Time to reconsider thromboembolic risk and anticoagulation in transthyretin cardiac amyloidosis?

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This article refers to 'Systemic embolism in amyloid transthyretin cardiomyopathy' by S. Vilches *et al.*, published in *Eur J Heart Fail* 2022;24:1387–1396.

Transthyretin cardiac amyloidosis (ATTR-CA) is considered an exemplar of 'restrictive cardiomyopathy' caused by extracellular deposition of amyloid fibrils derived from plasma transthyretin.[1] Whilst increased ventricular wall thickness is the hallmark of ATTR-CA, the atria are a frequently overlooked but common site of amyloid deposit.[2,3] Atrial fibrillation (AF) is the most common arrhythmia in ATTR-CA and exposes patients to the risk of thrombus formation and embolic events.[4,5] A remarkable incidence of atrial thrombi has been found in patients with ATTR-CA, either in the atrial appendage or attached to the atrial walls, also in a substantial number of those in sinus rhythm (SR).[4,5] Major advances in imaging such as bone tracer scintigraphy and cardiac magnetic resonance have transformed the non-invasive approach to diagnosis of ATTR-CA,[6,7] which has emerged as a much under-recognized cause of heart failure (HF) and mortality[8] in different clinical settings.[9–11] Nevertheless, solid evidence on the management of AF, estimation of thromboembolic risk and recommendations on initiation of oral anticoagulant therapy (OAT) in patients with ATTR-CA is lacking.

In the last issue of the Journal, we read with interest the study by Vilches *et al.*[12] that tries to shed light upon the current knowledge gap on systemic embolism in ATTR-CA. The authors conducted a multicentre, retrospective analysis among four international amyloid centres exploring the incidence, prevalence and factors associated with systemic embolism in a population of ≈1200 patients with ATTR-CA. They collected information on the development of AF, thromboembolic events – including stroke, transient ischaemic attack or peripheral embolism – and OAT at first clinical evaluation and during follow-up. The authors should be congratulated for their effort to collect a so well-characterized cohort of subjects who had at least two evaluations at their institutions. Previous literature on this topic is scarce, mostly coming from single-centre experience on small cohorts, predominantly with light-chain amyloidosis. Despite a number of methodological limitations, fairly addressed by the authors, the study is undoubtedly stimulating and raises relevant questions for clinical practice.

What is the incidence of systemic embolism in transthyretin cardiac amyloidosis?

Over a median follow-up of 20 months, 41 patients (3.44%) had an embolic event: 24 had AF at initial evaluation, 10 developed AF during follow-up and 7 did not have AF at initial evaluation nor during follow-up.[12] As expected, patients with AF had higher incidence rates of embolic events (per 100 patient-years) compared to those in SR: 0 among patients in SR with OAT, 1.3 in SR without OAT, 1.7 in AF with OAT, and 4.8 in AF without OAT.

Although the rate of systemic embolism was significant in patients with AF, the absolute number of events was low. Screening for development of AF was done by performing an electrocardiogram (ECG) at each clinical evaluation, in the event patients were admitted to hospital or by Holter ECG when deemed appropriate by the managing clinician. This approach might have missed some patients with paroxysmal AF that were considered as having SR. As the authors discuss, the presence of AF should be actively investigated with all available resources, including systematic interrogation of cardiac devices (i.e. loop recorders) that would have probably led to higher AF detection.[13]

On these premises, we would have expected an incidence of embolic events much higher based on patient characteristics and

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previous studies on consecutive cohorts of patients with ATTR-CA reporting an incidence of 8% over a similar median follow-up (19 months).[14] The authors recognized the retrospective nature of the study as a limitation and reported that several patients had to be excluded due to missing information or limited visits. Landmark studies changing clinical practice in ATTR-CA have been conducted among participating centres using overall mortality as main endpoint. However, the accurate collection of data on systemic embolism may be more challenging in retrospective studies, thus exposing to the risk of underestimating the number of embolic events. Interestingly, the results of this analysis might pave the way for dedicated future prospective studies.

Is sinus rhythm associated with lower risk of systemic embolism?

Vilches *et al.*[12] highlight the need to assess carefully patients with ATTR-CA as the incidence rate of systemic embolism in SR was similar to that in AF with OAT (1.3 vs. 1.7 events per 100 patient-years). This finding also suggests that ATTR-CA is a highly heterogeneous condition that requires a patient-tailored management. The typical phenotype of atrial remodelling in ATTR-CA includes significant infiltration of the atrial walls with progressive loss of atrial function and increased stiffness.[2] In a recent series from the National Amyloidosis Centre, 20% of patients with ATTR-CA had no atrial contraction while remaining in SR on the ECG, a condition defined as 'atrial electromechanical dissociation' (AEMD).[2] AEMD is a fascinating mechanism to systematically investigate in clinical practice that might also be useful to guide decision-making on initiation of OAT. Attempts to maintain SR by antiarrhythmic drugs and/or catheter ablation when the patient in SR with AEMD develop AF are likely not be associated with improved ventricular filling and cardiac output as atrial contraction was already absent when they were in normal SR.

Is CHA_2DS_2-VASc score reliable for estimating embolic risk in transthyretin cardiac amyloidosis?

In this study,[12] the CHA_2DS_2-VASc score did not predict embolic events in patients in SR whereas in patients with AF without OAT, only those with a score $\geq$4 had embolic events. This is in line with previous observations on the poor correlation of CHA_2DS_2-VASc score with clinical outcome in patients with ATTR-CA. For this reason, the authors suggest that this tool should not be used to assess thromboembolic risk in this population and to guide anticoagulation. The opinion of this panel of authors is of particular value as many among them are recognized experts in the field of amyloidosis.

Whilst the CHA_2DS_2-VASc score has some limitations, it includes factors known to be associated with global cardiovascular risk that, with different extent, promote the development of HF and AF. The low absolute number of embolic events did not allow Vilches *et al.*[12] to perform a comprehensive multivariable analysis. Notably, the parameters included in the score (except diabetes) were associated with systemic embolism at univariable analysis and those tested in the multivariable model (age and peripheral vascular disease) resulted independent prognostic predictors.

Finally, the limitation of the CHA_2DS_2-VASc score predominantly emerges in patients with ATTR-CA and a score of 0 and 1. In this population, the score does not reflect the risk of systemic embolism conferred by amyloid deposition in the atria that makes the endocardium more prone to thrombus formation. Those patients would not meet guideline criteria for initiation of OAT and could be exposed to a significant risk of thromboembolism. This might explain the poor correlation between low CHA_2DS_2-VASc score and embolic events found also by Vilches *et al.*[12] and suggest that ATTR-CA is an additional risk factor to be considered along with the CHA_2DS_2-VASc score, especially in patients with a score of 0 and 1. The findings of the present study highlight how challenging the prevention of systemic embolism in ATTR-CA might be in clinical practice. A prospective dedicated analysis is needed to investigate whether and how the CHA_2DS_2-VASc score should be used to guide the decision to start OAT in ATTR-CA.

Bleeding risk and oral anticoagulant therapy

In the analysis by Vilches *et al.*,[12] three patients died because of fatal bleeding. Although patients with ATTR-CA, especially those with AF, had an increased risk of systemic embolism, the authors pointed out that the bleeding risk of these patients should be taken into account in the decision to start OAT. Although no difference was observed among vitamin K antagonists and direct oral anticoagulants, the study cohort was retrospective and not statistically powered for this endpoint. Dedicated studies are required to investigate which is the most accurate tool to estimate the risk of major bleedings in ATTR-CA. In patients with contraindications to OAT or at high risk of bleeding precluding initiation of OAT, the safety and usefulness of left atrial appendage closure devices represent a grey area, despite in our opinion the likelihood of this approach to be effective is low considering the multiple and complex mechanisms involved in systemic embolism in ATTR-CA.

Towards a tailored management of atrial fibrillation in transthyretin cardiac amyloidosis

The findings from Vilches *et al.*[12] question whether the current approach to AF management endorsed by the European Society of Cardiology[15] is effective in ATTR-CA:

- Symptomatic patients with AF onset within 48 h can be treated with direct current cardioversion (DCCV).[15] This approach might be associated with an increased risk of systemic embolism and we believe it should be reserved to cases with haemodynamic instability;
- In patients not taking chronic OAT in whom AF has been present for >48 h or for an unknown duration and elective cardioversion is planned, a period of at least 3 weeks of therapeutic OAT or a transoesophageal echocardiography is needed before cardioversion.[15] We suggest the need for specific imaging, also following the period of OAT, to rule out cardiac thrombi before DCCV;
- CHA_2DS_2-VASc score of 0 and 1. Anticoagulation might be considered in these patients with ATTR-CA and AF, especially in presence of previous unexplained embolic events and low bleeding risk. In this setting, AEMD, severe systolic dysfunction and atrial dilatation might be additional factors to consider when estimating patients' embolic risk.

In conclusion, the study by Vilches *et al.* increases current knowledge on systemic embolism in ATTR-CA and has the ability to raise, explicitly or implicitly, a series of extremely challenging clinical and pathophysiological questions to be addressed in future dedicated analyses. A broad horizon of possibilities is unfolding and awaits discovery.

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