DOACs in LVT: To Be or Not To Be

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Learning Objectives:

1. Identify risk factors for the development of left ventricular thrombus
2. Summarize guideline recommendations for the treatment of left ventricular thrombus including the agent and duration of treatment
3. Select an appropriate treatment regimen for left ventricular thrombus taking into consideration patient specific factors

Background[1]:

Left ventricular thrombus (LVT): a blood clot in the left ventricle of the heart
Incidence by cause:

- Anterior myocardial infarction (MI): 25%
- ST-segment elevation myocardial infarction (STEMI): 15%
- Non-ischemic cardiomyopathies: 2 – 36%

Pathophysiology of LVT after MI[1]:

Virchow's Triad: blood stasis, endomyocardial injury, and hypercoagulability

- Blood stasis: Reduced contraction, wall motion abnormalities, diastolic dysfunction
- Endomyocardial injury: STEMI, poor reperfusion, extended period of ischemia
- Hypercoagulability: increased inflammation post MI, thrombocytosis, and leukocytosis

Risk Factors[1,2]:

- Lower left ventricular ejection fraction
- Severe diastolic dysfunction
- Large infarct size
- LV akinesia or dyskinesia
- LV apex involvement
- Anterior MI

Diagnosis[1]:

- Transthoracic echocardiogram (TTE) is routinely performed
    - Low sensitivity for LVT
- Transesophageal echocardiogram (TEE) can be performed
- Cardiac magnetic resonance with contrast
    - Gold standard
    - Not frequently used due to cost and availability

Clinical importance[1,3]:

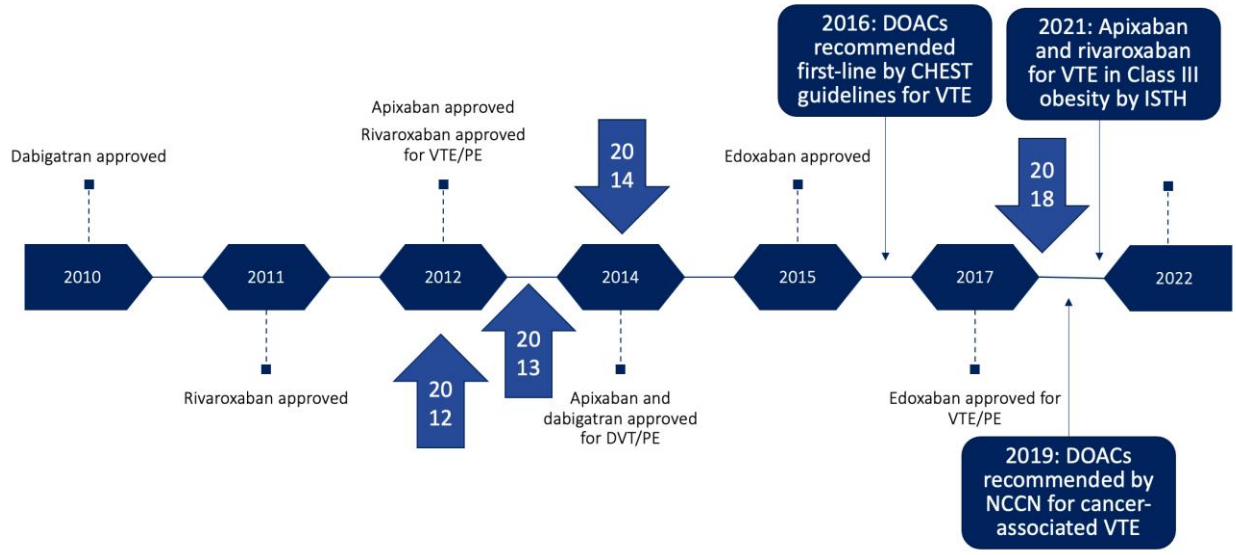
- LVT increases a patient's risk of having a stroke or systemic embolism
- This puts the patient at risk of higher morbidity and mortality
    - Risk of embolic event is ~10%
- The risk of LVT formation is highest in the first 2 weeks after MI and the risk of stroke or systemic embolism is highest within 3 to 4 months after MI

Guideline Recommendations[3-6]:

Guidelines	Recommendations
American College of Chest Physicians CHEST (2012)	Anterior MI and LVT or high risk for LVT: • Treatment with VKA for 3 months; goal INR of 2.0 - 3.0 (Grade 1B) DOACs: no mention of their use
American College of Cardiology ACCF/AHA (2013)	STEMI and asymptomatic LVT: • Treatment with VKA for 3 months; goal INR of 2.0 - 3.0 (Class IIa, Level of evidence C) STEMI and receiving DAPT: • Treatment with VKA for 3 months; goal INR of 2.0 - 2.5 (Class IIa, Level of evidence C) DOACs: no recommendation made
American Heart Association/American Stroke Association AHA/ASA (2014)	Ischemic stroke or TIA and acute MI complicated by LVT: • Treatment with VKA for 3 months; goal INR of 2.0 - 3.0 (Class I, Level of evidence C) Ischemic stroke or TIA and acute MI with LVT and other risk factors: • Either formation of LVT or anterior or apical wall-motion abnormalities with LV ejection fraction <40% and intolerance to VKA: ○ LMWH, dabigatran, rivaroxaban, or apixaban for 3 months (Class IIb; Level of evidence C)
European Society of Cardiology ESC (2018)	STEMI and LVT: • Treatment with oral anticoagulant for up to 6 months (Class IIa; Level of evidence C) • Duration of treatment should be guided by repeat imaging • If VKA is used, target lower part of regular goal INR • Non-VKA: use the lowest effective dose for stroke prevention

Warfarin vs DOAC Considerations[7,8]:

	Warfarin	**DOAC**
Advantages	• Affordable • Once daily dosing • No renal dose consideration	• Proven safe and effective • Rapid onset/offset of action • No routine monitoring
Disadvantages	• Drug-drug interactions • Drug-food interactions • Frequent lab monitoring • Bridging requirements • Variable dosing	• Drug-drug interactions • Twice daily dosing • Renal dose adjustment considerations • Can be expensive



Chest[9], NCCN[10], ISTH[11]

Clinical question: Are DOACs safe and effective for the treatment of left ventricular thrombus?

Literature Review:

Fleddermann AM, Hayes CH, Magalski A, Main ML. Efficacy of Direct Acting Oral Anticoagulants in Treatment of Left Ventricular Thrombus. *Am J Cardiol*. 2019;124(3):367-372.[12]			
Design	Intervention	Results	Conclusion
Single-center retrospective study	52 patients treated with a DOAC for LV thrombus Apixaban (n = 26, 50%) Rivaroxaban (n = 24, 46%) Dabigatran (n = 2, 4%)	The primary end point resolution of LV thrombus or death, major bleeding, ischemic stroke, or peripheral embolization • 83% of patients had resolution of thrombus • Average time to resolution of thrombus was 264 days • 1 cardioembolic event (TIA) • 8% of patients had major bleeding requiring transfusion	Findings are consistent with and add to earlier publications • DOAC therapy appears promising for the treatment of LV thrombus • Larger, prospective trials are needed to confirm these results

Drug	Dosing Regimen	Percent of patients on this regimen
Apixaban	2.5 mg BID	15.4
	5 mg BID	84.6
Rivaroxaban	15 mg daily	20.8
	20 mg daily	79.2
Dabigatran	150 mg BID	100

Analysis:

Strengths	Limitations
• Expert ECHO reviewer to verify resolution • Reported dosing regimens • Doubled the amount of patient data available • Similar results to previous literature	• Retrospective • No standard timing for follow up imaging • No details provided about determine DOAC dose

Robinson AA, Trankle CR, Eubanks G, et al. Off-label Use of Direct Oral Anticoagulants Compared With Warfarin for Left Ventricular Thrombi. *JAMA Cardiol*. 2020;5(6):685-692.[13]

Design

- Multicenter, retrospective cohort study

Purpose

- To compare the outcomes associated with the use of DOACs and warfarin for the treatment of LVT

Interventions

- Warfarin (n = 300)
- DOAC (n = 185)
    - Apixaban N = 141 (76.2%)
    - Rivaroxaban N = 46 (24.9%)
    - Dabigatran N = 9 (4.9%)

Inclusion Criteria

- LVT diagnosed by ECHO
- October 1, 2013 to March 31, 2019

Primary Outcome

- Clinically apparent stroke or systemic embolism (SSE)

Study Population:

- Warfarin = 300
- DOACs = 185
- Therapy-change = 64
    - DOAC to warfarin (19 patients): switched due to cost
    - Warfarin to DOAC (52 patients): switched due to convenience of DOACs
    - Some patients switched between groups more than one time confounding the total number of patients included in each arm
- Some patients did not receive a DOAC or warfarin
    - 50 patients with only parenteral agent and 43 patients with no anticoagulation

Outcomes:

Anticoagulant	SSE	Death	Bleeding Event
DOAC	17	14	8
Warfarin	14	32	19
Parenteral Agent	11	12	4
None	12	57	N/A
Total	**54**	**115**	**31**

Univariable Cox proportional hazards regression analysis		
Risk of SSE: (DOAC vs Warfarin)	(HR, 2.71; 95% CI, 1.31 - 5.57; P = 0.01)	Significantly higher risk with DOACs vs warfarin
Risk of SSE: (Prior SSE)	(HR, 2.13; 95% CI, 1.22 - 3.72; P = 0.01)	Significantly higher risk with prior SSE event

BMI, eGFR, race/ethnicity, LV ejection fraction, and thrombus size were not significantly associated with SSE events.

Author's conclusions

- DOAC treatment and prior SSE events were associated with increased risk of SSE events even after adjustment for other factors. These findings argue against the assumption of equivalence of DOACs and warfarin for LVT. Off-label use of DOACs for LVT should be used with caution.

Analysis

Strengths	Limitations
• Largest study to date • Standardized expert assessment of thrombi on ECHO	• Retrospective nature • Possibility for unmeasured confounders • No data about dosing • No adherence data or information about time in INR goal

Chen Y, Zhu M, Wang K, Xu Q, Ma J. Direct Oral Anticoagulants Versus Vitamin K Antagonists for the Treatment of Left Ventricular Thrombus: An Updated Meta-Analysis of Cohort Studies and Randomized Controlled Trials. *J Cardiovasc Pharmacol*. 2022;79(6):935-940.[14]

Design

- Meta-analysis, including 12 cohort studies and 3 randomized controlled trials

Purpose

- To compare the safety and efficacy of DOACs and VKAs in patients with LVT

Interventions

- Warfarin (n = 1705)
- DOAC (n = 629)
    - Apixaban, 40.4%
    - Rivaroxaban, 50.3%
    - Dabigatran, 8.8%
    - Edoxaban, 0.4%

Inclusion Criteria

- Cohort studies and RCTs
- Adults with LVT evaluated by TTE or cardiac magnetic resonance
- Comparison between DOACs and VKAs
- Evaluation of safety and efficacy

Data Collected

- Patient characteristics
- Publication year
- Study design and period
- Sample size
- Agent used
- Follow-up
- Outcomes

Individual Study Outcomes

- Thrombus resolution
- Stroke, systemic embolism
- Major bleeding
- All-cause mortality

Primary Outcomes

- Thrombotic events
- Thrombus resolution

Safety Outcomes

- Clinically significant bleeding
- All-cause mortality

Statistical Analysis

- Relative risk for each study with 95% confidence interval
- Statistical heterogeneity: $I2 > 50\%$
    - Significant heterogeneity: random effects model
- Sensitivity analyses were conducted

Study Population

- 15 studies included (12 cohorts and 3 RCTs)
- 2334 patients included

DOAC Dosing in RCTs

Alcalai et al	Apixaban 5 mg BID	Apixaban 2.5 mg BID[T]
T: two or more of the following criteria: age ≥80 years, weight ≤60 kg, or SCr ≥1.5 mg/dL or patients with advanced renal failure (CrCl 15 - 29 mL/min)		
Haniff et al	Apixaban 5 mg BID	Apixaban 2.5 mg BID[*]
*: two or more of the following criteria: age ≥75 years, weight ≤60 kg, or SCr ≥1.5 mg/dL		
Abdelnabi et al	Rivaroxaban 20 mg daily	

Outcomes

End Point	Risk Ratio and P-value
Resolution of LVT	RR = 1.01 (0.93 to 1.09) P = 0.48, I^2 = 0%
SSE	Pooled RR = 0.87 (0.11 to 1.55) P = 0.2, I^2 = 67.2%
Clinically significant bleeding	RR = 0.6 (-.39 to 0.9) P = 0.01, I^2 = 0%
All-cause mortality	RR = 0.9 (0.58 – 1.4) P = 0.65, I^2 = 0%

Author's Conclusions

DOACs are noninferior to warfarin for the treatment of LVT, however, they have a lower risk of clinically significant bleeding. This suggests that DOACs might be better alternatives to warfarin for LVT treatment

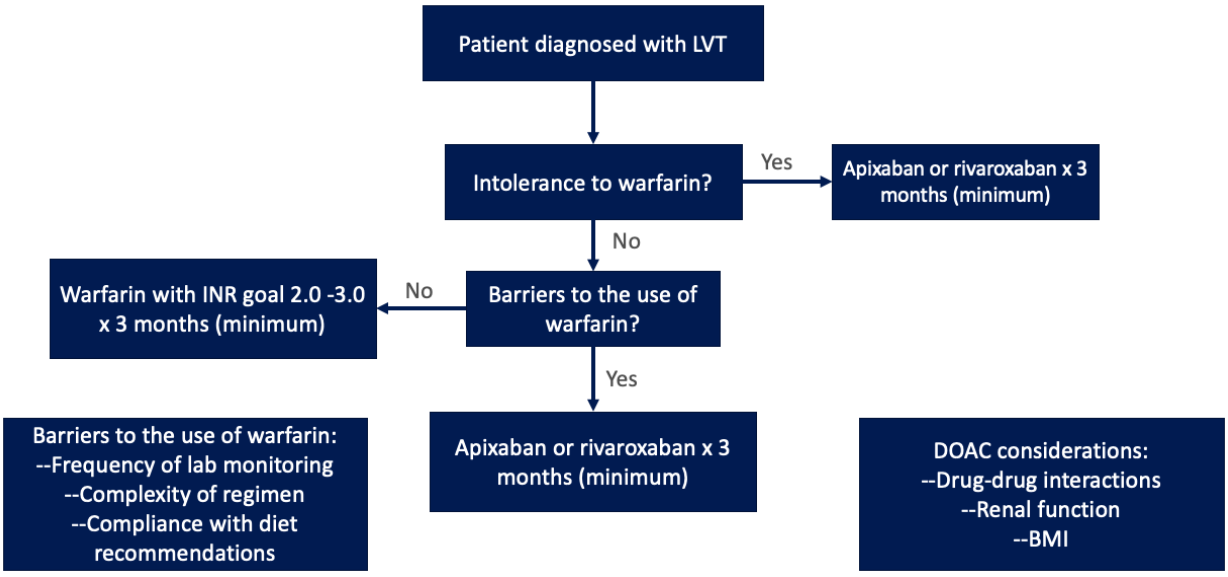
Analysis

Strengths	Limitations
• Largest study to date • Comprehensive of all current data including 3 RCTs • TTE as diagnostic tool increases generalizability	• Retrospective nature of most studies included • Small sample size in RCTs • Not all studies reported bleeding events • No information about dosing • No adherence data or information about time in INR goal • Stated non-inferiority, but did not perform any statistical tests

Main Takeaways:

- Use of DOACs in the treatment of LVT may have similar efficacy to warfarin
- Bleeding risks associated with DOACs as compared to warfarin may be more favorable
- In patients with intolerability to warfarin or barriers to the use of warfarin, DOACs may be a reasonable alternative

Proposed Treatment Algorithm



Remaining Questions

- What dosing regimen should be used?
- Is one agent preferred over another?

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