, because of the cross-sectional study design, information was limited to the clinical characteristics at the time of admission, and prognostic information was not obtained. Third, beyond AF, although the mechanism of embolic stroke may include thrombus formation in the left atrium, it was not possible to adequately evaluate causes of thrombus formation, such as enhancement of the coagulation system and stagnation of blood flow. Fourth, the study was a single-center retrospective observational study, and the time from AF onset to hospitalization was not available.

Conclusions

In conclusion, one-third of HCM patients with AF developed embolic stroke, and male HCM patients developed embolic stroke earlier than female HCM patients. In HCM patients with AF and embolic stroke, the prevalence of paroxysmal AF was significantly higher than that of chronic AF. Therefore, early introduction of anticoagulation treatment is recommended at first documentation of AF, even if only paroxysmal. The $CHADS_2$ score was not useful in predicting the development of embolic stroke in HCM patients with AF.

Sources of Funding

This study did not receive any specific funding.

Disclosures

H.K. is a member of *Circulation Reports*' Editorial Team. The remaining authors declare no conflicts of interest.

IRB Information

This study was approved by the Ethics Committee of Chikamori Hospital (Reference no. 369).

References

1. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implication on the projections for future prevalence. *Circulation* 2006; **114:** 119–125.
2. Kirchhof P, Benussi K, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC guidelines for the management of atrial fibril-

lation developed in collaboration with EACTS. *Eur Heart J* 2016; **37:** 2893–2962.
3. Vermond RA, Geelhoed B, Verweij N, Tieleman RG, Van der Harst P, Hillege HL, 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:** 1000–1007.
4. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation* 2001; **104:** 2517–2524.
5. Doi Y, Kitaoka H. Hypertrophic cardiomyopathy in the elderly: Significance of atrial fibrillation. *J Cardiol* 2001; **37**(Suppl 1)**:** 133–138.
6. Maron BJ, Olivotto I, Bellone P, Conte MR, Cecchi F, Flygenring BO, et al. Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002; **39:** 301–307.
7. Kubo T, Kitaoka H, Okawa M, Hirota T, Hayato K, Yamasaki N, et al. Clinical impact of atrial fibrillation in patients with hypertrophic cardiomyopathy: Results from Kochi RYOMA study. *Circ J* 2009; **73:** 1599–1605.
8. Siontis K, Geske JB, Ong K, Nishimura R, Ommen S, Gersh BJ. Atrial fibrillation in hypertrophic cardiomyopathy: Prevalence, clinical correlations, and mortality in a large high-risk population. *J Am Heart Assoc* 2014; **3:** e001002.
9. Eriksson MJ, Sonnenberg B, Woo A, Rakowski P, Parker TG, Wigle ED, et al. Long-term outcome in patients with apical hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002; **39:** 638–645.
10. Binder J, Attenhofer Jost CH, Klarich KW, Connolly H, Tajik AJ, Scott CG, et al. Apical hypertrophic cardiomyopathy: Prevalence and correlates of apical outpouching. *J Am Soc Echocardiogr* 2011; **24:** 775–781.
11. Guttmann OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: Systemic review. *Heart* 2014; **100:** 465–472.
12. MacIntyre C, Lakdawala NK. Management of atrial fibrillation in hypertrophic cardiomyopathy. *Circulation* 2016; **133:** 1901–1905.
13. Camm CF, Camm AJ. Atrial fibrillation and anticoagulation in hypertrophic cardiomyopathy. *Arrhythm Electrophysiol Rev* 2017; **6:** 63–68.
14. Kubo T, Hirota T, Baba Y, Ochi Y, Takahashi A, Yamasaki N, et al. Patients' characteristics and clinical course of hypertrophic cardiomyopathy in a regional Japanese cohort: Results from Kochi RYOMA study. *Circ J* 2018; **82:** 824–830.
15. Adabag AS, Casey SA, Kuskowski MA, Zenovich AG, Maron BJ. Spectrum and prognostic significance of arrhythmias on ambulatory Holter electrocardiogram in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005; **45:** 697–704.
16. Haruki S, Minami Y, Hagiwara N. Stroke and embolic events in hypertrophic cardiomyopathy: Risk stratification in patients without atrial fibrillation. *Stroke* 2016; **47:** 936–942.
17. Autore C, Bernabo P, Barilla CS, Bruzzi P, Spirito P. The prognostic importance of left ventricular outflow obstruction in hypertrophic cardiomyopathy varies in relation to the severity of symptoms. *J Am Coll Cardiol* 2005; **45:** 1076–1080.
18. Gruver EJ, Fatkin D, Dodds GA, Kisslo J, Maron BJ, Seideman JG, et al. Familial hypertrophic cardiomyopathy and atrial fibrillation caused by Arg663 His beta-cardiac myosin heavy chain mutation. *Am J Cardiol* 1999; **83**(Suppl 1)**:** 13–18.
19. Ogimoto A, Hamada M, Nakura J, Miki T, Hiwada K. Relation between angiotensin-converting enzyme II genotype and atrial fibrillation in Japanese patients with hypertrophic cardiomyopathy. *J Hum Genet* 2002; **47:** 184–189.
20. Tsutsui H, Kitaoka H, Isobe M, Ide T, Ueta H, Ono M, et al. JCS 2018 guideline on diagnosis and treatment of cardiomyopathies. https://www.j-circ.or.jp/cms/wp-content/uploads/2020/02/JCS2018_tsutsui_kitaoka.pdf (in Japanese) (accessed May 2020).
21. Klues HG, Schiffers A, Maron BJ. Phenotype spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: Morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. *J Am Coll Cardiol* 1995; **26:** 1699–1708.
22. Maron BJ, Olivotto I, Spirito P, Casey SA, Bellone P, Gohman TE, et al. Epidemiology of hypertrophic cardiomyopathy-related death: Revisited in a large non-referral-based patient population. *Circulation* 2000; **102:** 858–864.
23. Furlan AJ, Craciun AR, Raju NR, Hart N. Cerebrovascular complications associated with idiopathic hypertrophic subaortic stenosis. *Stroke* 1984; **15:** 282–284.
24. Higashikawa M, Nakamura Y, Yoshida M, Kinoshita M. Incidence of ischemic strokes in hypertrophic cardiomyopathy is markedly increased if complicated by atrial fibrillation. *Jpn Circ J* 1997; **61:** 673–681.
25. Guttmann OP, Pavlou M, O'Mahony C, Monserrat L, Anastasakis A, Rapezzi C, et al. Prediction of thrombo-embolic risk in patients with hypertrophic cardiomyopathy (HCM Risk-CVA). *Eur J Heart Fail* 2015; **17:** 837–845.
26. Rowin EJ, Hausvater A, Link MS, Abt P, Gionfriddo W, Wang W, et al. Clinical profile and consequences of atrial fibrillation in hypertrophic cardiomyopathy. *Circulation* 2017; **136:** 2420–2436.
27. Gersh BJ, Maron BJ, Bonow RD, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: Executive summary: A report of the America College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011; **124:** 2761–2796.
28. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014; **35:** 2733–2779.
29. Dominguez F, Climent V, Zorio E, Ripoll-Vera T, Salazar-Mendiguchia J, Garcia-Pinilla JM, et al. Direct oral anticoagulants in patients with hypertrophic cardiomyopathy and atrial fibrillation. *Int J Cardiol* 2017; **248:** 232–238.
30. Jung H, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation with hypertrophic cardiomyopathy: A nationwide cohort study. *Chest* 2019; **155:** 354–363.
31. Xao X, Abraham NS, Sangaralingham LS, Bellolio F, McBane RD, Shah ND, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *J Am Heart Assoc* 2016; **5:** e003725.
32. Larsen TB, Skjoth F, Nielsen PB, Kjaldgaard JN, Lip GYH. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: Propensity weighted nationwide cohort study. *BMJ* 2016; **353:** i3189.
33. JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with hypertrophic cardiomyopathy (JCS 2012): Digest version. *Circ J* 2016; **80:** 753–774.
34. Lip GY, Lane DA. Stroke prevention in atrial fibrillation: A systematic review. *JAMA* 2015; **313:** 1950–1962.
35. Okumura T, Kimura Y, Murohara T. Prediction of thromboembolism in patients with hypertrophic cardiomyopathy. *Circ J* 2020; **84:** 700–701.
36. Sivalokanathan S, Zghaib T, Greenland GV, Vasquez N, Kudchadkar SM, Kontari E, et al. Hypertrophic cardiomyopathy patients with paroxysmal atrial fibrillation have a high burden of left atrial fibrosis by cardiac magnetic resonance imaging. *JACC Clin Electrophysiol* 2019; **5:** 364–375.
37. Hohneek A, Overhoff D, Doesch C, Sandberg R, Rudic B, Tueluemen E, et al. Extent of late gadolinium enhancement predicts thromboembolic events in patients with hypertrophic cardiomyopathy. *Circ J* 2020; **84:** 754–762.
38. Bisbal F, Baranchuk A, Braunwald E, Bayes de Luna A, Bayes-Genis A. Atrial failure as a clinical entity: JACC review topic of the week. *J Am Coll Cardiol* 2020; **75:** 222–232.