

Atrial Fibrillation and Stroke in Patients with Hypertrophic Cardiomyopathy: Important New Insights

Jeffrey S. Borer¹ Dan Atar² Thomas Marciniak³ Moo Hyun Kim⁴ Victor Serebruany⁵

¹The Howard Gilman Institute for Heart Valve Disease and the Schiavone Institute for Cardiovascular Research, State University of New York Downstate Medical Center, Brooklyn, New York, United States

²Division of Medicine, Department of Cardiology B, Oslo University Hospital and Institute of Clinical Sciences, University of Oslo, Oslo, Norway

³Bethany Beach, Delaware, United States

⁴Department of Cardiology, Dong-A University, Busan, South Korea

⁵Department of Neurology, Johns Hopkins University, Baltimore, Maryland, United States

Address for correspondence Victor Serebruany, MD, PhD, Department of Neurology, Johns Hopkins University, Baltimore, MD 21204, United States (e-mail: vserebr1@jhmi.edu).

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Among the various non-ischaemic primary myocardial diseases recognized in humans, the most common is hypertrophic cardiomyopathy (HCM). Though first recognized more than 60 years ago because of the characteristic physical signs of its most dramatic form, idiopathic hypertrophic subaortic stenosis (IHSS),¹ the rapid dissemination of the echocardiogram 10 years later soon led to the recognition that IHSS was merely a part of a continuum of genetically determined hypertrophic anomalies, often without outflow obstruction.² The more characteristic haemodynamic abnormality is left ventricular diastolic dysfunction. This, in turn, can lead to left atrial dilatation which, if sufficiently severe, can contribute to the development of atrial fibrillation (AF).

Unless AF is recognized timely, the consequence frequently is left atrial thrombosis and embolization, leading to stroke or peripheral ischaemic sequelae. Thus, stroke prevention is central to the management of AF.³ Indeed, in a tragic and dramatic irony, Andrew G. Morrow, who devised the most widely employed surgical approach to IHSS at the National Institutes of Health more than 50 years ago,⁴ developed AF, was then found echocardiographically to have non-obstructive (i.e. inoperable) HCM, suffered a stroke and eventually died as a consequence.

The prevalence of AF has not been well defined in HCM, in part because of the difficulty in obtaining data from a sufficiently large and non-biased sample to ensure credibility. The study of Jung et al, published in the previous issue,⁵ provides some useful data concerning the extent to which HCM contributes to the global prevalence of AF.

Using a well-recognized national administrative database, these investigators provide a reasonable estimate of the prevalence of HCM among the Korean population with AF. Their more important finding was that the CHA₂DS₂-VASc score, commonly used to define risk of stroke in patients with AF and, therefore, a basis for the decision to prophylactically anticoagulate, has importantly different implications in patients with AF + HCM versus patients with AF without HCM.

The reason for this discrepancy is not clear and requires further study. It is possible that thrombogenesis of the endothelium in HCM hearts is enhanced by outflow obstruction, though no assessment of this possibility is yet available. Another speculative possibility is that thrombosis-inducing anti-cardiolipin antibody (aCLa) is produced by some cell line in the HCM heart when AF occurs; such abnormal aCLa production is seen in patients with non-rheumatic aortic valve disease⁶ and, when present, appears to be associated with a proclivity for thromboembolization and stroke, though the reason for this association is unclear.

Other possible pathophysiological factors might be hypothesized. In any case, additional study of these potential pathways now is appropriate because of the findings of Jung et al. In addition, despite the now apparent risk of stroke, a distressingly low proportion of those with AF + HCM actually were being anticoagulated in Jung et al's cohort. This finding suggests the need to revisit the guidelines for management of AF for patients with HCM and to emphasize the need for early aggressive anticoagulation once AF is found.

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The incidence of AF in HCM has been inferred from observational data to be approximately 25% of patients first seen without AF.⁷ However, a prospective assessment of the incidence of stroke in such patients has not been performed and is not available from the current study. The best available data were generated many years ago by a retrospective two-centre observational study involving 480 consecutive patients with HCM seen over 20 years and not managed according to any pre-set protocol or guideline.⁸ This study also revealed a 25% incidence of AF before the HCM diagnosis was made. After the diagnosis, 17% developed AF but the arrhythmia did not cluster in any temporal pattern. Rather, AF was found between 2 months and 29 years after the diagnosis and occurred at an average linearized rate of 2% per year. Further, in this series, stroke was unrelated to whether AF was paroxysmal or sustained. However, the relative risk of stroke in HCM + AF was almost 18-fold greater than among patients in the HCM cohort without AF. Coupled with the current data, these prior findings strongly suggest the appropriateness of long-term anticoagulation at the first evidence of AF.

A paucity of data also limits any conclusions about the utility of pharmacological anti-arrhythmic therapy, pulmonary vein isolation ('ablation') and the relative utility of these versus anticoagulation. Indeed, both the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines for management of patients with AF⁹ and the parallel European Society of Cardiology (ESC) guidelines¹⁰ offer relatively little definitive guidance for patients with HCM + AF. Both recommend lifelong anticoagulation after development of AF, though the ACC/AHA/HRS version specifically suggests anticoagulation irrespective of the CHA₂DS₂-VASc score. Jung et al's data support this suggestion because the risk of stroke in HCM + AF in the absence of CHA₂DS₂-VASc risk factors was similar to the stroke risk in patients without HCM but with CHA₂DS₂-VASc score of 3, generally considered a very strong indication for anticoagulation. Both American and European guidelines support attempts at rhythm control with pharmacological or ablation methods, though both appropriately note the absence of definitive studies to support this suggestion. Jung et al's data provide little guidance in this area and none with regard to the possible benefit of therapeutic reduction of outflow tract gradient when it exists (suggested without strong data by both guidelines for symptomatic patients with HCM + AF) because no pre-specified treatment protocol was employed in the study cohort and no randomization was attempted to facilitate data interpretation. Studies in this area now are needed.

In summary, the current study provides the most compelling data now available in support of a low threshold for lifelong anticoagulation in patients with HCM + AF at the initial discovery of AF, even if only a paroxysm. This study also supports the need for prospective efforts to define factors that can predict AF development in HCM to allow earlier effective prophylactic therapy and to identify the factors which render the addition of HCM to AF more likely

to cause stroke than AF in the absence of HCM. Finally, the potential use of direct oral anticoagulants (DOACs) instead of the vitamin K antagonists (e.g. warfarin) requires specific assessment. Though DOACs are far more convenient and, in theory, should be applicable in patients with HCM, the surprising finding of increased thrombogenesis and embolization with dabigatran in patients with prosthetic heart valves was unexpected, and has led to the contraindication of DOACs in the presence of valve prostheses. This issue will require direct study in HCM, rather than assumptions based on pharmacological data. On the other hand, there is no reason to believe that DOACs will perform worse in HCM than warfarin, as recently postulated for yet another disease state: rheumatic valvular disease including mitral stenosis.¹¹ After all, the HCM entity, in the previous ESC guideline on AF, was lumped together with rheumatic valvular heart disease, for the simple reason that a high embolic stroke rate was observed in both conditions.¹² Indeed, in a separate publication, Jung et al¹³ have reported that when compared with warfarin, patients with HCM and AF on DOACs had similar stroke and major bleeding risks, but lower all-cause mortality and composite fatal cardiovascular events. Thus, patients with HCM and AF can be safely and effectively treated with DOACs.

Conflict of Interest

Dr. Atar reports personal fees from Boehringer-Ingelheim, BMS/Pfizer, Bayer Healthcare, MSD (Merck) and AstraZeneca, and grants from Medtronic and BMS, outside the submitted work. Dr. Borer reports personal fees from Takeda USA, during the conduct of the study; AstraZeneca, Novartis, ARMGO, Abbott Laboratories, Amgen, Servier, GSK, Pfizer and other from Biomarin, outside the submitted work.

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