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VIEWPOINT

Risk Stratification in Hypertrophic Cardiomyopathy

Leveraging Artificial Intelligence to Provide Guidance in the Future

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Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disease occurring in 1:200 to 1:500 patients.[1] HCM is characterized by increased left ventricular (LV) wall thickness in the absence of abnormal loading conditions and infiltrative or storage disease processes, which can result in heart failure (HF), arrhythmias, and sudden cardiac death (SCD).[1,2] Although the overall risk of SCD is ~0.5%/y in the current era, there is at least more than a 2-fold increase of SCD in pediatric population compared to adults with HCM.[3,4] There is also a significant geographic variation of SCD events reflective of differential access to genetic testing, imaging used to guide diagnosis and risk stratification, and costly treatments such as device implants.[3] Timely HCM diagnosis and risk stratification assessment are key to prevent adverse outcomes including life-threatening arrhythmias. However, identification of patients who would derive the most benefit from implantable cardioverter-defibrillator (ICD) implant can be challenging and more enhanced risk stratification algorithms are needed.

CURRENT GUIDELINES

Current risk stratification models have evolved over time reflecting the challenges in capturing an individual's overall risk and increasing understanding of disease. Current 2020 American College of Cardiology (ACC)/American Heart Association (AHA) HCM Guidelines[2] and updated 2022 European Society of Cardiology (ESC) guidelines[5] for ventricular arrhythmias help guide risk stratification for SCD. According to guidelines, ICD is a Class I indication for patients with sustained ventricular arrhythmias, ventricular fibrillation, or cardiac arrest. Other individual factors are also used in the assessment of SCD risk in the 2020 ACC/AHA guidelines include family history of SCD in first-degree family members, unexplained syncope, nonsustained ventricular tachycardia, maximal wall thickness of ≥30 mm, LV end-stage remodeling with left ventricular ejection fraction <50%, left atrial size, left ventricular outflow tract obstruction, apical aneurysm, and significant late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging. In contrast, ESC risk assessment uses quantitative ESC 5-year SCD individual risk score with enhanced features such as apical aneurysm, significant LGE, ejection fraction <50% with abnormal blood pressure response with exercise and sarcomere status as key differentiating factors.

KNOWLEDGE GAPS IN OUR CURRENT MODELS: THE NEED FOR MORE ENHANCED PREDICTORS

Current models are limited and may underestimate risk among patients who have undergone septal reduction therapies, pediatric patients and underrepresented minorities. Genotype status may also confer risk of SCD based on observational studies; however, this association has not been well established. These tools also rely heavily on accurate

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assessment of maximal wall thickness, a continuous measure in the risk stratification models; however, expert interpretation has high inter-reader variability, and can be imprecise including the assessment of maximal wall thickness using transthoracic echocardiogram owing to erroneous inclusion of right ventricular myocardium, LV trabeculations, or papillary muscles. This has the potential to impact critical decisions on therapeutic interventions In one analysis, imprecise measurements, can contribute to inappropriate implantation of ICDs in approximately 1 in 7 patients leading to unintentional complications and costs[6] with a device complication rate of up to 2.1%/y.[7] In addition, degree of left ventricular outflow tract obstruction (continuous variable) is a risk predictor however this may not be necessarily reflective of one's overall risk as Black patients are more likely to be nonobstructive and have high degree of fibrosis on CMR (categorial variable).[8]

Validation studies have been performed to determine how well current models perform in prediction of SCD events which have previously shown variable sensitivity and specificity. An evaluation of 2,094 patients with primary prevention ICD incorporating 2020 ACC/AHA guideline risk factors including LGE and apical aneurysm had a sensitivity of 95% and specificity of 78% in comparison to sensitivity of 58% and specificity of 81% using the 2014 ESC criteria. Also, the C-statistics for discriminating patients with and without SCD was 0.81 for using ACC/AHA risk assessment vs 0.74 using 2014 ESC risk assessment with a more significant gap in refining risk in the intermediate risk cohort. Although the updated 2020 ACC/AHA algorithm is more sensitive in identifying very high risk patients, we need to better discriminate among lower risk patients evidenced by the fact that patients in the United States are implanted more frequently than patients at non-U.S. sites with less appropriate ICD therapies among patients managed in the United States.[9] More recently, 2022 ESC guidelines attempt to bridge some gaps by providing additional risk factors to be considered among intermediate and low risk groups including abnormal blood pressure response during exercise and sarcomere status beyond apical aneurysm, LGE and left ventricular ejection fraction <50%. However, use of abnormal blood pressure response, which was previously removed from 2020 ACC/AHA guidelines, and sarcomere status do not have strong evidence to support their use. Further studies are required to validate the current 2022 ESC model and optimize allocation of ICDs.

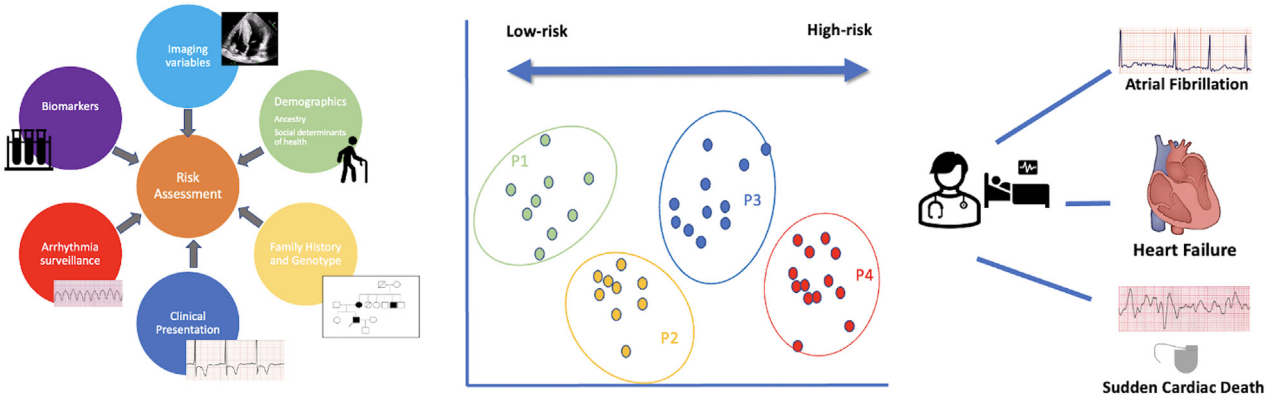
MACHINE LEARNING AND ENHANCING RISK STRATIFICATION ALGORITHMS

Machine learning (ML) is a type of artificial intelligence that learns from example data, and deep learning (DL) is a subtype of ML that utilizes neural networks to mimic the human brain. ML and DL approaches can automate echocardiographic analyses, interpretation and HCM detection. In a heterogeneous, progressive disease state such as HCM, ML may be a tool to: 1) accurately and precisely measure maximal wall thickness and quantify LGE on CMR that can be used for diagnosis and risk stratification; 2) identify additional 'high-risk' or 'low-risk' variables based on disease phenotypes; and 3) better enhance risk assessment using multiple variables reflecting different aspects of the disease to provide an accurate estimate of prognosis. In fact, ML can accurately measure maximal wall thickness and quantify scar quantification from CMR images with high correlation with expert analysis.[10,11] Prior studies have evaluated ML based risk stratification for ventricular arrhythmias and HF progression using clinical characteristics and echocardiographic features with sensitivity of 80% and specificity of 72% and C-statistic of 81%[12]; however, limitations include lack of well-represented population[13] and unexpected high event rates.[14] Sarcomeric status has also not been used in these models. Moreover, the ML model's performance in non-White patients who exhibit different phenotypes and factors such as social determinants of health is unknown. Regarding statistical approach, prior work has also found DL-based survival models to outperform regression approaches used for survival analysis in current risk stratification models which often assumes simplistic linear relationships between HCM and patient data.

INCREASING REPRESENTATION OF DIVERSE POPULATIONS

It is well known that Blacks with HCM have worse cardiovascular outcomes with higher risk of incident HF, HCM-related SCD and lower survival after out of hospital arrest comparative to their White counterparts.[15,16] Although recent studies attempt to bridge gaps in understanding disparities in diverse populations, studies are limited by significant referral bias highlighting differential access to care evidenced by lower genetic testing rates and lower referrals for septal reduction therapies among Black patients.[15] Large registry data from centers with community-

FIGURE 1 **Phenotyping and Risk Stratification Using Machine Learning in HCM**



Large registries including well-represented diverse populations can provide insight on various phenotypes and genotypes. Machine learning clustering on patients can be performed to categorize patient in phenogroups based on their risk profiles. This information can be used to guide development of risk stratification models to help identify patients who are highest risk for developing incident atrial fibrillation, heart failure, and sudden cardiac death so that timely treatment plans can be implemented. HCM = hypertrophic cardiomyopathy; P = phenogroup.

based networks with well-represented diverse populations is needed to determine the natural history of sarcomeric HCM including social determinants of health and ancestral data. This information can be used in addition to a priori risk factors to help inform us about a patient's overall risk beyond self-reported race. Further, as the cumulative burden of disease is primarily driven by incident HF and atrial fibrillation,[17] risk stratification tools in addition to SCD are also needed to identify patients at highest risk. Current registries and expanded registries representing diverse populations can provide more understanding of risk profiles and heterogenous HCM phenotypes. In turn, this information can then be used to help develop and advance risk stratification models for atrial fibrillation, HF, and SCD (**Figure 1**).

CONCLUSIONS

Decision of implantation of device therapy is complex and multifaceted, involving interplay of clinical reasoning, physician expertise, patient-centered shared decision-making model in management of a heterogenous disease process such as HCM. This is evidenced by the fact of varying clinical practices in ICD implantation rates in U.S. centers vs non-U.S. centers.[9] Current risk stratification tools have limitations and may not be widely applicable to all. Further, ML and DL have the potential to provide insight into individual's risk for susceptibility to malignant rhythms, and improve the precision of echocardiographic interpretation, early detection, and risk stratification in patients with HCM.[18-21]

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REFERENCES

1. Maron BJ, Desai MY, Nishimura RA, et al. Diagnosis and evaluation of hypertrophic cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022;79(4):372-389. https://doi.org/10.1016/j.jacc.2021.12.002

2. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2020;76(25):3022-3055. https://doi.org/10.1016/j.jacc.2020.08.044

3. Abdelfattah OM, Martinez M, Sayed A, et al. Temporal and global trends of the incidence of sudden cardiac death in hypertrophic cardiomyopathy. *J Am Coll Cardiol EP*. 2022;8(11):1417-1427. https://doi.org/10.1016/j.jacep.2022.07.012

4. Miron A, Lafreniere-Roula M, Steve Fan CP, et al. A validated model for sudden cardiac death risk prediction in pediatric hypertrophic cardiomyopathy. *Circulation*. 2020;142(3):217-229. https://doi.org/10.1161/CIRCULATIONAHA.120.047235

5. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022;43(40):3997-4126. https://doi.org/10.1093/eurheartj/ehac262

6. Captur G, Manisty CH, Raman B, et al. Maximal wall thickness measurement in hypertrophic cardiomyopathy: biomarker variability and its impact on clinical care. *J Am Coll Cardiol Img*. 2021;14(11):2123-2134. https://doi.org/10.1016/j.jcmg.2021.03.032

7. Maron MS, Rowin EJ, Wessler BS, et al. Enhanced American College of Cardiology/American Heart Association strategy for prevention of sudden cardiac death in high-risk patients with hypertrophic cardiomyopathy. *JAMA Cardiol*. 2019;4(7):644-657. https://doi.org/10.1001/jamacardio.2019.1391

8. Arabadjian ME, Yu G, Sherrid MV, Dickson VV. Disease expression and outcomes in Black and White adults with hypertrophic cardiomyopathy. *J Am Heart Assoc*. 2021;10(17):e019978. https://doi.org/10.1161/JAHA.120.019978

9. Nauffal V, Marstrand P, Han L, et al. Worldwide differences in primary prevention implantable cardioverter defibrillator utilization and outcomes in hypertrophic cardiomyopathy. *Eur Heart J*. 2021;42(38):3932-3944. https://doi.org/10.1093/eurheartj/ehab598

10. Augusto JB, Davies RH, Bhuva AN, et al. Diagnosis and risk stratification in hypertrophic cardiomyopathy using machine learning wall thickness measurement: a comparison with human test-retest performance. *Lancet Digit Health*. 2021;3(1):e20-e28. https://doi.org/10.1016/S2589-7500(20)30267-3

11. Navidi Z, Sun J, Chan RH, et al. Interpretable machine learning for automated left ventricular scar quantification in hypertrophic cardiomyopathy patients. *PLoS Digit Health*. 2023;2(1):e0000159. https://doi.org/10.1371/journal.pdig.0000159

12. Fahmy AS, Rowin EJ, Manning WJ, Maron MS, Nezafat R. Machine learning for predicting heart failure progression in hypertrophic cardiomyopathy. *Front Cardiovasc Med*. 2021;8:647857. https://doi.org/10.3389/fcvm.2021.647857

13. Smole T, Žunkovič B, Piculin M, et al. A machine learning-based risk stratification model for ventricular tachycardia and heart failure in hypertrophic cardiomyopathy. *Comput Biol Med*. 2021;135:104648. https://doi.org/10.1016/j.compbiomed.2021.104648

14. Kochav SM, Raita Y, Fifer MA, et al. Predicting the development of adverse cardiac events in patients with hypertrophic cardiomyopathy using machine learning. *Int J Cardiol*. 2021;327:117-124. https://doi.org/10.1016/j.ijcard.2020.11.003

15. Eberly LA, Day SM, Ashley EA, et al. Association of race with disease expression and clinical outcomes among patients with hypertrophic cardiomyopathy. *JAMA Cardiol*. 2020;5(1):83-91. https://doi.org/10.1001/jamacardio.2019.4638

16. Ntusi NAB, Sliwa K. Associations of race and ethnicity with presentation and outcomes of hypertrophic cardiomyopathy: JACC focus seminar 6/9. *J Am Coll Cardiol*. 2021;78(25):2573-2579. https://doi.org/10.1016/j.jacc.2021.10.020

17. Ho CY, Day SM, Ashley EA, et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). *Circulation*. 2018;138(14):1387-1398. https://doi.org/10.1161/CIRCULATIONAHA.117.033200

18. Zhang J, Gajjala S, Agrawal P, et al. Fully automated echocardiogram interpretation in clinical practice. *Circulation*. 2018;138(16):1623-1635. https://doi.org/10.1161/CIRCULATIONAHA.118.034338

19. Duffy G, Cheng PP, Yuan N, et al. High-throughput precision phenotyping of left ventricular hypertrophy with cardiovascular deep learning. *JAMA Cardiol*. 2022;7(4):386-395. https://doi.org/10.1001/jamacardio.2021.6059

20. Loncaric F, Garcia-Canadilla P, Garcia-Alvarez A, et al. Etiology-discriminative multimodal imaging of left ventricular hypertrophy and synchrotron-based assessment of microstructural tissue remodeling. *Front Cardiovasc Med*. 2021;8:670734. https://doi.org/10.3389/fcvm.2021.670734

21. Goto S, Solanki D, John JE, et al. Multinational federated learning approach to train ECG and echocardiogram models for hypertrophic cardiomyopathy detection. *Circulation*. 2022;146(10):755-769. https://doi.org/10.1161/CIRCULATIONAHA.121.058696

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