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EDITORIAL COMMENT

Atrial Fibrillation in Transthyretin Amyloid Cardiomyopathy

How Worried Should We Get?

Nowell M. Fine, MD, SM

The field of transthyretin amyloid cardiomyopathy (ATTR-CM) has witnessed remarkable advances in recent years, with respect to diagnostic approaches, disease-modifying therapy, and general awareness. Tafamidis, an oral transthyretin protein stabilizer that attenuates disease progression, is now the standard of care and has significantly improved clinical outcomes for patients with this disease. Although tafamidis is presently the only approved therapy for ATTR-CM, multiple other medications are in various stages of development, including a new transthyretin stabilizer, acoramidis; the second-generation transthyretin gene silencers eplontersen and vutrisiran; and new classes of therapies including depleters, aimed at reducing amyloid tissue deposits, and those based on the clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease system, designed to permanently reduce hepatic transthyretin production.

With all this exciting activity surrounding disease-modifying therapies for ATTR-CM, its important not to forget about the need for ongoing research to improve our understanding and management of the disease's complications. These include old and familiar foes such as heart failure, aortic stenosis, and atrial fibrillation. These disorders, though very common among all patients with cardiovascular disease, can present unique challenges for patients with ATTR-CM. For example, commonly used therapies for the treatment of patients with heart failure may be poorly tolerated or less effective among those with ATTR-CM compared with those with other heart failure etiologies.

Atrial fibrillation is another example of a cardiovascular complication that presents unique challenges for patients with ATTR-CM. It has been well described that atrial fibrillation is highly prevalent among patients with ATTR-CM, which is not surprising considering the structural and functional myocardial derangements associated with ATTR-CM (such as amyloid infiltration of atrial tissue, diastolic dysfunction, and others) and the frequently older age of patients. This is particularly true for those with wild-type ATTR, an age-related disorder occurring in the absence of a transthyretin gene mutation, but even those with hereditary ATTR, a familial condition caused by a transthyretin gene mutation, are also often diagnosed at an older age. Patients with ATTR-CM with atrial fibrillation are at a heightened risk for thromboembolic complications because of the highly thrombogenic texture of their endocardium, and systemic anticoagulation prophylaxis is recommended for all patients with atrial fibrillation irrespective of risk stratification score.[1] Furthermore, rate-controlling medications such as beta-blockers and calcium-channel blockers are often not well tolerated by patients with ATTR-CM, while rhythm-controlling strategies such as pulmonary vein ablation may be less effective compared with patients without ATTR-CM. Despite these unique challenges, the prognostic significance of atrial fibrillation for patients with ATTR-CM was generally considered to be low on the basis of prior research, the majority being of single-center retrospective study design.[2]

It is in this context that we consider the findings of Witteles et al[3] published in this issue of *JACC: CardioOnclogy*. The investigators performed a post hoc analysis of the ATTR-ACT (Tafamidis in

From the Libin Cardiovascular Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada.
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Transthyretin Cardiomyopathy Clinical Trial), a 30-month randomized placebo-controlled clinical trial examining the efficacy of tafamidis in ATTR-CM, to investigate the prognostic significance of a baseline history of atrial fibrillation (or atrial flutter) at the time of enrollment in the trial. The investigators also examined the impact of atrial fibrillation on the efficacy of tafamidis. They describe a high prevalence of atrial fibrillation at the time of enrollment, exceeding 70% among 441 patients with ATTR-CM (among whom the median age was 75 years, 90% were men, and 75% had wild-type ATTR), which is consistent with prior publications. Baseline or historical atrial fibrillation was significantly associated with an increased risk for all-cause mortality after adjusting for a limited number of covariates (including receiving tafamidis treatment, hereditary ATTR genotype, and NYHA functional class). However, when using a more expanded analysis that included 23 covariates, the prognostic importance of atrial fibrillation was no longer significant, nor did it affect the efficacy of tafamidis treatment.

What can we learn from these results? For one, they confirm the clinically intuitive notion that atrial fibrillation is a marker of more advanced disease in ATTR-CM and that it keeps bad company with other highly prognostic factors in ATTR-CM, similar to other causes of heart failure. However, it is reassuring that the presence of atrial fibrillation did not lessen the benefit of tafamidis therapy. And although these findings broaden our understanding of the significance of atrial fibrillation in ATTR-CM, like most research, these results bring many further questions. For example, the ATTR-ACT trial now represents an earlier era with respect to ATTR-CM diagnosis because nuclear scintigraphy using bone-seeking radiotracers (namely, technetium-99m-pyrophosphate and 3,3-diphosphono-1,2-propanodicarboxylic acid) were not yet available to confirm the presence of myocardial ATTR amyloid deposits. This noninvasive approach subsequently became the diagnostic standard of care, obviating the need for invasive biopsy confirmation in most patients (as long as light-chain amyloidosis is excluded). Biopsy confirmation of amyloidosis was still required to confirm the diagnosis for patients enrolled in ATTR-ACT.[4] Widespread use of nuclear scintigraphy resulted in a safer and easier path to diagnosis, which, combined with improved awareness, has contributed to an increased diagnostic rate of ATTR-CM in most regions. These factors also have contributed to more patients' being diagnosed at a relatively earlier stage of disease. This trend is reflected when comparing the patient populations of the ATTR-ACT trial with the more recently conducted ATTRibute-CM (Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy) trial, which did not require biopsy confirmation if the results of nuclear scintigraphy were positive. In ATTRibute-CM, patients had lower baseline medial N-terminal pro-B-type natriuretic peptide levels, and there was a lower proportion of patients in NYHA functional class III at the time of enrollment compared with patients in ATTR-ACT, despite their having a slightly higher mean age (although it is worth noting that a minority of patients received concomitant tafamidis treatment).[5] The findings of the present study most likely apply to a more modern cohort of patients with ATTR-CM, including those initiated on disease-modifying therapy from the time of diagnosis, but confirmation of this would be beneficial.

Another important question this study raises is, What happens to atrial fibrillation incidence and burden once treatment is initiated? Do they diminish, and are patients with ATTR-CM who do not have atrial fibrillation at the time of diagnosis less likely to subsequently develop it once they start treatment? Will other ATTR-CM treatments currently in development potentially influence this more or less than tafamidis? These questions will take additional time and research to adequately address but do have important implications for the management of ATTR-CM. Furthermore, the optimal approach for managing atrial fibrillation in ATTR-CM remains to be determined, including the importance (or futility) of pursuing a rhythm-control strategy and how best to do so. Given how common atrial fibrillation is among patients with ATTR-CM, addressing these knowledge gaps should be a priority for ATTR-CM research. In the meantime, we can conclude that atrial fibrillation has prognostic significance in ATTR-CM but that other factors carry far more importance.

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ADDRESS FOR CORRESPONDENCE: Dr Nowell M. Fine, University of Calgary, Libin Cardiovascular Institute, South Health Campus Hospital, 4448 Front Street SE, Calgary, Alberta T3M 1M4, Canada. E-mail: nmfine@ucalgary.ca.

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