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Research Paper

Atrial fibrillation and the risk of sudden cardiac arrest in patients with hypertrophic cardiomyopathy - A nationwide cohort study

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ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM), affecting 0.2% of the population, is the leading cause of sudden cardiac arrest (SCA). Incident atrial fibrillation (AF) is associated with an increased risk of SCA in general population. To determine whether AF is associated with an increased risk of SCA in patients with HCM.
Methods: This nationwide cohort study analyzed data from Registry for Catastrophic Illness, which encompassed almost 100% of the patients with HCM in Taiwan from 1996 to 2013. Follow-up and data analysis ended December 31, 2013. The main outcome was physician-adjudicated SCA, defined as death from a sudden, pulseless condition presumed due to a ventricular tachyarrhythmia. The secondary outcome was non-sudden cardiac death (NSCD), which was heart failure death, stroke death and non-HCM related death. We used Cox proportional hazards models to assess the association between AF and SCA/NSCD, adjusting for baseline demographic and cardiovascular risk factors.
Findings: A total 10,910 subjects participated in this study with mean age of 62 years. Among enrolled subjects, 1,169 (10.7%) developed AF, which was independently associated with elder age, female sex, and history of heart failure (HF) hospitalization. During follow-up (median, 8.5 years and 2th to 7th interquartile range, 3.6 to 16.5 years), 371 SCA (166 in AF and 205 in non-AF group) and 797 NSCD (417 in AF and 380 in non-AF group) events occurred. The crude incidence rates of SCA were 12.45/1000 person-years (with AF) and 3.57/1000 person-years (without AF). The crude incidence rates for NSCD were 31.29/1000 person-years (with AF) and 6.63/1000 person-years (without AF). The multivariable hazard ratios (HRs) (95% CI) of AF for SCA and NSCD were 3.633 (2.756–4.791) and 2.086 (1.799–2.418), respectively. Furthermore, among the etiologies of NSCD, subjects with AF was at most risk of stroke-related death (HR, 6.609; 95% CI, 3.794–9.725).
Interpretation: Incident AF is associated with an increased risk of SCA and NSCD in the HCM population. Early detection of AF may provide more comprehensive risk stratification of SCD in HCM population. Because of underuse of oral anticoagulants and the absence of primary prevention ICD therapy in our cohort, the application of our findings was limited for the general HCM population in the current clinical practice.
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1. Introduction

Patients of hypertrophic cardiomyopathy (HCM) have an annual incidence for cardiovascular death of 1 to 2% with sudden cardiac arrest (SCA), thromboembolism and heart failure being the main cause of death [1]. In terms of SCA, the majority of fatal arrhythmia is ventricular tachycardia or fibrillation and implantable cardioverter defibrillators (ICD) are indicated for primary prophylaxis in patients with high risk of SCA [1,2]. On the other hand, atrial fibrillation (AF) is the most common sustained arrhythmia in HCM population, with

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Research in context

Evidence before this study

We searched PubMed for studies published until December 31, 2020 using the terms: hypertrophic cardiomyopathy (HCM), atrial fibrillation and sudden cardiac arrest/sudden cardiac death. Three peer-reviewed studies investigated the impact of atrial fibrillation on sudden death in patients with HCM. While left atrial size is the determinant in assessing risk of sudden cardiac death and need for ICD in hypertrophic cardiomyopathy, the relation between the incident of atrial fibrillation and sudden death was not clear.

Added value of this study

The incident AF was associated tripling risk of SCD and doubling risk of NSCD. Among NSCD, HCM patients with AF had highest risk of stroke-related death. Among AF subjects, multivariable Cox regression revealed an association between the occurrence of SCD and the following: male sex, comorbidity of coronary artery disease and history of heart failure. On the other hand, NSCD was significantly related with female sex, age $\geq$ 75 years, hyperlipidemia and prior stroke.

Implications of all the available evidence

Because of underuse of oral anticoagulants and the absence of primary prevention ICD therapy in our cohort, the application of our findings was limited for the general HCM population in the current clinical practice. However, this study demonstrated the impact of AF on the outcomes of HCM patients, regardless of SCD and NSCD. Early detection of AF may provide more comprehensive risk stratification of SCD in HCM population.

reported prevalence around 20%. Predisposing factors include increased left atrial pressure and size, caused by diastolic dysfunction, left ventricular outflow tract obstruction and mitral regurgitation [1]. In the Atherosclerosis Risk in Communities (ARIC) Study and Cardiovascular Health Study (CHS), the incidence of AF is associated with an increased risk of SCA and non-sudden cardiac death (NSCD) in the general population [3]. In the Taiwan national cohort study, the risk of SCA and ventricular arrhythmia amongst AF patients is also higher compared to non-AF patients [4]. Compared with general population, AF is significantly more common in HCM patients and had higher risk of stroke [1,5,6]. Furthermore, AF in HCM has been regarded as a progressive arrhythmia responsible for a major impact on clinical course [6]. SCA and AF may share similar risk factors in HCM population. However, the relationship between the risk of SCA and AF has not been well studied in a nationwide cohort of HCM population and in an Asian cohort. We hypothesized that incident AF is associated with an increased risk of SCA and NSCD in the HCM population. We also aimed to identify important risk factors for SCA and NSCD among HCM patients with AF.

2. Methods

2.1. Study cohort

This large-scale, longitudinal cohort study used integrated medical and pharmacy claims data from National Health Insurance Research Database (NHIRD) in Taiwan. The National Health Insurance program has provided compulsory universal health insurance in Taiwan since 1995. Nearly 23 million residents were covered by the National Health Insurance (NHI) system, which offers comprehensive medical care coverage. The NHIRD contains nearly complete claims history of diagnosis and procedures, provided as the International Classification of Diseases Ninth Revision Clinical Modification (ICD-9-CM) codes, and drug dispensing for every beneficiary. This large sample size of this database provides a good opportunity to study whether incidence of AF in HCM patients is associated with increased risk of SCA and NSCD [7]. We investigated the database of NHIRD during year of 1996 to 2013. The index date for the study cohort was identified as the date of the first-time that had a diagnosis of HCM (ICD9-CM: 425.1). We identified all patients who were above 20 years old. Patients had AF before the diagnosis of HCM were excluded. Diagnosis of AF was based on ICD-9-CM coding (ICD9-CM code, 427.3) in consecutive two ambulatory visits or discharge diagnoses [8]. We divided 10,910 subjects in our cohort into two groups, those developing AF after HCM diagnosed (N = 1169) and without incidence of AF during follow-up (N = 9741) (Fig. 1).

2.2. Drug use, covariates, and outcomes

All subjects were then followed from the index date to the date of death, or Dec. 31, 2013 if no event occurred with a median follow-up duration of 8.5 years (25−75th interquartile range [IQR], 5.7− 12.1 years). We searched the database to see if they had hypertension (ICD-9-CM codes: 401.X-405.X), diabetes mellitus (250.X, 249.X), hyperlipidemia (272.X), coronary artery disease (ICD9-CM code, 411.X-414.X, V17.3, V81.0), heart failure hospitalization (ICD9-CM code, 428.0−428.3, 429.9), chronic kidney disease (ICD9-CM code, 585.X-588.X) and history of stroke (ICD9-CM code, 434.X, 430.X). Medications that were dispensed at time of index date, including antiplatelet, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), statins and oral anticoagulants were identified. The main purpose of the present study was to compare long-term outcomes of SCA and NSCD between HCM patients with and without AF. The diagnosis of SCA was defined as the occurrence of ventricular tachycardia/fibrillation (ICD9-CM code, 427.1, 427.4, 427.41, 427.42), implantation of ICD or CRT-implantable cardioverter-defibrillator (CRT-D) (procedure code, 0051−0056 and 3795−3798) and SCA (ICD9-CM code, 427.5, 798.X and V12.53) in any ambulatory visit and discharge diagnoses. The NSCD was defined as the occurrence of mortality not meeting SCA criteria. We classified NSCD into three secondary endpoints, which were heart failure death, stroke death and other non-HCM related death.

2.3. Statistical analysis

We report means with standard deviations for continuous variables and counts with percentages for categorical variables. For comparison of the baseline characteristics between two groups, the differences of continuous variables and nominal variables were assessed with unpaired two-tailed t-test and chi-squared test, respectively. Person-years at risk were calculated from the date of baseline until the date of SCA/NSCD, loss to follow-up, or end of follow-up, whichever occurred first. To estimate the association of AF with risks of SCA and NSCD, we calculated hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards model with AF as a time-dependent exposure variable. We performed Cox proportional hazards model adjusted for age, sex, comorbidities (Hypertension, diabetes, hyperlipidemia, chronic kidney disease, coronary heart disease, heart failure, stroke) and medications listed in Table 1. Independent predictors of SCA and NSCD in HCM patients with AF were identified by means of multivariable forward stepwise Cox regression analysis. Candidate variables selected for the model were those reflecting baseline clinical characteristics of patients at the time of listing that showed a statistically significant association with SCA and NSCD in univariable analyses. The cumulative incidence

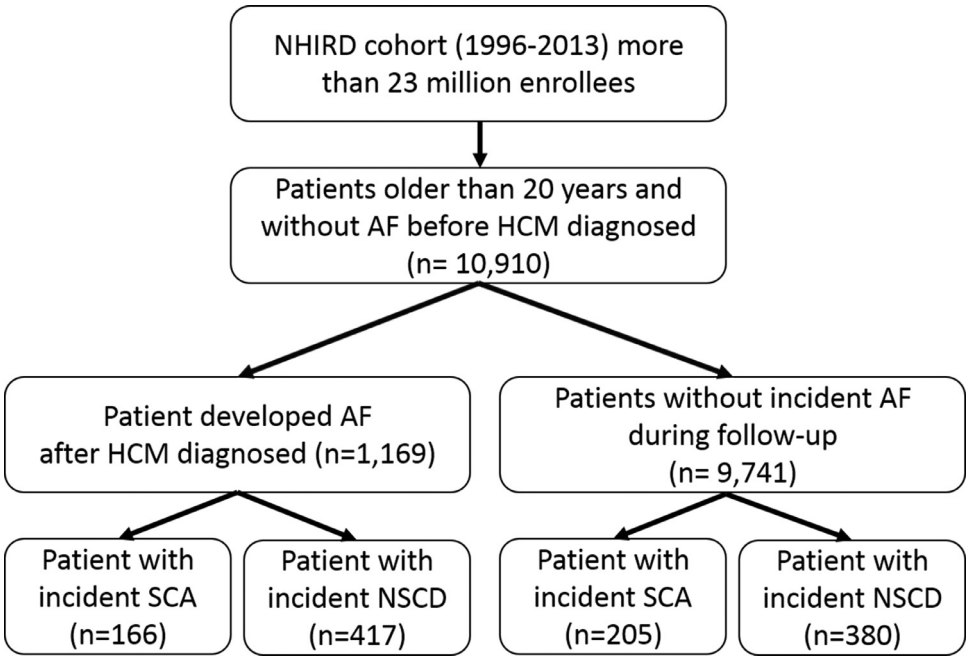

Fig. 1. Patient flow diagram. Abbreviations: AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy; NHIRD, National health insurance research database; SCA, sudden cardiac arrest and NSCD, non-sudden cardiac death.

curves of SCA and NSCD were plotted via the Kaplan-Meier method, with statistical significance examined by the log-rank test. Statistical significance was set at $P < 0.05$ for all comparisons. Statistical analyses were performed with SPSS 22 (SPSS Inc., Chicago, IL, USA).

2.4. Ethic review

In addition to protect the privacy of patients, the NHRI also has other restrictions on accessing the database. Every applicant seeking to use NHIRD must be a researcher or clinician from a university, research institute, or hospital, and the use of the data must be for research purposes only. All applications are to be reviewed by peer experts to ensure the rationality of the use. Researchers must follow the Computer-Processed Personal Data Protection Law and related regulations in Taiwan, and sign an agreement declaring that no attempt will be made to retrieve information potentially violating the privacy of patients or health care providers [9]. This study was approved from Institutional Review Board review of National Taiwan University Hospital (202010036RIN). We made our data, analytic methods, and study materials available for the purpose of reproducing our findings. All supporting data are available within the article and its online supplementary files.

2.5. Role of funding source

No funding was received to support this study. Dr Ting-Tse Lin and Dr Min-Tsun Liao had access to the data included in the manuscript and were responsible for submission of the manuscript.

3. Results

During the follow-up of median 8.5 years, 371 (3.4%) and 797 (7.3%) participants experienced SCA and NSCD, respectively. In the follow-up period, 1169 patients developed AF after diagnosis of HCM, with 166 (14.2%) experiencing SCA and 417 subjects (35.6%) experiencing NSCD. Among 9741 HCM patients without incident AF, 205 (2.1%) experienced SCA and 380 subjects (3.9%) experienced NSCD (Fig. 1). Baseline characteristics of HCM subjects with and without AF were listed in Table 1. AF patients were older and female predominant compared with non-AF patients. There were also more prevalent comorbidities of AF patients, except diabetes, chronic kidney disease and coronary artery disease. In terms of medications, except anti-platelet agents, there were more prescriptions of calcium channel blockers and oral anti-coagulants of AF patients. By contrast, non-AF patients had more frequent use of ACEI, ARB, beta-blockers, and statins. At last, AF patients had more likely to receive ICD implantation than non-AF patients (Table 1). Multivariable Cox regression showed an association between incident AF and the following: female sex, age, thyroid disease and history of HF hospitalization (Supplemental Table 1).

Compared with participants without AF, those with AF had higher incidence rates of SCA and NSCD. After adjustment for age, sex, comorbidities (hypertension, diabetes, hyperlipidemia, chronic kidney disease, coronary heart disease, heart failure, history of stroke) and medications, AF was significantly associated with an increased risk of SCA (hazard ratio [HR], 3.633; 95% confidence interval [CI], 2.756−4.791) and NSCD (HR, 2.086; 95% CI, 1.799−2.418) (Table 2). Overall, the presence of incident AF was associated with a tripling of the risk of SCA and doubling of the risk of NSCD. Overall, among 797 subjects experiencing NSCD, 126 had heart failure death, 193 had stroke death and 478 patients had non-HCM related death. We observed AF still independently associated with increased risk of heart failure death (HR, 1.322; 95% CI, 1.065−3.361), stroke death (HR, 6.609; 95% CI, 3.794 − 9.725) and non-HCM related death (HR, 2.092; 95% CI, 1.428 − 3.649) (Supplemental Table 2). On the other hand, because the follow-up duration was across two decades, we performed sensitivity analysis. The AF was still associated with increased risk of SCA and NSCD among different periods (Supplemental Table 3). The Kaplan-Meier survival curves were illustrated in Fig. 2. The log-rank test was significant in AF versus non-AF group in the respect of SCA (Fig. 2A) and NSCD (Fig. 2B) ($P < 0.001$). The results of subgroup analyses were demonstrated in Fig. 3. The incidence of AF was associated with around three to four times more likely to experience SCA across all subgroups. On the other hand, HCM patients with AF were at twice the risk of NSCD among all subgroups (Fig. 3). Among HCM patient with AF, male sex, coronary artery disease and hospitalization for heart failure were identified to be independent risk factors for SCA (Table 3). On the other hand, the

Table 1
Baseline characteristics according to atrial fibrillation status.

	Total	Without AF	With AF	*P* value
N	10,910	9741	1169	
Age, mean (SD), years	62 (13)	61 (15)	66 (12)	< 0.001
Female, n(%)	5182 (47.5)	4588 (47.1)	594 (50.8)	< 0.001
Diabetes, n(%)	2968 (27.2)	2650 (27.2)	318 (27.2)	0.824
Hypertension, n(%)	7572 (69.4)	6789 (69.7)	783 (66.9)	< 0.001
Hyperlipidemia, n(%)	4201 (38.5)	3818 (39.2)	383 (32.7)	< 0.001
CKD, n(%)	993 (9.1)	886 (9.1)	107 (9.1)	0.794
Thyroid disease, n(%)	867 (7.9)	779 (7.9)	88 7.5)	0.651
Coronary heart disease, n(%)	6099 (55.9)	5445 (55.9)	654 (55.9)	0.538
Heart failure hospitalization, n(%)	3175 (29.1)	2727 (28.0)	448 (38.3)	< 0.001
History of stroke, n(%)	860 (8.1)	425 (4.3)	455 (38.9)	< 0.001
No. patients with CIEDs, (%)	3054 (27.9)	2691 (27.6)	363 (31)	0.035
Pacemakers	2865 (26.2)	2487 (22.4)	378 (32.3(	0.024
CRTP	108 (0.98)	88 (0.9)	20 (1.7)	0.112
CRTD / ICDs, (%)	81 (0.72)	70 (0.70)	11 (0.94)	0.211
Anti-platelet, n(%)	6230 (57.1)	5572 (57.2)	658 (56.2)	0.336
ACEI / ARB, n(%)	6885 (63.1)	6186 (63.5)	699 (59.7)	0.002
Beta-blocker, n(%)	6645 (60.9)	5952 (61.1)	693 (59.7)	0.008
CCBs, n(%)	4692 (43.0)	4130 (42.4)	562 (48.0)	< 0.001
Statins, n(%)	3470 (31.8)	3156 (32.4)	314 (26.8)	< 0.001
OACs	1113 (10.2)	88 (9.0)	1025 (87.6)	< 0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; CCB, calcium channel blockers; CRTP, cardiac resynchronized therapy-pacing; ICD, implantable cardioverter defibrillator; OACs, oral anticoagulants; SD, standard deviation.

Table 2
Risk of sudden cardiac arrest and non-sudden cardiac arrest by atrial fibrillation status.

	Total	Without AF	With AF
Sudden cardiac death			
Number of events, *N*(%)	371 (3.4)	205 (2.1)	166 (14.2)
Person-year	70,185	57,323	13,327
Crude incidence rate (95% CI)[a]	5.286 (4.768–5.845)	3.576 (3.111–4.092)	12.455 (10.672–14.461)
Hazard ratio (95% CI)[b]		1	3.633 (2.756–4.791)
Non-sudden cardiac death			
Number of events, N(%)	797 (7.3)	380 (3.9)	417 (35.6)
Person-year	69,839	56,169	13,670
Crude incidence rate (95% CI)[a]	11.365 (10.597–12.164)	6.629 (5.987–7.322)	31.291 (28.396–34.412)
Hazard ratio (95% CI)[b]		1	2.086 (1.799–2.418)

[a] Per 1000 person-years of follow-up, 95% CI was estimated by Mid-P exact test.
[b] Cox proportional hazards model adjusted for age, sex, comorbidities (Hypertension, diabetes, hyperlipidemia, chronic kidney disease, coronary heart disease, heart failure, stroke) and medications.
Abbreviations: AF, atrial fibrillation; CI, confidence interval.

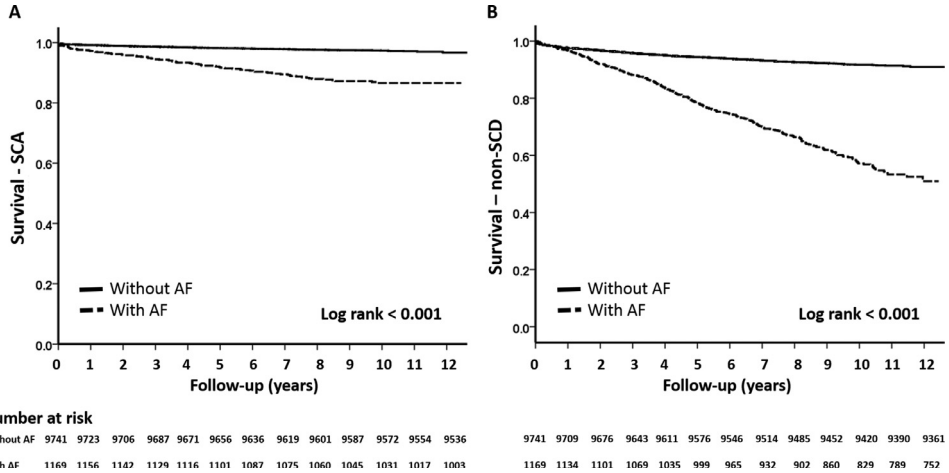

Fig. 2. Kaplan–Meier curves showing the development of (A) sudden cardiac death and (B) non-sudden cardiac death between patients with and without atrial fibrillation. The log-rank analysis showed significant different ($P < 0.001$) in both groups. Abbreviations: AF, atrial fibrillation and SCD, sudden cardiac death.

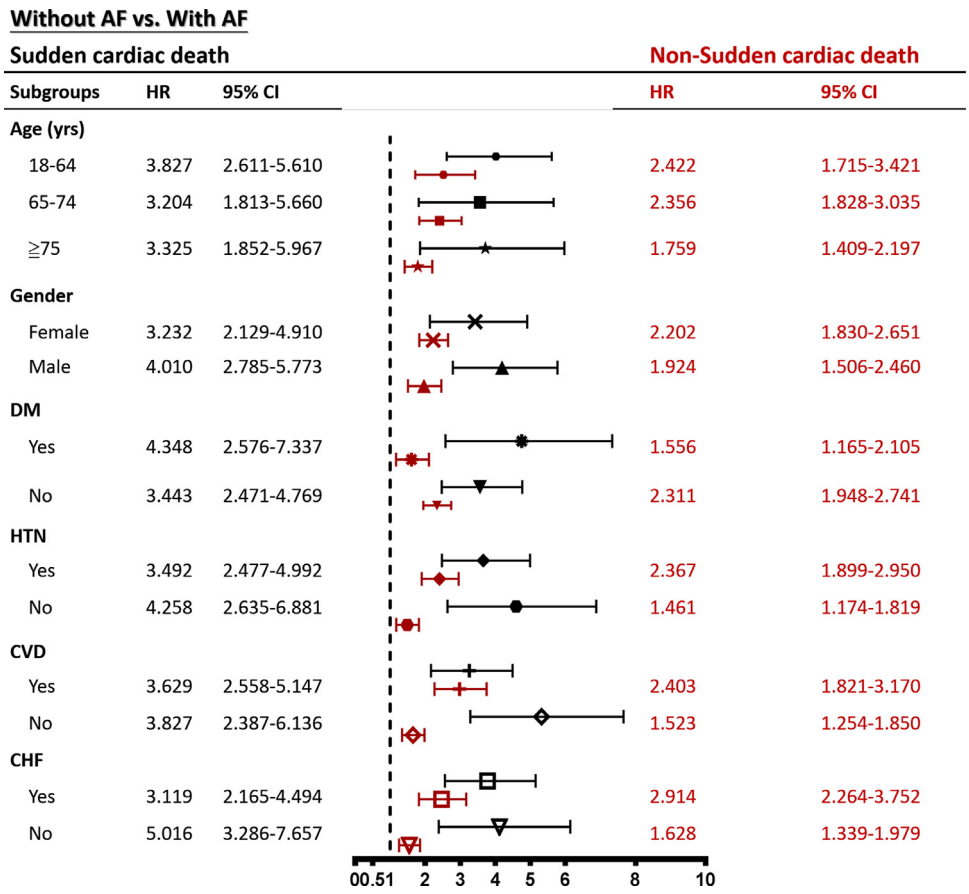

Fig. 3. Subgroup analyses. Hazard ratios of incidence of sudden cardiac death (black) and non-sudden cardiac death (red) in specific subgroups of patients with atrial fibrillation by using subjects without atrial fibrillation as reference group. Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; HTN, hypertension; CVD, cardiovascular disease and CHF, congestive heart failure (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

Table 3
Clinical predictors of sudden cardiac death among AF patients in the HCM cohort.

Variables	Univariate analysis		Multivariate analysis*	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age ≥ 65 years	0.892 (0.684–1.489)	0.542		
Male gender	1.403 (1.152–1.909)	0.034	1.810 (1.146–2.859)	0.033
CKD	0.948 (0.710–1.501)	0.743		
Diabetes	0.946 (0.755–1.884)	0.626		
Hypertension	1.052 (0.586–1.886)	0.866		
Hyperlipidemia	0.893 (0.702–1.935)	0.355		
CAD	1.894 (1.061–3.381)	0.031	1.822 (1.154–2.877)	0.01
Thyroid disease	1.561 (0.798 – 2.013)	0.125		
HHF	2.149 (1.747–2.643)	0.021	2.107 (1.719–2.883)	0.02
History of stroke	1.771 (0.494–1.901)	0.250		

* Variables with p values < 0.05 in the univariate analyses were included in the multivariate model which was adjusted for the use of medications listed in Table 1.
Abbreviations, AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; HHF, hospitalization for heart failure; HCM, hypertrophic cardiomyopathy.

independent risk factors associated with NSCD were age ≥ 75 years, female sex, hyperlipidemia and history of stroke (Table 4).

4. Discussions

In the present nationwide HCM cohort study, the annual incidence rate of SCA in patients with AF was 1.2%, which was 3.6-fold higher risk than non-AF patients after adjustment with several confounders. The incidence rate of NSCD was 3.1% which was 2.1-fold higher risk than non-AF patients. The increased risk of SCA and NSCD was consistently observed among different subgroups, including different age strata, sex and comorbidities. Of note, male HCM patients with AF were at risk to experience SCA. By contrast, female HCM patients with AF were associated with higher risk of NSCD. Other independent risk factors associated with SCA were coronary artery disease and HF hospitalization and factors associated with NSCD were older age and history of stroke.

In Taiwan, there are no special guidelines for patients with HCM. The treatment in patients with HCM is mainly based on the recommendation of AHA and ESC guideline [1,10,11]. Because of the NHIRD reimbursement in Taiwan, so far there is only secondary prevention for SCD without primary prevention of SCA in patients with HCM.

Table 4
Clinical predictors of non-sudden cardiac death among AF patients in the HCM cohort.

Variables	Univariate analysis		Multivariate analysis*	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age ≥ 75 years	1.590 (1.236–2.045)	< 0.001	1.702 (1.330–2.180)	0.001
Female gender	1.326 (1.116–1.854)	0.001	1.451 (1.184–1.862)	0.003
CKD	1.387 (0.927–2.076)	0.097		
Diabetes	1.004 (0.768–1.313)	0.978		
Hypertension	1.095 (0.812–1.477)	0.550		
Hyperlipidemia	1.587 (1.415–2.830)	0.003	1.682 (1.420–2.907)	0.001
CAD	0.798 (0.594–1.071)	0.133		
HHF	1.015 (0.779–1.324)	0.911		
History of stroke	1.317 (1.040–1.667)	0.022	1.298 (1.027–1.639)	0.029

* Variables with p values < 0.05 in the univariate analyses were included in the multivariate model which was adjusted for the use of medications listed in Table 1.
Abbreviations, AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; HHF, hospitalization for heart failure; HCM, hypertrophic cardiomyopathy.

The class IIb indications for primary prevention of SCA in patients with HCM recommended by 2002 ACC/AHA/NASPE pacemaker guideline or IIa indication of primary prevention recommended by 2011 AHA and 2014 ESC could not be enforced. Therefore, subsequent ICD implantation is mainly based on secondary prevention in Taiwan. In terms of using beta-blocker drug in the consensus' opinions in 2003 AHA/ESC [10], pharmacological treatment including beta-blockers or CCB is not recommended even if patients with HCM have no symptoms and low risk of SCA. This recommendation in 2011 AHA guideline still includes beta-blockers and CCB are not well established as Class IIb indication for management of asymptomatic patients with HCM [11]. As for asymptomatic patients with HCM and high risk of SCA, the current guidelines do not mention whether beta -blockers or CCBs are recommended. 2014 ESC HCM guideline recommends Class I indication to use beta-blocker in HCM patients with LVOTO or HF with EF <50% [1]. Therefore, in our cohort from 1996 to 2013, only 60.9% of patients had pharmacologic treatment with beta-blockers. The reasons may be that the symptoms are not obvious. In addition, younger patients with HCM mostly have no symptoms and their compliance is also an issue in the long-term use of beta-blocker.

In addition to compelling evidences of association between AF and cardiovascular mortality, a number of studies have shown that AF increases the risk of SCA in specific patient subgroups such as post-MI or heart failure patients. [8,12–14] Furthermore, in population-based and nationwide cohort, incident AF is associated with an increased risk of SCA [3,4]. Back to HCM population, left atrial size is regarded as a risk factor of SCA and a variable in HCM Risk-SCD calculator [1]. Given the high incidence and prevalence of AF in HCM population, AF has been regarded as a progressive arrhythmia responsible for a major impact on clinical course, including SCA, HF and stroke [6,15,16]. Some studies suggested the rhythms preceding ventricular arrhythmias were often sinus tachycardia or rapid atrial fibrillation [17,18]. On the contrary, it is previously reported an increased risk for HCM-related death in patients with AF but not sudden unexpected death [19,20]. Furthermore, Rowin et al. reported the generally favorable clinical course and outcome in the great majority of the study patients with AF [6,21]. Specifically, no differences were evident between patients with versus without AF regarding SCA event rate, all-cause or HCM-related mortality. By contrast, we observed tripling risk of SCA and doubling risk of NSCD in subjects with AF compared with those without AF. In Rowin's study, only 4% of patients with AF died of HCM-related causes (SCA, heart failure and stroke death), for an annual mortality rate of 0.7% while the annual SCA rate was 1.2% in the present study. The higher incidence rate of SCA and significantly associated with AF may be explained by the lower rate of ICD implantation in our cohort (46% vs. 0.72%). In Taiwan, the reimbursement of NHI for ICD implantation are mostly for secondary prevention of SCA survivors [22]. As a result, there was lower rate of ICD primary prevention in our cohort. In terms of NSCD, Rowin et al. also reported AF was not related to increased risk of HCM-related mortality. In our study, we found HCM patients with AF had doubling risk of HCM-related death compared with those without AF. The possible reason was higher prevalence of hypertension (29% vs. 69.4%) and CAD (13% vs. 55.9%) in our cohort, which may lead to more incident of NSCD. On the other hand, 87% of subjects with AF in our cohort were prescribed anti-coagulants, which was lower than Rowin's study (92%) and against the current guideline's suggestions. The possible reason was warfarin would cause more bleeding and labile INR in Asian population due to different genetic polymorphisms compared with Caucasians [23]. Therefore, physicians in Taiwan were reluctant to prescribe warfarin for stroke prevention. As a result, the underuse of oral anti-coagulants could increase the risk of NSCD in our population.

In the respect of variables related to the incident AF, most were consistent with clinical risks, including age, sex, history of heart failure and thyroid disease [24]. OF note, thyroid disease was significantly associated of AF incidence but was not correlated to the incident SCA/NSCD. In the multivariate analysis, predictors for SCA in HCM subjects with AF were male sex, comorbidities of CAD and history of heart failure hospitalization in our cohort, which are consistent with clinical risk predictors of non-HCM population [4,25]. In patients with susceptible comorbidities, such as CAD or HF, AF leads electrical remodeling in atrium with shorter action potential duration and refractoriness, which may also occur in ventricular myocytes and subsequently increase the risk of ventricular tachycardia or ventricular fibrillation [26]. The short-long-short sequences of ventricular conduction in atrial fibrillation may trigger ventricular arrhythmias [27]. Besides, AF may increase sympathetic tone and decrease parasympathetic tone because of their hemodynamic effects and favor VF development, especially in male patients [28,29].

A number of studies report substantial adverse outcomes attributed to AF and concluded this arrhythmia is independently associated with HCM-related heart failure and all-cause mortality [15,16,19,30,31]. In the present study, our findings supported that the incident AF was associated with an increased risk of NSCD, regardless of heart failure death, stroke death and non-HCM related death. Of note, the hazard ratio of stroke related death (HR, 6.609) was higher than that of non-HCM related death (HR, 2.092) and heart failure death (HR, 1.322). It suggests the predominant NSCD risk directly attributable to AF in HCM is the potential for thromboembolism, largely preventable by anticoagulation prophylaxis [5,32]. On the other hand, predictors for NSCD were elder age, female gender, hyperlipidemia and history of stroke. When HCM patients turning older, the risk of SCA was decreased and the risk of NSCD was increased [5]. While male patients may have more fibrosis on histological examination, and experience exercise-induced ventricular

arrhythmias more than their female counterparts, there is conflicting data about incident SCA [18]. Female sex has been reported associated with new-onset AF [16], and our finding suggests female AF patients may be associated with an increased risk of NSCD. This study confirms the impact of AF on the different outcomes of HCM patients. Our findings suggest that HCM patients with risks of female, elder age and heart failure possess higher risk of incident AF. They may undergo frequent ambulatory ECG monitoring to detect atrial arrhythmia and could be considered for early prophylactic anticoagulation. Furthermore, we found the incidence of SCA was independently associated with male sex, CAD and heart failure in HCM patients with AF. Therefore, patients with those risk factors should receive more detailed evaluation of the SCA risk. The principle strengths of this study include a nationwide cohort, long-term follow-up and large number of AF cases. However, several limitations should be noted. First, due to the nature of NHI data, the echocardiographic parameters and the subtype of AF were not available. Therefore, the cardiac hypertrophy due to hypertension would be considered in our study. To clarify the causal relation between hypertension and HCM, we identified subjects who had diagnosis of HTN before the diagnosis of HCM and only 131 (1.2%) subjects met the criteria. On the other hand, it is difficult to know the different treatment methods in various parts of Taiwan. The data is also limited without genetic data and SCD-risk score data recommended by ESC in 2014 [1], such as echocardiographic evaluation of left ventricular wall thickness and left ventricular outflow tract gradient, family history of SCA, non-sustained VT recorded by ECG or 24 h holter, and unexplained syncope. In addition, the diagnosis of SCD was based on the diagnostic codes registered in the database, and 0.72% of patients have ICDs in the index date, this may influence the study result. But because the number of patients with ICDs is small, the impact is not significant. Second, the implantation of ICD as primary prevention from SCA is not reimbursed in Taiwan. We recognized ICD implantation as endpoints, which were different from previous studies [33,34]. As a result, the real incidence of SCA may be underestimated. Third, there is the possibility that some other confounders such as body mass index, ethnicity, smoking, alcohol/drug abuse, or genetic data were not recognized and may therefore confound the analysis although we adjusted age, sex and important comorbidities. Fourth, our study enrolled only Taiwanese participants, and we do not know whether our result could be extrapolated to non-Asian populations. The AF prevalence in our HCM cohort was around 10%, lower than the prevalence reported by previous studies (around 20%) [35,36]. Like all electronic health databases, coding errors and purposely "upcoding" could be a problem of NHIRD [9]. Although large data sets could potentially overcome this problem, the diagnosis of AF might be ignored and underestimated. On the other hand, the prevalence of AF in Asia HCM population may be lower than non-Asia cohort. Choi et al. reported around 13% of prevalence of AF in Korea Using the Korean National Health Insurance Services database. Finally, our cohort spans 2 decades and the treatment for HCM is evolving, such as thromboembolic prophylaxis regardless of age, primary prevention with ICD and risk evaluation with HCM phenotype characterization. Furthermore, with adequate treatments, the rate of death associated with AF in patients with HCM is less than 1% per year, and thromboembolism without prophylactic anticoagulation accounts for virtually all such deaths [37].

In conclusion, AF is an important component of clinical course in many patients with HCM. Incident AF independently increases the risk of SCA and NSCD, especially stroke-related death. Our findings underscore the importance of AF-detection in HCM patients, followed by prophylaxis of oral anti-coagulants and the evaluation of SCA risk in those with diagnosed AF. However, because of the underuse of anticoagulants and the absence of primary prevention ICD therapy in our cohort, these limitations make our study not representative of the HCM cohort reported in other studies, which limits the application of our findings for the general HCM population in the current clinical practice.

Data sharing statement

The data used in this study were gathered from Taiwan National Health Insurance Research Database and available from the corresponding author upon reasonable request.

Author contributions

Conceptualisation, T.T.L., L.Y.L.; data curation, M.T.L., C.K.W.; formal analysis, M.T.L., T.T.L.; investigation, J.M.J., C.K.W.; methodology, M.T.L., T.T.L.; project administration, C.K.W., T.T.L.; resources, M.T.L., C.K.W.; software, M.T.L., T.T.L.; supervision, C.K.W., L.Y.L.; validation, J.M.J., C.K.W., L.Y.L.; visualization, J.M.J., C.K.W., L.Y.L.; writing – original draft, M.T.L., T.T.L.; and writing – review & editing, C.K.W., L.Y.L.

Declaration of Competing Interest

None declared.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.100802.

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