Thromboembolism and bleeding in systemic amyloidosis: a review

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Abstract

The assessment of both thromboembolic and haemorrhagic risks and their management in systemic amyloidosis have been poorly emphasized so far. This narrative review summarizes main evidence from literature with clinical perspective. The rate of thromboembolic events is as high as 5–10% amyloidosis patients, at least in patients with cardiac involvement, with deleterious impact on prognosis. The most known pro-thrombotic factors are heart failure, atrial fibrillation, and atrial myopathy. Atrial fibrillation could occur in 20% to 75% of systemic amyloidosis patients. Cardiac thrombi are frequently observed in patients, particularly in immunoglobulin light chains (AL) amyloidosis, up to 30%, and it is advised to look for them systematically before cardioversion. In AL amyloidosis, nephrotic syndrome and the use of immunomodulatory drugs also favour thrombosis. On the other hand, the bleeding risk increases because of frequent amyloid digestive involvement as well as factor X deficiency, renal failure, and increased risk of dysautonomia-related fall.

Keywords Amyloidosis; Thromboembolism; Bleeding; Anticoagulative therapy

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Introduction

Systemic amyloidosis is due to amyloid fibril deposits that involve numerous organs. More than 30 proteins are currently considered to be ‘amyloidogenic’, but the two most common forms of amyloidosis are variant (vATTR) or wild-type transthyretin (wtATTR) and immunoglobulin light-chain (AL).1,2 The incidence of AL amyloidosis is about 12 cases per million persons per year.3 TTR amyloidosis is more frequent (prevalence: 13% of heart failure with preserved ejection fraction (HFpEF)).4 5% of all hypertrophic cardiomyopathies).5 Amyloidosis can involve numerous organs, such as kidney, nerves, heart, digestive tract, liver, bone or joints, each of these leading to specific complications. Among amyloidosis-related complications are thrombotic and bleeding events6,11 whose prediction and management is particularly challenging. So far, there is no specific guideline about the use of antithrombotic treatment in amyloidosis.

The objectives of this narrative review are (i) to specify current epidemiological data on thrombotic and bleeding risks, (ii) to analyse main determinants and predictors of these two risks, and (iii) to review current evidence about antithrombotic treatment in amyloidosis.

Frequency and severity of thromboembolic events in amyloidosis

For 20 years, thrombotic events (TEs) have been described in amyloidosis and more particularly in patients with cardiac amyloidosis (CA).7,8,9,10,11 Indeed, cardiac involvement is particularly frequent (60–70%). TTR CA is estimated to be as high as 13% of patients with HFpEF.4 Cappelli et al.12 published the largest cohort including 406 patients with CA (134 AL, 73 vATTR, and 199 wtATTR) with a median follow-up of
19 months. The incidence of arterial TE was 7.6% (Table 1). Most events (29 out of 31) were cerebrovascular events (21 ischaemic strokes and 8 transient ischaemic attacks). TEs were the first disease manifestations in 10 patients. Eleven per cent of patients with CA and atrial fibrillation (AF) had a TE. The incidence rate of TE in patients with CA and AF was 3.2 per 100 patients per year. The only predictor of TE in Cox analysis was CHADS2-VAsc score ≥3 [hazard ratio 2.84, 95% confidence interval (CI) 1.02–7.92, \( P = 0.05 \)] especially in patients with sinus rhythm. The rate of events in sinus rhythm without history of AF was 32% (10 events).

Other types of TE occur in amyloidosis and appear always associated with poor prognosis. In a Mayo Clinic’s study\(^\text{13}\) involving 40 AL amyloidosis patients with TE, the authors reported that (i) 29 patients had deep vein thrombosis (73%) and 11 had arterial thrombosis (28%); (ii) embolic event preceded the diagnosis of amyloidosis in 11 patients (28%); (iii) TE were associated with a poor prognosis with death occurring in 8 patients 1 month after the event and 18 deaths in the year following the TE.

**Stroke as the first manifestation of cardiac amyloidosis**

A retrospective Mayo Clinic study\(^\text{14}\) carried out in 40 patients with systemic amyloidosis (37 AL and 3 ATTR) and stroke revealed that ischaemic stroke was the initial manifestation in 13 patients (33%). The median survival of patients in whom stroke was the first manifestation was 7 months. Stroke occurred 9.6 months before the diagnosis of amyloidosis. In most cases, the stroke was hemispherical (73%) and in a single vascular territory (68%). Amyloidosis, and particularly CA should therefore be considered in stroke patients, especially in the presence of features suggestive of transthoracic echocardiography (TTE) (left ventricular hypertrophy, dilated left atrium, restrictive filling pattern, pericardial effusion, aortic stenosis,\(^\text{15}\) and elevated cardiac biomarkers).\(^\text{16}\)

**Evidence for cardioembolic cause of thromboembolic events and mechanisms**

If recurrent cerebral embolism was described in amyloidosis patients even in the absence of AF or symptomatic heart failure, it is admitted that most are cardioembolic events. Feng et al.\(^\text{6}\) published a large study involving 116 autopsies of patients who had biopsy-proven CA (55 AL, 55 wtTTR, 4 AA-serum amyloid A protein and 2 vTTR). The prevalence of intracardiac thrombi in patients with CA was 33%. Patients with AL type CA were younger and had fewer supraventricular arrhythmias but had more frequent intracardiac thrombi than those with other types of CA (51% vs. 16%, \( P < 0.001 \)). AF and AL subtype were associated with a very high risk of thromboembolism (odds ratio 55; 95% CI

| Study, date | Population | Prevalence | Thromboembolic events details | Favours factors |
|------------|------------|------------|-------------------------------|-----------------|
| Capelli et al., 2020\(^\text{12}\) | N = 262, 134 AL, 73 vTTR, 199 wtTTR | 7.6% Prevalence of clinical events | 21 ischaemic stroke, 8 TIA, 2 peripheral events: 1 mesenteric and 1 femoral embolism | AF, LVEF <50%, CHADS2VASC > 2, Chronic kidney disease |
| Mitrani et al., 2020\(^\text{7}\) | N = 290 TTR | 6% Prevalence of clinical events, all had AF | 9 stroke, 8 TIA | AF |
| Donnellan et al., 2020\(^\text{12}\) | N = 382 TTR, 111 wtTTR, 271 vTTR | 16% 20% with AF vs 9% without AF | Cerebrovascular events | Increased CHADS2VASC score, No anticoagulation therapy |
| Feng et al., 2007\(^\text{6}\) | N = 116 autopsies, 55 AL, 55 wtTTR, 4 AA | 33% Intracardiac thrombi by autopsy | AL subtype | AF |
| Feng et al., 2009\(^\text{17}\) | N = 156, 80 AL, 73 TTR, 3 AA | 27% Intracardiac thrombi by ultrasound | AL subtype | Low systolic pressure, Low atrial emptying velocity, Diastolic dysfunction, Biventricular systolic dysfunction, Atrial dilation, Higher ECV, AF, AL subtype, AF |
| Martinez-Naharro et al., 2019\(^\text{18}\) | N = 324, 166 TTR, 155 AL | 6.2% Intracardiac thrombi by CMR | AL subtype | AF |
| Em Al et al., 2019\(^\text{19}\) | N = 58 | 28% Intracardiac thrombus (TEE) | AF, atrial fibrillation; AL, immunoglobulin light chain amyloidosis; CMR, cardiac magnetic resonance; TTR, transthyretin; wtTTR, wild type transthyretin; vTTR: variant transthyretin; TEE, transesophageal echocardiography; TIA: transient ischaemic attack. |
8–1134). TEs were a significant cause of death in patients with CA. Indeed, 19/23 emboli were considered to be fatal (14/53: 26% in the AL CA subgroup vs 5/59: 8% in the other types of CA, \( P < 0.001 \)). The same team studied the prevalence of intracardiac thrombi by transthoracic (TTE) and transoesophageal (TEE) echocardiography\(^\text{17}\) in all CA patients who underwent cardiac ultrasound in the Mayo Clinic database (from 1999 to 2007). One hundred sixty-five patients (80 AL, 73 ATTR, and 3 AA type) were studied; 58 thrombi were found in 42 patients (prevalence = 27%). The prevalence of intracardiac thrombi was higher in AL amyloidosis than ATTR or AA: 35% vs. 18%, \( P = 0.02 \). The prevalence of intracardiac thrombi assessed by cardiac magnetic resonance is 6.2% in a recent study of Martinez-Naharro et al. including 324 amyloidosis patients (166 TTR and 155 AL). Favouring factors of TE were biventricular systolic dysfunction, atrial dilatation, AF, higher extracellular volume, and AL subtype.\(^\text{18}\)

Comprehensive cardiac imaging should be considered in all patients with amyloidosis and TE events. Cardiac imaging could start with TTE and use of contrast agent in case of insufficient echogenicity. If there is no evidence of thrombus with this first examination, patients should be considered for TEE and/or computed tomography scan and/or cardiac magnetic resonance.

This high risk of cardiac thrombi and subsequent embolic events can be also related to supraventricular arrhythmia and also to specific involvement of atria by amyloidosis, that has been so-called atria myopathy.

**Supraventricular arrhythmia in amyloidosis**

Systemic amyloidosis increases the occurrence of AF or atrial flutter through several mechanisms: amyloid infiltration, impairment of ventricular and atrial compliance and relaxation with subsequent increase in left ventricular filling pressures resulting in LA enlargement and remodelling.

In published cohorts, the reported rate of AF varies between 20% and 75% (Table 2). Sanchis et al.\(^\text{19}\) reported AF prevalence as up to 44% in 238 patients with amyloid heart disease: 71% in wtATTR, 26% in AL and 19% in vATTR amyloidosis. Longhi et al.\(^\text{20}\) reported AF in 15% of 262 patients with CA: 40% in wtTTR, 9% in AL, and 11% in vATTR. Mitrani et al.\(^\text{21}\) reported the rate of AF as high as 74% of 290 patients with ATTR cardiomyopathy, higher in the wtATTR group than in the vTTR group (85% and 52%, respectively). In addition, Mitrani et al. reported a rate of 17 embolic events in 15 patients; all embolic events occurred in patients with AF. In a recent study including 382 patients with ATTR cardiomyopathy, Donellan et al. reported AF in 69% cases.\(^\text{22}\) Older age, male gender, history of heart failure, and advanced cardiac involvement were strongly associated with the risk of AF.\(^\text{20,22,23}\) AF was not associated with an increased mortality in most studies.

El-Am et al.\(^\text{24}\) studied AF-related thromboembolic risk through the comparison of TEE data between a cohort of 58 patients with CA and 114 patients without amyloidosis. All patients had AF, and the TEE was planned before electrical cardioversion. After TEE, the electrical cardioversion was cancelled in 16/58 (28%) CA patients vs 8/114 (7%) non-amyloid patients, \( P < 0.001 \). The main cause of cardioversion cancellation was intracardiac thrombus in 13/46 (28%) patients with CA. Among these 13 patients, 2 patients were in AF from less than 48 h, and 4 had had an INR in the therapeutic range for more than 3 weeks. This study suggests that AF in amyloid cardiomyopathy is associated with a higher risk of atrial thrombosis. The authors advised for systematic TEE before cardioversion in patients with amyloidosis. They also observed more complications from cardioversion in patients with CA: 6/42 (14%) vs. 2/106 (2%), \( P = 0.007 \) including 2 ventricular arrhythmias and 2 severe brady-arrhythmias requiring permanent pacemakers.

**Evidence of atrial amyloid myopathy**

Thirty years ago, Dubrey et al.\(^\text{25}\) reported three cases of patients with CA, sinus rhythm and atrial thrombi. These authors suggested that lack of atria mechanical function irrespective of sinus rhythm favoured intra-atrial thrombi. Indeed, they observed a very low velocity of the A wave suggesting that atrial contraction could be impaired by amyloid

| Study, date | Population | Overall prevalence | Prevalence in TTR | Prevalence in AL |
|------------|------------|--------------------|-------------------|-----------------|
| Longhi et al., 2015\(^\text{20}\) | N = 262 |
| Mints et al., 2018\(^\text{23}\) | N = 146 wtTTR |
| Sanchis et al., 2019\(^\text{19}\) | N = 238, 115 AL, 97 wtTTR, 26 hTTR |
| Martinez-Naharro et al., 2019\(^\text{18}\) | N = 324, 166 TTR, 155 AL |
| Mitrani et al., 2020\(^\text{21}\) | N = 290 TTR |
| Donellan et al., 2020\(^\text{22}\) | N = 265, 205 wt, 60 vTTR |

AL, immunoglobulin light chain amyloidosis; TTR, transthyretin; vTTR, variant transthyretin; wtTTR: wild type transthyretin.
tissue infiltration. Other evidence of left atrial dysfunction in patients with CA is reported below.

In a large pathological study, appendages were removed during cardiac surgery in 245 patients (median age 63 years old) and analysed by both Congo red staining and immuno-histochemistry: amyloid deposits were found in up to 16% of patients.26 Such atrial amyloidosis was independently associated with the occurrence of AF.

In their pathological studies, Feng et al. observed that predictors of intracardiac thrombi were severe diastolic dysfunction, low atrial emptying velocity in TEE, low systolic blood pressure, and the AL subtype.10,17 In other words, these studies suggested that the increase in thromboembolic risk was due to amyloid infiltration leading to impairment of atrial contractility and blood stasis, and the strong endothelial cytotoxicity of amyloid light-chains.

Several studies based on cardiac imaging highlighted the high rate and the role of atrial dysfunction in amyloidosis. Henein et al. showed that the LA strain rate during atrial contraction phase was the only predictor of the occurrence of AF on Holter-ECG recordings, independently of atrial size, in 46 patients with ATTR amyloidosis.29 Brand et al. showed that atrial mechanics assessed by strain were decreased in amyloidosis with a high accuracy for the diagnosis of CA in unexplained LV hypertrophy.27 Mohty et al. showed that impaired atrial function, assessed by TTE strain 3D28 and cardiac magnetic resonance imaging LA emptying function,29 worsened the prognosis of patients with AL amyloidosis. Indeed, 2 year survival was significantly reduced in patients with an LA emptying fraction <16% and that was associated with the prognostic classification of the Mayo Clinic.

However, no study has shown the predictive role of atrial dysfunction per se in the occurrence of thromboembolic events so far.

Non-cardiac factors associated with thromboembolic events in amyloidosis

Besides AF and CA, number of others causes or favouring factors can explain the high risk of TE in amyloidosis: nephrotic syndrome leading to urinary loss of natural anticoagulants factors (antithrombin, protein S) and increased synthesis of procoagulant factors (factor V, VII, fibrinogen), decreased mobility and chemotherapy. Hausfater et al.30 studied the causes of TE in a small cohort of patients with AL amyloidosis where 9 of the 15 patients had a TE: 3 strokes, 2 transient ischaemic attacks, 1 peripheral arterial embolism, 1 iliac thrombosis, 1 mesenteric ischaemia, and 1 ocular ischaemia. All patients were in sinus rhythm and only one patient had an intracardiac thrombus. The factors associated with TEs were oestrogen contraception, thalidomide, and growth factors. The authors postulated that all the elements of Virchow’s triad were implied, specifically the endothelial injury by endocardial amyloid deposits leading to parietal injury and valvular amyloid deposits, the stasis by restrictive cardiomyopathy characterized by slow diastolic filling and arrhythmias, and plasma hypercoagulability by a nephrotic syndrome, thrombocytosis related to hyposplenism, blood viscosity related to circulating monoclonal component. In the study of Haligan et al.,13 the main predictive factors of thrombosis were nephrotic syndrome, immobilization, heart failure, and tobacco use.

In AL amyloidosis, circulating levels of free light-chains and of β2-microglobulin were shown to be associated with TE risk.31 Plasma D-dimer level was also associated with a worse prognosis.32 An impairment of the thrombin–antithrombin (AT) pathway has also been evidenced in AL patients, with lower AT activity than AT antigen associated with reduced binding capacity to heparin, thus leading to a hypercoagulable state.33

The use of immunomodulatory drugs (IMIDs) also increases the risk of venous thromboembolism. Current recommendations advise the prescription of prophylactic antithrombotic treatment (vitamin K antagonist, low molecular weight heparin, or aspirin) in patients receiving IMID-based chemotherapy.34,35 An increased risk of thalidomide related TE has been shown in multiple myeloma and AL amyloidosis.36,37

Amyloidosis and bleeding risk

The most frequently reported bleedings are ecchymosis and purpura; bleedings from the gastrointestinal tract and the renal tract are also common8,9,39,40 (Table 3). Amyloid deposits can be found in digestive and mucous membranes. Perivascular amyloidosis deposits can lead to amyloid angiopathy that increases capillary fragility and impairs capillary vasomotion. Gastrointestinal bleeding is explained by amyloid deposits causing fragility of the vascular wall, muscle infiltration leading to increased vulnerability of the mucosa and/or intestinal ischaemia.42,33,43

Bleeding complications can also occur after an invasive procedure, such as biopsy. Laboratory characteristics reflect the clinical diversity in cohort studies44,45,46,47 (Table 4). Different clotting abnormalities have been described, as shown in Table 4. In a study including 337 patients with AL-amyloidosis, Mumford et al.44 reported in 51% of patients at least one abnormality in the semi-global clotting times, namely thrombin time (TT), prothrombin time (PT) or activated partial prothrombin time (aPTT), with substantial variation in the nature and magnitude of the defects. These results were confirmed in further studies.45,46,47 TT prolongation was potentially related by Mumford et al. to abnormal glycosylated fibrinogen resulting in dysfibrinogenemia combined with se-
vere hypoalbuminaemia, and subsequent abnormal fibrin polymerization, especially in patients with nephrotic syndrome, who represented 28% of patients in this cohort.44

The PT and aPTT prolongation were associated with acquired FX:C deficiency, more rarely FV deficiency. Overall, FX levels are reduced to below 20 to 50 IU/dL in a relatively small proportion of patients (5% to 10%) with systemic amyloidosis. The frequency of FX deficiency in AL amyloidosis varies across studies. Greipp et al.48 reported a frequency of FX below 20 IU/dL in 6 patients out of 95 patients

Table 3 Prevalence of bleeding events in systemic amyloidosis

| Study, date | Population | Prevalence of bleeding | Bleeding description | Favoursing factors |
|-------------|------------|------------------------|---------------------|-------------------|
| Yood et al., 198337 | 100 AL amyloidosis | 41/100 = 41% | 23% petechia and ecchymoses | 18% gastrointestinal tract bleeding |
| | | (3% cause of death) | | 8% after procedure |
| | | | | 3% haematuria |
| | | | | 2% haemoptysis |
| Mumford et al., 200044 | 337 AL amyloidosis | 28% | 18% cutaneous bleeding | Prolongation of thrombin time |
| | | | | 5% gastrointestinal bleeding |
| | | | | 1% post procedure |
| | | | | 7% of lower GI tract bleeding |
| | | | | 9% of upper |
| Kumar et al., 200140 | 45 AL amyloidosis treated with blood stem cell | 20% | 7% of lower GI tract bleeding | Multiorgan involvement |
| | | | | haemodialysis |
| Choufani et al., 200145 | 368 AL amyloidosis | 5%, all with FX deficiency | Frequency and severity worse with the lowest levels of FX | Labile INR |
| | 290 ATTR | | | |
| Mitrani et al., 202041 | 7% (all had anticoagulant therapy) | | FX deficiency < 50% |
| | | | |

AL, immunoglobulin light chain amyloidosis; GL, gastrointestinal; TTR, transthyretin; wTTR, wild type transthyretin; vTTR, variant transthyretin.

Table 4 Main studies investigating coagulation abnormalities in patients with AL-amyloidosis since 2000

| Reference | Study design | Number of patients/sex ratio (male/female) | Median age (years) | Coagulation abnormalities and relationships with clinical features |
|-----------|--------------|------------------------------------------|-------------------|------------------------------------------------------------------|
| Mumford AD et al., 200041 | Retrospective single-centre cohort study | 337/0.54 | 61.2 | -TT prolongation (32% of patients) associated with hepatic amyloid deposits ($P < 10^{-4}$), 24-h proteinuria ($P < 10^{-3}$), and hypoalbuminaemia ($P < 10^{-5}$) |
| | | | | -PT prolongation (24% of patients) associated with abnormal bleeding ($P = 0.001$) |
| | | | | -aPTT prolongation (14% of patients) |
| | | | | -FX:C deficiency (< 70 IU/dL): 22/154 (14%), of whom 7 (5%) < 20 IU/dL |
| | | | | -FX:Ag/FX:C 2.5 in patients with FX deficiency vs FX:Ag/FX:C 0.96 in patients without ($P < 10^{-3}$) |
| | | | | -Mild FVII:C deficiency in 2 patients (44 and 23 IU/dL) |
| | | | | -Absence of FX inhibitor |
| | | | | -TT prolongation (85% of patients) |
| | | | | -PT prolongation (22% of patients) |
| | | | | -aPTT prolongation (65% of patients) |
| | | | | -FX:C deficiency (< 65 IU/dL)(27% of patients) |
| Gamba G et al., 200042 | Prospective | 36/2.0 | NA | -Absence of FX inhibitor |
| | | | | -TT prolongation (85% of patients) |
| | | | | -PT prolongation (22% of patients) |
| | | | | -aPTT prolongation (65% of patients) |
| | | | | -FX:C deficiency (< 65 IU/dL)(27% of patients) |
| Choufani EB et al., 200143 | Prospective clinical trial | 368/1.5b | 58.0b | -FX:C deficiency (< 50 IU/dL): 32/368 (8.7%) of whom 12 < 25 IU/dL (9 with bleeding complications) |
| | | | | -Frequency and severity worse in the patients with the lowest levels of FX |
| | | | | -FX:C deficiency (< 50 IU/dL): 10/104 (9.6%) of whom 2 < 25 IU/dL |
| Patel G et al., 201944 | Retrospective single-centre cohort study | 104/0.54 | 63.4 | |

*Patients receiving vitamin K antagonist were excluded. |
| *Sex ratio and median age of patients with FX deficiency; TT: thrombin time. |
| aPTT: activated partial prothrombin time; Ag, antigen; F, factor; FX:C, FX clotting activity; NA, non-available; PT, prothrombin time. |
(7.6%). Mumford et al.\textsuperscript{44} reported a frequency of 14\% (<70 IU/dL), of whom 7 (5\%) were 20 IU/dL. In a cohort of 368 patients with AL-amyloidosis,\textsuperscript{46} 32 patients (7.8\%) had an FX level below 50 IU/dL, of whom 18 (56\%) had bleeding complications, mostly in those with an FX level below 25 IU/dL. Notably, aggressive chemotherapy combined with autologous haematopoietic cell transplantation improved the amyloid-related FX deficiency.\textsuperscript{46} More recently, Patel et al. reported an FX deficiency frequency of 9.6\% (< 50 IU/dL), with only two patients (2\%) with FX < 10 IU/dL.\textsuperscript{47} Compared with patients with normal FX activity, patients with FX deficiency were more likely to have a worse disease stage ($P = 0.05$), elevated higher biomarkers (NT-proBNP, $P = 0.002$; cardiac troponin T, cTNT, $P = 0.03$). Remarkably, all patients with the acquired FX deficiency had cardiac involvement, as compared with 70\% in the other group ($P = 0.06$).\textsuperscript{47} No bleeding occurred in the 10 patients with FX deficiency in the first 12 months of follow-up after FX was measured. (Table 2).

One hypothesis to explain FX deficiency is that FX is eliminated from the circulation by selective binding to amyloid deposits, especially in the perivascular tissues in the spleen. The correction of FX deficiency after splenectomy in some case reports supports this hypothesis.\textsuperscript{49} However, this simple FX adsorptive model cannot explain the discrepancy between circulating FX antigen and FX coagulant activity observed in some patients in Mumford's cohort. Additional mechanisms may be involved in FX functional impairment. Recently, the group of Christophe et al. have discovered new partners regulating FX circulating levels: they have identified scavenger receptor class A member I (SR-AI) as a receptor for FX at the macrophage surface and pentraxin-2 (PTX2), which forms a ternary complex with SR-AI and FX.\textsuperscript{50} PTX2 is essential to prevent internalization of FX by SR-AI. Like FX, PTX2 may be targeted to amyloid plaques. Because SR-AI/PTX2/FX complex is necessary to maintain normal plasma levels of FX and PTX2, a disequilibrium in the complex may contribute to a depletion in FX in systemic AL-amyloidosis.

### Antithrombotic drugs in amyloidosis

Currently, the main indications of anticoagulation in secondary prevention are AF, regardless of CHADS2-VaSC score, deep vein thrombosis and/or pulmonary embolism, nephrotic syndrome with hypoalbuminaemia < 20 g/L and unexpected intracardiac thrombus diagnosed during cardiac imaging (echocardiography, computed tomography scan, and magnetic resonance imaging).\textsuperscript{18} (Figure 1).

The situations that are to be considered for prescribing prophylactic anticoagulation are the prescription of IMIDs, heart failure hospitalization, a history of arterial thrombosis (stroke with presumed embolic origin, TIA) in the absence of a curable cause, a nephrotic syndrome with albuminuria > 20 g/L.

The contraindications to anticoagulant treatment are less well established. The most common are active digestive bleeding requiring blood transfusion (especially if linked to diffuse amyloid digestive involvement), coagulation disor-

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**Table 2**

| Pros | Cons |
|------|------|
| - History of venous thromboembolism or stroke | - Digestive involvement causing bleeding |
| - Atrial fibrillation | - TX deficiency, especially if < 50\% |
| - Atrial myopathy | - Severe cytopenias |
| - Heart failure | - Liver amyloidosis involvement |
| - Nephrotic syndrome in AL amyloidosis | - Dysautonomia leading to fall |
| - IMID based chemotherapy in AL amyloidosis | |

**Figure 1** Main determinants of thromboembolism and bleeding in systemic amyloidosis.
ders, especially FX < 50 IU/dL. Other risky situations that do not represent absolute contraindications to anticoagulant therapy are cytopenia, hepatic amyloid damage and renal failure.

There are important differences between AL and TTR amyloidosis (Table 5). Indeed, AL amyloidosis seems associated with a greater risk of haemorrhage because digestive involvement is more often present, association with a myeloma can lead to cytopenia, FX deficiency is associated with AL amyloidosis, renal failure is more common. There are also more interactions between anticoagulants and the treatments for AL amyloidosis (corticosteroids, chemotherapy: proteasome inhibitors, IMIDs, daratumumab). Conversely, tafamidis, the only approved treatment for ATTR cardiomyopathy, does not appear to interact with cytochrome CYP3A4.

Vitamin K antagonists

Vitamin K antagonist (VKA) response is marked by inter-patient and intra-patient variability. Acute illnesses, deterioration in chronic comorbidities or changes in associated drugs may dramatically impact anticoagulation control. Especially, VKAs interact with chemotherapy in AL amyloidosis. Thus, managing patients with amyloidosis may be challenging requiring a close monitoring of international normalized ratio (INR). INR takes the advantage of being widely available and cheap. In addition, there is an easy-to-use antidote for overdose. Finally, VKA is an inexpensive treatment that can be used in patients with severe renal failure (Figure 1). In the study by Mitrani et al., which included only TTR cardiomyopathies, INR lability was noted in 87% of patients. The event rate of major bleeds was 3.7 per 100 person years in this study as compared to 2.2–3.9 in the general population.51

Direct oral anticoagulants (DOACs)

The pharmacokinetics of the 3 most used direct oral anticoagulants (DOACs) are very different.52 Dabigatran has predominantly renal clearance (80%) and hepatic clearance (20%) and is not metabolized by cytochrome CYP3A4. Rivaroxaban and apixaban have predominantly hepatic clearance (65% and 73%, respectively). They also are both metabolized by CYP3A4.

The main advantages of DOACs are their easy use, rapid efficacy within a few hours after introduction, oral administration, and a wide therapeutic window. The data published in venous thrombosis in cancer patients have shown the efficacy and safety of DOACs.53,54 There are few safety data concerning apixaban use for venous thrombosis prevention in multiple myeloma treated with IMID-based chemotherapy55; indeed, no signal of ineffectiveness (little or no thrombosis) or higher risk of bleeding has been reported. Mitrani et al.21 have published the only available data on the use of DOACs in ATTR cardiomyopathy. There was no difference in thrombotic or haemorrhagic events compared to VKA treatment.

One of the main drawbacks of DOACs use is the management of patients with life-threatening bleedings or in emergency situations. The use of specific antidotes is expensive and may expose patients to an increased risk of thrombotic complications. Secondly, there are drug interactions with chemotherapy used in AL amyloidosis. For example, dexamethasone (CYP3A4 inducer) may decrease DOAC levels and lead to lower levels of anticoagulation. There is also an increased risk of gastrointestinal bleeding especially with dabigatran and rivaroxaban.56,57 However, the Amplify study53 showed the benefit of apixaban in major bleeding as compared with controls thanks to a decrease in gastrointestinal bleeding in cancer patients. In the general population, the rate of major bleeding in patients treated with DOAC is 2.9 to 4 per 100 person years.51,58 In Mitrani et al. data21 (TTR anticoagulated amyloidosis), this event rate was 5.2 per 100 patient years. Finally, xabans and dabigatran are contra-indicated in severe renal failure with creatinine clearance <15 and 30 mL/min, respectively, and 60% of AL amyloidosis patients have renal involvement. Furthermore, 10% to 15% of patients have liver damage which may also limit their prescription.

Direct oral anticoagulants could be used safely in TTR amyloidosis in the absence of severe renal failure. During the administration of chemotherapy containing dexamethasone,

![Table 5 Specific thrombotic and bleeding risks according to the type of amyloidosis](https://example.com/table5)

| Type of amyloidosis | Prothrombotic risk factors | Bleeding risk factors |
|--------------------|---------------------------|----------------------|
| AL  | - Nephrotic syndrome | - Digestive involvement |
|      | - Use of IMID | - Liver involvement |
|      | - Heart failure | - FX deficiency |
|      | - Higher free light chains and beta-2 microglobulin level | - Drug interactions (chemotherapy and oral anticoagulants) |
|      | - Atrial fibrillation | |
| TTR | - Atrial fibrillation | - Age |
|      | - Heart failure | - Risk of fall (dysautonomia, conductive disorder) |
|      | - Atrial myopathy | - Renal failure, haemodialysis |

AL, immunoglobulin light chain amyloidosis; IMID, immunomodulatory drugs; TTR: transthyretin.
anticoagulant therapy with low molecular weight heparin is preferred. On the other hand, once the patient is in remission and no longer receiving chemotherapy, anticoagulation by DOACs may be considered. Apixaban has shown a reduction in digestive bleeding in cancer patients with venous thromboembolism.53

Finally, the MYELAXAT59 study has tested the protective effect of apixaban (2.5 mg twice daily) for 6 months in multiple myeloma patients (all with creatinine clearance >30 mL/min) and treated with IMID (thalidomide and/or lenalidomide). In this non-controlled and non-randomized study, 104 patients were included. Two patients experienced a TE (the incidence of TE was 0.38 patient-months in the entire population, 95% CI 0.05–1.4). Neither arterial cardiovascular event, nor pulmonary embolism, and no death due to venous TE was observed. Eleven patients experienced bleeding: 10 clinically relevant non major bleedings [incidence 1.9% patient-months (95% CI 0.9–3.5)] and one major bleeding requiring blood transfusion [incidence 0.19% patient-months (95% CI 0.04–1.1)]. These preliminary data suggest the safety of this DOAC in myeloma patients.

Low molecular weight heparins

Low molecular weight heparin (enoxaparin and tinzaparin) are widely used. These treatments are easy to handle with a short half-life making it possible to stop them in case of bleeding. There are few drug interactions, especially with chemotherapy. However, low molecular weight heparin need subcutaneous injection and are contraindicated if creatinine renal clearance is below 15–20 mL/min. Moreover, a substantial decrease of AT activity may lead to a suboptimal effect of heparin derivatives.

Left atrial appendage closure

Some CA patients with AF with or without previous cardioembolic event have a history of severe bleeding, such as diffuse digestive bleeding. In these cases, a left atrial appendage closure has to be considered in order to stop or to avoid anticoagulation.

Conclusions

Thromboembolic and haemorrhagic events are frequent and major issues in cardiac AL and TTR amyloidosis. Physicians should systematically look for factors favouring thromboembolism such as heart failure, atrioopathy, supraventricular arrhythmias, history of a previous thromboembolic event, nephrotic syndrome, and thrombotic risk related to chemotherapy. The thrombotic risk has to be weighed with the haemorrhagic risk that is increased by amyloid digestive or liver involvement, coagulation disorders such as FX deficiency, renal failure, thrombopathy. Prospective studies are needed to specify when and how to prescribe preventive antithrombotic therapy in this specific population.

Conflict of interest

Nothing to declare.

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