Peer Review File

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Reviewer A:

Comment #1

The clinical implications of atrial fibrillation (AF) in hypertrophic cardiomyopathy (HCM) patients are relatively well defined. This paper also showed same finding which was presented in many papers.

Stroke risk score is not important in AF and HCM when we start OAC. It is already reported that HCM and without risk factors had higher annual stroke risk than AF only patients with CHA2DS-VASc score 2 in Korean AF patients (J Am Coll Cardiol. 2018 Nov 6;72(19):2409-2411)..

Therefore, CHA2DS-VASc score is not important when deciding OAC in AF with HCM patients. However, score and stroke risk showed linear correlation. It means than risk score is still good to predict stroke risk even in high stroke risk patients.

Response #1

Thank you for your thoughtful and constructive comment. We see your point that despite the low AUC of the CHA_2DS_2-VASc scoring system for discriminating stroke risk in HCM patients with AF, there is a trend for linear increase in stroke risk in proportion to the CHA_2DS_2-VASc scores and that especially patients with high scores had significantly elevated stroke risk. We rephrased the manuscript as below to make this clearer.

Results – *Performance of CHA_2DS_2-VASc score for predicting stroke in HCM patients not on anticoagulation* (page 7, paragraph 1)

"Incidence rates of stroke generally increased with higher CHA_2DS_2-VASc scores, and patients with very high CHA_2DS_2-VASc scores (≥6) had markedly elevated incidence rates of stroke. Due to the high incidence of stroke in HCM patients with low CHA_2DS_2-VASc scores, there were no statistically significant differences in risk of stroke among patients with CHA_2DS_2-VASc scores 1-5 compared to those with CHA_2DS_2-VASc=0, though

there was a trend for linear increase in stroke risk in proportion to CHA_2DS_2-VASc scores (***Figure 3A***). The risk of stroke was significantly increased only at very high CHA_2DS_2-VASc scores (≥6) in multivariable adjusted Cox regression analysis. Analyses in total AF patients showed similar results, with high incidence rates of stroke at low CHA_2DS_2-VASc scores, and no significant difference in stroke risk at CHA_2DS_2-VASc<6 (***Supplementary Table 2***). The CHA_2DS_2-VASc scoring system showed poor discrimination of stroke risk in HCM patients with AF (AUC 0.591, 95% CI 0.501-0.673) at three years of follow-up (***Figure 3B***).”

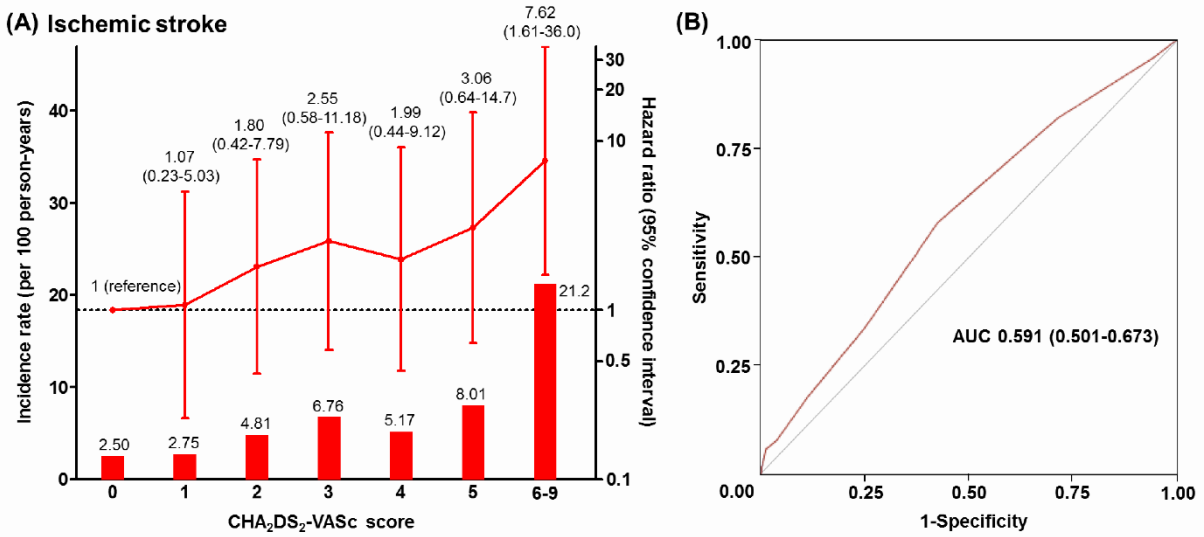


Figure 3. Performance of the CHA_2DS_2-VASc score for predicting stroke in hypertrophic cardiomyopathy patients with atrial fibrillation and without anticoagulation.

(A) Incidence rates (per 100 person-years) of stroke for each CHA2DS2-VASc scores are shown in bar graphs at the bottom with scales on the left. Hazard ratios with 95% confidence intervals representing the risk of stroke for each CHA2DS2-VASc scores are shown in line graphs with scales (base 10 logarithmic) on the right, with a dotted line at 1. (B) ROC curve for the prediction of stroke at 3 years of follow-up.

Reviewer B:

This study evaluate the clinical impact of atrial fibrillation in a nationwide cohort of hypertrophic cardiomyopathy. The paper is well written, easy to read, and data are of great clinical impact.
However there are two major limitations:

Comment #1-1

You should better clarify the study population. There is no definition of hypertrophic cardiomyopathy but only a code. This is a crucial bias. Moreover, most of your patients had hypertension so we can image that the hypertrophy was mainly secondary to hypertension.

Response #1-1

Thank you for your thoughtful and important comment. We agree that one of the limitations of studies utilizing big health insurance databases is the usage of operative definitions with diagnostic codes to define diseases, which may have variable reliability. Fortunately, a unique characteristic of the Korean NHIS database is that there are some rare diseases whose diagnostic codes are tightly controlled by the government because of billing issues, which increases the reliability of using diagnostic codes to define these rare diseases. We briefly explained this in the manuscript; a patient who is diagnosed with specific rare diseases is eligible to be enrolled in the 'RID (rare intractable disease)' welfare program which covers 90% of medical costs for the treatment of that rare disease. To be enrolled in that program, the attending physician must register the patient with clinical and imaging evidence, which is separately judged by medical experts and health insurance professionals working at the NHIS to decide whether the patient may or may not receive the RID program benefits. If the patient is judged to have the rare disease, he receives the RID code which is thereafter entered in combination with the ICD code to receive RID program benefits. Thus, for the rare diseases included in the RID list, the use of 'diagnostic codes + registration in the RID program (RID code)' provides a more reliable way to identify subjects with the disease. Hypertrophic cardiomyopathy is one of these rare diseases listed in the RID program. Thus, we used the ICD code + RID code to identify patients with HCM from the general population. This method, when verified with hospital data, showed a sensitivity of

91.5%, specificity of 100%, and accuracy of 92.6% for identifying true HCM patients (1). Also, when the definition of AF was validated with hospital data, the positive predictive value was 94.1% (2).

The proportion of hypertension was found to be 67.5% in our study population, which may seem high. For the definition of hypertension in our study, we used diagnostic codes + the prescription of anti-hypertensive drugs (thiazide, loop diuretics, aldosterone antagonist, alpha-/beta-blocker, calcium-channel blocker, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker). One of the explanations is that the mean age of the study population was 60.7 years old, including elderly patients with HCM. According to the governmental Korean Statistical Information Service (KOSIS), the Korea National Health and Nutrition Examination Survey in 2018 showed the prevalence of hypertension is 33.3% in the general population ≥30 years old, and 64.3% in the general population (URL: http://kosis.kr/statHtml/statHtml.do?orgId=117&tblId=DT_11702_N105). Specifically, the prevalence of hypertension was 20.6%, 34.7%, 46.0%, and 70.2% for subjects aged 40-49 years, 50-59 years, 60-69 years, and ≥70 years, respectively. To note, unpublished data from another study of 833 patients diagnosed with HCM at two tertiary hospitals that we are currently revising show the mean age of HCM patients to be 56.3 years old, and the prevalence of hypertension to be 42.0%.

The average age of our cohort was around 60 years old, which may seem higher than that of earlier studies. However, as shown in the Reviewer-only Table 1 below, HCM patients in a previous published claims data study from Germany (3) had a mean age of 63 years, similar to that of the current study, and the prevalence of hypertension approached 80.7%. Also, in a community-based cohort study without selection bias caused by selected referral to tertiary care centers, 25% of HCM patients were more than 75 years old (4). All of these findings are attributable to the increased awareness and late diagnosis of HCM at older age group, as well as increased longevity in HCM population in the contemporary management era (5). As a matter of fact, thanks to improved clinical care, the majority of deaths observed in the HCM population are unrelated to HCM itself (6). As such, the mean age of the studies published in the early 2000s was between 45 and 55 years; however, it became significantly higher in the studies after 2010, approaching 60 years old (53~63 years old), as shown in the Reviewer-only Table 1 below.

Reviewer-only Table 1. Age and comorbidities in patients with HCM reported previously

Previous study	Maron et al.(4)	Ho et al.(7)	Cecchi et al.(8)	Olivotto et al.(9)	Geske et al.(10)	Ingles et al.(11)	Cardim et al.(12)	Husser et al.(3)
Year	2003	2004	2005	2005	2017	2017	2018	2018
Country	United States	Hong Kong	Italy	United States, Italy	United States	Australia	Portugal	Germany
Study design	Single center cohort	Single center cohort	Registry data	Multi-center cohort	Single center cohort	Single center cohort	Registry data	Claims data
Number of patients	312	118	1677	969	3673	356	1042	4000
Age (years)	-	54 ± 18	44 ± 19	46 ± 20	55 ± 16	54 ± 16	53 ± 16	63 ± 17
Male (%)	55.1%	52.5%	62.0%	59.0%	55.0%	63.5%	59.0%	65.0%
Comorbidities (%)								
Hypertension	16.7%	-	-	-	46.0%	33.2%	-	80.7%
Diabetes	-	-	-	-	-	-	-	26.7%
Dyslipidemia	-	-	-	-	-	-	-	53.3%

Values presents as mean ± standard deviation and %

HCM=hypertrophic cardiomyopathy.

We believe that all of these findings are related to the high proportion of hypertension in HCM population. In summary, as we described above, the usage of ICD diagnostic codes + registration in the RID program showed high accuracy for identifying HCM in validation study using hospital data, and we do not believe that many patients with LV hypertrophy secondary to hypertension were included.

We rephrased the manuscript to make this clearer as below.

Methods – *Definitions* (page 3, paragraph 3)

"HCM was defined by 1) claims for diagnostic codes (I42.1 or I42.2) with at least one admission or outpatient clinic visit, and 2) registration in the rare intractable diseases (RID) program. The government-implemented RID program is a welfare policy extending health insurance coverage to 90% of medical costs for patients with specific rare diseases. Therefore, registration is tightly controlled by verification with clinical and imaging evidence, and reviews by medical experts and health insurance professionals. HCM was included in the rare diseases listed in the RID program since 2004. To be registered in the RID program, the patient must fulfill the criteria of HCM on echocardiography and the attending physician must provide clinical certification that the patient has HCM. When validated with hospital data (n=1110), the combination of ICD-10-CM codes and registration in the RID program showed a high positive predictive value and accuracy."

Comment #1-2

How many patients had a genetic hypertrophic cardiomyopathy? There was any difference in outcome, incidence and significance of AF in these two different populations?

Response #1-2

Thank you for your comment. To our regret, information on the genetics of HCM patients were not available in the NHIS database. Thus, we could not perform further analyses on whether there were differences in outcome according to the presence of known sarcomeric mutations in HCM.

Comment #2

Very few data are available on current anticoagulant regimen. There was any difference among patients taking warfarin or any other king of anticoagulant? Could you give us the cause of death of this population?

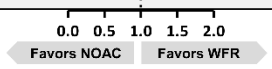
Response #2

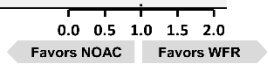
Thank you for this thoughtful comment. We recently published a study on the outcomes in HCM patients with atrial fibrillation on oral anticoagulation, including warfarin and NOACs (13). The study results showed that of 2397 patients with HCM and AF, 992 were prescribed warfarin and 1405 were prescribed NOACs for the primary prevention of embolic events. In the NOAC group, rivaroxaban was prescribed in 38.0% (n=534), dabigatran in 21.6% (n=303), apixaban in 26.6% (n=374), and edoxaban in 13.8% (n=194). NOAC use was associated with significantly lower risks of stroke, bleeding, and death. In separate analysis for individual NOACs, all NOACs were associated with lower risks of ischemic stroke, and apixaban showed the greatest decrease in GI bleeding, major bleeding, and death. The below figures show these main results of that study.

To our regret, our study database included information on only all-cause mortality, and did not have information on the specific causes of death.

Figures from Lee et al, *Stroke*, 2019.

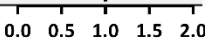
	Number of events* (IR†)		Hazard ratio‡ (95% CI)	Hazard ratio§ (95% CI)	
	Warfarin (n=992)	NOAC (n=1,405)	NOAC vs. warfarin (ref.)	Regular or reduced dose NOAC vs. warfarin (ref.)	
Ischemic stroke	111 (5.01)	39 (2.75)	0.47 (0.32-0.68)	Regular dose	0.76 (0.47-1.25)
				Reduced dose	0.36 (0.20-0.62)
Intracranial Hemorrhage	31 (1.34)	8 (0.54)	0.31 (0.14-0.69)	Regular dose	0.35 (0.10-1.18)
				Reduced dose	0.23 (0.08-0.70)
Gastrointestinal bleeding	69 (3.04)	33 (2.32)	0.62 (0.40-0.96)	Regular dose	0.69 (0.34-1.40)
				Reduced dose	0.82 (0.48-1.40)
Major bleeding	99 (4.42)	41 (2.87)	0.51 (0.35-0.75)	Regular dose	0.55 (0.30-1.02)
				Reduced dose	0.60 (0.37-0.95)
Death	119 (5.10)	42 (2.95)	0.45 (0.31-0.65)	Regular dose	0.76 (0.54-1.09)
				Reduced dose	0.80 (0.59-1.07)
Composite outcome	270 (12.5)	104 (7.53)	0.48 (0.38-0.61)	Regular dose	0.77 (0.59-1.02)
				Reduced dose	0.64 (0.50-0.82)





*Weighted events. †Weighted incidence rate, per 100 person-years.
‡Cox regression analysis in treatment groups balanced by inverse probability of treatment weighting.
§Cox regression analysis in unbalanced treatment groups with adjustment for age, sex, history of diabetes mellitus, hypertension, dyslipidemia, chronic heart failure, myocardial infarction, and peripheral artery disease.

	Treatment group	Number of events* (IR†)	Hazard ratio‡ (95% CI)
Ischemic stroke	Warfarin (n=992)	111 (5.01)	1 (ref.)
	Rivaroxaban (n=534)	19 (3.29)	0.56 (0.34-0.92)
	Dabigatran (n=303)	8 (2.76)	0.47 (0.23-0.96)
	Apixaban (n=374)	10 (2.24)	0.41 (0.21-0.80)
	Edoxaban (n=194)	1 (1.05)	0.17 (0.03-0.98)
Intracranial hemorrhage	Warfarin (n=992)	31 (1.34)	1 (ref.)
	Rivaroxaban (n=534)	4 (0.67)	0.38 (0.13-1.09)
	Dabigatran (n=303)	1 (0.20)	0.12 (0.01-1.44)
	Apixaban (n=374)	2 (0.45)	0.25 (0.06-1.12)
	Edoxaban (n=194)	1 (0.58)	0.32 (0.03-3.40)
Gastrointestinal bleeding	Warfarin (n=992)	69 (3.04)	1 (ref.)
	Rivaroxaban (n=534)	13 (2.17)	0.59 (0.32-1.09)
	Dabigatran (n=303)	15 (4.84)	1.31 (0.74-2.34)
	Apixaban (n=374)	3 (0.79)	0.21 (0.07-0.65)
	Edoxaban (n=194)	3 (2.06)	0.49 (0.14-1.76)
Major bleeding	Warfarin (n=992)	99 (4.42)	1 (ref.)
	Rivaroxaban (n=534)	17 (2.85)	0.52 (0.31-0.88)
	Dabigatran (n=303)	15 (5.05)	0.93 (0.54-1.60)
	Apixaban (n=374)	5 (1.24)	0.22 (0.09-0.55)
	Edoxaban (n=194)	3 (2.65)	0.43 (0.14-1.33)
Death	Warfarin (n=992)	119 (5.10)	1 (ref.)
	Rivaroxaban (n=534)	25 (4.17)	0.65 (0.42-1.01)
	Dabigatran (n=303)	9 (3.01)	0.47 (0.24-0.91)
	Apixaban (n=374)	8 (1.89)	0.30 (0.14-0.61)
	Edoxaban (n=194)	0	
Composite outcome	Warfarin (n=992)	270 (12.5)	1 (ref.)
	Rivaroxaban (n=534)	51 (8.92)	0.58 (0.43-0.78)
	Dabigatran (n=303)	27 (9.30)	0.60 (0.40-0.89)
	Apixaban (n=374)	22 (5.41)	0.35 (0.23-0.54)
	Edoxaban (n=194)	5 (3.70)	0.21 (0.08-0.53)



*Weighted events. †Weighted incidence rate, per 100 person-years.
‡Cox regression analysis in treatment groups balanced by inverse probability of treatment weighting.

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