DOAC Dynasty: Use of Direct Oral Anticoagulants in Patients with Left Ventricular Thrombus

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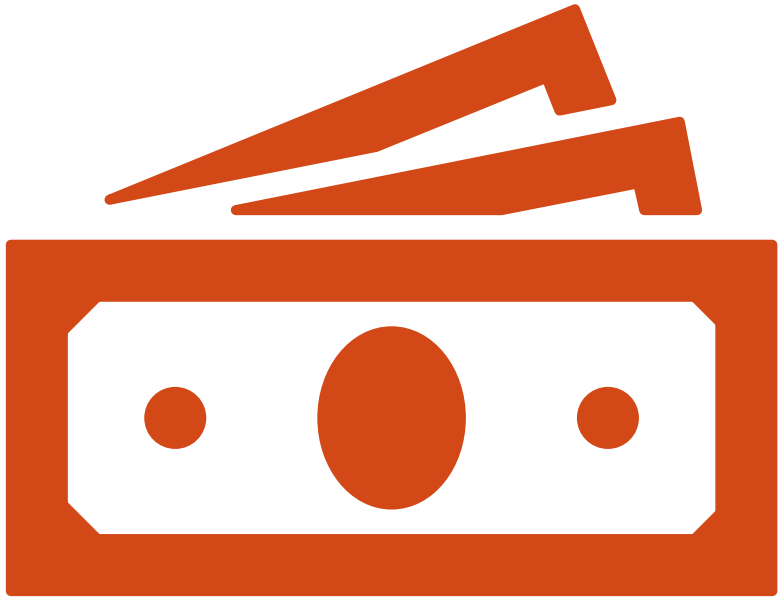


Financial Disclosure

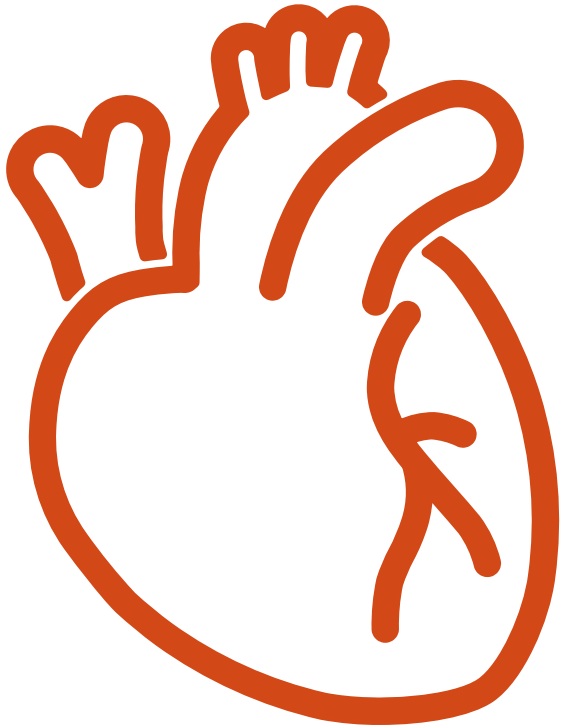
This Speaker has no financial conflicts of interest to disclose

Learning Objectives for Pharmacists

1. Discuss guideline recommendations regarding anticoagulation for the treatment of left ventricular (LV) thrombus
2. Interpret primary literature on the use of direct oral anticoagulants (DOACs) in patients with LV thrombus
3. Explain the risks and benefits of using DOACs compared to vitamin K antagonists for the treatment of LV thrombus
4. Assess a patient with LV thrombus and determine if the use of a DOAC is appropriate

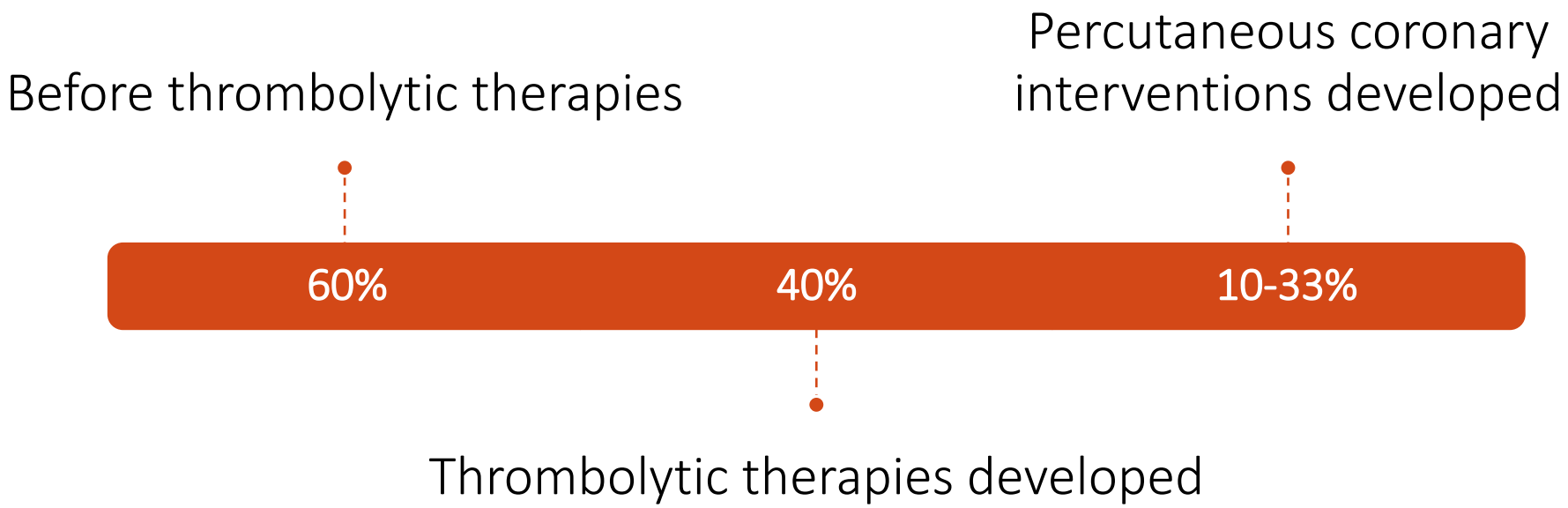
Learning Objectives for Technicians

1. Identify anticoagulants used in patients with LV thrombus
2. List DOACs studied in primary literature for patients with LV thrombus
3. Compare the risks and benefits of using DOACs compared to vitamin K antagonists for the treatment of LV thrombus



Overview of LV Thrombus

Epidemiology: Incidence of LV Thrombus after MI



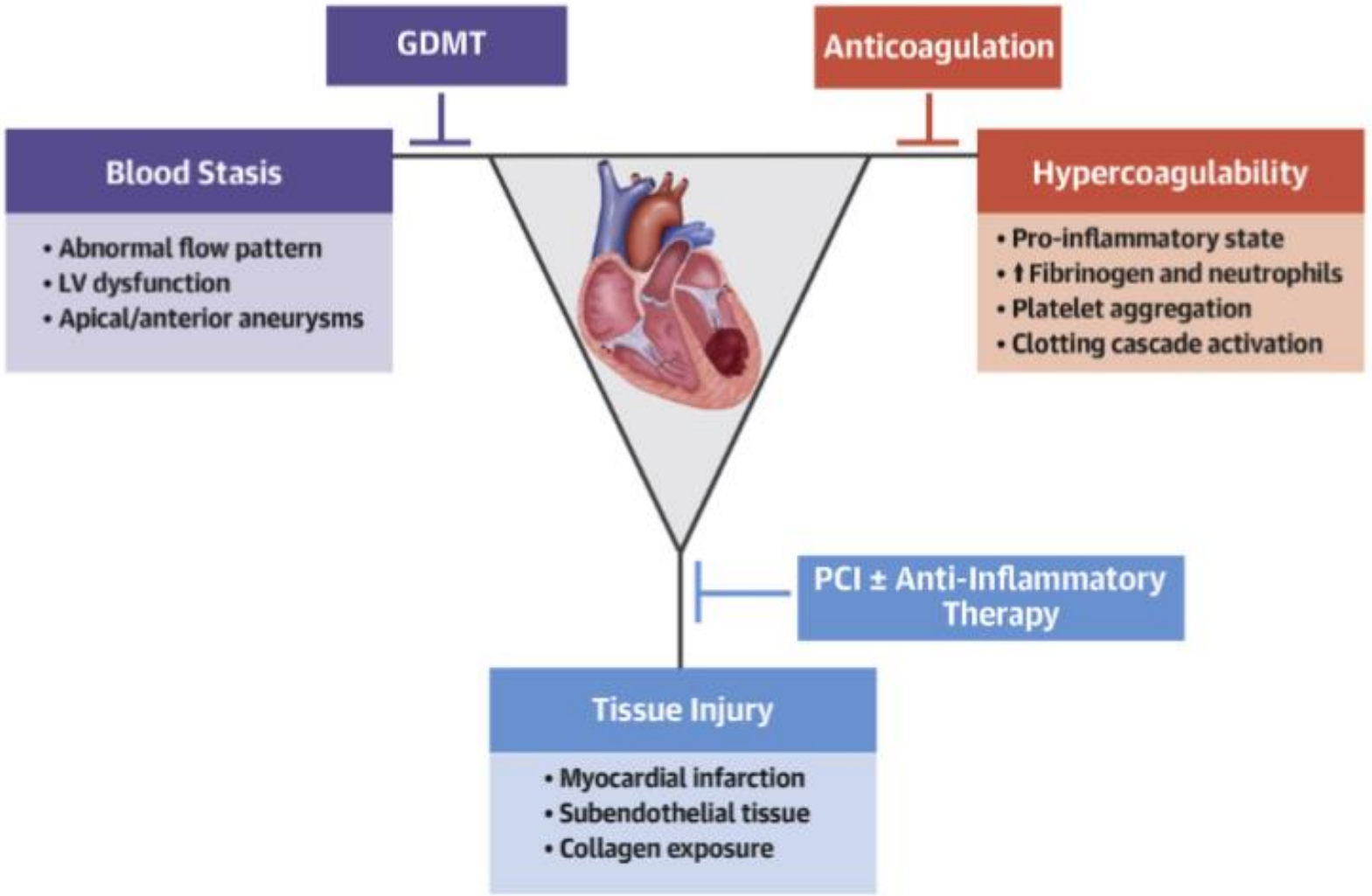
Epidemiology: Complications at One Year

13%

All-cause mortality

1.9%

Embolic events



Pathophysiology: Virchow's Triad

Pathophysiology

Acute myocardial infarction (MI)

Regional endocardial tissue injury, inflammation, and hypercoagulability

Heart Failure (HF)

Stasis due to globally reduced LV function

Knowledge Check

Which of the following contributes to LV thrombus formation?

A. Blood stasis caused by HF
B. Hypercoagulability that occurs during acute MI
C. Tissue injury during acute MI
D. All of the above

Knowledge Check

Which of the following contributes to LV thrombus formation?

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C. Tissue injury during acute MI
D. **All of the above**

Guideline Recommendations

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction (STEMI)

- Anticoagulant therapy with vitamin K antagonist (VKA) reasonable for patients with STEMI and asymptomatic LV mural thrombi
- Duration of VKA therapy can be limited to 3 months in patients with or at risk for LV thrombus (e.g., those with anteroapical akinesis or dyskinesis)

O'Gara et al. Circulation 2013

Warfarin Studies

Study	Design	Intervention/Comparator	Outcome
Weinreich et al.	Prospective observational	Warfarin (n = 25) vs. no anticoagulation (n = 18)	Mortality: 28% vs. 39%; NS Embolic complications: 0% vs. 39%; p<0.05
Keating, et al.	Prospective observational	Anticoagulation (9 warfarin and 1 aspirin/dypyridamole) vs. no anticoagulation	Anticoagulation = 80% resolution of thrombus No anticoagulation = 86% embolic events within 3 months
Vaitkus, et. al	Meta-analysis	Warfarin vs. no anticoagulation 7 studies with 270 patients	Embolic events: OR 0.14 (95% CI 0.04 to 0.52)

Weinreich et al. Ann Intern Med 1984
Keating et al. Am J Med 1983
Vaitkus et al.. J Am Coll Cardiol 1993

Knowledge Check

True or False. Per 2013 ACCF/AHA Guideline for the Management of STEMI, warfarin and DOACs can be used for the treatment of LV thrombus?

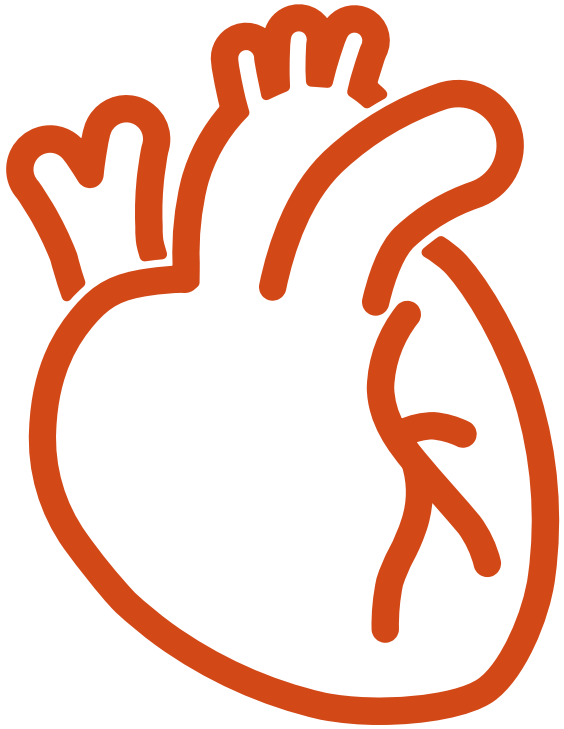
A. True
B. False

Knowledge Check

True or False. Per 2013 ACCF/AHA Guideline for the Management of STEMI, warfarin and DOACs can be used for the treatment of LV thrombus?

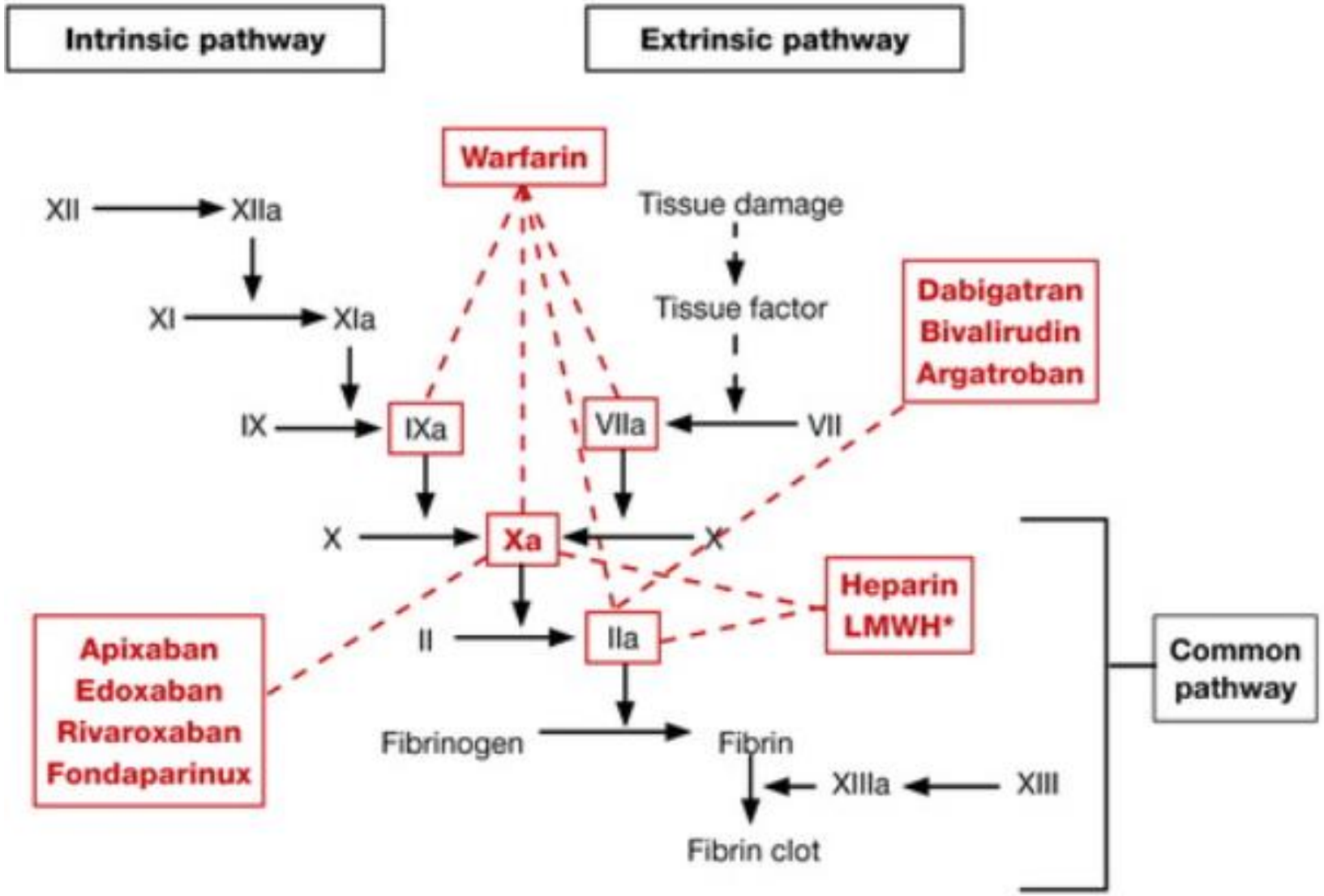
A. True

B. False



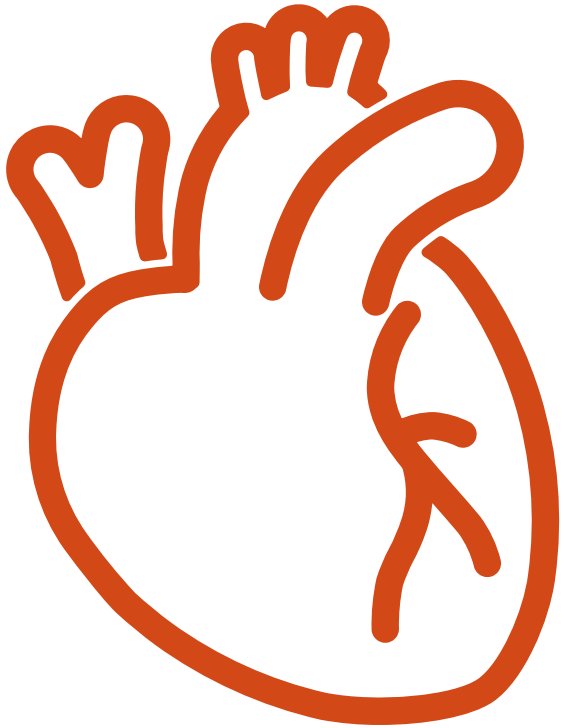
Oral Anticoagulants

Oral Anticoagulants & the Coagulation Cascade



Overview of anticoagulants

Drug	MOA	Indications	Dosing considerations
Warfarin	Vitamin K antagonist	Non-valvular AF Valvular AF Anticoagulation for mechanical heart valve DVT/PE	Based on INR Food/drug interactions
Apixaban	Factor Xa inhibitor	Non-valvular AF DVT/PE	Renal adjustment depending on indication Child-Pugh class C: Avoid use
Rivaroxaban	Factor Xa inhibitor	Non-valvular AF DVT/PE	Renal adjustment Child-Pugh class B or C: Avoid use
Edoxaban	Factor Xa inhibitor	Non-valvular AF DVT/PE	Renal adjustment Child-Pugh class B or C: Avoid use
Dagibatran	Direct thrombin inhibitor	Non-valvular AF DVT/PE	Renal adjustment



DOACs vs. Warfarin

DOAC vs. Warfarin

DOACs	Warfarin
Less monitoring	Frequent monitoring
Lower Bleeding risk	More drug-drug/food interactions
Higher cost	Lower cost

Drug-Drug/Food Interactions

Drug	Metabolism	Drug-Drug/Food Interactions
Apixaban	Primarily CYP3A4/5 P-gp substrate	**Strong inducers of CYP3A4 and P-gp (Avoid)** **Strong inhibitors of CYP3A4 and P-gp (Reduce dose)**
Rivaroxaban	Primarily CYP3A4/5 P-gp substrate	**Strong inducers of CYP3A4 and P-gp (Avoid)** **Strong inhibitors of CYP3A4 and P-gp (Avoid)**
Warfarin	Primarily CYP2C9 Minor: CYP2C8, 2C18/19, 1a2, and 3A4	**Increase potency or bleed risk**: NSAIDs, CYP2C9 inhibitors, cephalosporins, fluoroquinolones, tetracyclines **Decrease potency**: vitamin K rich foods, CYP2C9 inducers **Can adjust for drug and food interactions** with frequent INR monitoring

DOAC vs Warfarin Trials

Trial	Drug	Result	Bleeding
ARISTOTLE	Apixaban vs. Warfarin	Apixaban superior in preventing stroke or systemic embolism in patients with AF	Less major bleeding ↓ ICH GI bleeding: no difference
ROCKET-AF	Rivaroxaban vs. warfarin	Rivaroxaban non-inferior for prevention of stroke or systemic embolism in patients with AF	No difference in major bleeding ↓ ICH ↑ GI bleeding

Granger et al. NEJM 2011
Patel et al. NEJM 2011

DOAC vs Warfarin Trials

Trial	Drug	Result	Bleeding
ENGAGE AF-TMI 48	Edoxaban vs. warfarin	Edoxaban superior for prevention of stroke or systemic embolism in patients with AF	Less major bleeding ↑ GI bleeding (high-dose)
RE-LY	Dabigatran vs. warfarin	Dabigatran superior for prevention of stroke or systemic embolism in patients with AF	Less major bleeding ↑ GI bleeding (150 mg dabigatran)

Giugliano et al. NEJM 2013
Connolly et al. NEJM 2009

Knowledge Check

Which DOAC(s) showed superiority over warfarin for the prevention of systemic stroke and embolism in patients with atrial fibrillation?

A. Apixaban
B. Rivaroxaban
C. Dabigatran
D. A and C
E. All of the above

Knowledge Check

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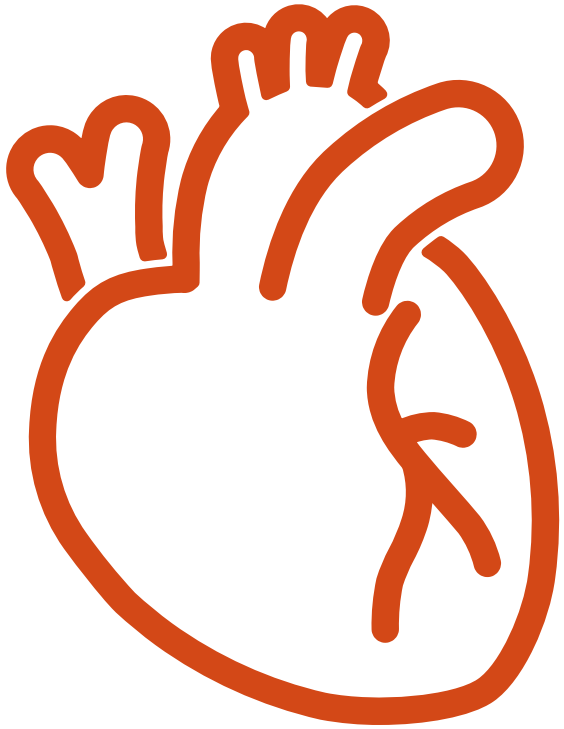


When are DOACs preferred for the treatment of LV thrombus?

Management of Left Ventricular Thrombi with Direct Oral Anticoagulants: Retrospective Comparative Study with Vitamin K Antagonists

Daher, et al. Clin Drug Investig 2020

Daher, et al.

Methods		
Overview	• Compared rate of LV thrombus resolution • Single center, observational, retrospective study	
Population	**Inclusion criteria** ▪ Patients with LV thrombi detected by transthoracic echocardiography (TTE)	**Exclusion criteria** ▪ None

Daher, et al.

Methods	

Intervention	▪ DOAC vs VKA (goal INR 2-3)
	▪ DOACs
	  ▪ Apixaban 2.5/5 mg BID
	  ▪ Rivaroxaban 15-20 mg/day
	  ▪ Dabigatran 110/150 mg BID
	▪ Patients who failed to respond to DOAC treatment (no thrombus resolution, n = 5) were switched to VKA (goal INR 3-4)

Primary Outcome	Rate of LV thrombus resolution

Daher, et al.

Results	

Baseline characteristics	▪ N = 59 patients
	▪ DOAC (n = 17, 28.8%)
	  ▪ Apixaban (n = 12)
	  ▪ Rivaroxaban (n = 4)
	  ▪ Dabigatran (n = 1)
	▪ VKA (n = 42, 71.2%)
	  ▪ Warfarin (n = 14), acenocoumarol (n = 12), fluindione (n = 16)
	▪ Mean (SD) age: 62 (14) years; sex: 16.9% women
	▪ Ischemic cardiomyopathy was present in 51 patients (86.5%) and dilated cardiomyopathy in eight patients (13.5%)

Daher, et al.

Variables	LV thrombus on DOACs (*n* = 59)	LV thrombus on VKAs (*n* = 42)	*p*-values
Age [mean ± SD (years)]	57 ± 14	61 ± 13	0.5
Sex, *n* (% female)	3 (17.6)	7 (17)	0.9
Hypertension [*n* (%)]	10 (59)	17 (40.5)	0.2
Diabetes mellitus [*n* (%)]	2 (12)	9 (21.4)	0.6
High blood cholesterol [*n* (%)]	5 (29.4)	18 (43)	0.5
Smoking [*n* (%)]	10 (59)	25 (59.5)	0.9
Structural heart disease [*n* (%)]	6 (100)	42 (100)	0.9
Ischemic cardiomyopathy [*n* (%)]	15 (88)	36 (74)	0.6
LVEF [mean ± SD (%)]	41 ± 8	36 ± 12	0.1

Daher, et al.

DOACs	VKAs
Complete thrombus resolution at 3 months	
Rivaroxaban (1/4 = 25%) Apixaban (11/12 = 92%) Dabigatran (0/1 = 0%)	Acenocoumarol (10/12 = 83.3%) Fluindione (13/16 = 81.3%) Warfarin (7/14 = 50%)
12/17 (**70.6%**)	42/59 (**71.2%**)
Not statistically significant difference (**p = 0.9**)	

Strengths

- Included doses that were prescribed (though not frequency of prescribing)

Limitations

- Single center, retrospective
- Small sample size
- No defined inclusion/exclusion criteria

Daher et al. Clin Drug Investig 2020

Key Takeaway

- DOACs (apixaban and rivaroxaban) can be used for treatment of LV thrombus
  - Single patient on dabigatran did not achieve thrombus resolution at 3 months
- Study focused on patients with ischemic cardiomyopathy and dilated cardiomyopathy

Off-label Use of Direct Oral Anticoagulants Compared With Warfarin for Left Ventricular Thrombi

Robinson, et al. JAMA 2020

Robinson, et al.

Methods		
Overview	▪ Multicenter, retrospective, cohort study	
Population	**Inclusion criteria** ▪ Echocardiographically diagnosed LV thrombus	**Exclusion criteria** ▪ None
Intervention	▪ DOAC vs warfarin	
Primary Outcome	▪ Embolic events defined as composite of clinically documented stroke or systemic embolism (SSE)	

Robinson, et al.

Results
▪ N = 514 patients ▪ Any DOAC (n=185) ▪ Apixaban (n = 141) ▪ Rivaroxaban (n = 46) ▪ Dabigatran (n = 9) ▪ Any warfarin (n = 300) ▪ Therapy change (n = 64)

Robinson, et al.

Results	
Baseline characteristics	▪ 379 men; mean [SD] age, 58.4 [14.8] years ▪ Type of cardiomyopathy: ischemic (59.9%), non-ischemic cardiomyopathy non otherwise specified (NICM NOS) (25.3%), unknown (7.8%), peripartum (2.1%), hypertrophic (1.6%), chemotherapy (1.4%), tachycardia (0.8%), stress (0.8%), familial (0.4%)

Characteristic	Patients, No. (%)			
	DOAC only (n = 121)	Warfarin only (n = 236)	Therapy change (n = 64)	*P* value
White race/ethnicity	73 (60.3)	119 (50.4)	32 (50.0)	0.04
Type 1 and 2 diabetes	36 (29.8)	92 (39.0)	26 (40.6)	0.21
Hypertension	86 (71.1)	177 (75.0)	47 (73.4)	0.99
Hyperlipidemia	71 (58.7)	126 (53.4)	29 (45.3)	0.32
Ischemic cardiomyopathy	66 (54.5)	148 (62.7)	36 (56.3)	0.34
Venous thromboembolism	25 (20.7)	38 (16.1)	19 (29.7)	0.02
Atrial fibrillation	30 (24.8)	45 (19.1)	23 (35.9)	0.04
Prior SSE	33 (27.3)	51 (21.6)	15 (23.4)	0.09
Presenting embolism	21 (17.4)	34 (14.4)	10 (15.6)	0.32
LV ejection fraction, mean (SD), %	27.7 (13.8)	28.2 (12.4)	25.1 (11.7)	0.33
Mobile thrombus	19 (15.7)	39 (16.5)	12 (18.8)	0.79
Thrombus size, mean (SD), cm^3	2.8 (2.1)	2.8 (2.5)	2.3 (1.5)	0.43
Antiplatelet therapy	77 (63.6)	164 (69.5)	38 (59.4)	0.42

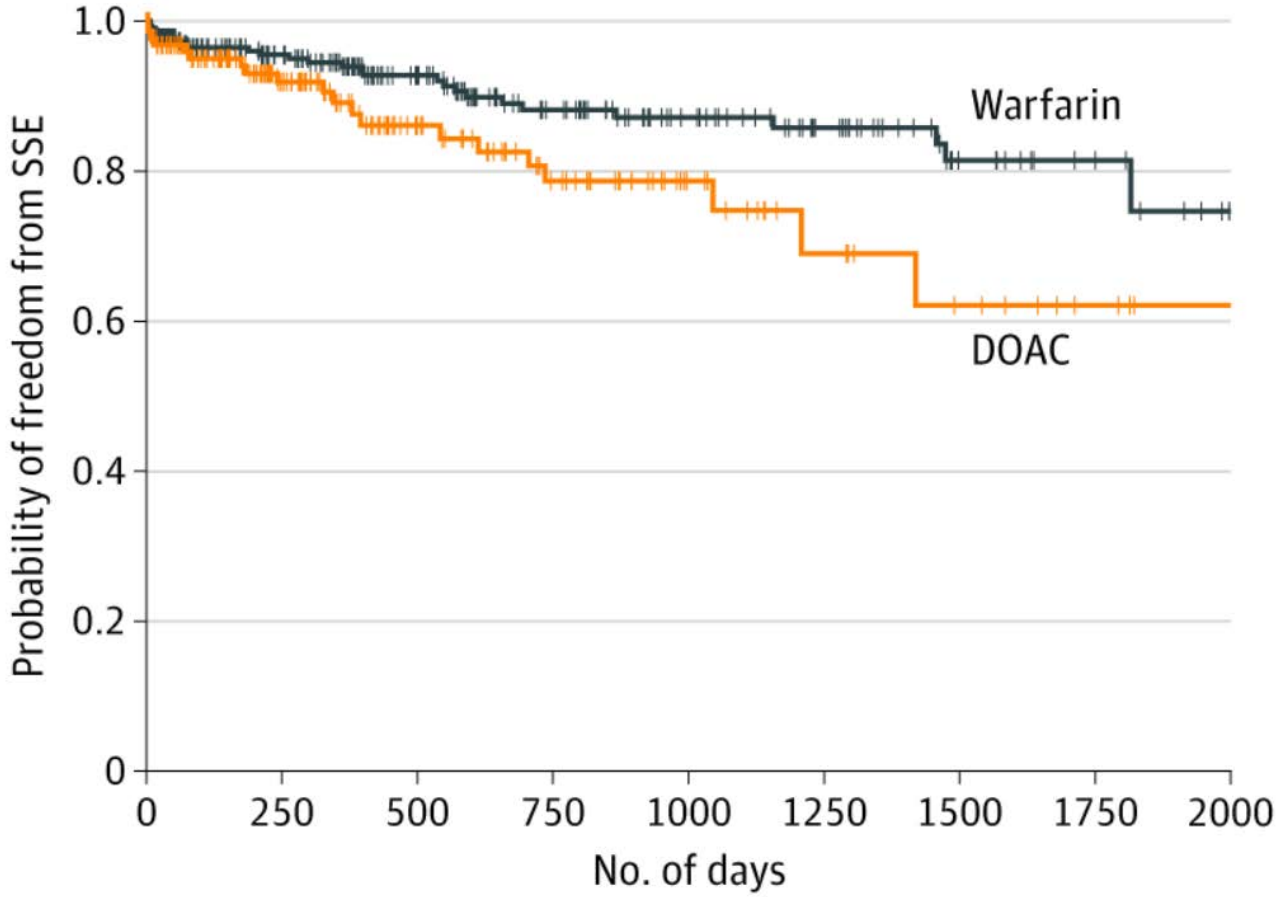
Robinson, et al.

Anticoagulant	Events, No.		
	SSE	Death	Bleeding event
DOAC	17	14	8
Warfarin	14	32	19
Parenteral agent	11	12	4
None	12	57	NA
Total	54	115	31

SSE

Cox proportional hazards regression analysis:
Univariable: HR, 2.71; 95% CI, 1.31-5.57; *P* = 0.01
Multivariable: HR 2.64; 95% CI, 1.28-5.43; *P* = 0.01

Risk of SSE



No. at risk									
Warfarin	87	193	138	99	73	59	33	28	17
DOAC	64	80	50	37	22	12	9	5	2

Robinson et al. JAMA 2020

Robinson, et al.

Within 3 months	Between 3 and 6 months
• Warfarin: 4 SSE events • DOACs: 5 SSE events • HR 2.33; 95% CI, 0.63-8.74; *P* = 0.21	• No SSE events

Strengths

- Relatively large trial
- Multi-centered
- Wide variety of etiology for LV thrombus study
- Multi-variable analysis

Robinson et al. JAMA 2020

Limitations

- Lack of randomization
- No defined inclusion/exclusion criteria
- Resolution of thrombus or discontinuation of oral anticoagulant not counted as a censoring event
- DOAC doses not reported
- Follow-up much longer than typical timeframe for resolution of thrombus

Robinson et al. JAMA 2020

Key Takeaway

- No difference in stroke and systemic embolism (SSE) between DOACs and warfarin for treatment of LV thrombus at 3 and 6 months

- Prior SSE significantly associated with SSE

Apixaban vs. warfarin in patients with left ventricular thrombus: a prospective multicenter randomized clinical trial

Alcalai, et al. European Heart Journal Cardiovascular Pharmacotherapy 2022

Alcalai, et al.

Methods	
Objective	▪ To assess if apixaban is as effective as warfarin for treatment of LV thrombus after acute MI
Study Design	▪ Multicenter, prospective, open-label, non-inferiority
Primary Outcome	▪ Presence of LV thrombus as assessed by 2D-TTE after 3 months of treatment
Secondary Outcome	▪ Major bleeding ▪ Stroke or systemic embolism ▪ Re-hospitalization for cardiovascular reasons and for non-cardiovascular reasons ▪ Death from any cause up to 3 months

Alcalai, et al.

Intervention
▪ Apixaban 5 mg BID vs. subcutaneous enoxaparin 1 mg/kg BID followed by dose adjusted warfarin to achieve target INR of 2.0-3.0 for three months ▪ All patients discharged with aspirin, clopidogrel, and anticoagulation (apixaban or warfarin according to randomization); aspirin was stopped after one month

Alcalai, et al.

Inclusion

- Evidence of LV thrombus as assessed by 2D-TTE during a period of 1–14 days following acute MI

Exclusion

- Contraindication to chronic anticoagulation
- Severe renal failure (CrCl < 15 mL/min)
- Other indications for chronic anticoagulation (e.g. AF, PE)

Baseline characteristics

	Apixaban N= 18	Warfarin N=17	*P*-value
Age, years (mean ± SD)	55.5 ± 12.9	58.8 ± 10.2	0.40
Gender (male)	13 (72.2)	15 (88.2)	0.40
Hypertension	7 (38.9)	7 (41.2)	0.89
Dyslipidemia	7 (38.9)	9 (52.9)	0.41
Current smokers	13 (72.2)	10 (58.8)	0.40
Diabetes	8 (44.4)	5 (29.4)	0.36
Obesity	4 (22.2)	4 (23.5)	1
Prior IHD	4 (22.2)	3 (17.7)	1
Prior CKD	3 (16.7)	1 (5.9)	0.32
Baseline EF (%)	35 ± 5	36 ± 7	0.74
Baseline thrombus size (length)	19.9 ± 9.4	18.5 ± 6.9	0.6
Baseline thrombus size (width)	12.4 ± 5.8	12.3 ± 4	0.96

Outcome at 3-month Follow-up

	Apixaban N= 17	Warfarin N=15	*P*-value
Complete resolution of thrombus	16 (94.1%)	14 (93.3)	1 (superiority); 0.026 (non-inferiority)
Major bleeding	0	2	N/A
Stroke/embolic event	0	1	N/A
All-cause mortality	1	0	N/A
Cardiovascular event	3	2	N/A
Other event	3	1	N/A
All events	7 (38.8%)	6 (40%)	0.8
Median follow-up time (days)	86.5 (IQR 85–93)	92 (IQR 85–102)	0.19
EF at end of follow-up (%)	40 ± 10	37 ± 9	0.48
Change in EF from baseline (%)	5 ± 9	1 ± 2	0.17

Strengths

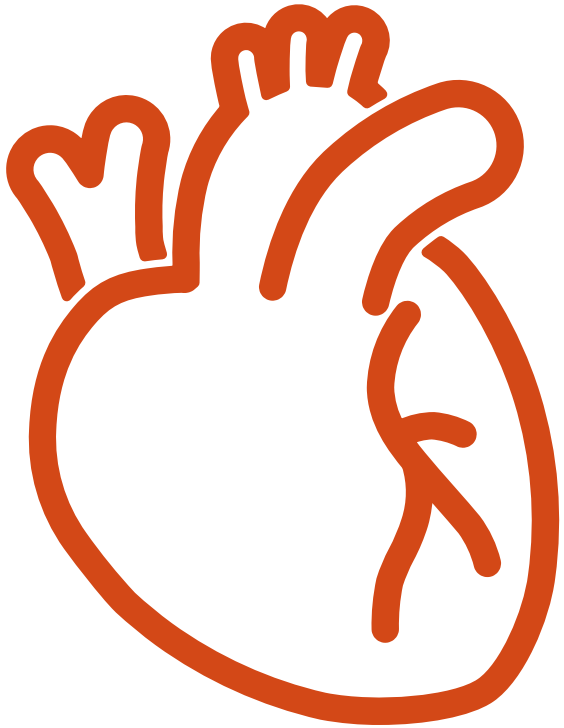
- First prospective, randomized trial
- Multicenter
- Clearly defined bleeding criteria

Limitations

- Small sample size
- Open label study (not blinded)

Key Takeaway

- Apixaban had similar efficacy compared to warfarin when used as treatment for LV thrombus in patients after an MI



Summary and Conclusions

2022 Management of Patients at Risk for and With Left Ventricular Thrombus: A Scientific Statement From the American Heart Association

- Therapeutic anticoagulation (**VKA or DOAC**) for treatment of LV thrombus after **acute MI**, typically for a **duration of 3 months**, with follow-up imaging

- **VKA or DOAC** in patients with LV thrombus in the setting of **dilated cardiomyopathy (DCM) for at least 3 to 6 months,** with **discontinuation if LVEF improves to > 35%**

- **Indefinite therapy if LV systolic function does not improve**

DOACs and Dosing Used in Studies

Apixaban	• 5 mg po BID • 2.5 mg po BID if ≥ 2 criteria: age ≥ 80 years, weight ≤ 60 kg, and SCr ≥ 1.5 mg/dL
Rivaroxaban	• 20 mg po daily • 15 mg po daily
Dabigatran	• 150 mg po BID • 110 mg po BID

Patient Considerations

Patients with indication for warfarin	Patients taking many medications	Patients with unreliable follow-up
• Heart valve replacement • Valvular atrial fibrillation	• DOACs have fewer drug-drug interactions • However, no standardized monitoring	• DOACs do not have routine monitoring

Recommendations

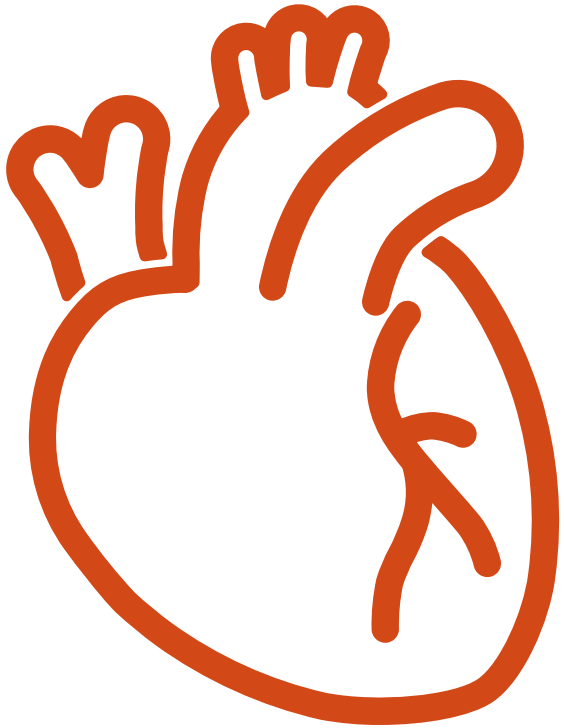
DOACs can be used for the treatment of LV thrombus

- Recommend apixaban or rivaroxaban

DOACs effective for duration of 3 to 6 months

- Recommend warfarin for LV thrombus use greater than 6 months

Warfarin preferred in patients with a history of SSE



Post Test Questions

1. Which anticoagulant is recommended in the 2013 guidelines for the treatment of left ventricular (LV) thrombus?

A. Apixaban
B. Warfarin
C. Heparin
D. Enoxaparin

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2. In the literature reviewed, which of the following is a DOAC dose commonly studied for the treatment of LV thrombus?

A. Apixaban 10 mg twice daily for 7 days followed by apixaban 5 mg twice daily
B. Dabigatran 150 mg daily
C. Apixaban 5 mg twice daily
D. Rivaroxaban 15 mg twice daily for 21 days followed by rivaroxaban 20 mg daily

2. In the literature reviewed, which of the following is a DOAC dose commonly studied for the treatment of LV thrombus?

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B. Dabigatran 150 mg daily
C. **Apixaban 5 mg twice daily**
D. Rivaroxaban 15 mg twice daily for 21 days followed by rivaroxaban 20 mg daily

3. Which of the following is a benefit of using a DOAC instead of warfarin for the treatment of LV thrombus?

A. Less frequent monitoring
B. Established monitoring assays
C. Superior efficacy compared to warfarin
D. All of the above

3. Which of the following is a benefit of using a DOAC instead of warfarin for the treatment of LV thrombus?

A. **Less frequent monitoring**
B. Established monitoring assays
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D. All of the above

4. AT is a 55-year-old male with a PMH of diabetes, hypertension, heart failure with an ejection fraction of 40% (2021). He has an inconsistent diet, frequently misses follow-up appointments and hates getting his fingers pricked. His home medications include carvedilol 3.125 mg BID, dapagliflozin 10 mg daily, losartan 50 mg daily, metformin 1000 mg BID, and spironolactone 25 mg daily. He is currently hospitalized for a heart failure exacerbation. A TTE showed a worsening EF of 20% and the presence of an LV thrombus. His CrCl is 95 ml/min. What anticoagulation would you recommend for this patient and for how long?

A. Initiate apixaban 5 mg twice daily indefinitely
B. Initiate warfarin 5 mg daily for 6 months
C. Initiate apixaban 2.5 mg twice daily for 3 months then repeat imaging to determine duration
D. Initiate rivaroxaban 20 mg daily for 3 months then repeat imaging to determine duration

4. AT is a 55-year-old male with a PMH of diabetes, hypertension, heart failure with an ejection fraction of 40% (2021). He has an inconsistent diet, frequently misses follow-up appointments and hates getting his fingers pricked. His home medications include carvedilol 3.125 mg BID, dapagliflozin 10 mg daily, losartan 50 mg daily, metformin 1000 mg BID, and spironolactone 25 mg daily. He is currently hospitalized for a heart failure exacerbation. A TTE showed a worsening EF of 20% and the presence of an LV thrombus. His CrCl is 95 ml/min. What anticoagulation would you recommend for this patient and for how long?

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C. Initiate apixaban 2.5 mg twice daily for 3 months then repeat imaging to determine duration
D. **Initiate rivaroxaban 20 mg daily for 3 months then repeat imaging to determine duration**

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