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REVIEW ARTICLE

Thromboembolic and bleeding risk in cardiac amyloidosis

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Abstract

Cardiac amyloidosis represents a spectrum of conditions characterized by the accumulation of insoluble fibrils, resulting in progressive deposition and myocardial dysfunction. The exact mechanisms contributing to the heightened risk of thromboembolic events and bleeding tendencies in cardiac amyloidosis remain unclear. Proteins such as transthyretin in transthyretin amyloidosis and light chains in light-chain amyloidosis, along with acute phase proteins in amyloid A (AA) amyloidosis, play complex roles in the coagulation cascade, affecting both coagulation initiation and fibrinolysis regulation. The increased occurrence of atrial fibrillation, systolic and diastolic left ventricular dysfunction, and atrial myopathy in patients with cardiac amyloidosis may predispose them to thrombus formation. This predisposition can occur regardless of sinus rhythm status or even with proper anticoagulant management. Bleeding events are often linked to amyloid deposits around blood vessels, which may increase capillary fragility and cause coagulation disturbances, leading to unstable international normalized ratio levels during anticoagulant therapy. Thus, comprehensive risk assessment for both thrombotic and hemorrhagic complications, especially before commencing anticoagulant therapy, is imperative. This review will explore the essential pathophysiological, epidemiologic, and clinical aspects of thromboembolic and bleeding risk in cardiac amyloidosis, evaluating the existing evidence and uncertainties regarding thrombotic and bleeding risk assessment and antithrombotic treatment.

KEYWORDS
anticoagulants, cardiac amyloidosis, hemostasis, pathophysiology, thrombosis

1 | INTRODUCTION

Amyloidosis, a systemic pathology precipitated by the aggregation of low-molecular-weight proteins, can lead to the formation of amyloid fibrils implicated in a spectrum of diseases affecting multiple organs, particularly the heart, kidneys, and nerves [1–5]. When the heart is involved, this condition is specified as cardiac amyloidosis (CA). Of the amyloid fibrils identified, only a subset has the potential to infiltrate the myocardium and induce cardiac damage [2]. The most prevalent amyloidosis subtypes with cardiac manifestation include hereditary

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transthyretin amyloidosis (hATTR) or variant transthyretin amyloidosis (vATTR), wild-type transthyretin amyloidosis (wtATTR), and amyloid light-chain (AL) amyloidosis [2–4]. Notably, wtATTR is associated with a significant proportion of hypertrophic cardiomyopathy and heart failure with preserved ejection fraction cases [6,7]. Thromboembolic events, encompassing arterial and venous thrombosis, are a critical aspect in the progression of CA, contributing significantly to morbidity and mortality, particularly within ATTR-CA subtypes [7,8]. Despite the high incidence of such events in ATTR-CA, existing epidemiologic and clinical data are disparate and often stem from limited cohort studies. This inconsistency is evident in the variation of intracardiac thrombosis incidence reported in autopsy studies (33%) compared to clinical assessments via echocardiography, which shows an incidence ranging from 8% to 30% [9–13]. This review aims to delve into the core clinical, epidemiologic, and pathophysiological characteristics of thromboembolic events in CA, addressing the current evidence and uncertainty surrounding anticoagulant therapy—particularly the choice between direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) for patients in sinus rhythm (SR) [14]. The elucidation of these aspects is essential for advancing our understanding of CA and refining therapeutic strategies.

2 | PATHOPHYSIOLOGY OF THROMBOEMBOLIC RISK IN CA

The pathophysiology of amyloidosis hinges on the aberrant production and impaired clearance of misfolded proteins, leading to their aggregation as amyloid deposits across various tissues. These deposits, depending on their location and abundance, precipitate a range of organ dysfunctions. In the heart, the deposition between cardiac muscle cells (myocytes) compromises diastolic function by reducing myocardial compliance, consequently elevating ventricular filling pressures [2,5]. Amyloid infiltration may also extend to the atria or the atrioventricular valves, causing their dilatation and sclerosis, respectively, which predisposes patients to rhythm abnormalities, predominantly atrial fibrillation (AF), and subsequent thromboembolic incidents like transient ischemic attacks (TIAs), stroke, or peripheral embolism, including femoral embolism [1–5,8,15]. Particularly vulnerable to thrombosis is the left atrial appendage (LAA), which becomes a predominant site for clot formation [1,9,10]. Cardiac magnetic resonance imaging of intracardiac thrombosis is illustrated in Figure 1.

ATTR patients are more susceptible to thromboembolic events and AF than those with AL amyloidosis, partly because of the restrictive atrial dysfunction from direct amyloid infiltration into the atrial wall, leading to impaired atrial reservoir function and contractility. Nochioka et al. [16] found that patients with wtATTR exhibited more pronounced declines in longitudinal strain and left atrial (LA) active emptying fraction than AL or hereditary ATTR. These findings underscore the relationship between decreased atrial function and cerebrovascular events, independent of AF. Differences in LA function between amyloid subtypes suggest that amyloid etiology plays a role in the pathophysiology of cardiac dysfunction and thromboembolic risk. Sinigiani et al. [17] further delineated the electrophysiological and functional harbingers of AF in CA patients. Their study underscored that interatrial conduction blocks, detected by electrocardiogram and compromised LA emptying fraction, measured by cardiac magnetic resonance are significant predictors of AF development. During a median 1.5-year follow-up, nearly one-third of patients with CA initially in SR developed AF. The combination of interatrial conduction block presence, patient age exceeding 78 years, and LA emptying fraction below 40% was associated with the highest risk of progressing to AF [17].

Progression of the disease can impair ventricular systolic function, leading to ventricular dilatation and a heightened risk of ventricular thrombi [9]. Furthermore, amyloid deposits can be patchy or widespread, leading to electrical isolation between atrial myocytes. This isolation can precipitate reentry arrhythmias and other supraventricular rhythm disturbances [2–4]. Stasis and thrombosis are further facilitated by the increased rigidity of the ventricular cavities involved in the deposits. The stretch of the atria under these conditions also induces elevated levels of atrial natriuretic peptide, which contributes to electrical isolation and creates an arrhythmogenic milieu, perpetuating a detrimental feedback loop [18].

Main pathophysiological mechanisms underlying thrombosis and bleeding in patients with ATTR-CA and AL amyloidosis are described in Table 1 and Figure 2.

Peripheral neuropathy accompanied by autonomic dysfunction frequently manifests in hereditary amyloidogenic transthyretin (ATTR) amyloidosis, as well as in primary immunoglobulin AL-derived amyloidosis [19]. Orthostatic hypotension (OH) is a significant indicator of cardiovascular autonomic dysfunction, stemming from the autonomic nervous system's inability to regulate postural hemodynamic equilibrium. Its frequency increases with advancing age and the presence of underlying pathologies such as neurodegenerative disorders, hypertension, diabetes, renal dysfunction, autoimmune diseases, and cancer. OH demonstrates a complex association with different phases of cardiovascular illness, culminating in severe cardiac ailments and cardiovascular-related mortality. Its manifestation notably correlates with left ventricular (LV) hypertrophy, inflammatory markers, atherosclerosis, and thrombotic events and independently forecasts adverse cardiovascular outcomes [20]. Recently, a novel classification for OH has been proposed, aiming to categorize various clinical conditions into 3 groups based on the predominant underlying pathophysiological mechanism: neurogenic, cardiogenic, and mixed [21]. OH also represents a condition of impaired hemodynamic homeostasis, wherein compensatory neuroendocrine mechanisms are intermittently engaged. These mechanisms may instigate the activation of additional biological pathways, such as platelets or the coagulation cascade, potentially predisposing individuals to cardiovascular or cerebrovascular events [22]. Supporting this notion, heightened activity of the endothelin system has been observed in patients experiencing syncope attributed to OH [23]. Consequently, physiological vasoconstrictors like endothelin-1 and vasopressin may serve as adaptive

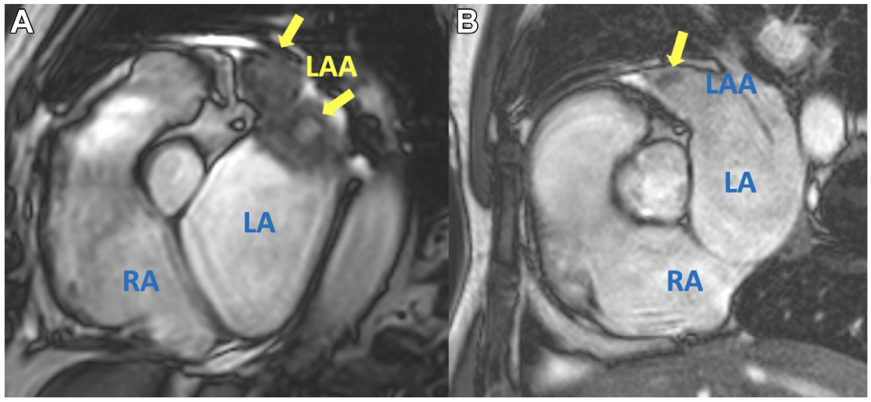

FIGURE 1 Left atrial appendage (LAA) thrombosis in cardiac amyloidosis. Cardiovascular magnetic resonance cine images documenting LAA thrombosis (yellow arrows) in (A) a 70-year-old man with wild-type transthyretin cardiac amyloidosis (CHA_2DS_2-VASc score, 1) and (B) a 64-year-old woman with light-chain cardiac amyloidosis (CHA_2DS_2-VASc score, 1). LA, left atrium; RA, right atrium.

responses to OH, albeit potentially promoting atherothrombosis in susceptible individuals [24].

Additionally, significant fluctuations in blood pressure and supine hypertension associated with OH may trigger intermittent ischemic episodes and increased afterload, resulting in irreversible damage such as LV hypertrophy and reduced renal function [25]. Intriguingly, among hypertensive individuals, isolated systolic OH is strongly linked to a heightened incidence of stroke, while isolated diastolic OH appears to pose greater risk to coronary circulation [26].

TABLE 1 Main pathophysiological mechanisms underlying thrombosis and bleeding in patients with ATTR-CA and AL amyloidosis.

Subtype	Thrombosis	Bleeding
AL	• IMIDs • Nephrotic syndrome with loss of natural anticoagulant factors and increased synthesis of procoagulant factors Impaired thrombin–antithrombinpathway • Heart failure/LV dysfunction • Hyperviscosity syndrome • Atrial fibrillation • Atrial myopathy or electromechanical dissociation	• GI tract involvement • Liver involvement • Factor X deficiency • Drug interactions (chemotherapy, oral anticoagulants) • Amyloid angiopathy
ATTR	• Atrial fibrillation • Heart failure/LV dysfunction • Atrial myopathy or electromechanical dissociation	• Age • Syncope and falls (autonomic neuropathy, OH, conductive disorder) • CKD, hemodialysis • Aortic stenosis (Heyde syndrome)

ATTR, transthyretin; ATTR-CA, transthyretin cardiac amyloidosis; AL, light-chain; CKD, chronic kidney disease; IMID, immunomodulatory imide drug; LV, left ventricle; OH, orthostatic hypotension; GI, gastrointestinal.

2.1 | Interaction between transthyretin and the coagulation system

Transthyretin (TTR) is a tetrameric protein primarily synthesized by the liver, albeit produced in lesser amounts by the choroid plexus and retinal pigmented epithelial cells, and it acts as a critical transporter protein for thyroxine and retinol-binding proteins [27]. In the context of ATTR, the pathologic aggregation of TTR in amyloid plaques seems to influence the activation and regulation of the coagulation and fibrinolytic system [28]. The etiology of ATTR amyloidosis is multifaceted and not fully elucidated, encompassing various mechanisms, with potential interplay between physiological fibrinolysis and amyloidogenesis. This relationship is particularly evident through the ability of plasmin to cleave TTR, leading to the formation of TTR fibrils closely resembling those seen *in vivo*. It has been noted that hyperfibrinolysis is more commonly observed in patients with AA and AL amyloidosis compared with those with TTR amyloidosis [28]. Additionally, TTR plays a multifaceted role, wherein amorphous extracellular protein aggregates bind to plasmin, facilitating its activation and protection from α2-antiplasmin inhibition, thereby establishing a feedback loop between amyloid and plasmin [29]. The presence of TTR in the fibrin clot supports the formation of truncated residues, which generate amyloid fibrils.

Amyloid deposits are particularly linked to spontaneous intracerebral hemorrhage in patients with cerebral amyloid angiopathy and hereditary cerebral amyloid angiopathy, impacting tissue plasminogen activator (tPA)-mediated plasminogen activation, clot structure, and fibrinolysis, with potential complications during recombinant tissue plasminogen activator (r-tPA) thrombolysis in acute ischemic stroke [30]. Furthermore, TTR plays a role in the coagulation system, where β-amyloid can induce structural changes in fibrin clots, rendering them resistant to fibrinolysis [31].

The vast majority of individuals afflicted with Alzheimer's disease (AD) experience compromised cerebral blood flow. A growing body of evidence indicates that fibrinogen, the primary constituent of blood clots, exerts a pivotal influence on this vascular dysfunction in AD. Fibrinogen engages with β-amyloid, culminating in the formation of aberrant blood clots resistant to plasmin degradation. Elevated fibrin deposition is discernible in the cerebral tissue of AD patients and

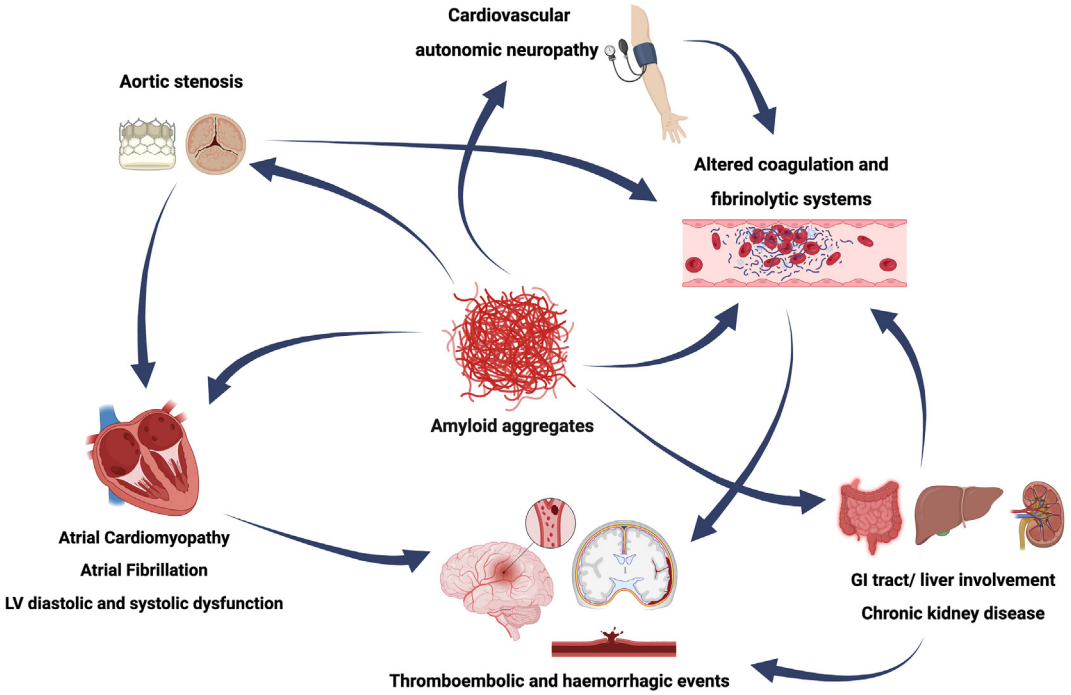

FIGURE 2 Pathophysiological mechanisms underlying thromboembolic and bleeding events in cardiac amyloidosis. GI, gastrointestinal; LV, left ventricle. Created with Biorender.com.

murine models [31]. Interestingly, the presence of amyloid binding to fibrin prolongs its proteolysis by plasmin, thus achieving a balance between amyloid activation and degradation [32]. Notably, elevated TTR levels are significantly associated with venous thromboembolism (VTE), indicating its potential utility as a biomarker [33]. Overall, the complex interactions between TTR, amyloid, and the coagulation and fibrinolytic systems underscore their roles in both thrombotic and hemorrhagic events, particularly in conditions such as familial amyloid polyneuropathy [34].

AL amyloidosis embodies a multifaceted interplay of molecular events, characterized by the dysregulation of plasma cell homeostasis and the ensuing overproduction of abnormal AL proteins. These proteins, instead of undertaking their conventional role in immunoglobulin assembly, undergo misfolding, predisposing them to aggregation and deposition of amyloid fibrils within various tissues and organs, culminating in organ dysfunction. Clinically, AL amyloidosis presents with a spectrum of systemic manifestations, reflecting the extensive distribution of amyloid deposits and encompassing complications such as cardiomyopathy and renal impairment. Efforts aimed at unraveling the intricate pathogenesis of AL amyloidosis have unveiled potential therapeutic targets aimed at attenuating aberrant AL production and mitigating the downstream consequences of amyloid deposition [7].

In AL amyloidosis, there is notable activation of the fibrinolysis system alongside excessive fibrinolysis. However, the precise mechanisms underlying this activation remain incompletely understood. In one study authors investigate whether the urokinase-type plasminogen activator (uPA), a key player in the fibrinolytic system, plays a role in the activation of fibrinolysis in AL amyloidosis. They conducted immunohistochemical analyses to examine the expression of uPA in bone marrow plasma cells. Notably, over 90% of bone marrow plasma cells from 5 distinct AL amyloidosis patients exhibited positive staining for uPA. Conversely, all bone marrow plasma cells from 7 different patients with multiple myeloma (MM) were devoid of uPA expression.

Furthermore, a patient diagnosed with AL amyloidosis, presenting with bleeding tendencies and excessive fibrinolysis accompanied by hypofibrinogenemia, underwent treatment with nafamostat mesilate—an agent known to inhibit uPA. Following administration of nafamostat mesilate, the patient's bleeding tendencies abated, and both excessive fibrinolysis and hypofibrinogenemia showed improvement. These findings strongly suggest a potential contribution of uPA expressed in plasma cells to the pathogenesis of excessive fibrinolysis in AL amyloidosis [35].

Pathophysiological mechanisms in AL amyloidosis include protein loss secondary to nephrotic syndrome with urinary dispersion of natural anticoagulants such as protein S and antithrombin is another cause [7], as well as an increase of the synthesis of procoagulant proteins such as factor (F)V, FVII, fibrinogen or an impairment between thrombin and antithrombin balance [7]. In patients with AL amyloidosis, some authors describe the hyperviscosity syndrome [36] or the use of chemotherapeutic agents as an additional cause [37]. Additionally, agents such as thalidomide, lenalidomide in patients with MM, or estrogens and other immunomodulatory drugs (IMIDs), granulocyte-macrophage colony–stimulating factor, and cytapheresis therapy can predispose to thromboembolism [38–40].

3 | incidence of Thromboembolic Events in CA

Several studies have assessed the risk of thromboembolic events in patients with CA. A summary and features of thromboembolic events among the main studies are listed in Table 2 [9,10,12–15,41,42]. Intracardiac thrombi are common in CA, particularly in patients with TTR amyloid cardiomyopathy (ATTR-CA), although incidence rates vary across studies. Feng et al. [10] showed a 33% incidence of intracardiac thrombi, higher in patients with AL-CA (51%) than other subtypes (16%) despite younger age and absence of AF. Co-occurrence of AL and AF significantly increased thromboembolic events (odds ratio [OR], 55.0; 95% CI, 8.1-1131.4). Another echocardiography study [10] identified AF, lower LAA emptying velocity, and reduced LV diastolic function as factors linked to thrombosis, and anticoagulant use was associated with a decreased risk (OR, 0.09; 95% CI, 0.01-0.51). El-Am et al. [12] reported a high rate of cancellation for direct current cardioversion in CA patients (81% vs 25% in control subjects) due to intracardiac thrombi, indicating its predictive value for cardioversion failure. Martinez-Naharro et al. [13] found a 6.2% incidence of intracardiac thrombi in CA, with no significant difference between ATTR-CA and AL-CA. A retrospective study on patients with LAA thrombosis treated with warfarin found a low-resolution rate (43%) at first follow-up transesophageal echocardiography (TEE) (median: 50 days). Subsequent TEE showed no further resolution [43].

A study by Vilches et al. [14] found an incidence rate of 0 per 100 patient-years among patients with a normal SR receiving oral anticoagulant therapy (OAT), 1.3 among those with a normal SR without OAT, 1.7 among those with AF on OAT, and 4.8 among those with AF not on OAT. Infiltration of amyloid into the left atrium can result in atrial mechanical dysfunction and endothelial damage, leading to blood flow stasis, particularly with atrial stiffness and electromechanical dissociation of the left atrium. Thrombus formation within the left atrium is infrequent among individuals exhibiting SR. However, cases of extensive CA presented large atrial thrombi were described, either within or extending into the LA body, as revealed by transthoracic echocardiography during SR. Doppler studies indicated the absence of an A wave in mitral inflow. Extensive infiltration of amyloid in both the atria and ventricles likely led to mechanical atrial standstill, thereby facilitating thrombus formation. These observations underscore the potential necessity for anticoagulant therapy in patients with severe CA exhibiting impaired atrial function [13,14,44].

3.1 | Stroke and TIA

ATTR-CA is the most common subtype related to intracardiac thrombosis and cerebrovascular events [4,8]. However, data regarding acute cerebrovascular events are very low. In a retrospective study conducted

TABLE 2 Thromboembolic risk in cardiac amyloidosis: summary of clinical studies.

Study	Population	Thromboembolic event	Incidence	Risk factors
Feng et al. [9], 2007	*N* = 116 autopsies (55 AL; 55 wtATTR; 4 AA)	Intracardiac thrombi at autopsy	33%	AF, AL subtype
Feng et al. [10], 2009	*N* = 156 (73 ATTR; 3 AA)	Intracardiac thrombi by Echo	27%	LV diastolic dysfunction, blunted LAA velocity, AF, AL subtype
Martinez-Naharro et al. [13], 2019	*N* = 324 (166 ATTR; 155 AL)	Intracardiac thrombi by CMR	6%	Biventricular systolic dysfunction, atrial dilatation, higher ECV, AF, AL subtype
El-Am et al. [12], 2019	*N* = 58 (29 AL; 25 wtATTR; 4 hATTR)	Intracardiac thrombi by Echo	28%	AF, AL subtype
Mitrani et al. [41], 2021	*N* = 290 (ATTR)	Ischemic stroke, *n* = 9; minor stroke, *n* = 8	6%	AF, labile INR
Cappelli et al. [15], 2021	*N* = 262 (134 AL; 73 hATTR; 199 wtATTR)	Stroke, *n* = 21; minor stroke, *n* = 8;	8%	AF, LVEF <50%, CHADS-VASc score >2, CKD
Bukhari et al. [42], 2021	*N* = 168 (68 wtATTR; 77 controls)	Stroke, *n* = 18; minor stroke, *n* = 4;	36% wtATTR; 19% control group	AF, LAVi, CHADS-VASc score >2; LV diastolic dysfunction
Vilches et al. [14], 2022	*N* = 1191 (990 wtATTR; 201 hATTR)	Stroke, *n* = 41	3%	AF, prior stroke, LV diastolic dysfunction

AA, amyloid A; AF, atrial fibrillation; AL, light-chain; ATTR, transthyretin; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category; CKD, chronic kidney disease; CMR, cardiac magnetic resonance; Echo, echocardiography; ECV, extracellular volume; hATTR, hereditary transthyretin amyloidosis; INR, international normalized ratio; LAA, left atrial appendage; LAVi, left atrial volume index; LV, left ventricle; LVEF, left ventricle ejection fraction; wtATTR, wild-type transthyretin amyloidosis.

on 40 patients with systemic amyloidosis (3 ATTR and 37 AL), almost 13 subjects (32.5%) had acute ischemic stroke as first clinical onset of systemic amyloidosis; specifically, authors pointed out that patients with neurologic symptoms as first presentation had worst prognosis, with a median survival of 6.9 months from diagnosis. Of 13 patients with amyloidosis and a neurologic event, almost 37% had recurrent stroke, especially cardioembolic (70%) and hemispherical (73%) [45].

In a retrospective study conducted between January 2004 and January 2018 by Donnellan et al. [46] on 382 patients with ATTR-CA (111 with wtATTR-CA, 271 with hATTR-CA), there was an incidence of thromboembolic and cerebrovascular events of 20% (n = 53) in AF patients and less in non AF patients (9%, n = 10), with a p = .005; in this study cerebrovascular events occurred in 63 patients (16%), and the absence of anticoagulants (hazard ratio [HR], 1.30; 95% CI, 1.01-1.63; p = .04) or higher CHA_2DS_2-VASc score [Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category] (HR, 2.80; 95% CI, 2.13-2.66; $p < .0001$) were linked to higher events rate.

In another study performed by Mitrani et al. [41] on 290 ATTR-CA patients, almost 217 of 290 (74.8%) had AF, 116 of 217 (53.5%) received novel oral anticoagulants (NOACs), and 78 of 217 (35.9%) were treated with warfarin. All patients with AF and ATTR-CA had 17 thrombotic complications; in particular, 8 had TIA and 9 had ischemic stroke. No patients without AF had a thrombotic event (p = .01).

3.2 | Arterial peripheral events

In literature, arterial peripheral events (AEs) in patients with systemic amyloidosis are less described: an Italian observational study that involved 5 centers and evaluated and followed 406 patients with CA (134 with AL-CA, 73 with hATTR-CA, and 199 with wtATTR-CA) found a total of 31 patients (7.6%) with AEs, in particular only 2 peripheral events (1 mesenteric and 1 femoral embolism). Most common AEs were neurologic, with a total of 21 ischemic strokes and 8 TIAs. These events were not linked to age, sex, or CA subtype, and 14 patients treated with anticoagulants had anyway AEs. Moreover, 10 of 31 patients with AEs (32.2%) were in SR; thus the best predictor of AEs was a high CHA_2DS_2-VASc score of ≥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 SR) [15]. In another retrospective study by Halligan et al. [47], the most common site was represented by femoral artery (n = 4 patients, 36%), followed by atria or multiple arteries in lower extremities (n = 2 patients, 18% for both); popliteal or ulnar involvement was noted in only 1 patient for both (9%).

3.3 | VTE

In contrast to ATTR subjects, patients with AL amyloidosis are more susceptible to VTE. In the retrospective study conducted on 2132 patients during the period between 1975 and 2000, the authors identified 40 subjects with biopsy-proven AL amyloidosis and a thrombotic event (11 arterial and 29 venous thromboses). The sites most commonly involved were pulmonary arteries (n = 15 patients, 52%), followed by calf veins (n = 5 patients, 17%), subclavian or popliteal vein (n = 3 patients, 10% for both), common femoral or inferior cava vein (n = 1 patient, 3% for both) [47].

Another retrospective study on 929 patients with immunoglobulin AL amyloidosis showed venous thromboembolic events in 65 patients (7%), especially those with lower albumin levels, with a HR of 4.30 (95% CI, 1.60-11.55; P = .0038); 8% of patients had an event within the first year from the diagnosis [48].

4 | THROMBOEMBOLIC RISK PREVENTION IN CA

Thromboembolic events are common in CA and are often associated with the presence of AF and intracardiac thrombi. Studies, previously mentioned, have consistently demonstrated the high incidence of AF among CA patients, which in turn significantly increases the likelihood of experiencing strokes and TIAs. The combined presence of AF and CA substantially heightens the risk of thromboembolic events, thus underscoring the critical importance of anticoagulation therapy as a primary preventive strategy.

The therapeutic use of anticoagulants has been associated with a reduction in the risk of thromboembolic events in CA patients. However, it is essential to carefully consider the potential for bleeding complications. Current clinical guidelines recommend the use of anticoagulation therapy in CA patients with AF, irrespective of their CHA_2DS_2-VASc score. Moreover, in SR patients with a high CHA_2DS_2-VASc score, anticoagulation therapy is also recommended. Several types of antithrombotic agents are available for use in CA patients, including DOACs, VKAs, and aspirin (ASA). The clinical evidence supports the efficacy of DOACs compared to VKAs in the prevention of thromboembolic events, with DOACs demonstrating lower rates of bleeding complications. In addition to CA, anticoagulation therapy is also recommended for patients with MM who are being treated with IMIDs. In this patient population, ASA is considered a viable alternative to low-molecular-weight heparin (LMWH) for the prophylaxis of VTE [49,50].

AF risk is significantly high among patients with CA and often correlates with cerebrovascular events, such as stroke or TIAs [3,4,12]. A study by Feng et al. [10] involving 156 CA subjects found that anticoagulants prescribed at the time of TEE were protective against thromboembolism (OR, 0.09; 95% CI, 0.01-0.51; $P < .006$), despite a heightened risk of bleeding linked to vessel wall fragility from amyloid fibril infiltration. In another Italian observational study by Cappelli et al. [15], the thromboembolic event rate was 3.2 per 100 patients/y among AF/CA patients. Anticoagulants appeared to be protective, with fewer adverse events observed in those treated (90.5% vs 66.7%; p = .006). The incidence of AEs in AF/CA patients did not significantly differ based on CHA_2DS_2-VASc score stages. A retrospective study by Mitrani et al. [41] showed no significant difference in thromboembolic event rates between CA patients treated

with warfarin and those treated with NOACs during a median follow-up of 2.4 years (range, 0.1-12). Similarly, Vilches et al. [14] found no substantial difference in the incidence of thromboembolic complications between AF/CA patients treated with VKAs and those treated with NOACs. The highest incidence of thromboembolic events (4.8 per 100 patients/y) was among AF/CA subjects not receiving oral anticoagulants [14]. These findings support the use of oral anticoagulants not only in CA patients with AF, regardless of CHA_2DS_2-VASc score, but also in SR patients with a high CHA_2DS_2-VASc score [2,49–51]. It is important to note that intracardiac thrombosis is still observed despite adequate anticoagulation, prompting many authors to recommend TEE before electrical cardioversion in CA patients with AF [12,28,29]. In patients with AL amyloidosis and MM, the risk of VTE is increased by IMIDs. Larocca et al. [39] proposed ASA as an alternative to LMWH for VTE prophylaxis in MM patients treated with IMIDs and found ASA to be effective in reducing the VTE incidence, with fewer episodes of major bleeding than LMWH.

The International Myeloma Working Group recommends ASA for MM patients with 1 or less VTE risk factors and LMWH for those with 2 or more risk factors, especially if receiving additional high-risk treatments [52].

4.1 | Heparin resistance in AL amyloidosis

More than half a century ago, AL amyloidosis was proposed as a potential instigator of heparin resistance [53]. Heparin, a naturally occurring polysaccharide, is synthesized and released by basophilic and mast cells. Heparan sulfate (HS), exhibiting a comparable molecular configuration albeit with lesser sulfation, is ubiquitously expressed on cell surfaces, extracellular matrices, and endothelial cell membranes as a constituent of HS proteoglycans [54]. Numerous biological functions within the human body rely on heparin or HS, with heparin-protein complexes assuming a pivotal role [55]. Accumulation of HS proteoglycans occurs at the interface between AA and AL amyloid fibrils with capillary membranes in murine and human tissues, suggesting a potential interplay between HS proteoglycans and amyloidogenesis or deposition [56–58]. The proximity of AL amyloid to significant blood flow in filtration organs might result in the binding of administered unfractionated heparin to AL amyloid, rendering it biologically inactive for anticoagulation. This conjecture is substantiated by the structural resemblance between unfractionated heparin and HS [59].

4.2 | DOAC vs VKA

The systematic review and meta-analysis by Lacy et al. [60] showed decreased thrombotic events and no difference in major bleeding in CA patients treated with DOACs vs VKAs. In a single-center retrospective analysis by Mitrani et al. [41], authors found similar rates of major bleeding and thrombotic events in ATTR-CA patients treated with DOACs vs VKAs. Cariou et al. [61], also observed fewer bleeding complications in CA patients on DOACs vs VKAs, with no significant difference in stroke events. Another study [14] found no differences in bleeding or embolic events between DOAC- and VKA-treated ATTR-CA patients. Finally, the ARCADIA trial (AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke trial) showed no significant difference in recurrent stroke risk between apixaban and ASA in cryptogenic stroke patients with evidence of atrial cardiopathy without AF [62].

5 | BLEEDING RISK IN CA

Bleeding events are relatively common in AL amyloidosis, but they have been also described as frequently related to TTR amyloidosis. Amyloid deposits in vessel walls can accelerate microcalcification and lead to vessel rupture [8,63]. The main bleeding manifestations include ecchymoses and petechiae, but hemorrhages from the gastrointestinal and renal systems are also quite common [64–67]. Amyloid accumulations are detectable within the gastrointestinal and mucosal linings. Perivascular deposition of amyloidosis can induce amyloid angiopathy, exacerbating capillary delicacy and disrupting capillary vasomotion. Gastrointestinal bleeding stems from amyloid deposits, which compromise vascular wall integrity, muscle infiltration heightening mucosal susceptibility, and/or intestinal ischemia [68,69]. The most prevalent dermatologic observations entail purpura and ecchymosis, stemming from vascular vulnerability and endothelial compromise likely attributable to amyloid accumulation and subsequent hemorrhagic susceptibility [70]. Instances of urinary tract bleeding have also been documented. Amyloid deposition beneath the superficial mucosa or within the urinary tract vasculature poses a significant hemorrhagic risk [71]. Among the prominent pathophysiological phenomena, notable examples include clotting abnormalities (mainly described in AL amyloidosis) like prolonged prothrombin time, activated partial thromboplastin time, and FX deficiency. Limited data on clotting abnormalities are available for ATTR amyloidosis. While the bleeding tendency in patients with TTR amyloidosis is generally less severe than in patients with AL and AA, anticoagulation treatment can exacerbate bleeding. Therefore, the potential benefits of anticoagulation must be carefully weighed against potential bleeding complications.

A study by Mitrani et al. [41] found no differences in the combined outcome of ischemic stroke, TIA, major bleeding, or death in patients with ATTR-CA and AF treated with warfarin vs DOACs. However, labile international normalized ratio was observed in 87% of patients, and the incidence rate of major bleeding events was higher in this study compared with the general population. Cariou et al. [61] analyzed 273 patients with CA and a history of atrial arrhythmias on long-term anticoagulant therapy: 69 (25%) had AL amyloidosis, 179 (66%) had wtATTR, and 25 (9%) had variant ATTR. Overall, 147 (54%) patients received VKA and 126 (46%) received DOAC therapy. In the wtATTR subgroup, VKA-treated patients had a significantly higher bleeding risk than DOAC-treated patients. However, there were no differences in ischemic events, and no strokes occurred during follow-up. On the

other hand, the bleeding risk in patients with AL amyloidosis was similar in the 2 groups, with no strokes during follow-up.

The most common hemorrhagic events in patients with wtATTR are hemorrhagic strokes and major extracranial bleeding. These incidents can occur irrespective of whether patients are taking DOACs or warfarin [8]. For instance, Bukhari et al. [42] reported hemorrhagic strokes in 4.4% and major extracranial bleeding in 7.3% of wtATTR patients with AF. Similarly, Vilches et al. [14] observed major hemorrhagic events in 46.9% of patients taking VKAs and in 12.5% of patients on DOACs during a median follow-up of 14.2 months (Table 3) [14,41,42,61].

6 | AMYLOIDOSIS AND RISK OF STROKE AFTER TRANSCATHETER AORTIC VALVE REPLACEMENT

Amyloidosis affects the heart valves and myocardium with accumulations of amyloid in these structures. This leads to inflammation due to lipid infiltration and structural stress, resulting in endothelial deformity, which in turn causes calcification, stiffness, fibrosis, and sclerosis of the aortic valve leaflets, leading to a progressive decline of the valve [72,73]. ATTR-CA ought to be considered in all instances of aortic stenosis (AS), especially in older male individuals exhibiting a medical background encompassing carpal tunnel syndrome, lumbar spinal stenosis, and unanticipated tendon ruptures, alongside premature pacemaker insertion, disproportionate symptoms of heart failure despite nonsevere AS, and signs suggestive of right ventricular failure. Low-flow, low-gradient AS is frequently encountered in CA [74]. In cases of discordant AS grading, European guidelines recommend confirming AS severity by using dobutamine stress echocardiography and/or aortic valve calcium score by computed tomography [75].

Individuals with CA may exhibit a comparatively reduced aortic valve calcium score in contrast to those without CA [76]. A retrospective evaluation involving patients diagnosed with AS-CA or isolated AS revealed notably diminished calcium scores in the CA-AS subgroup [77]. Consequently, reliance solely on aortic valve calcium threshold scores might prove unreliable due to the potential risk of underestimating the severity of AS in CA cases. An ongoing multicenter Italian investigation, known as the "Calcium score values of stenotic aortic valves in patients with and without cardiac amyloidosis" (CAUSATIVE) study, aims to delineate the optimal threshold values of valve calcification for CA diagnosis in AS patients [74]. Dobutamine stress echocardiography could serve as a valuable tool to affirm the presence of genuine severe AS in individuals with CA [78]. Nevertheless, further studies are warranted to validate these findings. In patients with amyloidosis, valvular repair is a therapeutic goal, often pursued through transcatheter aortic valve replacement (TAVR) rather than surgical aortic valve replacement due to age and comorbidities. In patients with both AS and ATTR-CA, recent evidence favors TAVR over surgical aortic valve replacement, although data on surgical and percutaneous approaches in ATTR-CA are limited [79]. Stroke prevention during TAVR is complex, with a 2% to 3% incidence at 30 days after procedure [80]. CA patients have been found to have a high frequency of intracardiac thrombosis and a high risk of thromboembolic events as previously described, with progressive amyloid deposition leading to atrial myopathy, atrial electromechanical dissociation, and acute decompensated AS. This evidence led to recommendations that CA patients with AF be anticoagulated regardless of their CHA_2DS_2-VASc score and that imaging-guided cardioversion be performed regardless of anticoagulation status [81,82]. Whether routine anticoagulation should also be considered in systemic amyloidosis, particularly in CA patients in SR with enlarged and dysfunctional atria and a low bleeding risk, remains to be determined [72].

Elzeneini et al. [83] conducted a retrospective analysis, finding that AS with preexisting amyloidosis is associated with a three-fold higher risk of acute ischemic stroke during TAVR compared to AS

TABLE 3 Bleeding events in patients with cardiac amyloidosis treated with oral anticoagulants.

Study	Population	Bleeding events	Incidence	Comments
Mitrani et al. [41], 2021	*N* = 290 (217 with AF)	Major bleeding	VKA: 3.7/100 PY; DOAC: 5.2/100 PY (*P* = NS)	Labile INR associated with increased hemorrhagic risk
Cariou et al. [61], 2021	*N* = 273 (69 AL; 179 wtATTR; 25 hATTR)	Major bleeding	wtATTR subgroup : 14% VKA; 2% DOAcs AL subgroup: 22% VKA, 13% DOAC	DOACs appear to be at least as effective and safe as VKAs
Bukhari et al. [42], 2021	*N* = 168 (68 wtATTR; 77 controls)	Hemorrhagic stroke Major extracranial bleedings	4.4% wtATTR vs 7.3% controls	No excess bleeding risk in wtATTR-AF
Vilches et al [14], 2022	*N* = 1191 (990 wtATTR; 201 hATTR)	Major bleeding	VKA: 3.2/100 PY DOAC:5.1/100 PY (p = NS)	No meaningful difference in bleeding risk DOACs vs VKAs

AF, atrial fibrillation; AL, light-chain; DOAC, direct oral anticoagulant; hATTR; hereditary transthyretin amyloidosis; INR, international normalized ratio; NS, not significant; PY, patient-years; VKA, vitamin K antagonist; wtATTR, wild-type transthyretin amyloidosis.

alone, irrespective of AF, prior stroke, or chronic heart failure. Further studies are needed to clarify the role of anticoagulation in systemic amyloidosis and to optimize stroke prevention during TAVR [83].

7 | CONCLUSIONS

The pathophysiology of thromboembolic risk in CA is complex, involving AF, atrial myopathy, autonomic neuropathy, and coagulation disorders. AF greatly increases the likelihood of thromboembolic events, highlighting the significance of anticoagulation therapy. Despite adequate anticoagulation, intracardiac thrombosis continues to be a significant concern, requiring imaging-guided interventions. Thromboembolic events, such as stroke and TIAs, are common in patients with CA, especially in those with TTR amyloid cardiomyopathy. Although AEs are less frequently described, VTE is more prevalent in AL amyloidosis. Anticoagulant therapy, especially DOACs, is critical in managing thromboembolic risk and is associated with a more favorable bleeding profile compared with that of VKAs. Hemorrhagic events, while less common, are significant in CA, demanding careful assessment of bleeding risks. Tailoring thromboembolic risk prevention strategies to individual risk factors is vital in optimizing outcomes for patients with CA. In this patient population, thromboembolic events contribute significantly to morbidity and mortality. Consequently, the approach to managing thromboembolic risk must be personalized by taking into account the complexity of each case. This involves a comprehensive assessment of thrombotic and bleeding risks, which includes evaluating patient history, degree of cardiac involvement, and the presence of concurrent conditions that may influence the therapeutic strategy. The use of DOACs, owing to their favorable bleeding profile, is often preferred over the use of VKAs. However, this preference must be balanced against individual patient characteristics, such as renal function and potential drug interactions. In the context of CA, where bleeding complications may occur, the decision to initiate and maintain anticoagulation therapy should be made judiciously. Close monitoring and regular reassessment of therapy efficacy and safety are integral to the management plan. It is crucial to engage in a multidisciplinary discussion that includes cardiologists, hematologists, geriatricians, neurologists, and other specialists to ensure informed clinical decision making and optimal patient care.

ETHICS STATEMENT

Not applicable.

AUTHOR CONTRIBUTIONS

M.T., C.T., D.R., F.R., E.P. have been involved in the draft and data preparation, made contributions to conception and design, and revised the work critically. All authors have fully contributed to the paper, agreed for all aspects, and approved the final publication.

DECLARATION OF COMPETING INTERESTS

There are no competing interests to disclose.

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REFERENCES

[1] Tana M, Tana C, Palmiero G, Mantini C, Coppola MG, Limongelli G, Schiavone C, Porreca E. Imaging findings of right cardiac amyloidosis: impact on prognosis and clinical course. *J Ultrasound*. 2023;26:605–14.

[2] Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, Burazor I, Caforio ALP, Damy T, Eriksson U, Fontana M, Gillmore JD, Gonzalez-Lopez E, Grogan M, Heymans S, Imazio M, Kindermann I, Kristen AV, Maurer MS, Merlini G, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2021;42:1554–68.

[3] Tana M, Tana C, Panarese A, Mantini C, Ricci F, Porreca E. Clinical and cardiovascular magnetic resonance imaging features of cardiac amyloidosis. *Rev Cardiovasc Med*. 2023;24:291.

[4] Tana M, Tana C, Guglielmi MD, Stefanelli A, Mantini C, Porreca E. Current perspectives on atrial amyloidosis: a narrative review. *Rev Cardiovasc Med*. 2024;25:73.

[5] Dogan A. Amyloidosis: insights from proteomics. *Annu Rev Pathol*. 2017;12:277–304.

[6] Aimo A, Merlo M, Porcari A, Georgiopoulos G, Pagura L, Vergaro G, Sinagra G, Emdin M, Rapezzi C. Redefining the epidemiology of cardiac amyloidosis. A systematic review and meta-analysis of screening studies. *Eur J Heart Fail*. 2022;24:2342–51.

[7] Nicol M, Siguret V, Vergaro G, Aimo A, Emdin M, Dillinger JG, Baudet M, Cohen-Solal A, Villesuzanne C, Harel S, Royer B, Arnulf B, Logeart D. Thromboembolism and bleeding in systemic amyloidosis: a review. *ESC Heart Fail*. 2022;9:11–20.

[8] Napolitano A, De Michieli L, Sinigiani G, Berno T, Cipriani A, Spiezia L. Thromboembolic and bleeding events in transthyretin amyloidosis and coagulation system abnormalities: a review. *J Clin Med*. 2023;12:6640.

[9] Feng D, Edwards WD, Oh JK, Chandrasekaran K, Grogan M, Martinez MW, Syed IS, Hughes DA, Lust JA, Jaffe AS, Gertz MA, Klarich KW. Intracardiac thrombosis and embolism in patients with cardiac amyloidosis. *Circulation*. 2007;116:2420–6.

[10] Feng D, Syed IS, Martinez M, Oh JK, Jaffe AS, Grogan M, Edwards WD, Gertz MA, Klarich KW. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. *Circulation*. 2009;119:2490–7.

[11] Banydeen R, Signate A, Tran TH, Monfort A, Neviere R, Inamo J. Cerebral ischemic events: an overlooked complication of transthyretin cardiac amyloidosis in Afro-Caribbean patients. *Front Neurol*. 2022;13:878292.

[12] El-Am EA, Dispenzieri A, Melduni RM, Ammash NM, White RD, Hodge DO, Noseworthy PA, Lin G, Pislaru SV, Egbe AC, Grogan M, Nkomo VT. Direct current cardioversion of atrial arrhythmias in adults with cardiac amyloidosis. *J Am Coll Cardiol*. 2019;73:589–97.

[13] Martinez-Naharro A, Gonzalez-Lopez E, Corovic A, Mirelis JG, Baksi AJ, Moon JC, Garcia-Pavia P, Gillmore JD, Hawkins PN, Fontana M. High prevalence of intracardiac thrombi in cardiac amyloidosis. *J Am Coll Cardiol*. 2019;73:1733–4.

[14] Vilches S, Fontana M, Gonzalez-Lopez E, Mitrani L, Saturi G, Renju M, Griffin JM, Caponetti A, Gnanasampanthan S, De Los Santos J, Gagliardi C, Rivas A, Dominguez F, Longhi S, Rapezzi C, Maurer MS, Gillmore J, Garcia-Pavia P. Systemic embolism in

amyloid transthyretin cardiomyopathy. *Eur J Heart Fail*. 2022;24:1387–96.
[15] Cappelli F, Tini G, Russo D, Emdin M, Del Franco A, Vergaro G, Di Bella G, Mazzeo A, Canepa M, Volpe M, Perfetto F, Autore C, Di Mario C, Rapezzi C, Musumeci MB. Arterial thrombo-embolic events in cardiac amyloidosis: a look beyond atrial fibrillation. *Amyloid*. 2021;28:12–8.
[16] Nochioka K, Quarta CC, Claggett B, Roca GQ, Rapezzi C, Falk RH, Solomon SD. Left atrial structure and function in cardiac amyloidosis. *Eur Heart J Cardiovasc Imaging*. 2017;18:1128–37.
[17] Sinigiani G, De Michieli L, Porcari A, Zocchi C, Sorella A, Mazzoni C, Bisaccia G, De Luca A, Di Bella G, Gregori D, Perfetto F, Merlo M, Sinagra G, Iliceto S, Perazzolo Marra M, Corrado D, Ricci F, Cappelli F, Cipriani A. Atrial electrofunctional predictors of incident atrial fibrillation in cardiac amyloidosis. *Heart Rhythm*. 2024;21:725–32.
[18] Vergaro G, Aimo A, Rapezzi C, Castiglione V, Fabiani I, Pucci A, Buda G, Passino C, Lupón J, Bayes-Genis A, Emdin M, Braunwald E. Atrial amyloidosis: mechanisms and clinical manifestations. *Eur J Heart Fail*. 2022;24:2019–28.
[19] Ikeda S-i. Amyloid neuropathy and autonomic dysfunction. *Neurol Clin Neurosci*. 2022;10:137–46.
[20] Fedorowski A, Ricci F, Sutton R. Orthostatic hypotension and cardiovascular risk. *Kardiol Pol*. 2019;77:1020–7.
[21] Fedorowski A, Ricci F, Hamrefors V, Sandau KE, Hwan Chung T, Muldowney JAS, Gopinathannair R, Olshansky B. Orthostatic hypotension: management of a complex, but common, medical problem. *Circ Arrhythm Electrophysiol*. 2022;15:e010573.
[22] Ricci F, Fedorowski A, Radico F, Romanello M, Tatasciore A, Di Nicola M, Zimarino M, De Caterina R. Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. *Eur Heart J*. 2015;36:1609–17.
[23] Fedorowski A, Burri P, Struck J, Juul-Möller S, Melander O. Novel cardiovascular biomarkers in unexplained syncopal attacks: the SYSTEMA cohort. *J Intern Med*. 2013;273:359–67.
[24] Berger R, Pacher R. The role of the endothelin system in myocardial infarction–new therapeutic targets? *Eur Heart J*. 2003;24:294–6.
[25] Shibao C, Biaggioni I. Orthostatic hypotension and cardiovascular risk. *Hypertension*. 2010;56:1042–4.
[26] Fedorowski A, Wahlstrand B, Hedner T, Melander O. Systolic and diastolic component of orthostatic hypotension and cardiovascular events in hypertensive patients: the Captopril Prevention Project. *J Hypertens*. 2014;32:75–81.
[27] Mangione PP, Verona G, Corazza A, Marcoux J, Canetti D, Giorgetti S, Raimondi S, Stoppini M, Esposito M, Relini A, Canale C, Valli M, Marchese L, Faravelli G, Obici L, Hawkins PN, Taylor GW, Gillmore JD, Pepys MB, Bellotti V. Plasminogen activation triggers transthyretin amyloidogenesis in vitro. *J Biol Chem*. 2018;293:14192–9.
[28] Bouma B, Maas C, Hazenberg BP, Lokhorst HM, Gebbink MF. Increased plasmin-alpha2-antiplasmin levels indicate activation of the fibrinolytic system in systemic amyloidoses. *J Thromb Haemost*. 2007;5:1139–42.
[29] Wieczorek E, Ożyhar A. Transthyretin: from structural stability to osteoarticular and cardiovascular diseases. *Cells*. 2021;10:1768.
[30] Mutimer CA, Keragala CB, Markus HS, Werring DJ, Cloud GC, Medcalf RL. Cerebral amyloid angiopathy and the fibrinolytic system: is plasmin a therapeutic target? *Stroke*. 2021;52:2707–14.
[31] Zamolodchikov D, Berk-Rauch HE, Oren DA, Stor DS, Singh PK, Kawasaki M, Aso K, Strickland S, Ahn HJ. Biochemical and structural analysis of the interaction between β-amyloid and fibrinogen. *Blood*. 2016;128:1144–51.
[32] Yaprak E, Kasap M, Akpinar G, Islek EE, Sinanoglu A. Abundant proteins in platelet-rich fibrin and their potential contribution to wound healing: an explorative proteomics study and review of the literature. *J Dent Sci*. 2018;13:386–95.
[33] Jensen SB, Hindberg K, Solomon T, Smith EN, Lapek JD Jr, Gonzalez DJ, Latysheva N, Frazer KA, Braekkan SK, Hansen JB. Discovery of novel plasma biomarkers for future incident venous thromboembolism by untargeted synchronous precursor selection mass spectrometry proteomics. *J Thromb Haemost*. 2018;16:1763–74.
[34] Takahashi R, Ono K, Ikeda T, Akagi A, Noto D, Nozaki I, Sakai K, Asakura H, Iwasa K, Yamada M. Coagulation and fibrinolysis abnormalities in familial amyloid polyneuropathy. *Amyloid*. 2012;19:129–32.
[35] Uchiba M, Imamura T, Hata H, Tatetsu H, Yonemura Y, Ueda M, Wada Y, Mitsuya H, Ando Y. Excessive fibrinolysis in AL-amyloidosis is induced by urokinae-type plasminogen activator from bone marrow plasma cells. *Amyloid*. 2009;16:89–93.
[36] Park H, Kim JW, Youk J, Koh Y, Lee JO, Kim KH, Bang SM, Kim I, Park S, Yoon SS. Serum free light chain difference and β_2 microglobulin levels are risk factors for thromboembolic events in patients with AL amyloidosis. *Clin Lymphoma Myeloma Leuk*. 2018;18:408–14.
[37] Tana M, Rizzo G, Porreca E. In: *Reference module in biomedical sciences. Risk factors and pathophysiology of venous thromboembolism in patient with malignancy. ISBN 9780128012383*. Elsevier; 2023. https://doi.org/10.1016/B978-0-443-15717-2.00034-2
[38] Osman K, Comenzo R, Rajkumar SV. Deep venous thrombosis and thalidomide therapy for multiple myeloma. *N Engl J Med*. 2001;344:1951–2.
[39] Larocca A, Cavallo F, Bringhen S, Di Raimondo F, Falanga A, Evangelista A, Cavalli M, Stanevsky A, Corradini P, Pezzatti S, Patriarca F, Cavo M, Peccatori J, Catalano L, Carella AM, Cafro AM, Siniscalchi A, Crippa C, Petrucci MT, Yehuda DB, et al. Aspirin or enoxaparin thromboprophylaxis for patients with newly diagnosed multiple myeloma treated with lenalidomide. *Blood*. 2012;119:933–9. quiz 1093.
[40] Hausfater P, Costedoat-Chalumeau N, Amoura Z, Cacoub P, Papo T, Grateau G, Leblond V, Godeau P, Piette JC. AL cardiac amyloidosis and arterial thromboembolic events. *Scand J Rheumatol*. 2005;34:315–9.
[41] Mitrani LR, De Los Santos J, Driggin E, Kogan R, Helmke S, Goldsmith J, Biviano AB, Maurer MS. 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.
[42] Bukhari S, Barakat AF, Eisele YS, Nieves R, Jain S, Saba S, Follansbee WP, Brownell A, Soman P. Prevalence of atrial fibrillation and thromboembolic risk in wild-type transthyretin amyloid cardiomyopathy. *Circulation*. 2021;143:1335–7.
[43] El-Am EA, Grogan M, Ahmad A, Patlolla SH, Klarich KW, AbouEzzeddine OF, Melduni RM, Maleszewski JJ, Dispenzieri A, Nkomo VT. Persistence of left atrial appendage thrombus in patients with cardiac amyloidosis. *J Am Coll Cardiol*. 2021;77:342–3.
[44] Dubrey S, Pollak A, Skinner M, Falk RH. Atrial thrombi occurring during sinus rhythm in cardiac amyloidosis: evidence for atrial electromechanical dissociation. *Br Heart J*. 1995;74:541–4.
[45] Zubkov AY, Rabinstein AA, Dispenzieri A, Wijdicks EFM. Primary systemic amyloidosis with ischemic stroke as a presenting complication. *Neurology*. 2007;69:1136–41.
[46] Donnellan E, Wazni OM, Hanna M, Elshazly MB, Puri R, Saliba W, Kanj M, Vakamudi S, Patel DR, Baranowski B, Cantillon D, Dresing T, Jaber WA. Atrial fibrillation in transthyretin cardiac amyloidosis: predictors, prevalence, and efficacy of rhythm control strategies. *JACC Clin Electrophysiol*. 2020;6:1118–27.
[47] Halligan CS, Lacy MQ, Vincent Rajkumar S, Dispenzieri A, Witzig TE, Lust JA, Fonseca R, Gertz MA, Kyle RA, Pruthi RK. Natural history of thromboembolism in AL amyloidosis. *Amyloid*. 2006;13:31–6.

[48] Bever KM, Masha LI, Sun F, Stern L, Havasi A, Berk JL, Sanchorawala V, Seldin DC, Sloan JM. Risk factors for venous thromboembolism in immunoglobulin light chain amyloidosis. *Haematologica*. 2016;101:86–90.
[49] Kittleson MM, Maurer MS, Ambardekar AV, Bullock-Palmer RP, Chang PP, Eisen HJ, Nair AP, Nativi-Nicolau J, Ruberg FL, American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. *Circulation*. 2020;142:e7–22.
[50] Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, Bezzina CR, Biagini E, Blom NA, de Boer RA, De Winter T, Elliott PM, Flather M, Garcia-Pavia P, Haugaa KH, Ingles J, Jurcut RO, Klaassen S, Limongelli G, Loeys B, et al. 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J*. 2023;44:3503–626.
[51] Fine NM, Davis MK, Anderson K, Delgado DH, Giraldeau G, Kitchlu A, Massie R, Narayan J, Swiggum E, Venner CP, Ducharme A, Galant NJ, Hahn C, Howlett JG, Mielniczuk L, Parent MC, Reece D, Royal V, Toma M, Virani SA, et al. Canadian Cardiovascular Society/Canadian Heart Failure Society Joint Position Statement on the evaluation and management of patients with cardiac amyloidosis. *Can J Cardiol*. 2020;36:322–34.
[52] Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, Harousseau J, Zonder JA, Cavo M, Zangari M, Attal M, Belch A, Knop S, Joshua D, Sezer O, Ludwig H, Vesole D, Bladé J, Kyle R, Westin J, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia*. 2008;22:414–23.
[53] Christiansen J, Lindqvist B. Heparin-resistance in amyloidosis. *Acta Med Scand*. 1967;181:723–4.
[54] Meneghetti MCZ, Hughes AJ, Rudd TR, Nader HB, Powell AK, Yates EA, Lima MA. Heparan sulfate and heparin interactions with proteins. *J R Soc Interface*. 2015;12:0589.
[55] Li JP, Kusche-Gullberg M. Chapter six - heparan sulfate: biosynthesis, structure, and function. In: Jeon KW, ed. *International review of cell and molecular biology, 325*. Academic Press; 2016:215–73.
[56] Moss J, Shore I, Woodrow D. AA glomerular amyloid. An ultrastructural immunogold study of the colocalization of heparan sulphate proteoglycan and P component with amyloid fibrils together with changes in distribution of type IV collagen and fibronectin. *Histopathology*. 1994;24:427–35.
[57] Snow AD, Bramson R, Mar H, Wight TN, Kisilevsky R. A temporal and ultrastructural relationship between heparan sulfate proteoglycans and AA amyloid in experimental amyloidosis. *J Histochem Cytochem*. 1991;39:1321–30.
[58] Stenstad T, Magnus JH, Kolset SO, Cornwell GG 3rd, Husby G. Macromolecular properties of glycosaminoglycans in primary AL amyloid fibril extracts of lymphoid tissue origin. *Scand J Immunol*. 1991;34:611–7.
[59] Van Ede ES, Hoeks MPA, Hofland J, Linssen VD, van Kuppevelt TH, Versteeg EM, Hafmans TG, Diepstra A, Kusters B, Vermorgen SMM. Heparin-resistance in AL amyloidosis: a case report. *BMC Anesthesiol*. 2023;23:217.
[60] Lacy SC, Kinno M, Joyce C, Yu MD. Direct oral anticoagulants in patients with cardiac amyloidosis: a systematic review and meta-analysis. *Int J Heart Fail*. 2023;6:36–43.
[61] Cariou E, Sanchis K, Rguez K, Blanchard V, Cazalbou S, Fournier P, Huart A, Roussel M, Cintas P, Galinier M, Carrié D, Maury P, Lavie-Badie Y, Lairez O. New oral anticoagulants vs. vitamin K antagonists among patients with cardiac amyloidosis: prognostic impact. *Front Cardiovasc Med*. 2021;8:742428.
[62] Kamel H, Longstreth WT Jr, Tirschwell DL, Kronmal RA, Marshall RS, Broderick JP, Aragón García R, Plummer P, Sabagha N, Pauls Q, Cassarly C, Dillon CR, Di Tullio MR, Hod EA, Soliman EZ, Gladstone DJ, Healey JS, Sharma M, Chaturvedi S, Janis LS, et al. Apixaban to prevent recurrence after cryptogenic stroke in patients with atrial cardiopathy: the ARCADIA randomized clinical trial. *JAMA*. 2024;331:573–81.
[63] Mumford AD, O'Donnell J, Gillmore JD, Manning RA, Hawkins PN, Laffan M. Bleeding symptoms and coagulation abnormalities in 337 patients with AL-amyloidosis. *Br J Haematol*. 2000;110:454–60.
[64] Yood RA, Skinner M, Rubinow A, Talarico L, Cohen AS. Bleeding manifestations in 100 patients with amyloidosis. *JAMA*. 1983;249:1322–4.
[65] Tanaka Y, Hosotani K, Fukushima M. A case of amyloid light-chain amyloidosis presenting with submucosal hematoma and bleeding in the upper gastrointestinal tract. *Clin Gastroenterol Hepatol*. 2020;18:e158–9.
[66] Sundaram S, Rathod R. Gastric amyloidosis causing nonvariceal upper gastrointestinal bleeding. *ACG Case Rep J*. 2019;6:3–4.
[67] Kumar S, Dispenzieri A, Lacy MQ, Litzow MR, Gertz MA. High incidence of gastrointestinal tract bleeding after autologous stem cell transplant for primary systemic amyloidosis. *Bone Marrow Transplant*. 2001;28:381–5.
[68] Gould M, Zarrin-Khameh N, Sellin J. Small bowel amyloidosis. *Curr Gastroenterol Rep*. 2013;15:350.
[69] Cowan AJ, Skinner M, Seldin DC, Berk JL, Lichtenstein DR, O'Hara CJ, Doros G, Sanchorawala V. Amyloidosis of the gastrointestinal tract: a 13-year, single-center, referral experience. *Haematologica*. 2013;98:141–6.
[70] Schrutka L, Avanzini N, Seirer B, Rettl R, Dachs T, Duca F, Binder C, Dalos D, Eslam RB, Bonderman D. Bleeding events in patients with cardiac amyloidosis. *Eur Heart J*. 2020;41(Suppl 2):ehaa946-2122.
[71] Jayakrishnan T, Kamran A, Shah D, Guha A, Salman Faisal M, Mewawalla P. Senile systemic amyloidosis presenting as hematuria: a rare presentation and review of literature. *Case Rep Med*. 2020;2020:5892707.
[72] Ricci F, Cipriani A, Khanji MY. Amyloidosis and risk of stroke after transcatheter aortic valve replacement: it takes two to tango? *JACC Adv*. 2023;2:100256.
[73] Jaiswal V, Agrawal V, Khulbe Y, Hanif M, Huang H, Hameed M, Shrestha AB, Perone F, Parikh C, Gomez SI, Paudel K, Zacks J, Grubb KJ, De Rosa S, Gimelli A. Cardiac amyloidosis and aortic stenosis: a state-of-the-art review. *Eur Heart J Open*. 2023;3:oead106.
[74] Aimo A, Camerini L, Fabiani I, Morfino P, Panichella G, Barison A, Pucci A, Castiglione V, Vergaro G, Sinagra G, Emdin M. Valvular heart disease in patients with cardiac amyloidosis. *Heart Fail Rev*. 2024;29:65–77.
[75] Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Gilard M, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43:561–632.
[76] Hussain M, Hanna M, Griffin BP, Conic J, Patel J, Fava AM, Watson C, Phelan DM, Jellis C, Grimm RA, Rodriguez LL, Schoenhagen P, Hachamovitch R, Jaber WA, Cremer PC, Collier P. Aortic valve calcium in patients with transthyretin cardiac amyloidosis: a propensity-matched analysis. *Circ Cardiovasc Imaging*. 2020;13:e011433.
[77] Hussain M, Hanna M, Rodriguez L, Griffin B, Watson C, Phelan D, Schoenhagen P, Jaber W, Cremer P, Collier P. Subthreshold aortic valve calcium scores in severe aortic stenosis and transthyretin cardiac amyloidosis. *JACC Case Rep*. 2020;2:2205–9.
[78] Ternacle J, Pibarot P, Clavel MA. Aortic stenosis and cardiac amyloidosis: watch out for traps!. *JACC Case Rep*. 2020;2:2210–2.

[79] Griffin JM, Rosenthal JL, Grodin JL, Maurer MS, Grogan M, Cheng RK. ATTR amyloidosis: current and emerging management strategies: JACC: CardioOncology state-of-the-art review. *JACC CardioOncol*. 2021;3:488–505.

[80] Muralidharan A, Thiagarajan K, Van Ham R, Gleason TG, Mulukutla S, Schindler JT, Jeevanantham V, Thirumala PD. Meta-analysis of perioperative stroke and mortality in transcatheter aortic valve implantation. *Am J Cardiol*. 2016;118:1031–45.

[81] Donnellan E, Elshazly MB, Vakamudi S, Wazni OM, Cohen JA, Kanj M, Hanna M, Baranowski B, Saliba W, Jaber W. No association between CHADS-VASc score and left atrial appendage thrombus in patients with transthyretin amyloidosis. *JACC Clin Electrophysiol*. 2019;5:1473–4.

[82] Di Lisi D, Di Caccamo L, Damerino G, Portelli MC, Comparato F, Di Stefano V, Brighina F, Corrado E, Galassi AR, Novo G. Effectiveness and safety of oral anticoagulants in cardiac amyloidosis: lights and shadows. *Curr Probl Cardiol*. 2023;48:101188.

[83] Elzeneini M, Gupta S, Assaf Y, Kumbhani DJ, Shah K, Grodin JL, Bavry AA. Outcomes of transcatheter aortic valve replacement in patients with coexisiting amyloidosis: mortality, stroke, and readmission. *JACC Adv*. 2023;2:100255.