Check for updates

ESC European Society of Cardiology

European Journal of Heart Failure (2022) **24**, 1387–1396
doi:10.1002/ejhf.2566

RESEARCH ARTICLE

Systemic embolism in amyloid transthyretin cardiomyopathy

Silvia Vilches[1†], Marianna Fontana[2†], Esther Gonzalez-Lopez[1], Lindsey Mitrani[3], Giulia Saturi[4], Mary Renju[2], Jan M. Griffin[3], Angelo Caponetti[4], Sahana Gnanasampanthan[2], Jeffeny De los Santos[3], Christian Gagliardi[4], Adrian Rivas[1], Fernando Dominguez[1], Simone Longhi[4], Claudio Rapezzi[5,6], Mathew S. Maurer[3], Julian Gillmore[2], and Pablo Garcia-Pavia[1,7,8,9*]

[1]Heart Failure and Inherited Cardiac Diseases Unit, Department of Cardiology, Hospital Universitario Puerta de Hierro, CIBERCV, Madrid, Spain; [2]National Amyloidosis Centre, University College London, London, UK; [3]Division of Cardiology, Department of Medicine, Columbia University Irving Medical Center, New York, NY, USA; [4]Department of Experimental, Diagnostic and Specialty Medicine – DIMES, University of Bologna, IRCCS Sant'Orsola Hospital, Bologna, Italy; [5]Cardiologic Center, University of Ferrara, Ferrara, Italy; [6]Maria Cecilia Hospital, GVM Care & Research, Ravenna, Italy; [7]Universidad Francisco de Vitoria (UFV), Pozuelo de Alarcon, Spain; [8]Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain; and [9]Universidad Autónoma de Madrid (UAM), Madrid, Spain

Received 6 December 2021; revised 24 May 2022; accepted 28 May 2022; online publish-ahead-of-print 11 July 2022

Aims Although systemic embolism is a potential complication in transthyretin amyloid cardiomyopathy (ATTR-CM), data about its incidence and prevalence are scarce. We studied the incidence, prevalence and factors associated with embolic events in ATTR-CM. Additionally, we evaluated embolic events according to the type of oral anticoagulation (OAC) and the performance of the CHA_2DS_2-VASc score in this setting.

Methods and results Clinical characteristics, history of atrial fibrillation (AF) and embolic events were retrospectively collected from ATTR-CM patients evaluated at four international amyloid centres. Overall, 1191 ATTR-CM patients (87% men, median age 77.1 years [interquartile range-IQR 71.4–82], 83% ATTRwt) were studied. A total of 162 (13.6%) have had an embolic event before initial evaluation. Over a median follow-up of 19.9 months (IQR 9.9–35.5), 41 additional patients (3.44%) had an embolic event. Incidence rate (per 100 patient-years) was 0 among patients in sinus rhythm with OAC, 1.3 in sinus rhythm without OAC, 1.7 in AF with OAC, and 4.8 in AF without OAC. CHA_2DS_2-VASc did not predict embolic events in patients in sinus rhythm whereas in patients with AF without OAC, only those with a score $\geq$4 had embolic events. There was no difference in the incidence rate of embolism between patients with AF treated with vitamin K antagonists (VKAs) ($n = 322$) and those treated with direct oral anticoagulants (DOACs) ($n = 239$) ($p = 0.66$).

Conclusions Embolic events were a frequent complication in ATTR-CM. OAC reduced the risk of systemic embolism. Embolic rates did not differ with VKAs and DOACs. The CHA_2DS_2-VASc score did not correlate well with clinical outcome in ATTR-CM and should not be used to assess thromboembolic risk in this population.

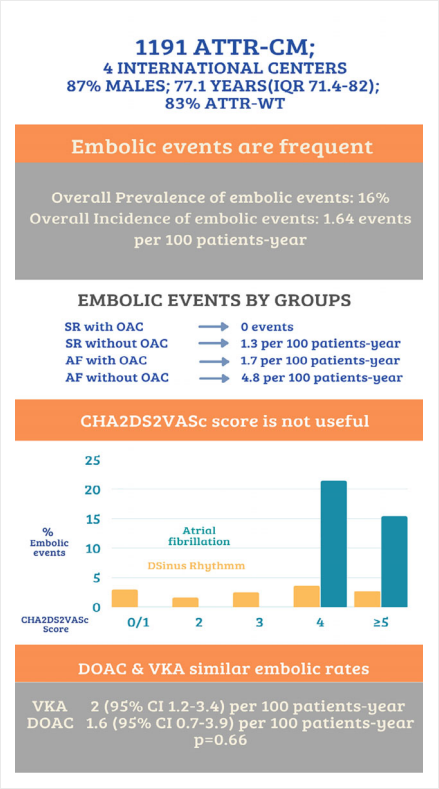
*Corresponding author. Department of Cardiology, Hospital Universitario Puerta de Hierro Manuel de Falla, 2. Majadahonda, Madrid 28 222, Spain. Tel: +34 911 917297, Fax: +34 911 917718, Email: pablo.garciap@uam.es

†Co-first authors.

© 2022 The Authors. *European Journal of Heart Failure* published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

18790844, 2022, 8, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2566 by University College London UCL Library Services, Wiley Online Library on [01/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Graphical Abstract



Systemic embolism in transthyretin amyloid cardiomyopathy (ATTR-CM). Incidence, prevalence and factors associated with embolic events were studied in 1191 ATTR-CM patients from four international centres. Systmic embolism is a common complication (16% prevalence). Incidence rate (per 100 patient-years) was 0 among patients in sinus rhythm (SR) with oral anticoagulation (OAC), 1.3 in SR without OAC, 1.8 in atrial fibrillation (AF) with OAC, and 4 in AF without OAC. CHA_2DS_2-VASc showed limited value to predict embolic events and vitamin K antagonists (VKA) and direct oral anticoagulants (DOAC) seemed equally effective to prevent embolisms. CI, confidence interval; IQR, interquartile range. ATTR-wt, wild-type transthyretin amyloidosis.

Keywords Transthyretin • Cardiac amyloidosis • Embolism • Atrial fibrillation • CHA_2DS_2-VASc • Anticoagulation

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an increasingly recognized progressive and frequently fatal cardiac disease caused by the accumulation of transthyretin (TTR), in its hereditary (ATTRv) or wild-type (ATTRwt) forms.[1]

Atrial arrhythmias and thromboembolic events are recognized complications of ATTR-CM and could be the first manifestation of the disease.[2–4] Atrial fibrillation (AF) is the most frequent arrhythmia detected in ATTR-CM and it is particularly common in ATTRwt, where the reported prevalence ranges from 43% to 67%.[5–7] Although AF appears less frequently in ATTRv, it is still a significant complication and could have great impact in these patients.[8]

Although data on the prevalence and incidence of thromboembolic events in ATTR-CM are scarce, concerns have emerged about the high incidence of intracardiac thrombus found in patients with ATTR-CM.[2,9,10] Moreover, atrial thrombi have also been identified in a substantial number of patients in normal sinus rhythm, complicating how to identify ATTR-CM patients who could benefit from the initiation of anticoagulation therapy.[9–11]

Furthermore, considering that the performance of the CHA_2DS_2-VASc score in predicting embolic events in ATTR-CM patients with and without AF is unknown and that ATTR-CM patients are frequently a fragile population at higher bleeding risk, the risk–benefit balance of initiating anticoagulation in ATTR-CM is particularly difficult to establish.

© 2022 The Authors. *European Journal of Heart Failure* published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.

18790844, 2022, 8, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2566 by University College London UCL Library Services, Wiley Online Library on [01/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

With new effective specific therapies to treat ATTR-CM already available in the clinic and others on the horizon, improvement of how to predict and prevent thromboembolic events in ATTR-CM patients constitutes an urgent unmet medical need.

In this study, we sought to describe the incidence and prevalence of thromboembolic events in a large international cohort of patients with ATTR-CM and determine which factors are associated with this complication. We also examined the performance of the CHA_2DS_2-VASc score in predicting thromboembolism in ATTR-CM patients with and without AF not receiving anticoagulation and evaluated the incidence of embolic events in patients with AF according to the type of anticoagulation therapy.

Methods

This study conforms to the principles of the Helsinki Declaration and all authors guarantee the integrity of data from their respective institutions. The study was approved by the ethics committee of Hospital Universitario Puerta de Hierro Majadahonda.

Cohort composition

This is a multicentre, longitudinal cohort study comprising ATTR-CM patients from four international referral amyloid centres: Alma Mater University of Bologna (Bologna, Italy), Columbia University Irving Medical Center (New York, NY, USA), National Amyloid Center (London, UK) and Hospital Universitario Puerta de Hierro Majadahonda (Madrid, Spain).

Each centre provided the data from a cohort of adult ATTR-CM patients (ATTRv or ATTRwt) with at least two evaluations at their institution. ATTR-CM was diagnosed by any of the following: (1) evidence of TTR amyloid deposits on endomyocardial biopsy; (2) evidence of TTR amyloid deposits on an extracardiac biopsy and at least one of the following: (i) increased left ventricular wall thickness (≥12 mm) by echocardiography, not explained by disturbances in loading conditions (i.e. hypertension, aortic stenosis); (ii) cardiac magnetic resonance (CMR) findings consistent with cardiac amyloidosis (i.e. diffuse subendocardial or transmural late gadolinium enhancement with abnormal gadolinium kinetics); (iii) cardiac uptake grade 2 or 3 on planar/single photon emission computed tomography 3,3-diphosphono-1,2-propanodicarboxylate/pyrophosphate/hydroxymethylene (SPECT DPD/PYP/HMDP) bone scintigraphy; (3) cardiac uptake grade 2 or 3 on planar/SPECT DPD/PYP/HMDP scintigraphy and no evidence of monoclonal protein in the presence of findings suggestive of amyloid on echocardiogram or CMR.[12–14]

In all cases, genetic testing confirmed the absence or presence of mutations in the *TTR* gene.

Data collection

Patients' databases from the four participating centres were checked for a list of pre-specified 100 variables. Centres were allowed to collect missing variables from available hospital records but only individuals with ≥80% of variables completed, with at least two evaluations at participating centres, and who had complete information about the presence of AF and embolic events at initial evaluation and during follow-up were included. Therefore, 858 individuals were excluded from the analysis. Patients excluded exhibited similar characteristics than those included, except for a higher number of females (19.5% vs. 12.9%, $p < 0.001$), ATTRv (52.8% vs. 16.8%; $p < 0.001$), African-Americans (75.8% vs. 24.2%; $p < 0.001$) and lower left ventricular ejection fraction (48%, interquartile range [IQR] 39–55 vs. 52%, IQR: 42–60; $p < 0.001$). Characteristics of individuals excluded versus those included can be found in online supplementary *Appendix S1*.

Age, type and date of ATTR-CM diagnosis and symptoms leading to diagnosis were collected. Previous history of embolism (defined as stroke, transient ischaemic attack [TIA] or peripheral embolism), heart failure, major bleeding, hypertension, vascular disease (peripheral, coronary, or aortic disease) and AF were also obtained. Baseline data also included renal function by creatinine clearance calculated by the Modification of Diet in Renal Disease-4 formula, cardiac biomarkers, presence of conduction abnormalities on the electrocardiogram (ECG) and echocardiographic parameters at first evaluation. The presence of intracardiac thrombi was not specifically evaluated.

Follow-up started at the time of first evaluation at each participating centre. AF appearance and thromboembolic events (stroke, TIA, or peripheral embolism) during follow-up were registered. Significant bleeding events under oral anticoagulation (OAC) were also collected. Significant bleeding was defined as any bleeding requiring hospitalization and/or causing a decrease in haemoglobin level of 0.2 g/L and/or requiring blood transfusion.

At participating centres, screening for AF is performed by ECG every time the patient comes to clinic or is admitted to hospital and by opportunistic screening with Holter ECG. Embolic events and major bleeding events were collected from medical records and medical records were completed when the patient attended regular visits. Information on patient's status at last follow-up was obtained from medical records. Overall and cardiovascular mortality was defined as mortality due to any cause or due to cardiac complications.

Statistical analysis

Normality was assessed using Shapiro–Wilk test. Variables that did not have a normal distribution were reported with median and IQR. Categorical data were reported as frequencies and percentages. Survival was evaluated from baseline evaluation with Kaplan–Meier curves and hazard ratios (HR) were estimated by Cox proportional hazards regression. Univariate Cox proportional hazards models were created to identify factors associated with embolic events during follow-up. Multivariable Cox proportional hazards modelling with variables that were statistically significant at the 0.1 α-level was subsequently performed to identify independent factors associated with embolic events during follow-up. Variables were excluded from multivariable analyses when the information was absent in ≥50% of individuals. Patients with AF who initiated or discontinued anticoagulation during follow-up were included in each group during the periods they were on/off anticoagulation accordingly. Similarly, patients who switched from one type of anticoagulant to another were included in the vitamin K antagonist (VKA) or the direct oral anticoagulant (DOAC) group during the periods they were on each medication. All tests were 2-tailed and a *p*-value of <0.05 was considered to be statistically significant in multivariable analysis. Statistical analysis was performed using STATA 14 (Stata Corp., College Station, TX, USA).

Results

The study cohort comprised 1191 individuals with ATTR-CM: 87.1% men, median age 77.1 years (IQR 71.4–82), 201 (16.9%) ATTRv and 990 (83.1%) ATTRwt. The diagnosis of ATTR-CM was established by biopsy in 477 (40%) patients (endomyocardial biopsy in 324 and extracardiac biopsy in 153) and using non-invasive

© 2022 The Authors. *European Journal of Heart Failure* published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.

18790844, 2022, 8, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2566 by University College London UCL Library Services, Wiley Online Library on [01/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1 Characteristics of the 1191 amyloid transthyretin cardiomyopathy patients included in the study

Clinical characteristics	
Male sex	1038 (87.2)
Race	
Caucasian	1069 (89.8)
African-American	102 (8.6)
Asian)	8 (0.7)
Other	12 (0.9)
Age at diagnosis, years	77.1 (71.5–82)
ATTR subtype	
ATTRv	201 (16.9)
ATTRwt	990 (83.1)
Type of ATTR diagnosis	
Histological confirmation	477 (40)
Non-invasive diagnosis	714 (60)
Hypertension	540 (45.4) (n = 1190)
Diabetes	180 (15.2) (n = 1186)
Body mass index, kg/m^2	26 (24–28.4) (n = 1160)
Peripheral vascular disease	216 (18.2) (n = 1184)
Liver disease/abnormal LFTs	7 (0.6) (n = 1158)
NYHA class	(n = 1049)
I	160 (15.3)
≥II	889 (84.7)
Prior embolism	162 (13.6)
AF at baseline	625 (52.5)
Oral anticoagulation	584 (49)
CHA_2DS_2-VASc score at baseline	(n = 1141)
0–1	157 (13.8)
2	270 (23.7)
3	291 (25.5)
4	236 (20.7)
≥5	187 (16.4)
Previous history of major bleeding	48 (4.1) (n = 1186)
Excessive alcohol intake	29 (2.5) (n = 1179)
Blood test results	
NT-proBNP, pg/ml	2523 (1221.9–4640) (n = 963)
eGFR, ml/min/1.73 m^2	64.2 (50.4–78.5) (n = 1126)
Electrocardiographic characteristics	
PR interval, ms	194 (168–226) (n = 384)
QRS interval, ms	108 (92–134) (n = 620)
Echocardiographic characteristics	
Interventricular septum wall thickness, mm	17 (15–19) (n = 1083)
Posterior wall thickness, mm	16 (14–18) (n = 1076)
E/A ratio	1.4 (0.9–2.5) (n = 197)
LA diameter, mm	46 (42–50) (n = 563)
Mitral regurgitation ≥2	399 (65.6) (n = 608)
Tricuspid regurgitation ≥2	359 (59.6) (n = 602)
Estimated systolic pulmonary artery pressure, mmHg	40 (35–50) (n = 246)
LVEF, %	52 (42–60) (n = 1096)

Data are shown as n (%), or median (interquartile range).
AF, atrial fibrillation; ATTR, transthyretin amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; eGFR, estimated glomerular filtration rate; LA, left atrial; LFT, liver function test; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

criteria in 714 (60%) patients. Baseline characteristics of the study cohort are shown in *Table 1* and online supplementary *Appendix S1*. A total of 625 (52.5%) patients had history of AF, 556 (88.7%) were receiving OAC and 162 (13.6%) had already had an embolic event at initial evaluation at participating centres.

During a median follow-up of 19.9 months (IQR 9.9–35.5), 41 (3.44%) patients had embolic events. Among them, 24 (57.1%) had AF at initial evaluation, 10 (26%) developed AF during follow-up (four before the embolic event, in two AF was diagnosed at the time of embolism and four several months after the embolic event), and 7 (16.7%) did not have AF at initial evaluation nor during follow-up (*Figure 1*). Total prevalence of embolic events in our cohort combining embolic events before initial evaluation and during follow-up was 16.2%.

Table 2 shows univariate and multivariate Cox regression analysis of factors associated with embolic events during follow-up. On multivariate analysis, the only factors associated with embolic events in the entire cohort including ATTR-CM patients with and without AF were age (HR 1.07; 95% confidence interval [CI] 1.02–1.12, $p = 0.002$), African-American race (HR 5.41; 95% CI 2.75–10.64, $p < 0.001$) and peripheral vascular disease (HR 2.48; 95% CI 1.3–4.75, $p < 0.006$). Interestingly, embolic events during follow-up were not associated with mortality (HR 0.88; 95% CI 0.55–1.42, $p = 0.61$).

Embolic events in patients without atrial fibrillation

In our cohort, 566 patients did not show history of AF at initial evaluation but 173 of them (30.6%) developed AF during follow-up. Seventeen of the 566 ATTR-CM patients who did not have AF at initial evaluation had an embolic event during follow-up. Four individuals had been diagnosed with AF before the embolic event. Interestingly, 26 patients without AF (4.6%) were receiving OAC (2 had a mechanical valve, 9 had previous embolic events, and in 15 anticoagulation was started under their doctor criteria) and none of them suffered an embolic event during follow-up. Thirteen of the 540 ATTR-CM patients (2.4%) who did not have history of AF and were not receiving anticoagulation had an embolic event during follow-up (six stroke, four TIA and four peripheral embolism, one patient had both a TIA and a stroke). The incidence rate of embolic events in ATTR-CM patients without AF not receiving anticoagulation was 1.3 embolic events per 100 patient-years (95% CI 0.8–2.3).

Application of the CHA_2DS_2-VASc score to the group of patients without AF at baseline not receiving OAC resulted in a deficient prediction of embolic events, as embolic events occurred similarly across all CHA_2DS_2-VASc scores (*Figure 2*). Three patients with a baseline CHA_2DS_2-VASc score 0–1 suffered embolic events during follow-up. These patients were Caucasian males aged 71, 72 and 67 years, did not show AF and did not have any additional CHA_2DS_2-VASc score factors except for age >65 years. Furthermore, they did not have significant valve disease and did not have chronic kidney or liver disease.

Embolic events in patients with atrial fibrillation

Overall, 625 patients had history of AF at initial evaluation. Of them, 558 (89.3%) received OAC without interruptions during follow-up, 40 (6.4%) received OAC during part of follow-up, and 27 (4.3%) did not receive OAC at any time during follow-up. Among the 598 (95.7%) individuals who had OAC at some point during

© 2022 The Authors. *European Journal of Heart Failure* published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.

18790844, 2022, 8, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2566 by University College London UCL Library Services, Wiley Online Library on [01/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

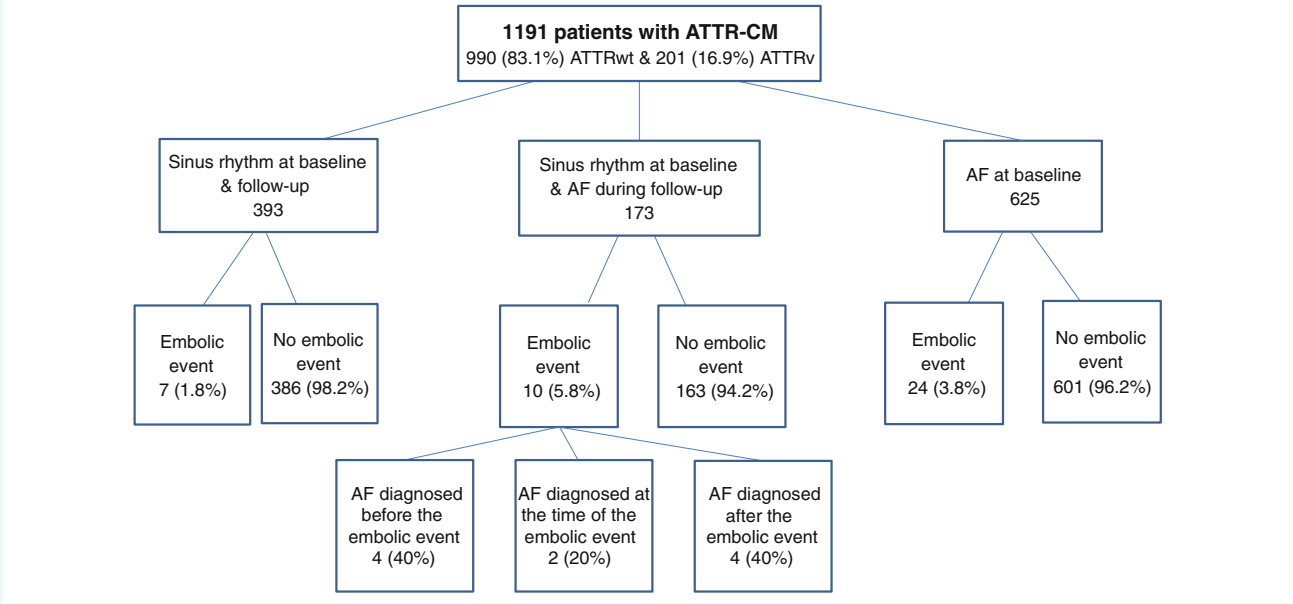


Figure 1 Atrial fibrillation (AF) and embolic events. Flowchart diagram showing the distribution of patients in our cohort according of the presence of AF and embolic events. ATTR-CM, amyloid transthyretin cardiomyopathy; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis.

follow-up, 19 (3.2%) had embolic events (ten stroke, seven TIA, two peripheral embolism) during a median follow-up under OAC of 16.3 months (IQR 8.04–33.8). Among the 67 (10.7%) who were not anticoagulated during follow-up, five had embolisms (three stroke and three TIA) during a median follow-up time without OAC of 17.1 months (IQR 5.7–24.4).

When comparing the incidence rate of embolic events in patients with AF receiving OAC to that of patients with AF without OAC, non-anticoagulated patients exhibited more embolic events than anticoagulated patients (4.8 embolic events per 100 patients-year [95% CI 2–11.6] vs. 1.7 embolic events per 100 patients-year [95% CI 1.1–2.6]).

Factors associated with embolic events in ATTR-CM patients with AF during the time they were not anticoagulated at Cox univariate analysis were: female sex, diabetes and previous hospital admission due to heart failure (online supplementary *Appendix S1*). Multivariate analysis was not performed due to the low number of embolic events.

When the CHA_2DS_2-VASc score was applied to predict embolic events in ATTR-CM patients with AF, only those who had a score ≥3 exhibited embolisms (*Figure 3*). Moreover, in the small subgroup of ATTR-CM patients with AF not receiving OAC, only those who had a score ≥4 exhibited embolisms (*Figure 2*).

Type of oral anticoagulation and embolic events

A total of 598 patients with history of AF received OAC. VKAs were prescribed in 322 subjects and DOACs in 239. Type of OAC was not available in 67 patients and 29 received both types of OAC during follow-up (not simultaneously). A total of 531 subjects with AF received either VKA (n = 322, 57.5%) or DOAC (n = 239, 42.5%) during a median follow-up of 19.1 months (IQR 9.9–36.7) vs. 11.9 months (IQR 6.3–21.1) for VKA and DOAC, respectively. Baseline characteristics are described in *Table 3*. Clinical characteristics did not differ between both groups except for a higher rate of previous heart failure hospitalizations, higher N-terminal pro-B-type natriuretic peptide level and worse estimated glomerular filtration rate among patients receiving VKA.

Incidence rate of embolic events with VKA and DOAC were 2 (95% CI 1.2–3.4) and 1.6 (95% CI 0.7–3.9), respectively. Nineteen patients suffered embolisms under OAC, 13 with VKAs (4%), 5 with DOACs (2.1%) and one with unknown type of OAC. There was no difference in the incidence of embolism between patients with AF treated with VKAs and those treated with DOACs during follow-up (p = 0.66) (*Figure 4*).

In patients with baseline AF treated with VKAs in whom information about control of the international normalized ratio (INR) was available (n = 235), 44 (18.7%) had labile INR or therapeutic time in range (TTR) <60% during follow-up. Six of them (13.6%) suffered embolic events during follow-up, compared to 5 (2.6%) in the group with good INR control (HR 7.14, 95% CI 2.2–23.5; p = 0.001).

Information about anticoagulation and major bleeding events was available in 273 patients with AF receiving VKA and in 216 receiving DOAC. A total of 32 patients suffered major bleeding events during a median follow-up of 14.2 months (IQR 6.7–30.8) while taking OAC, 18 with VKA and 14 under DOAC treatment. Gastrointestinal bleeding accounted for 46.9% of bleeding events and 12.5% corresponded to intracranial bleedings. Twenty-four patients (75%) were admitted to the hospital and

© 2022 The Authors. *European Journal of Heart Failure* published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.

18790844, 2022, 8, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2566 by University College London UCL Library Services, Wiley Online Library on [01/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 2 Clinical, analytical and echocardiographic characteristics of amyloid transthyretin cardiomyopathy patients with and without embolic events during follow-up

	No embolic event (n = 1150)	Embolic event (n = 41)	Univariate Cox HR (95% CI)	Multivariate Cox HR (95% CI)
Clinical characteristics				
Age, years	77 (71.4–82) (n = 1150)	79.6 (74.7–84) (n = 41)	**1.07 (1.02–1.1) p = 0.003**	**1.07 (1.03–1.12) p = 0.002**
Female sex	143 (12.4) (n = 143)	10 (24.4) (n = 41)	**2.24 (1.1–4.6) p = 0.027**	
African-American	90 (7.8) (n = 1150)	12 (29.3)	**5.1 (2.6–10) p < 0.001**	**5.4 (2.7–10.6) p < 0.001**
ATTR subtype	(n = 1150)	(n = 41)	0.7 (0.3–1.4) p = 0.313	
ATTRv	191 (16.6)	10 (24.4)		
ATTRwt	959 (83.4)	31 (75.6)		
Val142Ile variant	68 (5.9) (n = 1150)	8 (19.5) (n = 41)	4.9 (2.3–10.7) p < 0.001	
Hypertension	514 (44.7) (n = 1149)	26 (63.4) (n = 41)	**2.4 (1.3–4.5) p = 0.007**	
Diabetes	171 (14.9) (n = 1145)	9 (22) (n = 41)	1.7 (0.8–3.6) p = 0.15	
Body mass index, kg/m^2	26 (24–28.4) (n = 1122)	26.8 (25.4–28.3) (n = 38)	1 (0.9–1.1) p = 0.56	
Peripheral vascular disease	202 (17.7) (n = 1143)	14 (34.2) (n = 41)	**2.7 (1.4–5.2) p = 0.002**	**2.48 (1.3–4.8) p = 0.006**
Prior HF admission	408 (36.8) (n = 1109)	20 (48.8) (n = 41)	**1.95 (1.1–3.6) p = 0.033**	
NYHA class	(n = 1010)	(n = 39)	1.47 (0.6–3.6) p = 0.397	
I	154 (15.3)	6 (15.4)		
≥II	856 (84.7)	33 (84.6)		
Prior embolism	152 (13.2) (n = 1150)	10 (24.4) (n = 41)	**2.16 (1.1–4.4) p = 0.035**	
AF at baseline	601 (52.3) (n = 1150)	24 (58.5) (n = 41)	1.4 (0.8–2.8) p = 0.218	
OAC at baseline	562 (48.9) (n = 1150)	22 (53.7) (n = 41)	1.44 (0.8–2.7) = 0.243	
History of major bleeding	43 (3.8) (n = 1145)	5 (12.2) (n = 41)	**3.8 (1.5–9.8) p = 0.005**	
Blood tests				
NT-proBNP, pg/ml	2540 (1221–4640) (n = 938)	2265 (1228–4001) (n = 25)	0.99 (0.99–1) p = 0.569	
eGFR, ml/min/1.73 m^2	64.3 (50.7–78.7) (n = 1090)	56.4 (45.2–71.3) (n = 36)	0.99 (0.97–1) p = 0.069	
Echocardiographic characteristics				
Interventricular septum wall thickness, mm	17 (15–19) (n = 1044)	18 (15–19) (n = 39)	1 (0.92–1.1) p = 0.741	
LA diameter, mm	46 (42–50) (n = 533)	45.5 (43–48) (n = 30)	0.99 (0.93–1.05) p = 0.71	
Mitral regurgitation ≥2	378 (65.5) (n = 577)	21 (67.7) (n = 31)	1.35 (0.63–2.9) p = 0.433	
Tricuspid regurgitation ≥2	333 (58.3) (n = 571)	26 (83.9) (n = 31)	**4.9 (1.9–13) p = 0.001***	
Estimated systolic pulmonary artery pressure, mmHg	40 (35–50) (n = 233)	35 (25–40) (n = 13)	0.97 (0.92–1.02) p = 0.217	
LVEF, %	52 (43–60) (n = 1057)	50 (33–61) (n = 39)	**0.98 (0.95–0.99) p = 0.043**	

Data are shown as median (interquartile range), or n (%).
AF, atrial fibrillation; ATTR, transthyretin amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LA, left atrial; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OAC, oral anticoagulation.
*Tricuspid regurgitation was not included in the multivariate analysis as data were not available in ≥50% of individuals.

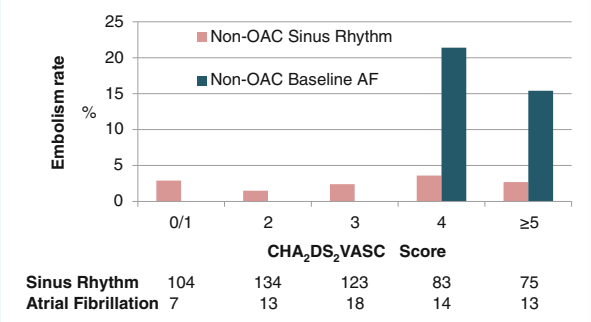


Figure 2 Prevalence of embolic events during follow-up in non-anticoagulated patients with atrial fibrillation (AF) and non-anticoagulated patients in sinus rhythm according to the CHA_2DS_2-VASc score. OAC, oral anticoagulation.

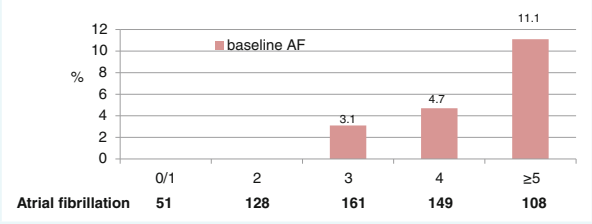


Figure 3 Prevalence of embolic events during follow-up in patients with atrial fibrillation (AF) according to the CHA_2DS_2-VASc score.

in three cases (9.8%) the bleeding episode (one gastrointestinal, one intracranial, one muscular) was related to the cause of death. Incidence rate of bleeding events in patients with OAC was 3.8 (95% CI 2.7–5.4) per 100 patient-years. Incidence rate of bleeding events according to the type of OAC was 3.2 per 100 patient-years (95% CI 2–5) in patients receiving VKAs and 5.1 per 100 patient-years (95% CI 3–8.5) in those treated with DOACs despite both groups exhibited similar baseline HAS-BLED scores. Major bleeding events during follow-up with DOAC compared

© 2022 The Authors. *European Journal of Heart Failure* published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.

18790844, 2022, 8, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2566 by University College London UCL Library Services, Wiley Online Library on [01/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 3 Clinical characteristics of amyloid transthyretin cardiomyopathy patients with atrial fibrillation treated with vitamin K antagonists and direct oral anticoagulants

	VKA (n = 322)	DOAC (n = 239)	Univariate analysis p-value
Clinical characteristics			
Age, years	77.8 (73.1–83.3) (n = 322)	77.3 (73.1–81.7) (n = 239)	0.3
Female sex, n (%)	35 (10.9) (n = 322)	23 (9.6) (n = 239)	0.63
African-American	15 (4.7) (n = 322)	12 (5) (n = 239)	0.84
ATTR subtype	(n = 322)	(n = 239)	0.87
ATTRv	27 (8.4)	21 (8.8)	
ATTRwt	295 (91.6)	218 (91.2)	
Hypertension, n (%)	151 (46.9) (n = 322)	105 (43.9) (n = 239)	0.47
Diabetes	47 (14.7) (n = 320)	37 (15.6) (n = 238)	0.78
Body mass index, kg/m^2	25.8 (23.9–28.1) (n = 313)	26.2 (24.3–28.5) (n = 239)	0.17
Peripheral vascular disease	63 (19.6) (n = 321)	44 (18.5) (n = 232)	0.74
Prior HF admission	160 (51.3) (n = 312)	87 (37.7) (n = 231)	**0.002**
NYHA class	(n = 293)	(n = 213)	0.86
I	23 (7.9)	17 (8)	
≥II	268 (92.1)	192 (92)	
Prior embolism	53 (16.5) (n = 322)	38 (15.9) (n = 239)	0.86
History of major bleeding	9 (2.8) (n = 320)	10 (4.2) (n = 239)	0.37
HAS-BLED	2 (1–2) (n = 204)	2 (1–2) (n = 103)	0.14
Blood tests			
NT-proBNP, pg/ml	3925 (2300–6809) (n = 255)	2869 (1704–4836) (n = 202)	**<0.001**
eGFR, ml/min/1.73 m^2	56.8 (45.4–70.3) (n = 306)	63.2 (51.7–75.8) (n = 228)	**<0.001**
Echocardiographic characteristics			
Interventricular septum wall thickness, mm	17 (15–19) (n = 302)	17 (15–19) (n = 219)	0.65
LA diameter, mm	48 (44–51) (n = 169)	47 (42–52) (n = 106)	0.4
Mitral regurgitation ≥2	137 (75.7) (n = 181)	80 (65.6) (n = 122)	0.06
Tricuspid regurgitation ≥2	126 (70.4) (n = 179)	76 (62.8) (n = 121)	0.17
Estimated systolic pulmonary artery pressure, mmHg	40 (30–45) (n = 105)	40 (35–50) (n = 54)	0.23
LVEF, %	48.7 ± 13.6 (n = 303)	47.7 ± 12.3 (n = 226)	0.2

Data are shown as median (interquartile range), mean ± standard deviation, or n (%).
AF, atrial fibrillation; ATTR, transthyretin amyloidosis; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; HF, heart failure; LA, left atrial; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OAC, oral anticoagulation; VKA, vitamin K antagonist.

with VKA did not significantly differ (HR 1.92, 95% CI 0.94–3.96; p = 0.074).

Discussion

This international multicentre study describes the prevalence, incidence and predictors of embolic events in patients with ATTR-CM. To our knowledge, this is by far the largest study to date to examine embolic events in ATTR-CM. Major findings of our study are that embolic events are common in patients with ATTR-CM (16.2% prevalence) with an overall incidence rate of 1.64 embolic events per 100 patient-years (95% CI 1.2–2.2). Both patients with and without AF suffered embolic events with incidence rates increasing across the clinical spectrum from patients in sinus rhythm not receiving OAC to patients with AF with OAC and patients with AF not anticoagulated (1.3, 1.7 and 4.8 embolic events per 100 patient-years, respectively). Additionally, this study shows that the CHA_2DS_2-VASc score had limited value to predict embolic events in ATTR-CM with and without AF and that VKAs and DOACs seem equally effective in preventing embolism in this particular setting (Graphical abstract).

Studies describing the prevalence and incidence of embolic events in ATTR-CM are scarce and mostly performed in small and single-centre cohorts.[4,10,15,16] Moreover, they rarely include only ATTR-CM patients and usually combine both ATTR-CM and amyloid light-chain cardiomyopathy (AL-CM) patients.[4,10,15] Our study provides more precise data by including only ATTR-CM patients, avoiding the possible confounding factor of combining data from two different diseases with potentially different thrombogenic risks. This difference is relevant as previous studies examining the presence of intracardiac thrombus by transoesophageal echocardiography or more recently using CMR have shown a higher rate of intracardiac thrombi in AL-CM than in ATTR-CM.[9,10] Our results provide a solid ground to design strategies and interventions to reduce embolic events in ATTR-CM and would be very useful to design prospective clinical trials in this field, particularly now that

© 2022 The Authors. *European Journal of Heart Failure* published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.

18790844, 2022, 8, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2566 by University College London UCL Library Services, Wiley Online Library on [01/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

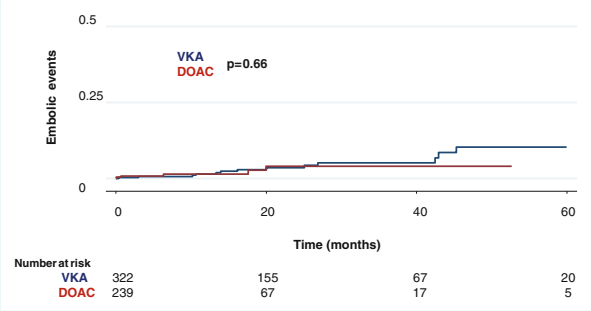


Figure 4 Embolic events during follow-up in amyloid transthyretin cardiomyopathy patients with atrial fibrillation according to the type of oral anticoagulation (vitamin K antagonist [VKA] vs. direct oral anticoagulant [DOAC]) (hazard ratio 0.79, 95% confidence interval 0.3–2.3, $p = 0.66$).

specific disease-modifying therapies have become available and will expand patient survival.[17]

Intracardiac thrombi are a recognized complication of cardiac amyloidosis previously described by several groups.[2,4,9,10] Most of these groups found an association with the presence of history of AF.[10,15] Our study confirms the high thromboembolic risk of AF in ATTR-CM. The systemic embolism rate among non-anticoagulated patients with AF found in our study (4.8 embolic events per 100 patient-years) was higher to that found in other heart conditions with recognized high thromboembolic risk like hypertrophic cardiomyopathy were an incidence of 3.75 embolic events per 100 patient-years has been reported in a meta-analysis combining data of 10 studies.[18]

Moreover, the incidence rate found in non-anticoagulated patients with AF is similar to that described in patients with non-valvular AF without OAC therapy and a CHA_2DS_2-VASc score of 3 (3.9% in 1 year) and the incidence in ATTR-CM patients without AF and not receiving OAC was almost as high as that of patients with non-valvular AF with a CHA_2DS_2-VASc score of 1 (1.6% in 1 year).[19]

Exploratory analyses performed provide evidence for a reduction of embolic events with OAC therapy in ATTR-CM. Unfortunately, OAC therapy in patients with AF did not protect completely from embolic events in our study in line with a recent Italian study of 406 AL and ATTR patients.[4] However, the incidence rate of embolisms in patients with AF without OAC almost doubled that of patients with AF receiving OAC and none of the small group ($n = 26$) of patients without AF who were under OAC therapy in our study had embolic events during follow-up.

We did not find significant differences in the rate of embolisms according to the type of OAC. However, patients with labile INR or TTR <60% suffered a remarkable higher rate of embolism underlining the importance of an appropriate anticoagulation control in this vulnerable and fragile population.

In our study, the CHA_2DS_2-VASc score showed limited ability to identify patients at risk of embolic complications and failed to correctly identify patients without AF who had embolic events during follow-up in line with recent reports of intracardiac thrombus prevalence at transoesophageal echocardiography prior to electrical cardioversion/AF ablation.[20] Therefore, based on our findings, the CHA_2DS_2-VASc score should not be used to assess embolic risk and to decide anticoagulation in ATTR-CM.

Our findings contrast with the abovementioned Italian study by Cappelli *et al.*[4] in which a CHA_2DS_2-VASc score ≥3 was associated with embolic events in patients without AF. Possible explanations for this difference might be related to the heterogeneous type of cardiac amyloidosis included in the Italian study or to the different embolic risk profile of patients evaluated in both studies as 33.9% of their cohort had AF at initial evaluation and only 3.4% have had previous embolic events (52.5% and 13.6% in our cohort, respectively). More work is needed in this area to identify ATTR-CM patients without AF who are at higher risk of embolic events and who could benefit from close atrial thrombus/AF screening or early treatment with OAC. In this regard, identification of atrial dysfunction by strain echocardiography that has been found to be present in cardiac amyloidosis irrespectively of atrial cavity size, diastolic dysfunction and electrical atrial activity should be explored.[21–23] Unfortunately, atrial strain echocardiography data were not available in our cohort.

The persistence of atrial thrombus despite appropriate OAC has been described in cardiac amyloidosis.[10] If an intra-cardiac thrombus is detected, appropriate anticoagulation therapy must be pursued, and if this is still insufficient, other strategies like switching OAC, achieving a higher INR threshold or adding antiplatelet therapy, seem reasonable despite these strategies may exacerbate the haemorrhagic tendency that is known in amyloid patients due to fragile blood vessel walls secondary to amyloid deposition and coexisting coagulopathy. In our cohort, the incidence rate of major bleeding during follow-up was high and clinical consequences were severe in some patients. In patients with baseline AF, incidence rates of major bleeding in those receiving OAC, VKA and DOAC were 3.8, 3.2 and 5.1 per 100 patient-years, respectively. Surprisingly, these rates are similar to that of embolic events in ATTR-CM patients with AF and without OAC (4.8 per 100 patient-years) highlighting the complex conundrum of assessing the risk–benefit balance in these patients. Our study supports the use of either VKAs or DOACs to prevent thromboembolism in ATTR-CM with similar embolic rates with both types of OAC in line with two smaller studies recently published.[24,25] Interestingly, in one of these studies patients receiving VKA showed more bleeding events[25] whereas in our study we did not find significant differences regarding major bleeding rates in both groups and, in fact, the group of patients receiving DOAC showed a non-significant higher rate of major bleeding.

Limitations

Significant limitations to this investigation are worth noting. Due to the retrospective nature of the study, several patients from the participating centres had to be excluded due to missing information or limited visits. Patients excluded were more frequently African-Americans and affected by ATTRv limiting generalization of our findings to other cohorts with other characteristics. However, this is by far the largest cohort of patients ensembled to investigate

© 2022 The Authors. *European Journal of Heart Failure* published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.

18790844, 2022, 8, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2566 by University College London UCL Library Services, Wiley Online Library on [01/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

embolic events in ATTR-CM and comes from three European countries and the US reflecting, in our opinion, real-world data in this complex scenario. Also, there was not a uniform protocol to detect AF onset and rhythm assessment was clinically decided as per local practice. Although the AF screening performed at participating centres reflects the most frequent approach in clinical practice, a systematic use of implantable loop recorders or wearable devices would probably have lead to higher AF detection. Moreover, decision to initiate/stop/switch OAC and type of OAC prescribed in each patient was decided at each centre based on perceived embolic/bleeding risk and patient preferences influencing allocation to treatment groups and outcomes. Furthermore, information on the type of DOAC and the time that INR was on target were not always available and could have affected our results. Lastly, participating centres are highly specialized amyloidosis centres and referral and survival bias cannot be excluded.

Conclusions

This study shows that embolic events are a frequent complication in ATTR-CM affecting up to 16% of patients. It also provides embolic and bleeding rates in ATTR-CM according to the presence of AF and treatment with OAC. This information would be highly useful for the design of future trials in the field. Exploratory analyses show evidence of a reduction of systemic embolism with OAC therapy with similar embolic rates observed with VKAs and DOACs. The CHA_2DS_2-VASc score does not appear to correlate well with clinical outcome in patients with ATTR-CM and should not be used to assess thromboembolic risk in this population.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Funding

This study has been funded by Instituto de Salud Carlos III (ISCIII) through the projects "PI18/0765 & PI20/01379" (Co-funded by European Regional Development Fund/European Social Fund "A way to make Europe"/"Investing in your future"). The CNIC is supported by the ISCIII, MCIN, the Pro-CNIC Foundation, and the Severo Ochoa Centers of Excellence program (CEX2020-001041-S).

Conflict of interest: E.G.L. reports speaking fees from Pfizer and Alnylam; consulting fees from Pfizer and Proclara; research/educational support to his institution from Pfizer, Bridgebioand Alnylam. C.R. reports grant support from Pfizer and speaker fees from Pfizer, Akcea, and Alnylam. M.S.M. reports grant support from NIH R01HL139671, R21AG058348 and K24AG036778; has had consulting income from Pfizer, Eidos, Prothena, Akcea, GSK, Intellia, Regeneron and Alnylam, and his institution received clinical trial funding from Pfizer, Prothena, Eidos and Alnylam. P.G.P. reports speaking fees from Pfizer, Bridgebio, and Alnylam; consulting fees from Pfizer, Bridgebio, Attralus, Novonordisk, Neuroinmmune, Alnylam, and AstraZeneca; research/educational support to his institution from Pfizer, Bridgebioand Alnylam. All other authors have nothing to disclose.

References

1. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2021;**42**:1554–68.
2. Feng DL, Edwards WD, Oh JK, Chandrasekaran K, Grogan M, Martinez MW, et al. Intracardiac thrombosis and embolism in patients with cardiac amyloidosis. *Circulation*. 2007;**116**:2420–6.
3. González-López E, Gagliardi C, Dominguez F, Quarta CC, de Haro-Del Moral FJ, Milandri A, et al. Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. *Eur Heart J*. 2017;**38**:1895–904.
4. Cappelli F, Tini G, Russo D, Emdin M, Del Franco A, Vergaro G, et al. Arterial thrombo-embolic events in cardiac amyloidosis: a look beyond atrial fibrillation. *Amyloid*. 2021;**28**:12–8.
5. López-Sainz Á, Hernandez-Hernandez A, Gonzalez-Lopez E, Domínguez F, Restrepo-Cordoba MA, Cobo-Marcos M, et al. Clinical profile and outcome of cardiac amyloidosis in a Spanish referral center. *Rev Esp Cardiol*. 2021;**74**:149–58.
6. Connors LH, Sam F, Skinner M, Salinaro F, Sun F, Ruberg FL, et al. Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: a prospective, observational cohort study. *Circulation*. 2016;**133**:282–90.
7. Giancaterino S, Urey MA, Darden D, Hsu JC. Management of arrhythmias in cardiac amyloidosis. *JACC Clin Electrophysiol*. 2020;**6**:351–61.
8. Donnellan E, Wazni OM, Hanna M, Elshazly MB, Puri R, Saliba W, et al. Atrial fibrillation in transthyretin cardiac amyloidosis: predictors, prevalence, and efficacy of rhythm control strategies. *JACC Clin Electrophysiol*. 2020;**6**:1118–27.
9. Feng DL, Syed IS, Martinez M, Oh JK, Jaffe AS, Grogan M, et al. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. *Circulation*. 2009;**119**:2490–7.
10. Martinez-Naharro A, Gonzalez-Lopez E, Corovic A, Mirelis JG, Baksi AJ, Moon JC, et al. High prevalence of intracardiac thrombi in cardiac amyloidosis. *J Am Coll Cardiol*. 2019;**73**:1733–4.
11. Dubrey S, Pollak A, Skinner M, Falk RH. Atrial thrombi occurring during sinus rhythm in cardiac amyloidosis: evidence for atrial electromechanical dissociation. *Heart*. 1996;**75**:426.
12. Perugini E, Guidalotti PL, Salvi F, Cooke RMT, Pettinato C, Riva L, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. *J Am Coll Cardiol*. 2005;**46**:1076–84.
13. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation*. 2016;**133**:2404–12.
14. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 2 of 2 – Diagnostic criteria and appropriate utilization. *J Nucl Cardiol*. 2020;**27**:659–73.
15. El-Am EA, Grogan M, Ahmad A, Patlolla SH, Klarich KW, AbouEzzeddine OF, et al. Persistence of left atrial appendage thrombus in patients with cardiac amyloidosis. *J Am Coll Cardiol*. 2021;**77**:342–3.
16. Selvaraj S, Claggett B, Minamisawa M, Windham BG, Chen LY, Inciardi RM, et al. Atrial fibrillation and ischemic stroke with the amyloidogenic V122I transthyretin variant among Black Americans. *J Am Coll Cardiol*. 2021;**78**:89–91.
17. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al.; ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;**379**:1007–16.
18. Guttmann OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. *Heart*. 2014;**100**:465–72.
19. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest*. 2010;**137**:263–72.
20. Donnellan E, Elshazly MB, Vakamudi S, Wazni OM, Cohen JA, Kanj M, et al. No association between CHADS-VASc score and left atrial appendage thrombus in patients with transthyretin amyloidosis. *JACC Clin Electrophysiol*. 2019;**5**:1473–4.

© 2022 The Authors. *European Journal of Heart Failure* published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.

18790844, 2022, 8, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2566 by University College London UCL Library Services, Wiley Online Library on [01/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

21. Bandera F, Martone R, Chacko L, Ganesananthan S, Gilbertson JA, Ponticos M, et al. Clinical importance of left atrial infiltration in cardiac transthyretin amyloidosis. *JACC Cardiovasc Imaging*. 2022;**15**:17–29.
22. Nochioka K, Quarta CC, Claggett B, Querejeta Roca G, Rapezzi C, Falk RH, et al. Left atrial structure and function in cardiac amyloidosis. *Eur Heart J Cardiovasc Imaging*. 2017;**18**:1128–37.
23. Minamisawa M, Inciardi RM, Claggett B, Cuddy SAM, Quarta CC, Shah AM, et al. Left atrial structure and function of the amyloidogenic V122I transthyretin variant in elderly African Americans. *Eur J Heart Fail*. 2021;**23**:1290–5.
24. Mitrani LR, De Los Santos J, Driggin E, Kogan R, Helmke S, Goldsmith J, et al. Anticoagulation with warfarin compared to novel oral anticoagulants for atrial fibrillation in adults with transthyretin cardiac amyloidosis: comparison of thromboembolic events and major bleeding. *Amyloid*. 2021; **28**:30–4.
25. Cariou E, Sanchis K, Rguez K, Blanchard V, Cazalbou S, Fournier P, et al. New oral anticoagulants vs. vitamin K antagonists among patients with cardiac amyloidosis: prognostic impact. *Front Cardiovasc Med*. 2021;**8**:742428.

© 2022 The Authors. *European Journal of Heart Failure* published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.

18790844, 2022, 8, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2566 by University College London UCL Library Services, Wiley Online Library on [01/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License