

Original Article



Direct Oral Anticoagulants in Patients With Cardiac Amyloidosis: A Systematic Review and Meta-Analysis

Spencer C. Lacy , MD, MPH¹, Menhel Kinno , MD, MPH², Cara Joyce, PhD¹, and Mingxi D. Yu , MD²

¹Department of Internal Medicine, Loyola University Medical Center, Maywood, IL, USA

²Division of Cardiovascular Medicine, Loyola University Medical Center, Maywood, IL, USA



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Correspondence to

Spencer C. Lacy, MD, MPH

Department of Internal Medicine, Loyola University Medical Center, 2160 S. First Ave, Maywood, IL 60153, USA.

Email: spencer.c.lacy@luhs.org

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ABSTRACT

Background and Objectives: Atrial fibrillation is common in patients with cardiac amyloidosis. However, the optimal anticoagulation strategy to prevent thromboembolic events in patients with cardiac amyloidosis and atrial fibrillation is unknown. This systematic review and meta-analysis compares direct oral anticoagulants (DOACs) vs. vitamin K antagonists (VKAs) in patients with cardiac amyloidosis and atrial fibrillation.

Methods: We performed a systematic literature review to identify clinical studies of anticoagulation therapies for patients with cardiac amyloidosis and atrial fibrillation. The primary outcomes of major bleeding and thrombotic events were reported using random effects risk ratios (RRs) with 95% confidence interval (CI).

Results: Our search yielded 97 potential studies and evaluated 14 full-text articles based on title and abstract. We excluded 10 studies that were review articles or did not compare anticoagulation. We included 4 studies reporting on 1,579 patients. The pooled estimates are likely underpowered due to small sample sizes. There was no difference in bleeding events for patients with cardiac amyloidosis and atrial fibrillation treated with DOACs compared to VKAs with a RR of 0.64 (95% CI, 0.38–1.10; p=0.10). There were decreased thrombotic events for patients with cardiac amyloidosis and atrial fibrillation treated with DOACs compared to VKAs with a RR of 0.50 (95% CI, 0.32–0.79; p=0.003).

Conclusions: This systematic review and meta-analysis suggests that DOACs are as safe and effective as VKAs in patients with cardiac amyloidosis and atrial fibrillation. However, more data are needed to investigate clinical differences in anticoagulation therapy in this patient population.

Keywords: Anticoagulation; Cardiac amyloidosis

INTRODUCTION

Atrial fibrillation and thromboembolic events are significant complications of cardiac amyloidosis.^{1,2)} The frequency of atrial arrhythmias is highest in wild-type transthyretin amyloidosis (ATTRwt), followed by variant transthyretin amyloidosis, and light chain amyloidosis (AL).²⁾

There is a high incidence of intracardiac thrombus in patients with cardiac amyloidosis and these thrombi have even been identified in patients in normal sinus rhythm.^{1,3} Patients with AL have been shown to have a higher rate of intracardiac thrombus compared to transthyretin amyloidosis by transesophageal echocardiography and cardiac magnetic resonance imaging.^{4,5} Furthermore, the congestive heart failure, hypertension, age above 75, diabetes, stroke, vascular disease, age above 65, sex (CHA₂DS₂-VASc) score is not reliable in patients with cardiac amyloidosis, and likely underestimates the true risk of thromboembolism.⁶

Direct oral anticoagulants (DOACs) have been established as alternatives to vitamin K antagonists (VKAs) for stroke prevention in patients with atrial fibrillation.⁷ However, the safety and efficacy of anticoagulation therapy for stroke prophylaxis is not well studied in the cardiac amyloidosis population.

In this systematic review and meta-analysis, we examine DOACs vs. VKAs in patients with cardiac amyloidosis and atrial fibrillation. The main objective of this review was to assess the safety and efficacy of anticoagulation in patients with cardiac amyloidosis and atrial fibrillation.

METHODS

This study did not require ethical approval because only public published data were used. The reporting of this systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.⁸ This review was submitted to PROSPERO for registration.

Search strategy

We performed a systematic literature review to identify randomized and nonrandomized clinical studies that reported clinical outcomes from anticoagulation therapy in patients with cardiac amyloidosis and atrial fibrillation. Searches were limited to peer-reviewed articles published in English up to July 9th, 2023. This search was limited to studies with human subjects and those that described the clinical impact of anticoagulation therapy on patients with cardiac amyloidosis and atrial fibrillation. We developed the search strategy according to available guidance from the Cochrane Collaboration.⁹

The search strategy in PubMed explored Medical Subject Heading (MeSH) terms related to anticoagulation in patients with cardiac amyloidosis and atrial fibrillation. The exact search strategy was “(“anticoagulants”[Pharmacological Action] OR “anticoagulants”[MeSH Terms] OR “anticoagulants”[All Fields] OR

“anticoagulant”[All Fields] OR “anticoagulate”[All Fields] OR “anticoagulated”[All Fields] OR “anticoagulating”[All Fields] OR “anticoagulation”[All Fields] OR “anticoagulations”[All Fields] OR “anticoagulative”[All Fields]) AND (“cardiacs”[All Fields] OR “heart”[MeSH Terms] OR “heart”[All Fields] OR “cardiac”[All Fields]) AND (“amyloid”[MeSH Terms] OR “amyloid”[All Fields] OR “amyloids”[All Fields] OR “amyloidal”[All Fields] OR “amyloidic”[All Fields])”. The articles found to be relevant during the search were stored in EndNote (Clarivate Analytics, London, UK). References from full-text articles were also evaluated and considered for inclusion.

Study selection

Articles were selected for inclusion based on predefined criteria, including the comparison of DOACs and VKAs in patients with cardiac amyloidosis and atrial fibrillation. The primary outcomes were major bleeding and thrombotic events. We excluded case reports and studies that did not provide patient numbers for event data.

Three authors (Lacy SC, Kinno M, and Yu MD) independently completed literature searches and screened abstracts to choose potentially relevant articles. Selected articles underwent a full evaluation to assess their potential inclusion in the systematic review.

Risk for bias

The risk of bias for non-randomized trials was evaluated using the ROBINS-I tool.¹⁰ Two independent reviewers (Lacy SC, Yu MD) assessed the risk for bias.

Endpoints

Each included study defined the primary endpoints of bleeding and thrombotic events separately. In general, major bleeding required hospitalization or blood transfusion. Thrombotic events included stroke, transient ischemic attack, or peripheral embolism.

Statistical analysis

Review Manager software 5.4 (Cochrane, London, UK) was used for data analysis. The meta-analysis outcomes were pooled using Mantel-Hansel methods due to sparse event rates. The DerSimonian and Laird approach was used for random effects model estimation of the average effect across the studies.¹¹ Pooled estimates were presented as risk ratios (RRs) with 95% confidence intervals (CIs). A χ^2 test of heterogeneity was calculated for each pooled analysis. The I^2 measure of statistical heterogeneity relative to sampling error between studies was also estimated, with higher I^2 values representing greater heterogeneity. All statistical tests were 2-sided and p values <0.05 were considered significant.

RESULTS

Literature search

Our search yielded 97 abstracts. We excluded 83 studies at the abstract level and selected 14 full-text articles for detailed assessment. We excluded 6 studies based on case report, editorial, or review article status and 4 studies did not report anticoagulation comparison data. We ultimately included 4 studies in our systematic review and meta-analysis. **Figure 1** describes the flow-chart of included studies.

Baseline characteristics of the studies

Table 1 shows the baseline characteristics of the included studies. All studies were published between 2020 and 2022. The 4 studies included 1,579 patients and the median age of the participants was 77.2 years interquartile range (IQR) (76.6–77.7). The median percentage of men was 85.8 IQR (70.7–88.9). The median percentage of ATTRwt was 80.0 IQR (75.3–89.4). The median percentage of hypertension was 47.0 IQR (46.2–48.3). The median percentage of diabetes mellitus was 15.6 IQR (14.3–20.1). The median percentage of prior embolism was 16.2 IQR (12.0–17.9).

Risk for bias

The risk for bias revealed appropriate study designs for pre-intervention, at-intervention, and post-intervention domains in the non-randomized clinical trials included in this study. Overall, the risk for bias for clinical outcomes was low.

Anticoagulation in cardiac amyloidosis

The included studies reported clinical outcomes in patients with cardiac amyloidosis and atrial fibrillation treated with anticoagulation as summarized in **Table 2**. Mitrani et al.¹²⁾ completed a single-center retrospective analysis on anticoagulation therapy in patients with transthyretin cardiac amyloidosis (ATTR-CA) and atrial fibrillation. There was no difference in major bleeding and thrombotic events between patients treated with warfarin and DOACs. The thrombotic event rate was 3.9 per 100 person-years for patients treated with DOACs compared to 2.9 per 100 person-years for patients treated with VKAs ($p=0.74$) and the bleeding event rate was 5.21 per 100 person-years for patients treated with DOACs compared to 3.74 per 100 person-years for patients treated with VKAs ($p=0.45$) as shown in **Table 3**.¹²⁾ Cariou et al.¹³⁾ reported a single-center retrospective analysis

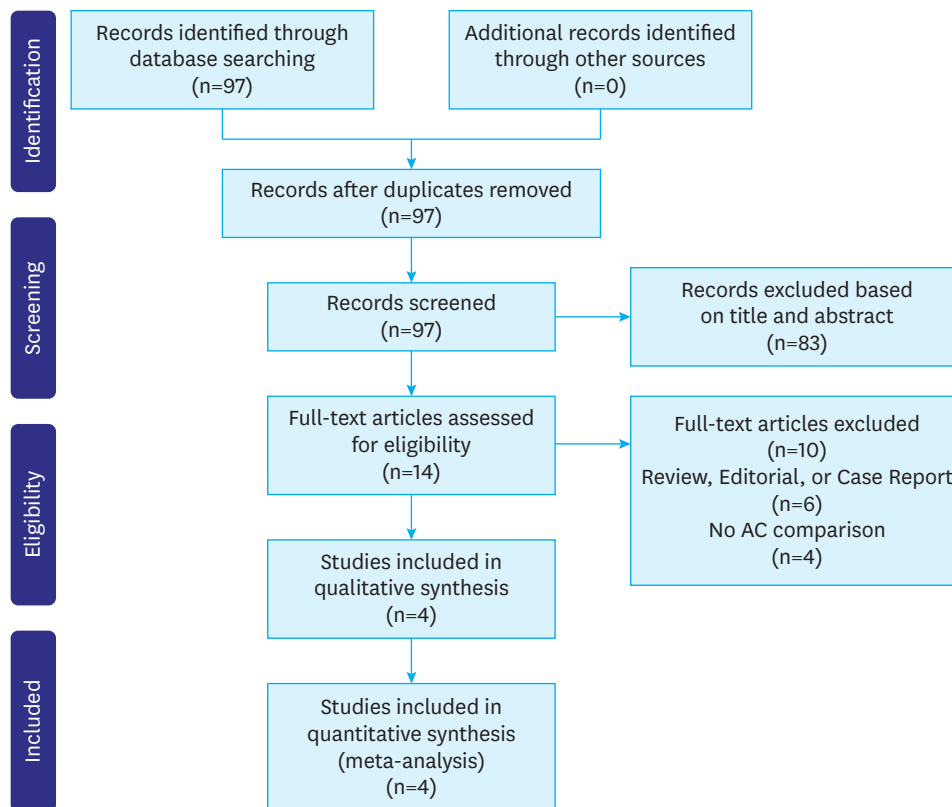


Figure 1. Flow chart of the included studies.

Anticoagulation in Cardiac Amyloidosis

Table 1. Baseline characteristics of the included studies

Characteristics	Study author, Year							
	Mitrani et al., 2020 ¹²⁾		Cariou et al., 2021 ¹³⁾		Mentias et al., 2021 ¹⁴⁾		Vilches et al., 2022 ¹⁵⁾	
Sample size	194		273		551		561	
Group	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA
Group size	116	78	126	147	338	213	239	322
Mean/Median age (years)	75.3±7.6	54.9±7.9	79±8	77±11	77.6±9.1	77.0±9.7	77.3 (73.1–81.7)	77.8 (73.1–83.3)
Men (%)	88.8	88.5	83	73	63.6	60.6	90.4	89.1
BMI (kg/m ²)	27.1±4.2	26.1±3.4	25±4	25±4	NR	NR	26.2 (24.3–28.5)	25.8 (23.9–28.1)
ATTRwt (%)	84	76	75	58	NR	NR	91.2	91.6
ATTRv (%)	16	24	13	5	NR	NR	8.8	8.4
AL (%)	0	0	12	37	NR	NR	0	0
Hypertension (%)	52.6	48.7	46	47	NR	NR	43.9	46.9
Diabetes mellitus (%)	15.5	9.0	13	16	32.5	33.8	15.6	14.7
Vascular disease (%)	NR	NR	25	21	NR	NR	18.5	19.6
Prior embolism (%)	12.1	20.5	17	21	9.1	11.7	15.9	16.5
CHA ₂ DS ₂ -VASC	3.8±1.2	3.7±1.2	4±1	4±1	5 (4–6)	5 (4–6)	NR	NR
HAS-BLED	2.5±0.7	3.1±0.9	NR	NR	NR	NR	2 (1–2)	2 (1–2)
eGFR (mL/min/1.73 m ²)	NR	NR	55±18	39±22	NR	NR	63.2 (51.7–75.8)	56.8 (45.4–70.3)
LVEF (%)	NR	NR	51±12	46±12	NR	NR	47.7±12.3	48.7±13.6

DOAC = direct oral anticoagulant; VKA = vitamin K antagonist; BMI = body mass index; ATTRwt = wild-type transthyretin amyloidosis; ATTRv = hereditary transthyretin amyloidosis; AL = light chain amyloidosis; CHA₂DS₂-VASC = congestive heart failure, hypertension, age above 75, diabetes, stroke, vascular disease, age above 65, sex; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NR = not reported.

Table 2. Summary of study design for the included studies

Characteristics	Study author, Year			
	Mitrani et al., 2020 ¹²⁾	Cariou et al., 2021 ¹³⁾	Mentias et al., 2021 ¹⁴⁾	Vilches et al., 2022 ¹⁵⁾
Location	Single-center (NY, USA)	Single-center (France)	Single-center (OH, USA)	Multicenter (4; Italy, USA, UK, Spain)
Sample size	194	273	551	561
Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort
Study population	Transthyretin cardiac amyloidosis and atrial fibrillation	Cardiac amyloidosis and atrial arrhythmia	Cardiac amyloidosis	Transthyretin cardiac amyloidosis and atrial fibrillation
Follow-up duration	2.4 years (range 0.1–12)	18 months (IQR 8–43)	444 days (IQR 170–823)	19.9 months (IQR 9.9–35.5)
Primary outcome	Time to event analysis for combined outcome of stroke, TIA, major bleed, or death	All-cause and cardiovascular mortality	All-cause mortality	Incidence and prevalence of thromboembolic events
Definition of major bleeding	Bleed requiring hospitalization, intracranial bleeding, or any drop in hemoglobin necessitating a transfusion	Symptomatic bleeding or bleeding causing a fall in hemoglobin level of 2 g/dL	Hospitalization associated with a code for bleeding and reported bleeding overall and by site, including gastrointestinal and intracranial	Bleeding requiring hospitalization and/or causing a decrease in hemoglobin level of 0.2 g/L and/or requiring blood transfusion
Definition of thrombotic events	Stroke or TIA by combination of CT, MRI, chart review, and patient reporting	Stroke	Stroke	Stroke, TIA, or peripheral embolism

TIA = transient ischemic attack; CT = computed tomography; MRI = magnetic resonance imaging; IQR = interquartile range.

Table 3. Thrombotic and bleeding event rates for patients with cardiac amyloidosis and atrial fibrillation receiving anticoagulation with DOACs or VKA

Rates	Study	DOACs	VKA	p value
Thrombotic event rates	Mitrani et al., 2020 ¹²⁾	3.9 per 100 person years	2.9 per 100 person years	0.74
	Vilches et al., 2022 ¹⁵⁾	1.6 per 100 patient-years	2 per 100 patient-years	NR
Bleeding event rates	Mitrani et al., 2020 ¹²⁾	5.21 per 100 person years	3.74 per 100 person years	0.45
	Vilches et al., 2022 ¹⁵⁾	5.1 per 100 patient-years	3.2 per 100 patient-years	NR

DOAC = direct oral anticoagulant; VKA = vitamin K antagonist; NR = not reported.

on anticoagulation therapy in patients with cardiac amyloidosis and atrial arrhythmia. There were increased bleeding complications in patients treated with VKAs when compared to DOACs, but no difference for stroke events. This was the only included study that evaluated patients with AL and transthyretin amyloid.

Subgroup analysis of patients with AL showed no difference in bleeding or stroke events between anticoagulation groups in this patient population.¹³⁾ Mentias et al.¹⁴⁾ completed a single-center retrospective analysis on anticoagulation therapy in patients with cardiac amyloidosis and atrial fibrillation. There was a de-

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creased risk of all-cause mortality, major bleeding, and stroke in patients treated with DOACs when compared to VKAs.¹⁴ Vilches et al.¹⁵ reported a multicenter retrospective analysis on embolic events and anticoagulation therapy in patients with ATTR-CA. In ATTR-CA patients with atrial fibrillation, there was no difference in bleeding or embolic events between those treated with VKAs or DOACs. The thrombotic event rate was 1.6 per 100 patient-years for patients treated with DOACs compared to 2.0 per 100 patient-years for patients treated with VKAs and the bleeding event rate was 5.1 per 100 patient-years for patients treated with DOACs compared to 3.2 per 100 patient-years for patients treated with VKAs as shown in **Table 3**.¹⁵

Meta-analysis of the included studies revealed a non-significant trend towards decreased bleeding events for patients with atrial

fibrillation and cardiac amyloidosis treated with DOACs compared to VKAs with a RR of 0.64 (95% CI, 0.38–1.10; p=0.10). The forest plot for bleeding events is shown in **Figure 2**. The statistical heterogeneity was moderate for bleeding events with an I² value of 61%. There were decreased thrombotic events for patients with atrial fibrillation and cardiac amyloidosis treated with DOACs compared to VKAs with a RR of 0.50 (95% CI, 0.32–0.79; p=0.003). The forest plot for thrombotic events is shown in **Figure 3**. The statistical heterogeneity was low for thrombotic events with an I² value of 0%. Subgroup analysis for patients with ATTR-CA revealed no difference in major bleeding or thrombotic events with RRs of 0.63 (95% CI, 0.26–1.54; p=0.31) and 0.59 (95% CI, 0.31–1.14; p=0.12), respectively. The subgroup analysis forest plots for bleeding and thrombotic events are shown in **Figures 4** and **5**.

Study or Subgroup	DOAC		VKA		Weight	Risk Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
Mitrani 2020	12	116	9	78	23.7%	0.90 [0.40, 2.03]	2020
Cariou 2021	3	126	17	147	14.3%	0.21 [0.06, 0.69]	2021
Mentias 2021	21	338	23	213	33.3%	0.58 [0.33, 1.01]	2021
Vilches 2022	14	216	18	273	28.7%	0.98 [0.50, 1.93]	2022
Total (95% CI)		796		711	100.0%	0.64 [0.38, 1.10]	
Total events	50		67				
Heterogeneity: Tau ² = 0.14; Chi ² = 5.78, df = 3 (P = 0.12); I ² = 48%							
Test for overall effect: Z = 1.62 (P = 0.10)							

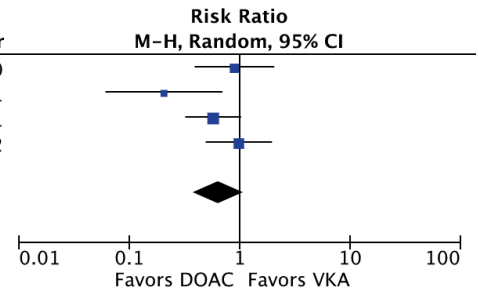


Figure 2. Forest plot of bleeding events for DOAC vs. VKA in cardiac amyloid patients. DOAC = direct oral anticoagulant; VKA = vitamin K antagonist; CI = confidence interval.

Study or Subgroup	DOAC		VKA		Weight	Risk Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
Mitrani 2020	8	116	6	78	19.2%	0.90 [0.32, 2.48]	2020
Cariou 2021	2	126	6	147	7.9%	0.39 [0.08, 1.89]	2021
Mentias 2021	16	338	24	213	53.7%	0.42 [0.23, 0.77]	2021
Vilches 2022	5	239	13	322	19.2%	0.52 [0.19, 1.43]	2022
Total (95% CI)		819		760	100.0%	0.50 [0.32, 0.79]	
Total events	31		49				
Heterogeneity: Tau ² = 0.00; Chi ² = 1.68, df = 3 (P = 0.64); I ² = 0%							
Test for overall effect: Z = 3.02 (P = 0.003)							

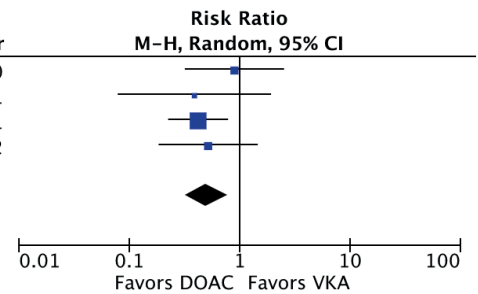


Figure 3. Forest plot of thrombotic events for DOAC vs. VKA in cardiac amyloid patients. DOAC = direct oral anticoagulant; VKA = vitamin K antagonist; CI = confidence interval.

Study or Subgroup	DOAC		VKA		Weight	Risk Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
Mitrani 2020	12	116	9	78	37.1%	0.90 [0.40, 2.03]	2020
Cariou 2021	2	94	12	85	21.9%	0.15 [0.03, 0.65]	2021
Vilches 2022	14	216	18	273	41.1%	0.98 [0.50, 1.93]	2022
Total (95% CI)		426		436	100.0%	0.63 [0.26, 1.54]	
Total events	28		39				
Heterogeneity: Tau ² = 0.39; Chi ² = 5.57, df = 2 (P = 0.06); I ² = 64%							
Test for overall effect: Z = 1.01 (P = 0.31)							

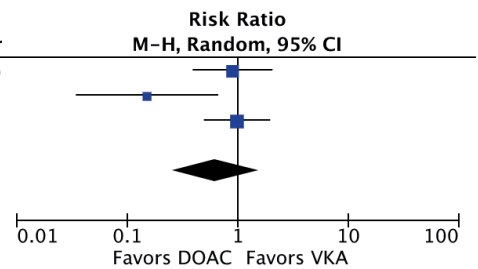


Figure 4. Forest plot of bleeding events for DOAC vs. VKA in transthyretin cardiac amyloid patients. DOAC = direct oral anticoagulant; VKA = vitamin K antagonist; CI = confidence interval.

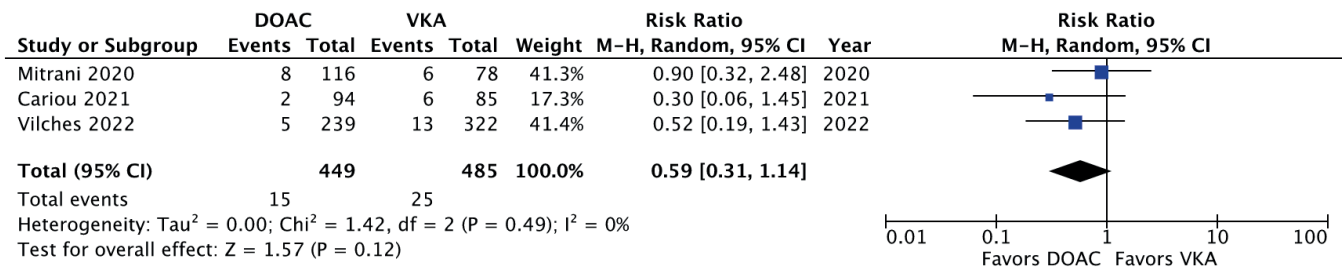


Figure 5. Forest plot of thrombotic events for DOAC vs. VKA in transthyretin cardiac amyloid patients. DOAC = direct oral anticoagulant; VKA = vitamin K antagonist; CI = confidence interval.

DISCUSSION

This is the first systematic review and meta-analysis on the safety and efficacy of anticoagulation therapy in patients with cardiac amyloidosis and atrial fibrillation. Our findings are derived from 4 studies reporting clinical outcomes in 1,579 patients with cardiac amyloidosis and atrial fibrillation. There were decreased thrombotic events and no difference in major bleeding in patients with cardiac amyloidosis treated with DOACs when compared to VKAs.

The initial landmark randomized clinical trials established the non-inferiority of DOACs compared to VKAs for anticoagulation in atrial fibrillation.^{16,49} Several recent meta-analyses have shown DOACs to have decreased systemic embolism, major bleeding, hemorrhagic stroke, and all-cause mortality when compared to VKAs.²⁰⁻²² Patients with cardiac amyloidosis warrant particular consideration for DOAC anticoagulation therapy since they have an increased risk of both thromboembolism and bleeding.^{1,23} Our study demonstrates decreased thrombotic events and a non-significant trend towards decreased major bleeding events for DOACs when compared to VKAs in patients with cardiac amyloidosis and atrial fibrillation.

VKAs require frequent laboratory monitoring to maintain efficacy and patients treated with VKAs have been shown to only spend about 55–68% of time in therapeutic range.²⁴ The included studies by Mitrani et al.¹² and Vilches et al.¹⁵ reported 87% and 19% of patients treated with VKAs had labile international normalized ratio, respectively. Interestingly, the included study by Cariou et al.¹³ did show increased risk of bleeding for VKAs when compared to DOACs that was not demonstrated in our meta-analysis. The authors proposed the increased bleeding rate to be from impaired renal function, but this was not seen in the multivariate analysis. These findings suggest it may be reasonable to consider DOACs as an alternative to VKAs given the challenges of maintaining therapeutic INR in patients with cardiac amyloidosis and atrial fibrillation. Randomized clinical trials are needed to study anticoagulation therapy in patients with cardiac amyloidosis and

atrial fibrillation before guideline recommendation changes can be made for this specific patient population.

The mechanism behind the increased risk of thromboembolism is related to amyloid deposition causing increased left ventricular filling pressures and resulting in left atrial enlargement and remodeling. This atrial remodeling leads to blood stasis and turbulence that predisposes to the development of intracardiac thrombi.²⁵ Additionally, amyloid infiltration causes myocardial injury and endothelial dysfunction, which can trigger cytokines and the prothrombotic inflammatory cascade.²⁶ AL has additional thromboembolic mechanisms compared to ATTR due to the systemic nature of the disease. In AL, nephrotic syndrome leads to urinary loss of anticoagulant factors and increased synthesis of procoagulant factors. Hyposplenism leads to thrombocytosis and there is increased blood viscosity and procoagulant activity due to circulating monoclonal proteins.²⁵ There are multiple mechanisms for the increased risk of bleeding in cardiac amyloidosis. Perivascular amyloid deposition causes vascular fragility causing amyloid angiopathy. Advanced kidney dysfunction in amyloidosis can lead to uremia-induced platelet dysfunction. In AL, clotting abnormalities due to circulating monoclonal proteins and chemotherapy-induced bone marrow suppression contribute to bleeding risk. Dysautonomia from amyloidosis also increases fall risk in this patient population.²⁵

The limitations of this systematic review and meta-analysis are influenced by the limitations of the included studies. CIs for estimates were wide in spite of pooling due to low event rates in the included studies. The pooled estimates are likely underpowered and more data are needed to further investigate clinical differences between anticoagulation groups in this patient population. Variations in clinical settings, population characteristics, follow-up time, and endpoint definitions are potential sources of heterogeneity. We used a random effects model to account for these variations. All of the included studies are likely influenced by between-center variability and lack of centralized independent assessment of outcomes. The inclusion of patients with AL and




ATTR-CA likely influences the generalizability of the aggregate data as outcomes vary by each subtype of cardiac amyloidosis. However, subgroup analysis of only ATTR-CA patients showed similar results to the aggregate data. The study by Vilches et al.¹⁵⁾ is a multicenter study that included the same single-center patient population reported earlier by Mitrani et al.¹²⁾ We did not have access to patient-specific data, so were unable to remove patients previously accounted for in the pooled estimates. This likely lead to double counting of some cases and introduced statistical error to our results. However, analysis with the Mitrani et al.'s study¹²⁾ excluded revealed similar results.

In this systematic review and meta-analysis, there were decreased thrombotic events and no difference in major bleeding events in patients with cardiac amyloidosis and atrial fibrillation treated with DOACs when compared to VKAs. This suggests DOACs are as safe and effective as VKAs for anticoagulation therapy in this specific patient population.

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ORCID iDs

Spencer C. Lacy 
<https://orcid.org/0000-0002-6909-9139>
 Menhel Kinno 
<https://orcid.org/0000-0003-0468-8271>
 Mingxi D. Yu 
<https://orcid.org/0000-0002-6581-7914>

Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Lacy SC, Kinno M, Yu MD; Data curation: Lacy SC; Formal analysis: Lacy SC, Joyce C; Investigation: Lacy SC, Yu MD; Methodology: Lacy SC, Joyce C, Yu MD; Software: Lacy SC; Supervision: Kinno M, Joyce C, Yu MD; Writing - original draft: Lacy SC, Kinno M, Yu MD; Writing - review & editing: Lacy SC, Kinno M, Yu MD.

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