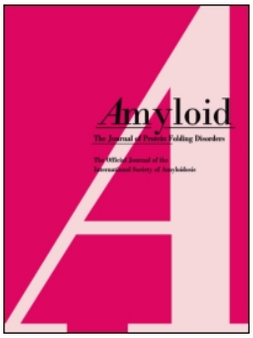

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ARTICLE

Arterial thrombo-embolic events in cardiac amyloidosis: a look beyond atrial fibrillation

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ABSTRACT

Background: Intracardiac thrombosis is reported to occur frequently in cardiac amyloidosis (CA). However, data regarding arterial thrombo-embolic events (AEs) in CA are limited. We aimed at assessing prevalence, clinical characteristics and predictors of AEs in a large multicentric CA cohort.

Methods and results: Four-hundred-six consecutive CA patients (134 AL, 73 ATTRm and 199 ATTRwt) from 5 Italian referral centres were retrospectively evaluated and followed-up for a median time of 19 months. Thirty-one patients (7.6%) suffered from an AE, of whom 10 (32.2%) were in sinus rhythm and had no history of AF. There were no significant differences in terms of age, gender and type of CA between patients with or without AEs. Fourteen (7.6%) of 185 patients on anticoagulation had an AE despite therapy. Anticoagulation therapy did not appear to fully protect from the risk of events (HR 1.23, 95%CI 0.52–2.92, $p = .64$). The only predictor of AEs, in particular among CA patients in sinus rhythm, was a CHA2DS2-VASC score ≥ 3 (HR 2.84, 95%CI 1.02–7.92, $p = .05$ in overall population; HR 10.13, 95%CI 1.12–91.19, $p = .04$ in patients in sinus rhythm).

Conclusions: In our large, multicentric, real-world cohort, prevalence and incidence rate of AEs was high. A consistent proportion of events occurred despite anticoagulation therapy or in patients in sinus rhythm. A higher CHA2DS2-VASc score might identify patients at risk of AEs also among those in sinus rhythm.

Abbreviations: AEs: arterial thrombo-embolic events; AF: atrial fibrillation; AL: light chain amyloidosis; CA: cardiac amyloidosis; CKD: chronic kidney disease; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; TIA: transient ischaemic attackTTR: transthyretin

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Cardiac amyloidosis; atrial fibrillation; arterial thrombo-embolic events; stroke; anticoagulation

Introduction

Systemic amyloidosis represents a group of heterogeneous diseases characterised by the extracellular deposition of insoluble protein fibrils composed of beta-pleated sheets in diverse organs, included the heart. Nearly all cases of cardiac amyloidosis (CA) result from immunoglobulin light-chain amyloidosis (AL) or transthyretin (TTR) amyloidosis, categorised as mutant (ATTRm) or wild-type (ATTRwt) depending on the genetic sequence of the TTR protein [1]. Cardiac involvement dictates clinical course of systemic amyloidosis and is mainly characterised by heart failure. However, amyloid infiltration causes a wide extent of myocardial derangement which may result in several other cardiac manifestations [2,3]. Autoptic [4] and *in vivo* studies [5–7] have reported a considerable prevalence of intracardiac thrombi in CA, even in patients with sinus rhythm or in atrial fibrillation (AF) patients adequately on anticoagulation. Despite these findings, data regarding arterial thrombo-embolic events (AEs) in CA are lacking, limited to monocentric and small studies [4,8–10].

In our study, we investigated the occurrence of AEs in CA and AL, ATTRm and ATTRwt disease subgroups. We also aimed at describing features of CA patients with AEs, and at identifying predictors of them.

Methods

Study population

Four-hundred and six CA patients from 5 Italian referral centres (Tuscan Regional Amyloid referral centre, AOU

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Supplemental data for this article can be accessed here.

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Careggi, Florence, $n = 192$; Azienda Universitario Ospedaliera Sant'Andrea, Rome $n = 95$; Fondazione G. Monasterio, CNR Pisa $n = 75$; University Hospital G. Martino, Messina $n = 24$; IRCCS Ospedale Policlinico San Martino, Genova $n = 20$) were retrospectively evaluated from 2004 to 2019. All patients were managed in accordance with the Declaration of Helsinki and signed an informed consent for the processing of personal data for scientific research purposes. Demographic data, baseline neurological and cardiological assessment, and follow-up events were collected in a centralised anonymized database.

Cardiac amyloidosis assessment

Diagnosis of AL amyloidosis was confirmed by biopsy of abdominal fat pad or of an involved organ with amyloid deposits characterised as AL type by immunohistochemistry, optic/immunoelectron microscopy, or proteomics. Cardiac involvement in AL amyloidosis was established according to current guidelines [11]. Diagnosis of TTR-related CA was made when diastolic interventricular septum thickness was >12 mm on echocardiography without other causes of left ventricular hypertrophy, in the presence of documented TTR amyloid deposits in at least one involved organ or according to non-invasive algorithms [12,13].

Cardiological assessment included New York Heart Association (NYHA) classification and CHA_2DS_2-VASc score calculation. This score ranges from 0 to 9 points and includes the following clinical characteristics: congestive heart failure or left ventricular dysfunction (1 point), hypertension (1 point), age ≥75 years (2 points), diabetes (1 point), stroke/TIA (2 points), vascular disease (1 point), age 65–74 years (1 point), and sex category (female; 1 point). The sum of all factors provides the individual patient's thromboembolic risk [14]. Electrocardiography and echocardiography evaluations were performed in all individuals.

As per each Institution practice, patients underwent routine 24-h Holter ECG monitoring every 6 to 12 months as part of the cardiological follow-up.

Arterial thrombo-embolic events

Ischaemic stroke was defined as neurologic impairment due to vascular ischaemia, including episodes lasting 24 h or less, which were regarded as transient ischaemic attacks (TIAs) [15]. Patients with cerebral or subarachnoid haemorrhage, as well as those with neurologic dysfunction due to non-vascular causes (i.e. brain tumor) were excluded from the present analysis. Moreover, given the retrospective nature of the study, and the well-acknowledged conundrum of determining the aetiology of ischaemic stroke subtypes, no attempt was made to distinguish cardioembolic stroke from other ischaemic subtypes [16]. Even if an adjudication of ischaemic stroke cases was not performed at the time of analysis, the clinical records of all patients reported a neurological evaluation from the time of the event, which adjudicated all events as embolic with sufficient probability. Peripheral embolizations (i.e. to non-central nervous system sites) were also considered and confirmed by Doppler vascular ultrasound and/or angiography. For the purpose of this study, ischaemic strokes, TIAs and peripheral events were considered together as AEs.

Statistical analysis

Data are presented as the mean ± SD or as frequencies. Student *t*-test was used to compare groups with normally distributed continuous variables, and the χ^2 or Fisher exact test (when an expected value was <5) was used to compare nominally scaled variables. Mann–Whitney *U*-test was used to compare ordinal variables. A *p*-value less than or equal to .05 was considered as statistically significant.

Incidence rates of AEs were calculated by dividing the number of new events by the total number or person-years accumulated during follow-up in the study population.

The role of demographic, clinical, morphological and biomarker baseline features as determinants of AEs was tested by univariate Cox regression analysis. Patients who experienced an AE at first evaluation were excluded from this analysis. AE-free curves were estimated using the Kaplan–Meier method, and differences between curves were assessed by log-rank tests. Statistical analysis was performed using SPSS statistical software version 25 (SPSS Inc., Chicago, IL).

Results

Four-hundred and six patients (79.6% males, mean age at diagnosis: 72.6 ± 11.0 years) were included in the present analysis. Overall CA population was composed of 134 AL, 73 ATTRm (most common mutations: 21 Ile68Leu, 28.8%; 16 Glu89Gln, 21.9%;13 Val122Ile, 17.8% and 8 Phe64Leu, 11.0%) and 199 ATTRwt amyloidosis. Main characteristics of overall population and by CA subgroup are summarised in Supplementary Table 1s.

Prevalence and incidence rate of arterial thrombo-embolic events

Thirty-one out of 406 patients (7.6%) suffered from an AE: there were 29 cerebrovascular events (8 TIAs and 21 ischaemic strokes) and 2 peripheral events (1 mesenteric and 1 femoral embolism). Of the 31 patients with AEs, 9 were AL (9/134: 6.7%), 6 ATTRm (6/73: 8.2%) and 16 ATTRwt amyloidosis (16/199: 8.0%). Ten patients experienced the AE as the first presentation of CA, while the remaining 21 experienced the event over a median follow-up of 19 months (*range*: 4–187), with an incidence rate of 2.2 per 100 patients/year (95%CI 1.4–3.3). Six patients (6/31: 19%) had a recurrent AE.

Clinical and morphological characteristics of patients with arterial thrombo-embolic events and comparison among cardiac amyloidosis subgroups

Characteristics of patients with and without AEs are reported in Table 1. There were no significant differences

Table 1. Characteristics of cardiac amyloidosis patients with versus without arterial thrombo-embolic events.

	No AEs $n = 375$	AEs at first presentation $n = 10$	AEs during follow up $n = 21$	p^a
Age at diagnosis	72.5 ± 11.2	74 ± 5.0	73.7 ± 8.9	.80
Age ≥75 years	217 (57.9)	5 (50.0)	13 (61.9)	.84
Males	298 (79.5)	7 (70.0)	18 (85.7)	.83
Type of CA				.71
AL	125 (33.3)	3 (30.0)	6 (28.0)	
ATTRm	67 (17.9)	2 (20.0)	4 (19.0)	
ATTRwt	183 (48.8)	5 (50.0)	11 (52.4)	
Previous arterial thrombo-embolic event	13 (3.5)	0 (0)	1 (4.8)	.79
BMI	24.9 ± 3.9	23.0 ± 2.0	25.1 ± 3.0	.30
NYHA functional class III–IV at first evaluation	116 (30.9)	2 (20.0)	6 (28.6)	.46
Any atrial fibrillation at first evaluation	125 (33.3)	7 (70.0)	6 (28.6)	.05
LV ejection fraction (%)	53.5 ± 9.0	49.0 ± 8.0	50.7 ± 12.2	.19
≤50%	146 (38.9)	5 (50.0)	11 (52.4)	.39
IVS (mm)	16.7 ± 3.5	15.8 ± 3.0	17.0 ± 3.0	.66
Left atrial dimension (mm)	45.1 ± 6.4	47.0 ± 6.0	46.9 ± 4.7	.42
Restrictive pattern	138 (36.8)	4 (40.0)	8 (38.1)	.47
BNP (ng/ml)	475 (176–1100)	335 (245–335)	395 (236–522)	.32
NT-proBNP (ng/ml)	3125 (1271–6607)	4527 (2633–9049)	2483 (684–3892)	.23
Troponin I (ng/ml)	0.07 (0.04–0.15)	0.08 (0.02–0.17)	0.07 (0.03–0.08)	.33
CKD	170 (45.3)	6 (60.0)	13 (61.9)	.13
CHA_2DS_2-VASc score				<.0001
0	8 (2.0)	0 (0)	0 (0)	
1–2	131 (34.9)	0 (0)	5 (23.8)	
≥3	236 (62.8)	10 (100.0)	16 (76.2)	
NYHA functional class III–IV at follow-up[b]	192 (51.2)	4 (40.0)	14 (66.7)	.29
Any atrial fibrillation at follow-up[b]	178 (47.7)	7 (70.0)	14 (66.7)	.03
LV ejection fraction ≤50% at follow-up[b]	164 (43.7)	7 (70.0)	15 (71.4)	.03
Anticoagulation therapy[b,c]	171 (45.6)	2 (20.0)	12 (57.1)	.17
Death	111 (29.6)	2 (20.0)	8 (38.1)	.94

AE: arterial thrombo-embolic event; CA: cardiac amyloidosis; LV: left ventricular; IVS: interventricular septum; CKD: chronic kidney disease.
[a]Comparing patients without AEs versus all patients with AEs.
[b]At the time of the AE or at last evaluation.
[c]Data available for 360 patients.

in terms of age, gender and type of CA among patients with or without events. CHA_2DS_2-VASc score ($p < .0001$) was higher in patients with AEs. Moreover, presence of any (either paroxysmal or chronic) AF ($p = .03$) and LV ejection fraction ≤50% at follow-up ($p = .03$) were more frequent in patients with AEs, as compared to those without.

In the AL subgroup, patients with AEs were more frequently females ($p = .03$), showed higher CHA_2DS_2-VASc score (CHA_2DS_2-VASc ≥3 in 77.8% vs. 42.4%, $p = .01$), and had more frequently the presence of any AF (66.7% vs. 24.4%, $p = .01$) and LV ejection fraction ≤50% at follow-up (77.8% vs. 37.6%, $p = .04$), as compared to AL patients without events (Supplementary Table 2s).

In the ATTRm subgroup, patients with AEs showed lower LV ejection fraction at first evaluation (42.0 ± 11.0% vs. 54.0 ± 11.0%, $p = .02$), had more commonly chronic kidney disease (66.7% vs. 22.4%, $p = .04$) and presence of any AF (83.3% vs. 35.8%, $p = .03$) (Supplementary Tables 3s).

All patients with AEs in the ATTRwt subgroup had a CHA_2DS_2-VASc score ≥3 (100% vs. 83.6% in patients without events, $p = .004$). No other significant differences were found between ATTRwt patients with and without events (Supplementary Tables 4s).

When comparing patients with AEs among CA subgroups, those with AL amyloidosis were generally female, while subjects with ATTRwt amyloidosis were older and with higher CHA_2DS_2-VASc score (Figure 1).

Impact of atrial fibrillation and anticoagulation on arterial thrombo-embolic events

Data regarding the occurrence of AF were available for 404 patients; the remaining 2 patients with missing information did not have AEs. One hundred ninety-nine patients had at least one episode of any AF, of whom 138 already at first evaluation. Twenty-one AF patients (10.6%) had an AE. The incidence rate of AEs in patients with AF was 3.2 per 100 patients/year (95% CI 1.9–5.3). There were no significant differences between AF patients with and without AEs, except for anticoagulation therapy which was less common in AF patients with AEs (66.7% vs. 90.5%, $p = .006$). In patients with AEs not on anticoagulation ($n = 7$), AF was detected together with or after the event (5 as the first presentation of CA, and 2 during the clinical course).

Out of 205 patients in sinus rhythm, 10 (4.9%) experienced an AE. The incidence rate of AEs in patients in sinus rhythm was 1.3 per 100 patients/year (95% CI 0.7–2.8). Patients in sinus rhythm with AEs had a significantly higher CHA_2DS_2-VASc score (CHA_2DS_2-VASc ≥3 in 50.7% vs. 90.0%, $p = .02$). No other significant differences were found between patients in sinus rhythm with and without AEs.

One hundred eighty-five patients were on anticoagulation, and 14 (7.6%) of them had an AE despite therapy. All these 14 patients were on anticoagulation due to known AF. Half of them were taking vitamin K antagonists ($n = 7$), while the others were taking direct oral anticoagulants

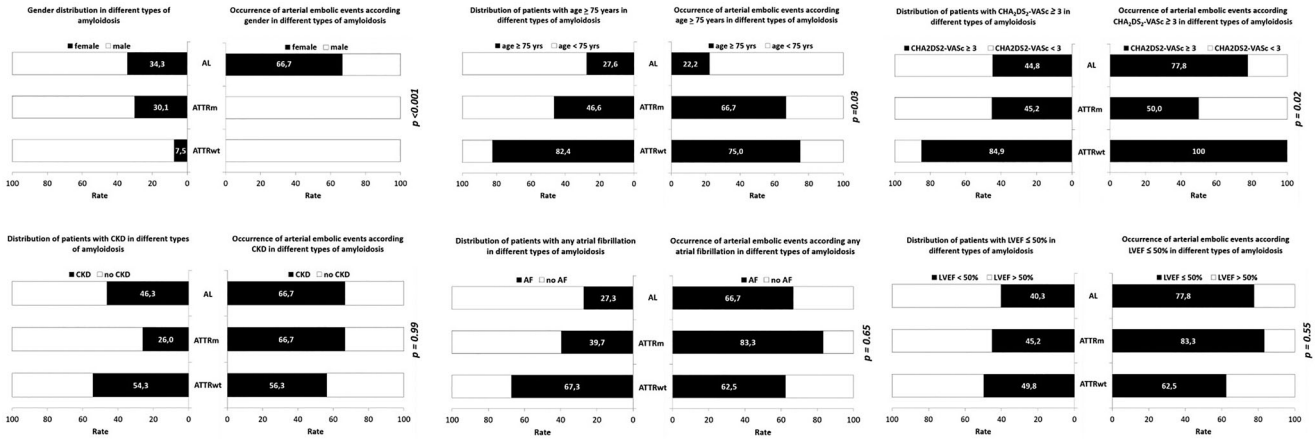

Figure 1. Comparison of patients with arterial thrombo-embolic events among cardiac amyloidosis subgroups. Distribution of gender, older age and CHA_2DS_2-VASc score in patients with AEs was significantly different among CA subgroups: AL patients with events were more frequently females (upper panel, left), while ATTRwt patients with events had frequently ≥75 years of age (upper panel, centre) and CHA_2DS_2-VASc score ≥3 (upper panel, right). On the contrary, distribution of CKD (lower panel, left), presence of any (paroxysmal or chronic) AF (lower panel, centre) and LVEF ≤50% (lower panel, right) in patients with AEs did not differ among CA subgroups. AEs: arterial thrombo-embolic events; CA: cardiac amyloidosis; AL: light-chain amyloidosis; ATTRwt: wild-type transthyretin amyloidosis; CKD: chronic kidney disease; AF: atrial fibrillation; LVEF: left ventricular ejection fraction

Table 2. Relationship between clinical, morphologic and functional features at initial evaluation and occurrence of arterial thrombo-embolic events in patients with cardiac amyloidosis.

	Univariate		
	Hazard ratio	95% CI	*p*
Female sex	0.53	0.16–1.82	.31
Transthyretin cardiac amyloidosis	0.50	0.13 – 1.92	.31
Age ≥75 years	1.34	0.55–3.24	.52
Chronic kidney disease	1.94	0.77–4.87	.16
Atrial fibrillation at first evaluation	1.65	0.80–3.39	.17
CHA_2DS_2-VASc score ≥3	2.84	1.02–7.92	.05
Left ventricular ejection fraction ≤50% at first evaluation	1.95	0.83–4.60	.13
Anticoagulation therapy	1.23	0.52–2.92	.64

($n = 5$) and (weight-adjusted) low molecular weight heparin ($n = 2$). Finally, 5 of the six patients with a recurrent AE were on anticoagulation (3 were taking vitamin K antagonists and 2 direct oral anticoagulants). In all patients taking vitamin K antagonists, INR was in range at the time of the event. Anticoagulation therapy did not appear to fully protect from the risk of AEs (HR 1.23, 95%CI 0.52–2.92, $p = .64$).

Predictors of arterial thrombo-embolic events

At univariate Cox regression analysis, CHA_2DS_2-VASc score ≥3 (HR 2.84, 95%CI 1.02–7.92, $p = .05$) was the only significant predictor of AEs (Table 2). This finding was particularly pronounced among patients in sinus rhythm (HR 10.13, 95%CI 1.12–91.19, $p = .04$), but it was not significant among those in AF (HR 1.73, 95%CI 0.58–5.20, $p = .33$, Supplementary Tables 5s). Kaplan–Maier estimates of the risk of events according to CHA_2DS_2-VASc score (<3 vs. ≥3) are shown in Figure 2. AEs were not associated with death (HR 1.11, 95%CI 0.58–2.12, $p = .76$).

Discussion

This multicentric observational study provides an estimate of prevalence and incidence of AEs in a large cohort of consecutive patients with CA from different aetiologies. Our results show that AEs in CA are not limited to patients in AF and that anticoagulation therapy does not appear to fully protect from this serious complication. We found that the CHA_2DS_2-VASc score may represent a possible tool to identify patients at higher risk of AEs.

Studies addressing the epidemiology of AEs in CA are scarce and mostly limited to monocentric and small observations, mainly in the AL subgroup. In our study, about 8% of CA patients had an AE, with an incidence rate of 2.2 per 100 patients/year, and in 10 patients the AE was the trigger that led to CA diagnosis. We confirmed that the occurrence of AEs in CA is substantial, as previously reported [8], and we observed no significant difference in AEs prevalence among the etiologic subgroups. In our cohort, the incidence rate of AEs appeared slightly higher than that of stroke among patients with heart failure [14,17], suggesting that in CA, other different, specific mechanisms could be involved in the pathogenesis of arterial thromboembolism. However, we found no peculiar features related to the occurrence of AEs in the overall CA population and in the disease subgroups. In our study, patients who experienced AEs frequently presented at least one episode of AF, either paroxysmal or permanent, in their clinical course or had lower LV ejection fraction. Moreover, patients with AEs, mainly in AL and ATTRwt subgroups, had higher

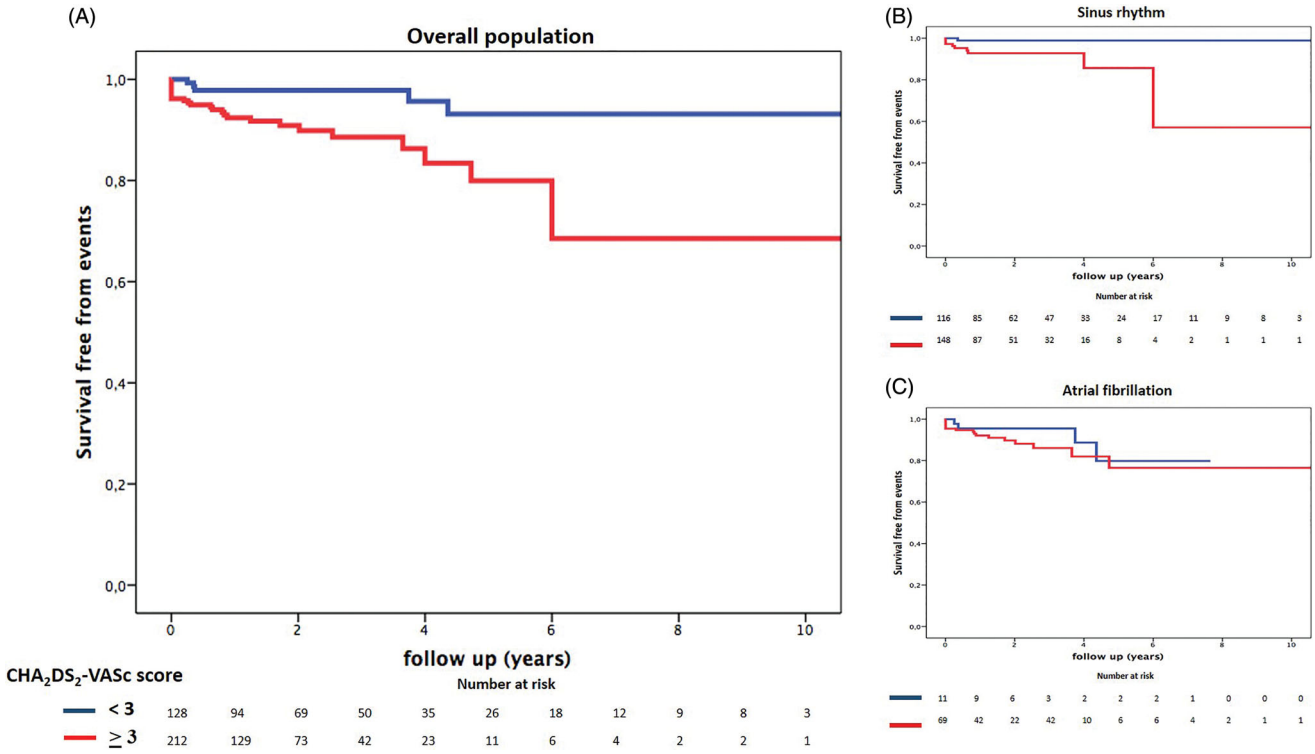

Figure 2. Kaplan–Maier estimates of the risk of events according to CHA_2DS_2-VASc score (<3 vs. ≥3). In the overall study population (A), in patients in sinus rhythm (B) and in patients in atrial fibrillation (C).

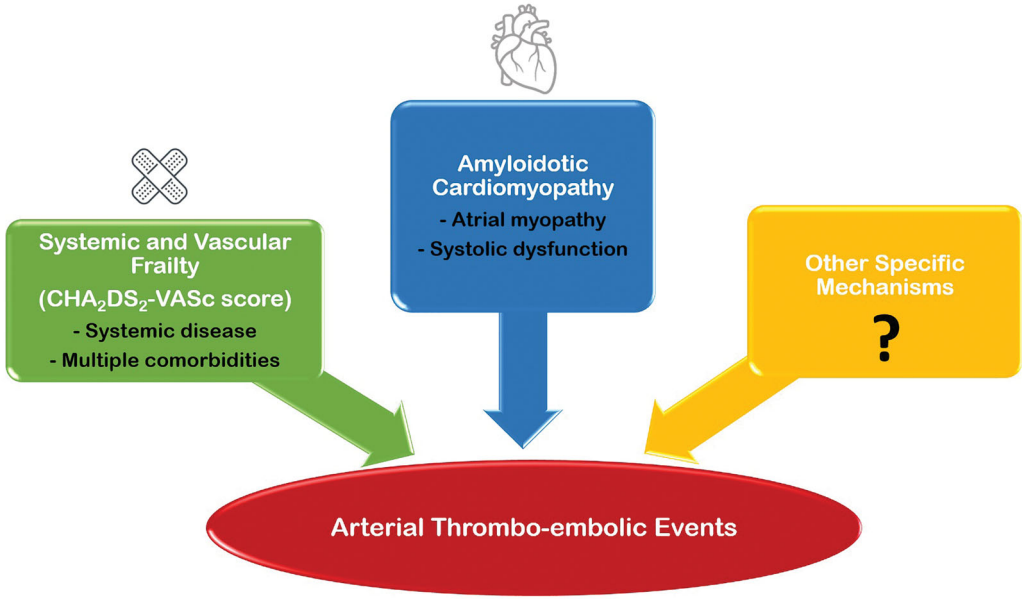

Figure 3. Pathogenic mechanism of arterial thrombo-embolic events in cardiac amyloidosis. Intracardiac thrombi formation and arterial thrombo-embolic events occurrence in cardiac amyloidosis result from a complex interplay, only partially understood, involving systemic and vascular frailty, as represented by higher CHA_2DS_2-VASc scores; advanced amyloidotic cardiomyopathy, with both atrial and ventricular dysfunction; and other, unknown mechanisms, likely specific of the amyloidotic disease.

CHA_2DS_2-VASc scores than those without events. These findings show that, in the first instance, patients at increased thromboembolic risk are frailer, with an advanced amyloidotic cardiomyopathy and a higher burden of cardiovascular comorbidities.

Notably, even if AF was more frequent in CA patients with AEs, almost one-third of events occurred in patients in sinus rhythm and without any evidence of arrhythmia. Moreover, nearly half of AEs were found in patients on adequate anticoagulation. Previous studies demonstrated an increased prevalence of intracardiac thrombi in patients with CA despite the absence of AF or atrial flutter [4,6]. Moreover, in a recent series of CA patients receiving transoesophageal echocardiography before a scheduled direct cardioversion, 46% of those with intracardiac thrombi either had therapeutic levels of anticoagulation for more than

3 weeks or had arrhythmia onset 48 h before the planned cardioversion [7].

A fundamental contribution to intracardiac thrombi formation in CA may be represented by atrial myopathy. Atrial myocardial dysfunction, demonstrated by strain echocardiography, was found to be present in CA irrespectively of atrial cavity size, diastolic dysfunction and electrical atrial activity [18,19]. Therefore, atrial myopathy may explain the detection of thrombi and events in patients in sinus rhythm, or despite adequate anticoagulation. Furthermore, atrial cavity size and severe diastolic dysfunction were not associated with thrombi formation in previous studies [4] neither with events in our analysis. Mechanisms by which atrial myopathy induces thrombo-embolism may not completely overlap with those involved in AF, and thus may not be adequately hampered by anticoagulation therapy [20]. In Figure 3 is proposed a schematic diagram depicting the pathogenetic mechanisms of AEs in CA, resulting from a complex interplay between frailty and myocardial amyloidotic involvement.

Interestingly, atrial myopathy has been recognised as a possible contributor in the pathogenesis of cryptogenic stroke [20,21]. In fact, as up to 90% of cases of cryptogenic strokes are deemed embolic, and defined 'embolic strokes of undetermined source', cardio-embolic aetiologies may play an important role in its pathogenesis [22,23]. In about 15% of cryptogenic stroke cases, prolonged cardiac rhythm monitoring unveils AF episodes [23]. This also happened in our cohort: in 2 patients, AF was detected only >1 year after the event. Nevertheless, embolic strokes of undetermined source may occur in the absence of (detected) AF. Historically, indexes of atrial dysfunction have been linked to the risk of stroke [24,25]. As such, atrial myopathy may represent a substrate for thrombo-embolism even in the absence or before the occurrence of AF [20]. In a wider, provoking perspective, it has been postulated that AF may not be the primary cause of thrombo-embolism, rather a marker of atrial myopathy, which is itself, ultimately, the underlying determinant of thrombo-embolism [26,27].

However, it should be reminded that CA patients display an increased risk of atherosclerotic events, given the older age, the male preponderance and the frequent cardiovascular comorbidities. Thus, even if AEs in our cohort were adjudicated as embolic at index time, carotid or other atherosclerotic sources may also play a role in AEs pathogenesis in CA.

Our study underlines the open question about the management of anticoagulation therapy in CA. Anticoagulation confers a protection towards AEs, though not optimal: in our study, among CA patients on anticoagulation, those experiencing AEs represented a minority (7.6%). Unquestionably, in AF, anticoagulation must be started as soon as possible, at the first recognition of arrhythmia. In this regard, a stricter screening with ECG Holter monitoring may be advised to early identify (silent) AF. Among patients in sinus rhythm, we found that the only predictor of AEs was CHA_2DS_2-VASc score $\geq$3. As reported in other cardiac diseases, even if not specifically developed for non-AF settings, the CHA_2DS_2-VASc score may reliably identify the risk of stroke beyond the presence of AF [28,29], likely representing a proxy of vascular frailty. Although the benefit from anticoagulation in the specific setting of CA patients without AF remains to be clarified, the potential usefulness of this score in driving the decision of searching for atrial thrombi at transoesophageal echocardiography or at cardiac magnetic resonance might be considered and warrants further investigations.

Our findings depict a complex scenario for clinical and therapeutic management of CA patients, and represent a call for action to better understand the pathophysiology and the management of AEs in this condition.

Limitations

Due to the retrospective nature of this observational study, data regarding anticoagulation therapy were not available in 46 patients, all without events. The information was available for all patients with events. Patients with missing data on anticoagulation were excluded from the presented analyses. However, we also performed separate analyses, in which: (i) patients with missing data were assigned as not on anticoagulation, (ii) patients with missing data were assigned as on anticoagulation. In both cases, results were not appreciably different. In 2 patients, both without events, data regarding the occurrence of AF was missing. Information in regard to haematologic therapies received by AL patients were not complete for all subjects, and therefore were not included in our analysis.

Furthermore, both BNP and NT-proBNP were assessed, depending on centre practice, this possibly leading to a non-uniformity of biomarker data results. INR values at the time of AEs were available for all patients taking vitamin K antagonists, but information regarding time in therapy range during treatment and before the AE were not available.

Finally, it should be again underlined that despite a sufficient probability of the embolic aetiology of AEs in our cohort, given the retrospective nature of the study a neurologic adjudication was not performed at the time of analysis, but only at index time. CA patients display an increased risk of atherosclerotic events, and carotid or other atherosclerotic sources may play a role in AEs occurrence. Further, prospective analyses should take into account this consideration and perform thorough neurologic event adjudication.

Conclusions

This is the first study systematically investigating the occurrence of AEs in CA. In our large, multicentric, real-world cohort, prevalence and incidence rate of AEs were high. A significant proportion of events occurred despite anticoagulation therapy or in patients in sinus rhythm. The only predictor of AEs, in particular among CA patients in sinus rhythm, was a CHA_2DS_2-VASc score $\geq$3. The pathogenesis of AEs in CA remains an important gap in knowledge.

Further, larger studies are warranted to better define the prediction and prevention of AEs in CA.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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