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DOAC Failure in Cardiac Amyloidosis

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Abstract

Cardiac amyloidosis, as the extracellular deposition of amyloid proteins in the cardiac tissue, is associated with a high risk for thromboembolic events, with the highest risk being in those with wild-type transthyretin amyloidosis, followed by variant transthyretin and light-chain amyloidosis. The CHA2DS2-VASc score, as used traditionally to guide anticoagulation in atrial fibrillation, has been shown to be untrustworthy in this cohort as it underestimates the true thromboembolic risk. While direct oral anticoagulants (DOACs) have demonstrated a certain advantage in reducing thrombotic events compared to vitamin K antagonists (VKAs), their efficacy remains less than optimal due to the complex interplay of prothrombotic mechanisms in cardiac amyloidosis.

This article presents a comprehensive literature review of anticoagulation in cardiac amyloidosis, supplemented by a case report of an 80-year-old female with wild-type transthyretin amyloidosis who, under DOAC therapy, developed acute lower limb arterial occlusion. The case reinforces the multifactorial etiology of thrombosis in cardiac amyloidosis, including left atrial enlargement, blood stasis, and amyloid-induced endothelial dysfunction. Postoperative course and challenges in anticoagulant therapy demonstrate the need for patient-specific treatment strategies.

The authors underscore the distinctive thromboembolic mechanisms in transthyretin and light-chain amyloidosis and the limitations of the current therapeutic approaches. The paper concludes by calling for randomized clinical trials to create firm, evidence-based guidelines for anticoagulation therapy in this high-risk population. This research aims to close the knowledge gap and improve clinical outcomes in cardiac amyloidosis patients.

Keywords: Cardiac Amyloidosis, Thromboembolism, Direct Oral Anticoagulants (DOACs), VitaminK Antagonists (VKAs), Atrial Remodeling, Anticoagulation Therapy, Amyloid Cardiomyopathy, Endothelial Dysfunction

Introduction

Cardiac amyloidosis is a rare but increasingly recognized etiology of arrhythmias and heart failure caused by the deposition of amyloid fibrils in the myocardium. The disease is associated with a heightened risk of thromboembolic events, which can manifest as intracardiac thrombi, systemic embolism, or venous thromboembolism. Among the subtypes, wild-type transthyretin amyloidosis (ATTRwt) demonstrates the highest frequency of clot formation, followed by variant transthyretin (ATTRv) and light-chain (AL) amyloidosis. The pathogenesis of thrombosis in cardiac amyloidosis is multifactorial and involves remodeling of the left atrium, blood stasis, endothelial dysfunction, and prothrombotic inflammatory pathways.

Despite these known thrombotic risks, anticoagulation strategies that are effective in this

population are lacking. The conventional tools, such as the CHA2DS2-VASc score, used to predict thromboembolic risk in the context of atrial fibrillation, are less helpful when applied to individuals with cardiac amyloidosis. Such tools have a tendency to underestimate due to the different pathophysiologic processes in amyloidosis, i.e., atrial remodeling without arrhythmia and hyperviscosity caused by circulating amyloid proteins. Consequently, anticoagulation decision-making in this group is particularly challenging clinically.

There is some nascent evidence in the form of systematic reviews and meta-analyses to favor the use of direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) for the prevention of thrombotic events in cardiac amyloidosis. However, this is a modest and not always consistent benefit, a reflection of the weakness of both interventions in opposing the multifaceted process of thrombogenesis in the disease. This is also tempered by the risks of bleeding from anticoagulation, which is especially relevant in elderly populations with comorbid illness.

In the face of these challenges, there is a dire necessity for detailed investigations with the goal of improving the knowledge of thromboembolic risk in cardiac amyloidosis as well as developing individualized anticoagulation approaches. In this paper, these challenges are explored more through an integration of evidence from the literature and a detailed case report that illustrates the limitations of current anticoagulation approaches and offers directions for future investigations.

Case Description

Clinical Presentation

An 80-year-old female with a history of wild-type transthyretin amyloidosis (ATTRwt), undergoing tafamidis therapy, presented with acute onset of severe pain and weight in the left lower extremity. She had a number of comorbidities that included atrial flutter managed with a Medtronic dual-chamber ICD (implanted following a resuscitated ventricular fibrillation event), monoclonal gammopathy of undetermined significance (MGUS), hypertension, hyperlipidemia, non-obstructive coronary artery disease, and previous upper extremity deep vein thrombosis (DVT) for which she was on rivaroxaban. She also had a history of squamous cell carcinoma of the base of the tongue treated with radiation, hysterectomy, and cardiac arrest in the past.

Diagnostic Findings

Upon presentation, physical exam was notable for pallor, coolness, and decreased pulses of the left lower extremity. Laboratory findings were notable for elevated prothrombin time (PT) of 21.6 seconds (reference range: 12.1–15.4 seconds) and INR of 1.8 (reference range: 0.8–1.2), demonstrating anticoagulant effect but potentially subtherapeutic levels. Imaging studies confirmed complete occlusion of the left common femoral artery, superficial femoral artery, and popliteal artery.

Interventions

The patient underwent emergent left groin cutdown with thrombectomy of the common femoral artery, superficial femoral artery, and profunda femoris artery. She also underwent a left lower extremity angiogram and compartment fasciotomy for management of ischemia and prevention of compartment syndrome. She was admitted to the intensive care unit (ICU) postoperatively for hourly neurovascular checks.

Despite the interventions, her postoperative course was complicated by persistent drops in hemoglobin levels, exacerbated by her refusal of blood transfusion on religious grounds. Bilateral lower extremity DVT scans were negative. The patient was started on intravenous iron therapy for five days for anemia and was subsequently switched to oral dabigatran on postoperative day (POD) 6.

Fasciotomy wounds were managed with Gelfoam packing and wound vacs.

Outcome and Discharge

Abdominal and pelvic CT scans ruled out causes of bleeding but identified a number of draining hematomas up to 8.4 cm in the left inguinal region, which on ultrasound were confirmed to be non-pulsatile hematomas without pseudoaneurysm. Hemoglobin stabilized with iron therapy, and pain was well-controlled. The patient was discharged in stable condition on POD 7 with follow-up instructions for vascular surgery and hematology.

Key Data Summarized in Tables

Table 1: Laboratory Findings on Admission

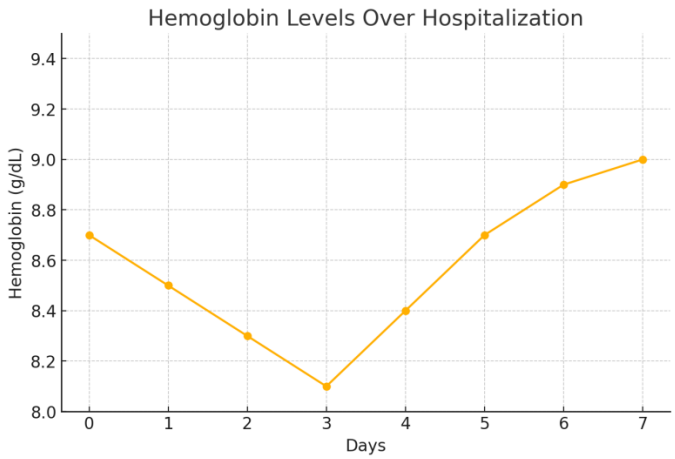
Test	Patient Value	Reference Range
Prothrombin Time (PT)	21.6 seconds	12.1–15.4 seconds
INR	1.8	0.8–1.2
Hemoglobin (Hb)	8.7 g/dL	12.0–15.5 g/dL

Table 2: Timeline of Key Events

Day	Event
Day 0	Presentation with acute limb ischemia, thrombectomy performed.
Day 1	Post-op ICU care, hourly neurovascular checks initiated.
Day 3	Fasciotomy wound packed with Gelfoam, hematomas identified.
Day 6	Transitioned from heparin drip to oral dabigatran.
Day 7	Discharged in stable condition with outpatient follow-up planned.

Illustrative Graph: Hemoglobin Trends During Hospitalization

Below is a graph illustrating the patient's hemoglobin levels over the postoperative period, highlighting the impact of intravenous iron therapy:



The graph visualizes the stabilization of hemoglobin levels following the initiation of iron therapy.

Case Implications

This case underscores the multifaceted challenges associated with managing anticoagulation in patients with cardiac amyloidosis, especially when complicated by thrombotic events. The stabilization of hemoglobin levels following iron therapy highlights the potential for non-transfusion-based management of anemia, accommodating patients with specific beliefs or medical limitations.

Key insights from this case include:

1. **Complex Pathophysiology**: The interplay of amyloid-related endothelial dysfunction, atrial remodeling, and blood stasis contributes to both thrombosis and anticoagulant resistance, necessitating a nuanced approach to treatment.
2. **Anticoagulation Challenges**: Standard anticoagulant therapies may provide suboptimal protection, as demonstrated by the incomplete efficacy of rivaroxaban and dabigatran in this patient.
3. **Individualized Treatment**: Personalized management strategies, including tailored anticoagulation regimens and non-transfusion anemia management, are critical in addressing the unique needs of this population.

Research Needs

The limitations encountered in this case emphasize the necessity for:

- Robust clinical trials to define evidence-based anticoagulation protocols for cardiac amyloidosis.
- Innovative approaches to mitigate thrombotic risk while minimizing bleeding complications.
- Enhanced understanding of the interaction between amyloid pathology and anticoagulant pharmacodynamics.

By addressing these gaps, clinicians can improve outcomes for patients with cardiac amyloidosis experiencing thrombotic complications.

Discussion

Thromboembolism is a major complication of cardiac amyloidosis, due to a multifactorial pathophysiologic predisposition to increased clotting in such patients. The mechanisms are outlined herein, highlighting the variations between light-chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) and relating them to clinical findings in the case.

Mechanisms Promoting Thromboembolism

Atrial Remodeling and Blood Stasis

Amyloid infiltration of the myocardium increases the left ventricular filling pressures, and this leads to left atrial enlargement and dysfunction. This atrial remodeling is often observed without overt arrhythmias but still leads to blood stasis and turbulence that predispose to thrombus formation. Unlike other causes of atrial enlargement, the CHA2DS2-VASc score cannot predict thromboembolic risk in cardiac amyloidosis since it cannot account for these amyloid-related mechanisms.

Endothelial Dysfunction and Prothrombotic State

Amyloid deposits damage the endothelium, causing cytokine release and a proinflammatory cascade. The inflammatory process exacerbates the prothrombotic state by activating platelets and clotting factor synthesis. In the case described, endothelial dysfunction and a high INR level (1.8) on rivaroxaban were likely key contributors to the thrombotic event.

Additional Factors in AL Amyloidosis

AL amyloidosis contributes additional thromboembolic risks through systemic effects:

- **Nephrotic Syndrome**: Loss of anticoagulant proteins in urine and increased synthesis of procoagulant factors.
- **Hyposplenism**: Leads to thrombocytosis and increased platelet activity.
- **Monoclonal Proteins**: Directly raise blood viscosity and the activity of clotting factors.

Therapeutic Challenges

Both VKAs and DOACs are suboptimal in cardiac amyloidosis due to the multifactorial nature of thromboembolism. Despite the safer bleeding profile of DOACs, they may be insufficient in individuals with very severe endothelial dysfunction or nephrotic syndrome, as is the case in AL amyloidosis. The case highlights the need for alternative anticoagulant strategies in amyloidosis patients.

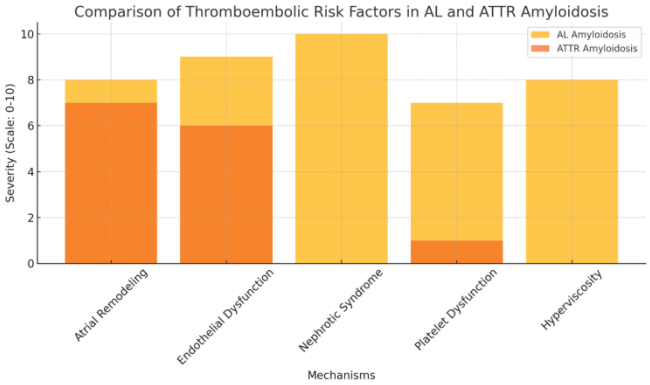
Table 3: Comparison of Mechanisms in AL and ATTR Amyloidosis

Mechanism	AL Amyloidosis	ATTR Amyloidosis
Amyloid Deposition	Widespread systemic deposition, including nephrotic syndrome.	Primarily localized to the heart, leading to atrial remodeling.
Coagulopathy	Loss of anticoagulant proteins, increased procoagulant synthesis.	Limited coagulopathy; primarily atrial enlargement-induced stasis.
Platelet Dysfunction	Enhanced by thrombocytosi	Minimal platelet dysfunction.

	s from hyposplenism.	
Inflammatory Response	Strong systemic inflammatory cascade.	Predominantly localized inflammation.
Thrombotic Risk	Higher due to systemic and cardiac contributions.	Moderate, predominantly cardiac-related thromboembolism .

Graph: Thromboembolic Risk Factors in Cardiac Amyloidosis

A bar graph can illustrate the relative contributions of different mechanisms to thromboembolic risk in AL and ATTR amyloidosis.



This visual representation emphasizes the higher systemic involvement in AL compared to ATTR amyloidosis.

Clinical Implications

The discussion emphasizes the need for randomized trials to study:

- The application of biomarkers to risk-stratify thromboembolic.
- Efficacy of tailored anticoagulant routines, including new drugs such as factor Xa inhibitors or thrombin antagonists.

This case substantiates the complexity of thromboembolism in cardiac amyloidosis and individualized anticoagulation strategies based on the amyloid subtype and involved mechanisms.

Conclusion

Cardiac amyloidosis presents a new and challenging problem in the management of thromboembolism, which is rooted in its distinct pathophysiological mechanisms. The inability of traditional risk stratification tools, such as the CHA2DS2-VASc score, and the unpredictable effectiveness of current anticoagulants highlight significant gaps in clinical management for this high-risk cohort.

This article has reviewed the interplay among amyloid deposition, atrial remodeling, endothelial dysfunction, and systemic prothrombotic mechanisms that cumulatively heighten the risk for thromboembolism in cardiac amyloidosis. Despite the fact that direct oral anticoagulants (DOACs) have shown a limited advantage over vitamin K antagonists (VKAs) for prevention of thrombotic events, their effectiveness remains variable and context-dependent, particularly in patients with additional systemic complications such as nephrotic syndrome in AL amyloidosis.

The case illustrated here underscores the practical dilemmas of anticoagulation management in cardiac amyloidosis, including the risk of thrombosis in the setting of anticoagulant therapy and the challenge of balancing efficacy and bleeding risk in elderly patients with many comorbid conditions. The findings demonstrate that one-size-fits-all anticoagulation does not fit this diverse group of patients.

To improve outcomes, randomized clinical trials with the exclusive aim of evaluating anticoagulation strategies in cardiac amyloidosis are urgently required. The trials should:

- Describe the thromboembolic risk profiles of the different amyloid subtypes (e.g., ATTRwt, ATTRv, AL).
- Discuss the comparative effectiveness and safety of DOACs versus VKAs in these subtypes.
- Explore the potential application of novel anticoagulants or composite therapies that

are specifically tailored to the unique mechanisms of amyloidosis thromboembolism.

Additionally, biomarkers such as atrial strain imaging, D-dimer levels, and amyloid-specific inflammatory markers can be included in trial designs to help further risk stratify and guide personalized treatment approaches.

Ultimately, the formation of evidence-backed anticoagulation guidelines in cardiac amyloidosis is central to reducing thrombotic as well as bleeding complications, improving quality of life, and survival in this vulnerable population. Such developments shall address existing gaps in knowledge and equip clinicians with robust tools for optimal patient management.

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