








## Protocol

# Left atrial appendage thrombus with severe mitral stenosis, responders and non-responders with anticoagulation, a prospective cohort study.

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## Abstract

**Background:** One of the most frequently observed valvular heart lesions is Mitral stenosis (MS), characterized by left ventricular inflow tract obstruction at the mitral valve level caused by different etiologies. Early detection of symptomatic mitral stenosis with a thrombus in LAA, not responding to anticoagulation in due course of time are sent for Mitral valve replacement rather than undergoing PTMC. The current study aims to see the anticoagulation response in different types of left atrial appendages so that non-responders can be referred for surgery on the first TEE and Cardiac CT.

**Methodology:** The current study will observe the frequency of left atrial appendage (LAA) thrombus resolution after three months of anticoagulation in patients with severe MS. It will assess the response rate in different morphologies of LAA so that non-responders can be referred for surgery on the very first TEE and Cardiac CT. Consecutive MS patients with thrombus in LAA detected via transesophageal echocardiography will be included in the study. According to the standard procedure, TEE followed by Cardiac CT will be performed after obtaining informed consent from the patients.

**Discussion:** Detecting the anticoagulation response using follow-up TEE in different types of left atrial appendages might be helpful for the non-responders that can be referred for surgery after TEE and Cardiac CT on first examination and TEE only at the end of three months.

**Trial registration number:** The trial was registered on ClinicalTrials.gov (NCT05186649).

## Keywords

Left Atrial Appendage, Severe Mitral Stenosis, Anticoagulation, Transesophageal Echocardiography, Cardiac CT.



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## Introduction

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Rheumatic Mitral stenosis is one of the most frequently observed valvular heart lesions, whose main characteristics include left ventricular inflow tract obstruction at the mitral valve level because of the structural defect of the mitral valve apparatus. A transesophageal echocardiogram detects thrombus in LAA in patients with Mitral Stenosis undergoing PTMC<sup>1</sup>. According to current guidelines<sup>2,3</sup>, treatment of vitamin K antagonist (VKA) is recommended in such cases with a therapeutic international normalized ratio (INR) between 2.0 to 3.0, including characteristics of thrombus i.e., organized and non-organized, along with a follow-up TEE to confirm the resolution of the thrombus. Warfarin is the treatment of choice among the treating physicians to resolve existing thrombus<sup>4-9</sup>. A study by Srimannarayana et al. observed that only 2 of the 17 patients (11.8%) with the left atrial thrombus successfully dissolved the clot after anticoagulation for six months<sup>10</sup>.

In a study, the left atrial appendage thrombus disappeared in 31 patients out of 33(93.9%). Rheumatic heart diseases (RHD) and mitral stenosis (MS) are prevalent in the South Asian population, especially in Pakistan, India, and Bangladesh. Early detection of symptomatic mitral stenosis with a thrombus in the left atrium not responding to anticoagulation and referral to surgery on the first TEE and Cardiac CT investigation may decrease morbidity and mortality. Studies suggest that atrial thrombus patients risk developing events related to thromboembolism<sup>11</sup>. Therefore, LAA's morphological delineation/classification is more predictive of upcoming events, and its treatment for such patients is still unclear.

Over the last decade, TEE has been briefly extended since its introduction in terms of its usage and indications. Moreover, the main drawbacks and issues of TEE are very rare, including insertion and manipulation of the probe of TEE resulting in esophageal, pharyngeal or oral trauma and arrhythmias. These also include conscious sedation complications. Since the interpretation and acquisition of images that are conducted inaccurately can lead a case to wrong clinical

decisions, for the success of TEE, an experienced operator is essential<sup>12</sup>. Still, TEE has considered the gold standard for detecting left atrial and LAA thrombus, along with the presence of thrombus. Anticoagulation for this purpose is used in patients with LAA and atrial fibrillation to prevent atrial thrombi embolization. So, it can be said that anticoagulation's beneficial and effective mechanism for the resolution of the thrombi is not well define<sup>8</sup>. Using the TEE database of 958 consecutive studies, a study suggests that left atrial thrombus associated with the mitral valve's pathology were efficiently detected using TEE.

Few reports suggest the effectiveness of anticoagulant treatment for the resolution of LAA thrombus. The results suggest that most physicians recommend the titration dosage of the anticoagulants or Warfarin for thrombus in LAA, suggesting that increased frequency of LAA thrombi can be resolved with a very lower rate of ischemic stroke incidence after treatment from oral anticoagulant<sup>13</sup>.

The current study aims to observe the anticoagulation response in different types of left atrial appendages so that non-responders can be referred for surgery after TEE and Cardiac CT on the first examination and TEE only at the end of three months.

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## Methodology

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### Objective

- **Primary Objective**

The primary objective will be to assess the left atrial appendage (LAA) thrombus resolution frequency after three months of anticoagulation in severe mitral stenosis patients.

- **Secondary Objective**

The secondary objective will be to assess the response rate in different anatomies of LAA.

### Study Design

The current study will be conducted as a prospective, observational, cohort multicenter study (Appendix I).

### Ethics

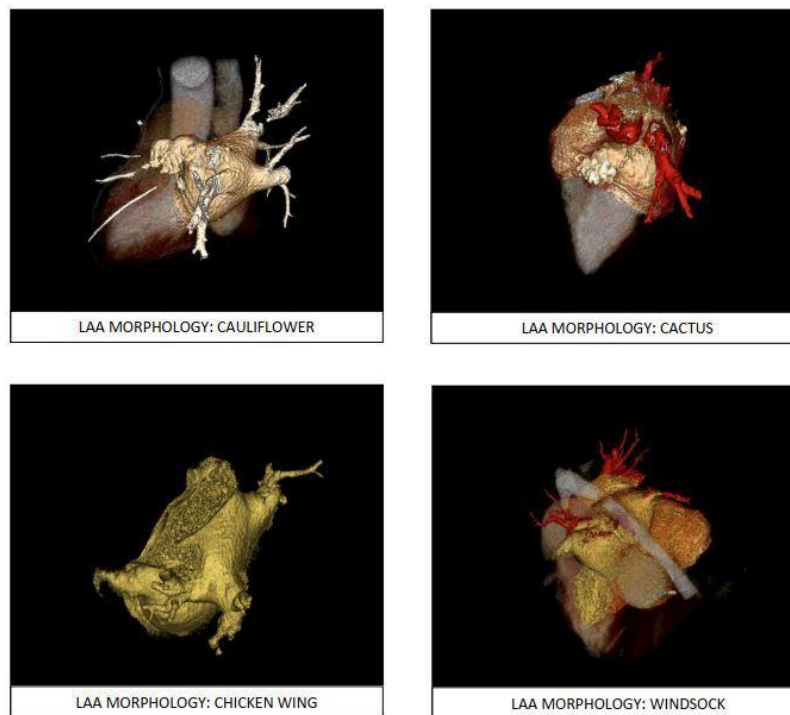
Ethical approval was obtained from PMA Ethics Committee (Reference no. JZ/036/SRO/05; Dated: 20th December 2021).

### Study registration

The study protocol was registered at ClinicalTrials.gov, with trial registration number NCT05186649.

### Participants

All consecutive patients with a severe thrombus in LAA, between 18 to 65 years of both genders, will be screened for the study. The duration of the study will be six months from the start of enrollment of the patient in the study. Patients will be enrolled in the study on the detection of 4 types of LAA that are classified as cauliflower, windssock, cactus, and chicken wing (Figure 1).



**Figure 1: 4 Different LAA morphologies as shown by Cardiac CT: Cauliflower, Cactus, Chicken Wing, and Windssock**

### Eligibility criteria

Patients meeting the eligibility criteria and providing written informed consent will be included in the study. Before inclusion, the study's purpose, procedure, risk, and benefits will be explained to all participants by the principal investigator. Following will be the inclusion and exclusion criteria of the study:

### Inclusion Criteria

- Age between 18 to 65 years.
- Both male and female.
- Patients with severe mitral stenosis.

- Patients with LAA thrombus on first TEE and Cardiac CT.

### Exclusion Criteria

- Patients with severe Mitral Regurgitation.
- Patients with severe Aortic Stenosis.
- Patients with NYHA class IV.
- Patients with valve morphology precluding Percutaneous transvenous mitral commissurotomy (PTMC).
- Contraindications to warfarin therapy.

## Assessment Procedures

### • Study Proforma

The study proforma includes the patient's demographic details, weekly INR monitoring, and baseline and follow-up TEE details.

### • Procedure

Consecutive patients visiting the hospital with severe mitral stenosis and a thrombus in the left atrial appendage (LAA) detected on first transesophageal echocardiography (TEE) and Cardiac CT, fulfilling the inclusion criteria, will be included in this study. After the informed consent, TEE followed by Cardiac CT will be performed as per the standard settings of the procedure. The demographic profile of the patients will be recorded, like gender and age. Baseline TEE will be interpreted, and parameters such as the mean of Mitral Valve Area (MVO) ( $\text{cm}^2$ ), MPG (mmHg), and LA size (AP diameter, cm) will be recorded. LAA morphologies will be classified as per the operational definition.

Every patient will be put on an oral dose of anticoagulation with Warfarin. The INR will be maintained between 2.5 and 3.5. Patients will be prescribed Warfarin initially with 5 mg of daily dosage. Weekly INR monitoring will be performed via weekly calls to each patient, and their INR level will be obtained. Warfarin daily dosage will be adjusted at each test based on the target INR range. Repeat TEE will be performed in all patients after three (3) months. The presence and absence of thrombus in different types of LAA will be recorded (Figure 2).

## Operational Definitions

### • Severe Mitral Stenosis (MS)

Severe MS will be defined as valve area  $< 1 \text{ cm}^2$  with the supportive finding of mean gradient  $> 10$  mmHg on Transthoracic Echocardiogram (TTE).

### • Anticoagulation

Patients on warfarin therapy (oral dose = 5 mg, frequency = once a day after one hour of breakfast, duration = three months).

### • NYHA Class IV

The incompetence of carrying out any activity physically without the feeling of discomfort. Symptoms and signs of heart failure (such as fatigue, palpitation, or dyspnea) at rest and symptoms aggravate on involved in any less than ordinary activity (such as walking short distances 20-100 yards).

### • Thrombus resolution

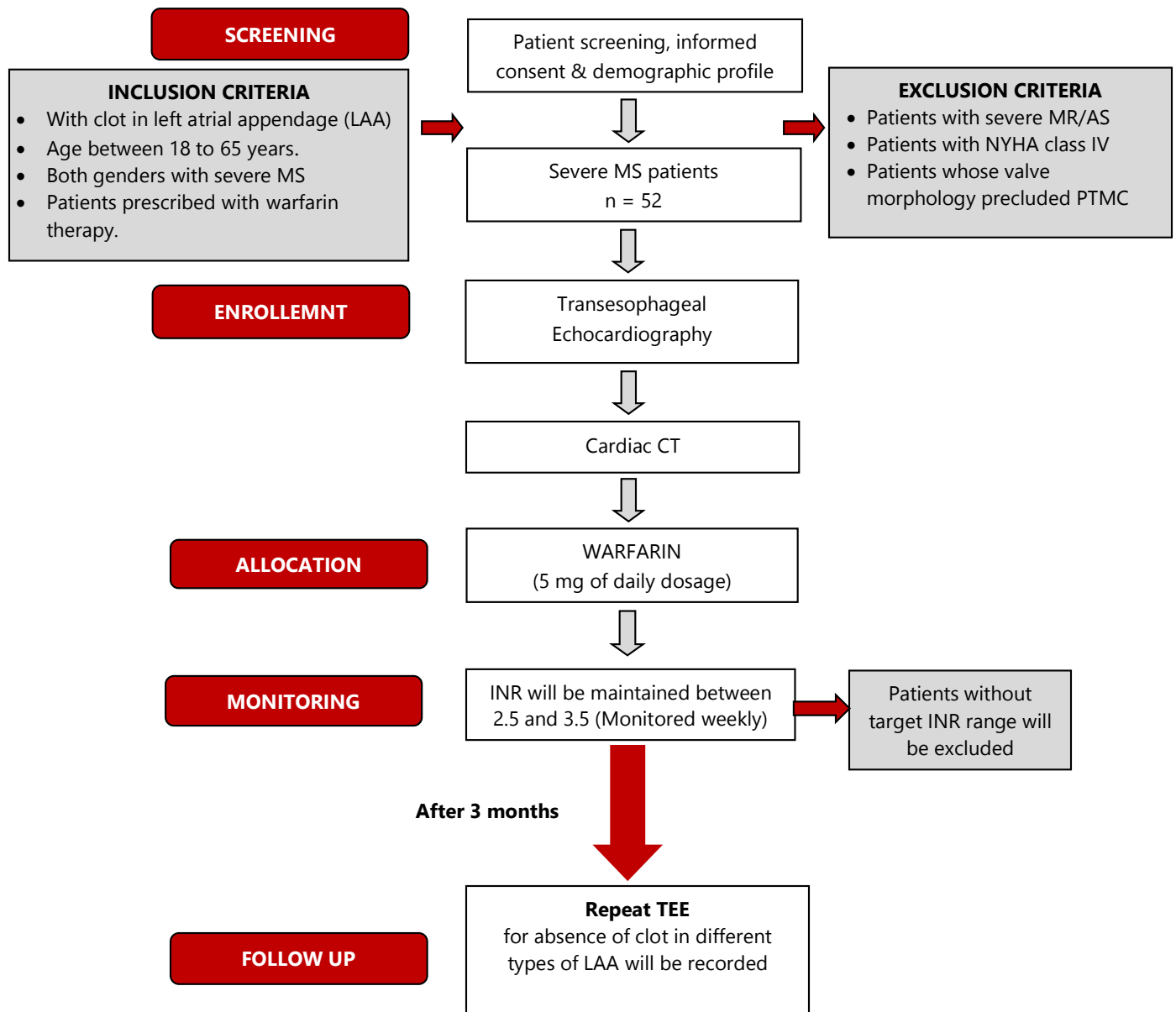
Thrombus resolution is a significant element in the etiology of post-thrombotic syndrome. Both neutrophils and monocytes are involved in thrombus resolution because they can control the production and activity of plasmin, which is essential for fibrinolysis or the breakdown of the fibrin network.

## Outcome Measures

A possible resolution of LAA thrombus on repeat transesophageal echocardiographic (TEE) after three months of anticoagulation (warfarin therapy) is supposed to be observed.

## Sample Size

The sampling will be conducted using the non-probability, consecutive sampling technique. With a 95% confidence interval, 7% of absolute precession, and 93.9% of expected prevalence (p), a minimum of 45 severe MS patients with a thrombus in the LAA will be required. With the addition of 15% of patients in an account of loss to follow-up, a total of  $n = 52$  severe MS patients with a thrombus in the LAA will be recruited for this study.



### Statistical Analysis

Data will be entered and analyzed using the SPSS version 22.0. To determine the hypothesis of normality for quantitative (continuous) variables like age (years), MVO (cm<sup>2</sup>), MPG (mmHg), and LA size (AP diameter, cm), the Shapiro-Wilk test will be applied. While the quantitative (continuous) variables will be expressed using descriptive statistics by determining mean  $\pm$  SD, median, skewness, maximum and minimum, etc. For

categorical variables like gender, age group, types of LAA, and presence and absence of thrombus, frequency and percentages will be calculated. An appropriate Fisher exact or chi-square test will determine the post-stratification. For statistical significance, a two-sided p-value of  $\leq 0.05$  will be taken.

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## Discussion

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To date, few studies have examined the embolic risks of thrombi in LA while referring to anticoagulants. The current study aims to observe the anticoagulation response in different types of left atrial appendages so that non-responders can be referred for surgery on the first TEE and Cardiac CT. Studies suggest that atrial fibrillation is associated with the thrombi development of LAA, that are the main cause of systemic embolisms and stroke. Studies suggest that in patients with atrial fibrillation, the formation of thrombus and state of hypercoagulable or prothrombotic may be promoted by the major complications, including poor LA contractile or atrial systole failure triggering stasis<sup>13</sup>. Moreover, studies suggest that LAA is considered the most usual site of thrombus intra-atrial since the anatomy of LAA helps provide the blood stasis environment<sup>14</sup>.

Studies in the past have reported that patients with LAA thrombus tend to have a history of heart disease, dimension of LA, and transient ischemic attack. TEE has been suggested to reflect the abnormal blood stasis in LA and LAA as an independent risk factor for thromboembolism in patients with atrial fibrillation<sup>15</sup>. Concerning using anticoagulants for thrombi resolution, many case series and reports show that thrombi of LA and LAA in most patients disappear after oral anticoagulation treatment and its prolonged usage, with a duration longer than 3-4 weeks<sup>16</sup>.

In today's world, not all patients with LAA thrombi are keen to receive the TEE follow-up, be it short-term, to determine LAA status, since this process cause great discomfort. However, TEE has suggested a procedure with low risk, few complications of trauma related to dental and some esophagus and upper gastrointestinal tract injuries, but in cases where the patients do not cooperate<sup>17</sup>. In using an anticoagulant for LAA, the follow-up may get prolonged, even though the guidance suggests a follow-up TEE period of 3-4 weeks. This is recommended as a class 1 recommendation, which is evidence C level<sup>18</sup>. A meta-analysis of LAA patients suggests that computed tomography cannot evaluate, and the

spontaneous echo was detected, in contrast to TEE. Therefore, TEE is still considered the necessary tool to evaluate the intra-atrial thrombus with an extended duration of TEE follow-up. The present study's possible outcome will be the LAA thrombus resolution, observed on repeat transesophageal echocardiographic (TEE) after three months of anticoagulation (warfarin therapy).

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## Conflicts of Interest

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The authors have declared that no competing interests exist.

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