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# Hypertrophic cardiomyopathy and atrial fibrillation: the Cardiomyopathy/Myocarditis Registry of the EURObservational Research Programme of the European Society of Cardiology

Katarzyna Mizia-Stec,[1] Juan R Gimeno ,[2] Philippe Charron ,[3] Perry M Elliott,[4] Juan Pablo Kaski,[5] Aldo Pietro Maggioni ,[6] Michal Tendera,[7] Luigi Tavazzi,[8] Maciej T Wybraniec ,[9] Cécile Laroche,[10] Alida Caforio,[11] on behalf of the EORP Cardiomyopathy Registry Investigators

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For numbered affiliations see end of article.

**Correspondence to**
Dr Katarzyna Mizia-Stec; kmiziastec@gmail.com

## ABSTRACT

**Background** Hypertrophic cardiomyopathy (HCM) is commonly associated with atrial fibrillation (AF), but its impact on outcomes in real-world practice is uncertain. The aim of the study was to evaluate the clinical profile and prognosis of patients with HCM and AF.

**Methods** Overall, 1739 adult patients with HCM (40.9% women; median age: 55.5 years) were enrolled in the EURObservational Research Programme (EORP) Cardiomyopathy/Myocarditis Registry. Clinical characteristics at baseline and cardiovascular endpoints at 1 year were prospectively assessed.

**Results** At baseline, AF was present in 478 (27.5%) patients; an additional 48 patients (2.8%) developed AF at 1-year follow-up. Oral anticoagulants (OAC) were administered at baseline in 69.5% of the patients. Patients with AF were older and more symptomatic, had higher body mass index, more prevalent cardiovascular risk factors, a history of sustained ventricular tachycardia and implantable cardioverter-defibrillator, lower left ventricular ejection fraction (LVEF), larger left atria (LA) and more advanced LV diastolic dysfunction (pp<0.001 for all). Age at enrolment (OR=1.068, p<0.001), symptom: palpitations (OR=2.191, p<0.001), LVEF (OR=0.978, p<0.001) and LA diameter (OR=1.094, p<0.001) were independent predictors of AF in HCM population. Patients with AF had a higher annual incidence of stroke/transient ischaemic attack (2.6 vs 0.9%, p=0.009) and a trend towards increased all-cause mortality in comparison to the non-AF cohort (3.4 vs 1.7%, p=0.053).

**Conclusions** AF affects nearly one-third of patients with HCM and is associated with higher symptom burden, increased prevalence of comorbidities, myocardial remodelling and increased annual risk of cerebral ischaemic events. In spite of this, the utilisation of OAC was suboptimal.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Atrial fibrillation is common in patients with hypertrophic cardiomyopathy, but its prevalence and risk factors and clinical sequelae are not well described in European population.

### WHAT THIS STUDY ADDS

⇒ The study showed the high prevalence of atrial fibrillation in patients with hypertrophic cardiomyopathy, especially in patients with hypertrophic cardiomyopathy coexisting with other comorbidities or advanced structural and functional remodelling. The study demonstrated the significant increase in the risk of stroke along with inadequate use of oral anticoagulation.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The clinical characteristics of patients with hypertrophic cardiomyopathy and atrial fibrillation support the complex approach of 'CC To ABC' and highlight the need for further increase of use of oral anticoagulants in this population.

## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common cardiomyopathy[1 2] and is associated with an increased risk of sudden cardiac death (SCD) related with ventricular arrhythmias, progressive heart failure and symptoms from left ventricular outflow tract obstruction (LVOTO).[2] Apart from prevention of SCD with implantable cardioverter defibrillators and septal reduction therapies for LVOTO, the management of patients with HCM also focuses on detection and treatment of atrial fibrillation (AF).[3] Recent data suggest that AF may be the first manifestation of certain genetic variants of HCM prior to expression of hypertrophic phenotype.[4]

AF in HCM constitutes an independent predictor of thromboembolic events[5] and is

an indication for chronic oral anticoagulation (OAC)[1] regardless of CHA2DS2-VASc score.[2 6] Furthermore, regular ambulatory electrocardiographic monitoring is recommended in order to detect clinically silent AF.[1 2 7] Regardless of the increasing data on AF in HCM, here are some discrepancies between current recommendations and real-life data on the management of AF in patients with HCM.[8]

The EURObservational Research Programme (EORP) Cardiomyopathy/Myocarditis Registry, conceived by the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Disease, is a prospective observational multinational registry of consecutive patients presenting to centres in European countries. The Registry is designed to provide insight into clinical presentation and management of contemporary patients with heart muscle disease across a large range of centres in Europe to improve clinical service provision and therapy.[9] The Registry comprises a representative population of adult patients with cardiomyopathies. The aims of this study were to perform a focused analysis of the prevalence of AF and AF risk factors in patients with HCM; to compare current recommendations for OAC with real-life practice and assess the risk of stroke.

## METHODS

The protocol of the EORP Cardiomyopathy/Myocarditis Registry and data on participating centres are presented elsewhere.[9] The study complies with the Declaration of Helsinki and all *participating centres obtained the approval of national or regional ethics committees or Institutional Review Boards, according to local regulations*. Written informed consent was obtained from all participants before collection of any data. All diagnostic or therapeutic procedures and decisions were left to the discretion of attending physicians.

Baseline and 1-year follow-up data (including demographic, clinical, cardiac, genetic, therapeutic data) were collected prospectively using a web-based system with an electronic case report form. The variables analysed in the study included data on anticoagulation and antiplatelet therapy. The EORP department of the ESC was responsible for study management, data quality control and statistical analyses.

Patients with HCM were recruited between 1 December 2012 and 30 December 2016 in 68 centres located in 18 countries; the obligatory number of enrolled patients was 40 per centre. The inclusion criteria comprised participants aged 18 years and above, willingness and ability to give informed consent, and fulfilment of standard diagnostic criteria for HCM in probands and relatives. General clinical characteristics of HCM were reported in the first publication of the registry data.[9] HCM was defined as a left ventricular wall thickness of ≥15 mm in one or more myocardial segments in the absence of inappropriate loading conditions. For the purpose of familial screening, HCM in first degree relative was diagnosed in line with previously published criteria.[10]

A history of paroxysmal, persistent or permanent AF was obtained from medical records or confirmed on 12-lead ECG, ambulatory electrocardiographic monitoring or implantable loop recorders. Atrial high rate episodes in cardiac implantable electronic devices (dual chamber pacemaker, implantable cardioverter-defibrillator) as an indirect marker of AF was not obtained in the analysis. Following the registry enrolment, patients were followed up at 1 year for the onset of adverse clinical endpoints, including stroke/transient ischaemic attack (fatal ischaemic stroke and non-fatal stroke/transient ischaemic attack (TIA)), death from any cause, death from heart failure, death from ischaemic stroke, death from haemorrhagic stroke and death from systemic haemorrhage.

### Statistical analysis

Analysis of baseline demographic and clinical variables and predefined clinical endpoints was stratified by the presence of any AF. Univariate analysis was applied to both continuous and categorical variables. Continuous variables were reported as mean±SD. Among-group comparisons were made using the non-parametric test (Kruskal-Wallis test). Categorical variables were reported as percentages. Among-group comparisons were made using the $\chi^2$ test or a Fisher's exact test if any expected cell count was less than five. Stepwise multivariable logistic regression analyses were performed to establish the relationship between the patient characteristics and the presence of AF, including into the model, all the candidate variables (variables with p<0.10 in univariate). The candidate variables for the prediction of AF included age at enrolment, age at first evaluation in the centre, body mass index (BMI), NYHA class, palpitations, history of sustained ventricular tachycardia, history of atrioventricular block, history of bundle branch block, history of stroke or TIA, arterial hypertension, diabetes mellitus, hyperlipidaemia, renal impairment, chronic obstructive pulmonary disease, anaemia and level of physical activity. A significant level of 0.05 was required for a variable to stay in the model. No interaction was tested. To verify that the models were optimal, Hosmer and Lemeshow Goodness-of-Fit test and per cent concordant were calculated. A two-sided p value of less than 0.05 was considered as statistically significant. All analyses were performed using SAS statistical software V.9.4 (SAS Institute, Cary, North Carolina).

## RESULTS

### Baseline characteristics

1739 adult patients with HCM (40.9% women; median age: 55.5) were recruited. Follow-up data at 1 year were obtained in 1420 patients (87.7%) (table 1).

### Rate of AF in HCM population

AF was present at baseline in 478 (27.5%) individuals. Paroxysmal AF was the most common form of AF in

**Table 1** Prevalence of AF in patients with HCM

| | HCM |
|---|---|
| AF at baseline | 478/1739 (27.49%) |
| Baseline—type of AF | |
| Paroxysmal | 245/448 (54.69%) |
| Persistent | 79/448 (17.63%) |
| Permanent | 124/448 (27.68%) |
| AF at 1-year follow-up | 526/1739 (30.25%) |

AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy.

patients with HCM (54.7%). Newly diagnosed AF was registered during follow-up in 48 (2.8%) individuals with HCM. The proportion of patients with AF at baseline and at follow-up in different cardiomyopathies is presented in table 1.

### Demographic and clinical characteristics of AF and non-AF HCM patients at baseline

Baseline characteristics of HCM patients with and without AF was outlined in table 2. Age at enrolment (59.6±13.8 vs 50.8±16.1 years, p<0.001) and age at the first evaluation in the centre (53.9±15.5 vs 46.9±17.0 years, p<0.001) were greater in HCM subjects with AF. Patients with AF had larger BMI (27.7±5.1 vs 26.6±4.6 kg/m$^2$, p<0.001). New York Heart Association (NYHA) class was more advanced in AF (NYHA I/II/III/IV: 19.3/55.8/22.5/2.4%) than in non-AF subjects (NYHA I/II/III/IV: 39.2/47.0/12.9/0.8%, p<0.001). History of arrhythmias: sustained ventricular tachycardia (10.8 vs 6.4%, p=0.001), atrioventricular block (12.3 vs 8.4%, p=0.043) and bundle branch block (19.3 vs 12.3%, p=0.003) were more frequent in AF than in non-AF HCM population. History of stroke/TIA was positive more frequently in AF population (11.5% vs 3.3%, p<0.001).

The following comorbidities were more prevalent in patients with AF: arterial hypertension (43.4 vs 34.6%, p<0.001), diabetes mellitus type I or II (14.6 vs 8.2%, p<0.001), hyperlipidaemia (42.0 vs 34.1%, p=0.002), renal impairment (15.4 vs 6.4%, p<0.001), chronic obstructive pulmonary disease (6.7 vs 2.6%, p<0.001) and anaemia (7.5 vs 3.4%, p<0.001). Patients with AF reported less physical activity than those without AF (40.0 vs 53.3%, p<0.001).

### Echocardiographic characteristics of AF and non-AF HCM patients at baseline

Patients with AF had lower LVEF (59.5±12.3 vs 63.5±10.7%, p<0.001), left atrium (LA) dilatation (48.9±9.1 vs 42.4±7.7 mm, p<0.001), increased pulmonary artery systolic pressure (37.8±13.7 vs 29.6±12.6 mm Hg, p<0.001), other *pattern of LV hypertrophy* (AF vs non-AF: septal 70.9 vs 74.6%, concentric 15.6 vs 11.4%, apical 8.4 vs 8.2%, other 5.1 vs 5.8%; p=0.031), more advanced LV diastolic dysfunction (AF vs non-AF: normal 14.8 vs 27.5%, grade I/impaired relaxation 38.3 vs 43.6%, grade II/pseudonormalisation 29.8 vs 24.0%, grade III/restriction 17.2 vs 5.0%; p<0.001) and more frequent LV outflow tract resting gradient (38.8 vs 30.7%, p<0.001).

### Predictors of AF in HCM population

Multivariate logistic regression analysis revealed that the independent predictors of AF in the HCM population were age at enrolment (OR 1.068, p<0.001), symptom—palpitation (OR 2.151, p<0.001), left ventricular ejection fraction (LVEF) (OR 0.978, p<0.001) and LA diameter (OR 1.094, p<0.001) (table 3).

### OAC and antiplatelet therapy in HCM population with AF

OAC was administered at baseline in 69.5% of HCM patients with AF: 48.5% patients were treated with vitamin K antagonists (VKA) and 21.0% with DOAC (figure 1). Antiplatelet therapy was administered in 20.3% of AF patients, of whom 90.7% received aspirin. Detailed data on anticoagulant and antiplatelet therapy in HCM patients with AF are presented in table 4.

### Clinical endpoints in AF and non-AF patients with HCM

At 1-year follow-up, the incidence of stroke/TIA was higher in patients with AF compared with non-AF patients (2.6 vs 0.9%, p=0.009). There was a trend towards increased death from any cause in patients with AF (3.4 vs 1.7%, p=0.053). Comparison of other endpoints—death from ischaemic stroke, death from haemorrhagic stroke and death from systemic haemorrhage did not differ between the AF and non-AF HCM populations (table 5).

## DISCUSSION

We present data from the EORP Registry on the prevalence of AF and AF risk factors in a contemporary European population of HCM patients. Our study extends a previous analysis on AF prevalence in patients with cardiomyopathies.[11] The study confirms the high prevalence of AF (particularly paroxysmal) in patients with HCM and the association between AF and stroke risk. The presence of AF corresponded with more advanced symptoms, increased prevalence of comorbidities and structural and functional heart remodelling. Oral anticoagulants were administered in less than 70% of patients with AF. Data on AF prevalence in patients with cardiomyopathies are limited. According to the EORP Registry, 29.4% of cardiomyopathy patients were affected by AF. These findings are similar to those of a previous analysis,[12] which showed a prevalence of AF in patients with inherited cardiomyopathies ranging from 11% to 33%, with the highest values in patients with HCM and familial DCM.[13] Other data indicate 5%–15% AF prevalence in HCM.[5 14]

The recently introduced HCM-AF Risk Calculator allows the prognosis of AF occurrence in HCM patients for the nearest 2 and 5 years.[15] The score considers four clinically relevant variables: LA diameter, the presence of heart failure (HF) symptoms, age at HCM diagnosis and age at current clinical evaluation. Thus, it corresponds to our observation. On the other hand, the HCM-AF Risk

**Table 2** Demographic and clinical characteristics in AF and non-AF populations of HCM patients

| Variable | AF (N=526) | Non-AF (N=1213) | P value | OR (95% CI) | OR P value |
|---|---|---|---|---|---|
| Age at enrolment (years), mean±SD | 59.6 (±13.8) | 50.8 (±16.1) | <0.001 | 1.039 (1.031 to 1.046) | <0.001 |
| Age at first evaluation in the centre (years), mean±SD | 53.9 (±15.5) | 46.9 (±17.0) | <0.001 | 1.027 (1.020 to 1.034) | <0.001 |
| Sex—female | 224/526 (42.59%) | 487/1213 (40.15%) | 0.342 | 1.106 (0.899 to 1.361) | 0.342 |
| Body mass index (kg/m²), mean±SD | 27.7 (±5.1) | 26.6 (±4.6) | <0.001 | 1.046 (1.023 to 1.070) | <0.001 |
| NYHA class | | | | | |
| NYHA I | 90/466 (19.31%) | 373/951 (39.22%) | <0.001 | reference | reference |
| NYHA II | 260/466 (55.79%) | 447/951 (47.00%) | | 2.411 (1.829 to 3.178) | <0.001 |
| NYHA III | 105/466 (22.53%) | 123/951 (12.93%) | | 3.538 (2.499 to 5.008) | <0.001 |
| NYHA IV | 11/466 (2.36%) | 8/951 (0.84%) | | 5.699 (2.227 to 14.579) | <0.001 |
| History of arrhythmias : | | | | | |
| History of sustained VT | 57/526 (10.84%) | 77/1213 (6.35%) | 0.001 | 1.793 (1.252 to 2.568) | 0.001 |
| History of resuscitated VF/cardiac arrest | 18/526 (3.42%) | 31/1213 (2.56%) | 0.316 | 1.351 (0.749 to 2.437) | 0.318 |
| History of AV block | 39/316 (12.34%) | 62/742 (8.36%) | 0.043 | 1.544 (1.010 to 2.360) | 0.045 |
| History of BBB | 61/316 (19.30%) | 91/742 (12.26%) | 0.003 | 1.712 (1.200 to 2.441) | 0.003 |
| Family history of sudden death | 111/495 (22.42%) | 239/1167 (20.48%) | 0.374 | 1.122 (0.870 to 1.448) | 0.374 |
| History of stroke: TIA or stroke | 60/523 (11.47%) | 40/1205 (3.32%) | <0.001 | 3.774 (2.494 to 5.712) | <0.001 |
| Co-morbidities : | | | | | |
| Arterial hypertension | 228/526 (43.35%) | 420/1213 (34.62%) | <0.001 | 1.445 (1.172 to 1.781) | <0.001 |
| Diabetes mellitus I or II | 77/526 (14.64%) | 99/1213 (8.16%) | <0.001 | 1.930 (1.405 to 2.651) | <0.001 |
| Hyperlipidaemia | 221/526 (42.02%) | 414/1213 (34.13%) | 0.002 | 1.398 (1.134 to 1.725) | 0.002 |
| Renal impairment | 81/526 (15.40%) | 77/1213 (6.35%) | <0.001 | 2.684 (1.929 to 3.736) | <0.001 |
| Chronic obstructive pulmonary disease | 35/526 (6.65%) | 32/1213 (2.64%) | <0.001 | 2.629 (1.609 to 4.295) | <0.001 |
| Anaemia | 39/522 (7.47%) | 41/1195 (3.43%) | <0.001 | 2.273 (1.448 to 3.568) | <0.001 |
| Lifestyle : | | | | | |
| Physical activity | 167/418 (39.95%) | 505/948 (53.27%) | <0.001 | 0.584 (0.462 to 0.737) | <0.001 |
| Physical activity | | | | | |
| None | 251/418 (60.05%) | 443/948 (46.73%) | <0.001 | reference | reference |
| Occasionally | 112/418 (26.79%) | 277/948 (29.22%) | | 0.714 (0.546 to 0.934) | 0.014 |
| Regularly | 51/418 (12.20%) | 195/948 (20.57%) | | 0.462 (0.327 to 0.652) | <0.001 |
| Intensely | 4/418 (0.96%) | 33/948 (3.48%) | | 0.214 (0.075 to 0.611) | 0.004 |
| Alcohol use (any amount) | 101/426 (23.71%) | 265/961 (27.58%) | 0.132 | 0.816 (0.627 to 1.063) | 0.132 |
| Smoking (current or former) | 144/482 (29.88%) | 357/1104 (32.34%) | 0.332 | 0.891 (0.707 to 1.125) | 0.332 |

AF, atrial fibrillation; BBB, bundle branch block; NYHA, New York Heart Association; TIA, transient ischaemic attack; VF, ventricular fibrillation; VT, ventricular tachycardia.

Score seems to be useful in the prediction of the general clinical outcomes in HCM patients, but in some populations, it underestimates the real-life high level of AF incidence.[16]

Our analysis also revealed that HCM patients with AF were older, more symptomatic and had more cardiovascular risk factors and comorbidities. Moreover, the median age varied between AF and non-AF subjects being lower in non-AF population. The age distribution and disease severity may also partially explain differences in the prevalence of AF. Many cardiovascular diseases as well as unhealthy lifestyle are associated with a risk of AF and its complications.[8 17] We should be aware that the Registry HCM population was relatively old with a high percentage of comorbidities. The recently published data[18–20] show the similar age and characteristics of the HCM patients registered in the healthcare system. The clinical characteristics of HCM-AF patients indicate that the ESC recommended complex AF approach 'CC To ABC' is appropriate in this population. Thus, identification of comorbidities as well as their treatment is important to prevent AF also in patients with HCM.

**Table 3** Multivariate logistic regression analysis of different baseline demographic and clinical variables associated with the overall presence of AF in HCM patients

| Variable | Global P value | OR (95% CI) | OR P value |
|---|---|---|---|
| Age at enrolment | <0.001 | 1.068 (1.042 to 1.094) | <0.001 |
| Symptom: palpitations | <0.001 | 2.151 (1.589 to 2.911) | <0.001 |
| History of stroke/TIA | | | |
| Stroke vs no | <0.001 | 2.750 (1.339 to 5.648) | 0.300 |
| TIA vs no | | 3.188 (1.389 to 7.315) | 0.151 |
| LVEF (%) | <0.001 | 0.978 (0.966 to 0.990) | <0.001 |
| Left atrium diameter (mm) | <0.001 | 1.094 (1.073 to 1.115) | <0.001 |
| Sample size : 1050/1739 | | | |
| Hosmer-Lemeshow goodness of fit : Stat=13.00 with 8DF and 10 groups. P value=0.112 | | | |

AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; TIA, transient ischaemic attack.

### OAC and antiplatelet therapy in AF population

Almost a third of patients with HCM and AF did not receive anticoagulants during the observation period. This is consistent with data from the EORP-AF pilot registry,[21] in which OAC was used in 80.1% of patients with AF. Other contemporary registries presenting data on OAC in the general AF population report rates of anticoagulation that vary from 46% to 97%.[22 23] Anticoagulation is associated with a lower incidence of thromboembolic events[24] and the $CHA_2DS_2$-VASc score is used as a method of stratifying patients with AF for therapy.[8] However, retrospective evidence in HCM suggests that $CHA_2DS_2$-VASc performs suboptimally with respect to stroke prediction.[7 25] Currently, HCM is incorporated into $CHA_2DS_2$-VASc score and constitutes a surrogate of heart failure in the scoring system.[8] Given that AF increases the risk of thromboembolic events in patients with HCM to a greater extent than in the general population, the first occurrence of AF should be an indication for lifelong OAC and HCM.[26 27] While there is more experience with VKA, DOAC can currently be used in these patients.[26] Although antiplatelet agents are not indicated for prevention of thromboembolic events,[8] 17.5% of our AF patients received this therapy.

We may suspect only that in some patients stroke/TIA in case history, or coexistence of diabetes mellitus were the indications for the therapy. Probably in most cases, the antiplatelet therapy was used improperly instead of OAC. The registry highlights the need for further education on OAC in prevention of thromboembolic events in HCM-AF population.

### Clinical endpoints and risk factors for stroke/TIA

The EORP Registry confirmed impaired prognosis for the population with HCM and concurrent AF. The present results suggest more than three times higher annual incidence of stroke/TIA in AF than in non-AF patients with HCM (2.65 vs 0.85%), and the annual incidence of stroke/TIA is comparable to the adjusted stroke rate (3.2%/year) in non-valvular AF population with a $CHA_2DS_2$-VASc score of 3 (population not receiving OAC).[8] Our results are concordant with the meta-analysis by Guttmann *et al*,[7] which

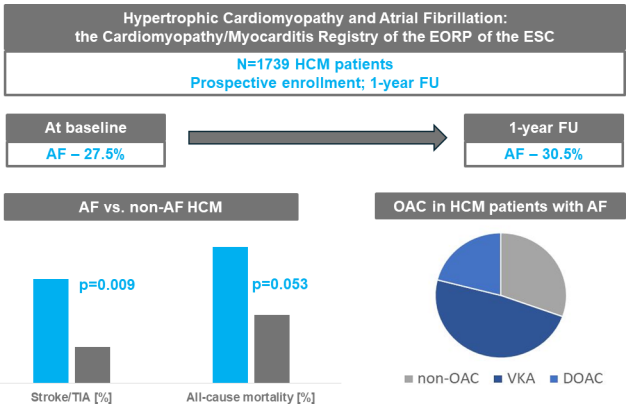


**Figure 1** Prevalence of atrial fibrillation and anticoagulation in patients with the diagnosis of hypertrophic cardiomyopathy at baseline and in 1-year follow-up. AF, atrial fibrillation; DOAC, direct oral anticoagulants; EORP, European Observational Research Programme; ESC, European Society of Cardiology; FU, follow-up; HCM, hypertrophic cardiomyopathy; OAC, oral anticoagulants; TIA, transient ischaemic attack.

**Table 4** Current anticoagulation regimen (VKA/DOAC) in patients with HCM and AF

| Variable | HCM with AF (N=526) |
|---|---|
| Oral anticoagulant treatment | 364/524 (69.47%) |
| Oral anticoagulant treatment | |
| No treatment | 160/524 (30.53%) |
| DOAC | 110/524 (20.99%) |
| VKA | 254/524 (48.47%) |
| Antiplatelet therapy | 107/526 (20.34%) |
| Aspirin | 97/514 (18.87%) |

AF, atrial fibrillation; DOAC, direct oral anticoagulants; HCM, hypertrophic cardiomyopathy; VKA, vitamin K antagonists.

Table 5 Incidence of adverse cardiovascular endpoints in 1-year follow-up among AF and non-AF populations of HCM patients

| Variable | AF | Non-AF | P value | OR (95% CI) | OR P value |
|---|---|---|---|---|---|
| Stroke/TIA | 11/417 (2.64%) | 8/945 (0.85%) | 0.009 | 3.173 (1.267 to 7.948) | 0.014 |
| Death from any cause | 15/443 (3.39%) | 17/976 (1.74%) | 0.053 | 1.977 (0.978 to 3.996) | 0.058 |
| Death from heart failure | 4/439 (0.91%) | 9/973 (0.92%) | 1.000 | 0.985 (0.302 to 3.216) | 0.980 |
| Death from ischaemic stroke | 1/439 (0.23%) | 1/973 (0.10%) | 0.525 | 2.219 (0.138 to 35.557) | 0.573 |
| Death from haemorrhagic stroke | 0/439 (0.00%) | 0/973 (0.00%) | NC | NC | NC |
| Death from systemic haemorrhage | 0/439 (0.00%) | 0/973 (0.00%) | NC | NC | NC |

AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy; NC, not calculable; TIA, transient ischaemic attack.

demonstrated the annual incidence of thromboembolic events of 3.75% in patients with HCM and AF. According to a Korean database,[25] the risk of stroke in HCM population with AF and without any $CHA_2DS_2$-VASc risk factors was similar to that of AF general population with $CHA_2DS_2$-VASc score of 3. In the study by Maron and coworkers on 900 patients with HCM, overall annual incidence of systemic thromboembolic events in HCM population was 0.8%/year, 1.9%/year in patients >60 years and 2.5%/year in patients with AF.[5] This data confirm the requirement for prompt introduction of chronic OAC in patients with HCM and AF irrespective of the risk estimated using $CHA_2DS_2$-VASc score. The clinical vigilance in terms of screening for silent AF is vital and should be performed according to current ESC recommendations.[28]

Comparison of other clinical endpoints, that is, death from ischaemic stroke, death from haemorrhagic stroke, death from systemic haemorrhage that may be related to AF or anticoagulation did not reveal any differences, which may be linked to a limited number of events.

It is well-documented that AF coexists and interacts with other cardiovascular risk factors both in general[9] and in cardiomyopathy population.[22] Thus, AF itself and AF as an element of complex interactions may worsen the prognosis for AF population. We found that classic cardiovascular risk factors, that is, age, diabetes mellitus and renal impairment were associated with the incidence of stroke/TIA in the HCM population. The AF at baseline, previous incidence of stroke and anaemia were independent risk factors for the stroke/TIA on follow-up. It suggests that both monitoring for AF diagnosis and complex 'up-stream therapy' including modification of life-style risk factors and treatment of comorbidities are necessary to prevent cerebral events in patients with cardiomyopathies.

### Limitations

The limitations for the analysis of the EORP Cardiomyopathy/Myocarditis Registry data have been described previously.[9] Considering the selection bias related with tertiary reference centres involved in the registry, the use of anticoagulation in patients with HCM and AF might have been overestimated. The actual use of OAC in this population may thus be lower with further deleterious impact on the risk of thromboembolic events. The protocol did not impose on centres the strict requirement for screening for AF, thus, the registry represents real-world data on the prevalence of AF in this population.

The data in the EORP Registry have been collected between 2012 and 2016,[9] and the anticoagulation was administered according to the current recommendations. However, we should be aware that specific recommendations have been set for patients with HCM and AF.[2 26] Nowadays, we administer anticoagulation for all HCM subjects with AF since HCM is considered as surrogate of HF in CHA2DS2-VASc score.

Data on appropriate anticoagulation are important for the assessment of the risk of thromboembolic events. The registry did not include information about OAC doses or INR in VKA patients. We also have no data on genetic tests or familiar HCM appearance that would be of great importance regarding a potent separate analysis of predisposing factors for AF in a sarcomeric form of cardiomyopathy.

The relatively short follow-up constitutes another limitation of the study. Since there are not many subjects who experienced a stroke/TIA during follow-up, the analysis of risk factors for stroke/TIA was limited.

## CONCLUSIONS

The EORP Cardiomyopathy/Myocarditis Registry showed high prevalence of AF in patients with HCM that corresponds with more advanced symptoms, increased prevalence of comorbidities, structural and functional heart remodelling along with inadequate anticoagulation and a significant increase in the risk of stroke. The clinical characteristics of HCM-AF patients indicate that the ESC-recommended complex AF approach 'CC To ABC' is appropriate in this population.

**Author affiliations**
[1]First Department of Cardiology, Medical University of Silesia School of Medicine in Katowice, Katowice, Poland
[2]Cardiac Department, Virgen de la Arrixaca University Hospital, El Palmar, Spain
[3]Cardiology and Genetics, Pitié-Salpêtrière University Hospital, Paris, France
[4]Cardiology, University College London, London, UK
[5]Inherited Cardiovascular Diseases, Great Ormond Street Hospital for Children, London, UK

[6]Research Center, ANMCO, Firenze, Italy
[7]Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland
[8]Maria Cecilia Hospital SpA, Cotignola, Italy
[9]First Department of Cardiology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland
[10]EurObservational Research Programme Department, European Society of Cardiology, Sophia Antipolis, France
[11]Department of Cardiological Thoracic and Vascular Sciences, University of Padua, Padova, Italy

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**ORCID iDs**
Juan R Gimeno http://orcid.org/0000-0001-5818-1754
Philippe Charron http://orcid.org/0000-0002-1782-1118
Aldo Pietro Maggioni http://orcid.org/0000-0003-2764-6779
Maciej T Wybraniec http://orcid.org/0000-0003-1151-8385

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