



Comparison of Safety and Outcomes of Warfarin Versus Rivaroxaban for treating Left Ventricular Thrombus

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ABSTRACT

Objective: We aimed to compare the Outcomes and Safety of Rivaroxaban versus Warfarin for the treatment of left ventricular thrombus.

Methodology: This Prospective, Cohort study was conducted at AFIC/NIHD Rawalpindi, from July 2022 to December 2022. 196 patients of both genders, aged between 40-80 years, diagnosed with left ventricular thrombus on Transthoracic echo (TTE), were included. Patients were divided into two treatment groups using stratified random sampling; warfarin-treated and rivaroxaban treated. The outcomes were assessed at 1, 3, and 5 months. Echocardiographic evidence of thrombus resolution defined the treatment outcome while Safety was assessed in terms of increasing bleeding risk.

Results: The patients were equally divided into warfarin and rivaroxaban-treated group. The mean age was 56.29 ±11.04. Echocardiography was done on 1,3 and 5 months and revealed an odds ratio of 1.04(95%CI 0.62-2.13) for thrombus resolution when comparing warfarin to DOACS while the relative risk ratio(RR) of bleeding in patients was 1.2(95%CI 0.51-2.39)in patients treated with warfarin.

Conclusions: DOACS appeared non-inferior to warfarin for treating LVT without difference in bleeding complications.

Keywords: Left ventricular thrombus (LVT), Direct oral anticoagulants (DOAC)/ Novel oral anticoagulants (NOAC)s, Outcomes.

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INTRODUCTION: Left ventricular thrombus (LVT) is common in patients with severe left ventricular dysfunction following myocardial

infarction (MI), and nonischemic cardiomyopathies. This condition may be life-threatening, due to association with a high risk of systemic embolization[1] and stroke.



Appropriate anticoagulation (DOACS/warfarin) can significantly reduce the risk of embolization and associated complications [2].

Virchow's triad refers to three prerequisites for thrombus formation, i.e., blood stasis, endothelial injury, and hypercoagulability, and can occur as early as within 24 hours to 3 months following myocardial infarction [3]. LV regional wall akinesia or dyskinesia is generally recognized in two-dimensional echocardiography, and it plays a key role in the pathogenicity of LVT. Secondly in heart failure with reduced ejection fraction, a hypercoagulable state is noted with an increased incidence of LVT and a high risk of thromboembolism[4]

Anticoagulation using warfarin has long been established as the gold-standard level of care in guidelines of the American College of Cardiology but the advent of DOACs prompts a re-examination of literature. The question we seek to answer lies in the efficacy and safety of these drugs while treating LVT. Achieving adequate anticoagulation with warfarin requires adherence, dietary consistency, and laboratory monitoring. These disadvantages have led to increased adoption of DOACs for anticoagulation treatment of thromboembolic disease .and current evidence advocates the safety and efficacy of DOACS as an alternative to warfarin[5,6]. The use of DOACS is becoming the ultimate choice among physicians[7,8]. Backed by their efficacy, lack of monitoring, and safety profile, DOACs have overtaken VKAs in current clinical practices. Though the effectiveness and safety of the DOACS are still debatable due to the lack of wide-scale studies and meta-analysis[9], some studies advocate an early and better response for thrombus resolution by DOACS [10]

Bleeding complications may mimic the outcome and response to treatment. Several clinical evidence-based studies point towards a higher risk in the case of warfarin therapy due to bleeding management. Such risk can

be evaluated using Bleeding Academic Research Consortium (BARC) criteria [11], Figure 1. This study aims to compare the Outcomes and Safety of Rivaroxaban versus Warfarin for the treatment of left ventricular thrombus.

MATERIALS AND METHODS:

After getting permission from Institute Ethical Review Board, this prospective, cohort study was conducted at the Armed Forces Institute of Cardiology and National Institute of Heart Diseases at Rawalpindi from 1st July 2022 to 1st December 2022. A total of 196 patients of 40 to 80 years of age of both sexes were included in the study. All the patients with De Novo Left Ventricular Thrombus, diagnosed with TTE were enrolled in the study. Exclusion criteria were any contra-indication against the use of Rivaroxaban/warfarin, i.e., clotting disorders, antiphospholipid antibody syndrome, patients with a history of atrial fibrillation, deep vein thrombosis/pulmonary embolism who remained on anticoagulation therapy, deranged renal functions with GFR<30 Platlets<50., Chronic Liver Disease(CLD) with deranged Liver Function Tests / Child-Pugh(Class B & C), pregnancy and breastfeeding. Patients with hypersensitivity to warfarin and rivaroxaban were also excluded.

Patients with diagnosed LVT were distributed in two groups according to choice of drug.i.e. warfarin(n=98) and rivaroxaban(n=98). In the warfarin group, patients were bridged with enoxaparin 1mg/kg twice daily until reaching the international normalization ratio(INR) of 2 to 3. The Rivaroxaban group received a 20 mg daily dose. The Outcome was assessed by LVT resolution by TTE at 1,3 and 5 months. All three TTEs were performed by the same operator for every single patient to avoid operational measurement errors. Thrombus resolution was further categorized as complete, partial, and unresolved, based on echocardiographic measurements.

Bleeding risk was further graded as BARC bleeding score, Figure 1.

After the initial evaluation and management of LVT, the patient's

demographic information were collected, table1. Demographic data were presented as simple descriptive statistics giving mean and standard deviation for age, weight, and BMI. Mean reported for the normally distributed quantitative variables. Frequencies and percentages were calculated for the

qualitative variable like gender and obesity status.

All collected data were entered into a CRF that has already been created, as per ICH-GCP guidelines. Data were examined and processed using SPSS-25. The appropriate Chi-square test was then used.

Figure 1

Type Definition of BARC Bleeding (Primary end Point)

Type 1: No evidence of bleeding.

Type 2: Bleeding that is not actionable.

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 Type 2: Any overt, actionable sign of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that does not fit the criteria for Types 3, 4, or 5, but does meet at least one of the following criteria: (1) requiring non-surgical, medical intervention by a health care professional, (2) leading to hospitalization or increased level of care, (3) prompting evaluation

Type 3

Type 3a

Overt bleeding plus haemoglobin drop of 3 to <5*g/dL (provided haemoglobin drop is related to bleed)
 Any transfusion with overt bleeding

Type 3b

Overt bleeding plus haemoglobin drop ≥ 5*g/dL (provided haemoglobin drop is related to bleed)
 Cardiac tamponade
 Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)
 Bleeding requiring intravenous vasoactive drugs

Type 3c

Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal)
 Subcategories; confirmed by autopsy or imaging or LP
 Intra-ocular bleed compromising vision

Type 4: CABG-related bleeding

Perioperative intracranial bleeding within 48 h
 Reoperation following closure of sternotomy for the purpose of controlling bleeding
 Transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48 period**
 Chest tube output ≥ 2 L within a 24 h period

RESULTS

There were 76(77.55%) and 81(78.79%) males in warfarin group while 22(22.49%) and 17(17.34%) females in rivaroxaban group. The association of LVT with clinical characters and comorbidities is given in table 1. The proportion of males and females in two groups was almost similar ranging 77 to 81% for males and 17 to 22 % for females.

Table 1 : Baseline characters of study participants with LVT (N=196)

Characteristic	Warfarin 5mg daily (INR=2-3) N= 98	Rivaroxaban 20mg/day N=98	P-Value
Age	56.29 ±11.04	56.29 ±11.04	0.50



Gender			
Male	76(77.55%)	81(78.79%)	0.299
Female	22(22.49%)	17 (17.34%)	
Weight	81.4±16.63	80.6±16.74	0.443
BMI (kg/m²)	26±5.0	26.5±4.5	0.468
Hypertensive	66(64.68%)	68(66.64%)	0.386
Diabetic (HbA_{1c} >6.5)	63(61.74%)	65(66.33%)	0.251
Smoking status	28(28.57%)	23(23.47%)	0.207
Heart Failure	11(11.12%)	13(13.27%)	0.3220

Thrombus resolution:

There were 76(77.55%) and 81(78.79%) males in warfarin group while 22(22.49%) and 17(17.34%) females in rivaroxaban group. The association of LVT with clinical characteristics and comorbidities is given in Table 1. The proportion of males and females in the two groups was almost similar ranging from 77 to 81% for males and 17 to 22 % for females.

Bleeding risk was identified and recorded using Bleeding Academic Research Consortium (BARC) criteria. Major bleeding (BARC type 4) occurred in 5 patients (5.102 %) in the warfarin group and 4 patients (4.08 %) in the rivaroxaban group. It was noted that pooled odds ratio of 1.2 (95% CI 0.51-2.39), and did not reach statistical significance (p=0.36).

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Bleeding Risk Assessment:

Table 2 : Details of outcome (thrombus resolution) and bleeding complications

LV Thrombus resolution	Warfarin	Rivaroxaban	P-Value
Completely Resolved	76(77.5%)	73(74.49%)	0.310
Partially Resolved	12(12.24%)	19(19.39%)	0.085
Un-resolved	10(10.20%)	6(6.12%)	0.1484

Bleeding complications	Warfarin	Rivaroxaban	P-Value
Major bleed (BARC type 4)	5(5.102%)	4(4.08%)	0.366
Minor bleed (BARC type 1-2)	18(18.37%)	14(14.29%)	0.2198

DISCUSSION

The current study compares warfarin with rivaroxaban in terms of outcomes and safety,



for treating LVT in a leading tertiary care hospital in Rawalpindi. We found that there is no significant statistical difference in thrombus resolution and risk of bleeding complications. Our findings suggest that rivaroxaban(DOAC) is non-inferior to warfarin in treating left ventricular thrombus. These findings are also consistent with prior studies where the safety and efficacy of warfarin were compared with DOACS[11,12,13].

The risk of LVT is quite higher in ST-segment elevation myocardial infarction (STEMI), more commonly involving the anterior wall [14]. The incidence of LVT may be as high as 15% in patients with STEMI and up to 25% in patients with anterior wall infarction. The higher embolic potential is associated with protruding configuration and patterns of mobility of LVT [15]. Though it may occur in both ischemic and non-ischemic cardiomyopathies. Akinesia following myocardial tissue necrosis is a key element in pathogenesis. Adequate anticoagulation therapy plays a vital role as there is an associated higher risk of mural thrombi in patients with anterior wall myocardial infarction [16,17].

DOACS are now widely being used in clinical practice for treating venous thromboembolism and non-valvular atrial fibrillation. As they are easy to administer and there are no dietary restrictions, they are considered reasonable for treating LVT patients. More commonly used factor Xa inhibitors are apixaban, rivaroxaban, and edoxaban.

In our study, the pooled odds ratio of thrombus resolution was 3% higher with 1% more risk of bleeding in warfarin vs rivaroxaban groups. But neither outcome resulted in statistical significance. In terms of bleeding events, rivaroxaban had a similar risk of bleeding events which were clinically relevant in patients with LVT, as compared to warfarin. This is by previous studies [18,19,20]. Based on the findings of this study, the two treatments may share a similar safety profile. The result of this study is a hypothesis-generating for further studies to

evaluate the comparative effectiveness of warfarin vs DOACS.

Limitations:

Our study had several limitations which need to be addressed. First, LVT was evaluated by TTE, which has limited sensitivity. Secondly, the study was conducted on a relatively smaller number of patients. Lastly, due to limited information on the duration of thrombus resolution, we were not able to fully conclude the period for treatment. The best strategy to treat organized LV thrombus is yet to be defined.

Conclusions:

Our findings suggest that rivaroxaban (a Direct Oral Anticoagulant) is non-inferior or at least as effective as warfarin in the treatment of left ventricular thrombus. DOACS can be considered in patients with LV thrombus. However, for further confirmation of these findings, large randomized studies comparing the effectiveness of DOACS to warfarin are still needed.

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