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Editorial

Stroke in ATTR cardiac amyloidosis: Does only rhythm matter?

Transthyretin amyloidosis (ATTR) is frequently associated with cardiac involvement in the wild type form (wtATTR) as well as in the mutated form (variant ATTR, vATTR). Although left ventricular (LV) pseudohypertrophy is currently considered the most relevant structural abnormality in cardiac amyloidosis (CA), atrial involvement due to both amyloid infiltration and secondary to LV overload and remodeling, is another key feature and a major determinant of decompensation, especially when associated with atrial arrhythmias [1]. Atrial fibrillation (AF) is very common in CA, being detectable in up to 40% of cases depending on the specific amyloid subtype, with the highest prevalence among wtATTR-CA patients [2]. AF is a major cause of the formation of intraatrial thrombi, which expose the patients to a higher risk of cardioembolic events. Nonetheless, the amyloid involvement of atria, and the subsequent structural and electrical remodeling also contribute to the development of thrombosis [3]. Feng and Colleagues reported that severe diastolic dysfunction, low atrial emptying velocity at transesophageal echocardiography (TEE), and amyloid immunoglobulin-light chain (AL) subtype were predictors of intracardiac thrombi [4]. Other non-cardiac factors may also contribute to thrombogenesis, such as decreased mobility and the loss of anticoagulant factors (antithrombin, protein S) and increased synthesis of procoagulant factors (factor V, VII, fibrinogen) whenever a nephrotic syndrome is present [3].

Current expert consensus by the European Society of Cardiology (ESC) suggests that ambulatory ECG monitoring should be repeated yearly in patients with ATTR-CA, or following the development of symptoms, to detect new-onset brady- or tachyarrhythmias, including AF [5]. The use of anticoagulants is suggested in patients with ATTR-CA and AF irrespective of CHADS-VASc score. The expert consensus by the ESC also recommends "to consider [anticoagulation] in selected cases in sinus rhythm" [5], and the American Heart Association suggests that patients with decreased A-wave amplitude and left atrial (LA) appendage velocities on echocardiography may warrant empirical anticoagulation even in sinus rhythm [6]. Still, the role of anticoagulation in patients with sinus rhythm is an unmet need in the management of patients with ATTR-CA.

In this issue of the Journal, Masri and Colleagues performed a retrospective analysis on patients with ATTR-CA referred to a single Center in the United States to determine the prevalence of AF and atrial flutter (AFL) [7]. All patients without known AF/AFL at baseline were randomly followed-up through either ECG Holter monitoring (1 to 3 days), ambulatory monitoring (5 to 14 days) or 30-day monitoring every 6 months, while those with cardiovascular implantable electronic devices had device interrogations. Among the 84 patients collected between 2005 and 2019, 40 had AF/AFL before ATTR-CM diagnosis, while 21 were subsequently diagnosed with AF/AFL. During a mean 28-month follow-up, stroke occurred in 9 patients. In most cases ($n = 5$), strokes were attributed to cardio-embolic events presenting in either non-anticoagulated patients with new-onset AF/AFL or patients with known AF/AFL not on appropriate dosage of anticoagulants, while no ischemic stroke occurred in patients receiving anticoagulant therapy.

The paper by Masri et al. highlights the epidemiological relevance of AF in with ATTR-CA and the need for a tailored approach in the monitoring and therapeutic management. Notably, no strokes were observed in anticoagulated patients with AF/AFL. This is somehow conflicting with findings from a large Italian cohort of 406 patients with either AL or ATTR-CA, in whom anticoagulation did not appear to fully protect from thrombo-embolic events [8]. In the same study, around 1/3 of patients who experienced events were in sinus rhythm and had no history of AF, albeit an under detection of atrial arrhythmias cannot be excluded [8].

While the question of the Authors is reasonable (i.e. how common is AF/AFL and how common is stroke in patients with CA?), the most relevant issue concerns the prevention of thromboembolic events in these patients. The mechanisms of disease, regarding atrial remodeling and electromechanical dissociation, together with some clinical evidence on the higher thromboembolic risk on patients with amyloidosis, suggests that current risk stratification criteria should not be applied *sic et simpliciter* in these patients. Indeed, whether the documentation of atrial arrhythmias should be deemed necessary for the initiation of anticoagulant therapy is a matter of debate [3,8]. We have recently shown that strain parameters, such as peak LA-longitudinal strain and LA-peak contraction strain are profoundly impaired in patients with ATTR-CA compared with those with AL-CA or age- and sex-matched controls [9]. The perspective of predicting interatrial thrombosis and thromboembolic events through strain parameters and other echocardiographic measures (such as LA dilation) in patients without a history of AF/AFL is intriguing and should be examined in dedicated studies.

In conclusion, the paper by Masri et al. provides novel insights into the epidemiology of atrial arrhythmias and cerebral thromboembolic events in ATTR-CA. Nonetheless, several questions on the management of AF/AFL and stroke prevention in patients with CA remain unanswered, such as the preferred therapeutic strategy to prevent thromboembolism (i.e., warfarin vs. than non-vitamin K antagonists [NOAC]), the target international normalized ratio or the optimal dosages of NOACs, the role of ablation therapy, and the importance to routinely perform TEE before cardioversion even in anticoagulated patients [10].

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