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Editorial

Stroke risk stratification in hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM), a common inherited cardiac disease, is defined by the presence of left ventricular (LV) wall thickness which is not solely explained by abnormal loading conditions.[1] The prevalence of HCM is 1 in 500 in most studies, but using combined clinical parameters and genetic carriers, HCM could affect 1 in 200.[2] Patients with HCM have excess mortality compared with general population,[3] the pooled 5- and 10-year survival rate of HCM is 82.2% and 75%, respectively.[4] Sudden cardiac death, heart failure and stroke are the major mortality risks with thromboembolic events occurring in 1 to 4 per 100 person-years.[5-11] Population-based cohorts observed progressively increased incidence of stroke among HCM patients following their diagnosis.[12,13] Prompt risk stratification for thromboembolism is thereby of great importance.

Atrial fibrillation (AF) is the most common cardiac arrhythmia in HCM, affecting 20-25% of patients with HCM, with incidence of 2.5% new cases annually.[6,13-16] In patients with HCM, AF is associated with the pooled 7-fold increase in thromboembolism, 3-fold increase in heart failure, 2.5-fold increased risk of mortality as compared to HCM patients with sinus rhythm in a recent systematic review.[16] Given the high risk of thromboembolism in patients with HCM, the European Society of Cardiology (ESC) guideline recommended anticoagulation for all HCM patients with co-existing AF, irrespective of their CHA_2DS_2-VASc score.[1,17] Indeed, HCM reflects substrate abnormalities when evaluating the patient with AF, and invariably is associated with heart failure with preserved ejection fraction (HFpEF).[18]

Oral anticoagulation (OAC) is associated with markedly reduced pooled incidence of total thromboembolism in patients with HCM compared with the use of antiplatelet therapy or no treatment (9.5% vs 22.1%). Among OACs, the direct oral anticoagulants (DOAC) outperformed Vitamin K antagonists (VKA) in the association with lower thromboembolic event (4.7% vs 8.7%), major bleeding event (3.8% vs 6.8%), and all-cause mortality (4.1% vs 16.1%) among patients with HCM.[19]

Various risk factors such as presence of AF, left atrial (LA) size, age, and CHA_2DS_2-VASc score have been identified based on different cohort studies on HCM (see Table 1). Both $CHADS_2$ and CHA_2DS_2-VASc scores have been applied in cohorts of HCM.[8,11] In a population-based cohort of 17,371 patients with HCM with absence of AF at baseline, CHA_2DS_2-VASc score 0-2 was associated with 1.5-2 fold increase in ischaemic stroke compared with general population with AF, whereas no significant difference was noted in stroke rate between HCM patients with CHA_2DS_2-VASc score$\geq$3 as compared with control.[12] Other risk scores have been proposed, one incorporated the $CHADS_2$ score, left ventricular outflow tract gradient (LVOTG), and presence of permanent AF,[7] while the HCM Risk-CVA score included parameters such as age, presence of AF, interaction between age and AF, prior thromboembolism, the New York Heart Association Functional classification (NYHA) II or III/IV, LA diameter, vascular disease, maximal wall thickness (MWT) and the square of MWT.[8] The HCM Risk-CVA score has been validated in a cohort of 417 patients with HCM, results showing limited value for clinical utility[10] (see Table 1).

In this issue of *Hellenic Journal of Cardiology*, Wang et al. presented their study which validated the R-CHA_2DS_2-VASc score in a cohort of 446 patients with HCM.[20] The CHA_2DS_2-VASc score (congestive heart failure, hypertension, age $\geq$75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and female sex) is most commonly used in the risk stratification for stroke in AF,[21] although the female sex (Sc) criterion is a risk modifier rather than a risk factor.[22] The R-CHA_2DS_2-VASc score was previously proposed for stroke risk estimation in patients with myocardial infarction, which included additional components such as renal function including blood urea nitrogen (BUN) and estimated glomerular filtration rate (eGFR), performance of a revascularization procedure, and presence of AF on the basis of CHA_2DS_2-VASc score.[23]

In this study by Wang et al,[20] a moderate discriminative value in thromboembolism was demonstrated with C-statistic 0.77 (95% confidence interval: 0.65-0.89) using the R-CHA_2DS_2-VASc score. This significant improvement in risk stratification for thromboembolism as compared to previous cohorts using CHA_2DS_2-VASc score[8,12] is most likely due to the addition of AF into the risk scheme, rather than the letter "R" (renal function). Whereas HCM has been recognized as an independent risk factor for end-stage renal disease,[24] there is no evidence supporting reduced renal function as an independent risk factor for thromboembolism in patients with HCM. Also, many of the determinants of renal impairment are represented by the components of CHA_2DS_2-VASc, eg. age, hypertension, diabetes, vascular disease etc. Furthermore, in this study, eGFR 30-59% (16.5% of the cohort) was risk factor for thromboembolism on univariate analysis (only 2.9% of the cohort had eGFR<30%), and BUN was not a risk factor for thromboembolism. Hence, kidney disease is unlikely to have contributed significantly to the discriminative power of the clinical risk score. Additionally, only 2.5% of the cohort had revascularization to add the additional component in the R-CHA_2DS_2-VASc score.

Clinical risk stratification is an evolving field, and much focus has been directed to improve clinical risk prediction. Given the limitations of clinical risk scores, the aim of clinical risk stratification for thromboembolism has shifted to initially identify the true low-risk patients, which is perhaps especially relevant in HCM. The high-risk group of HCM patients with AF is already advised to be offered anticoagulation and HCM patients at the very

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Table 1
Risk factors and risk schemes for thromboembolism in hypertrophic cardiomyopathy

Study	No. of patients	Location	Design	Age (mean, years)	Follow-up (median, years)	AF at baseline (%)	Anticoagulation therapy, %	Accumulative TE incidence (95% CI)	Significant risk factors* for TE	Risk models tested
Higashikawa 1997[5]	83	Single centre, Japan	Retrospective, longitudinal cohort	55.5	8	22.9	10.8	23% in AF vs 5.9% in non-AF over 5 years	AF, beta-blocker	
Maron 2002[6]	900	4 centres in US and Italy	Retrospective, longitudinal cohort	46	7	21	9.1 (in AF group) Unreported figure in non-AF	5.7%	Woman, age, NYHA functional class, AF	
Benchimol Barbosa 2013[7]	172	Brazil	Prospective cohort	40 (median)	12.3	Not reported	Not reported	4% per year	$CHADS_2$>1, LVOTG>38 mmHg, permanent AF	New risk scheme: $CHADS_2$>1 (score 2), LVOTG>38 mmHg (score 3), permanent AF (score 3)
Tian 2013[28]	654	Single centre, China	Prospective cohort	50	4.2	17	3	Not reported (in figure)	(In patients without previous stroke): AF and age	
Guttmann 2015[8]	4,821	7 European centres	Retrospective, longitudinal cohort	49	6	12.46	9.2	5 year: 2.9% (2.37%-3.48%) 10 year: 6.4% (5.42%-7.53%)		HCM Risk-CVA score): C-statistic 0.75 (0.70-0.80), D-statistic 1.30 (1.05-1.56) CHA_2DS_2 VASc: unsatisfactory stratification on incidence of TE
Haruki 2016[9]	593	Single centre, Japan	Prospective cohort	51	10.7	27.3	Not reported	1.0% per year	(In patients without previous AF): Age, enlarged LA	
Zegkos 2017[29]	509	Single centre, Greece	Retrospective, longitudinal cohort	51	9	23.3	15.9	Not reported	LA size (optimal cut-off at 4.2 cm)	
Choi 2018[13]	~3,000 (2005)-11,500 (2015)	Korean national health insurance service database	Nationwide, population-based study	61.5	10 (total)	13.39	58 (HCM with AF)	AF-associated stroke: 2.94% per year	(In patients with new onset AF): Sex, age (trend), CHA_2DS_2-VASc (trend)	
He 2019[10]	417	Single centre, China	Prospective cohort	55.2	3.5	15.8	8.4	1.6% per year		HCM Risk-CVA score[8] C-statistic: 0.67 (0.55-0.79) Subgroup without AF:C-statistic: 0.67 (0.51-0.83)
Hirota 2019[11]	293	Japan, regional HCM register (Kochi Ryoma study)	Prospective cohort	63	6.1	29	27	5.5% over 5 years		$CHADS_2$ score: non-significant predictive accuracy for TE
Lin 2019[12]	17,371	Taiwan, national health insurance research database	Nationwide, population-based longitudinal study	61	7.3	0 (HCM without AF)	Not reported	0.59% per year for ischaemic stroke	Age, CHA_2DS_2-VASc, sudden cardiac death	CHA_2DS_2-VASc: significantly raised stroke rate in HCM with score≤2† Similar stroke rate with score≥3†

HCM Risk-CVA score: consists of age, AF, interaction between age and AF, prior TE, NYHA II or III/IV, LA diameter, vascular disease, MWT, MWT^2.
CI: confidence interval, HR: hazard ratio, LA: Left atrial size, LVOTG: left ventricular outflow tract gradient, MWT: Maximal wall thickness, NYHA: New York Heart Association Functional classification, TE: thromboembolic event.
* Significant association with thromboembolic event in multivariate analysis.
† compared with matched general population with AF.

minimum should score 1 point on the C criterion (due to HFpEF) using the CHA_2DS_2-VASc score, as defined for AF.

Increasingly complex clinical risk scores may improve prediction at least statistically, but this needs to be balanced against simplicity and practicality for used in busy everyday clinical settings. Addition of biomarkers (whether urine, blood or imaging ones) will always improve on clinical risk prediction, again statistically but the clinical difference is marginal, especially in real world clinical practice.[25] Many biomarkers are non-specific, being predictive of outcomes beyond those of interest.[26,27] Indeed, statistical significance is not the same as clinical significance.

Conflict of interest

TP: Consultant for Bayer/Jansen and BMS/Pfizer (no fees). GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Boehringer Ingelheim, Verseon and Daiichi-Sankyo. Speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.

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