STUDY OF OUTCOMES IN PATIENT WITH PROSTHETIC VALVE THROMBOSIS

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DM CARDIOLOGY

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STUDY OF OUTCOMES IN PATIENTS WITH PROSTHETIC VALVE THROMBOSIS

A THESIS SUBMITTED BY

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TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

DM CARDIOLOGY

2022

DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr.Nitin Naik hereby certify that I had personally carried out the work depicted in the thesis titled, “STUDY OF OUTCOMES IN PATIENTS WITH PROSTHETIC VALVE THROMBOSIS”.

No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

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The thesis entitled, "Study of Outcomes in patients with prosthetic valve thrombosis" was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

*Clearance was obtained from the Institutional Ethics Committee / Institutional Animal Ethics / Institutional Committee for Stem Cell Research / Other appropriate committees (if any, specify) for carrying out the study.

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The work under the thesis entitled, “Study of the outcomes in patients with prosthetic valve thrombosis.” was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

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Signature
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Date

APPROVAL OF THE THESIS

The thesis entitled

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Submitted by

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LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
1	BAV	Bicuspid aortic valve
2	BHV	Bioprosthetic heart valves
3	CC-TGA	Congenitally corrected transposition of great arteries.
4	CHPV	Chitra prosthetic valve
5	DVR	Dual valve replacement
6	FT	Fibrinolytic therapy
7	INR	International normalized ratio
8	IU	International Units
9	MHV	Mechanical heart valves
10	NYHA	Newyork Heart Association
11	OAC	Oral anticoagulation
12	PASP	Pulmonary artery systolic pressure
13	PHTN	Pulmonary Hypertension
14	PT	Prothrombin time
15	PV	Prosthetic valve
16	PVT	Prosthetic valve thrombosis
17	SJM	St.Jude Medical valve
18	SVR	Surgical valve replacement

19	TAVR	Transcatheter aortic valve replacement
20	t-PA	Tissue plasminogen activator
21	TEE	Transesophageal echocardiography
22	TTE	Transthoracic echocardiography
23	UHMW-PE	Ultrahigh molecular weight polyurethane

SYNOPSIS

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BY

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SYNOPSIS

Prosthetic valve thrombosis is a serious but rare complication of prosthetic valve replacement. There are no randomized control trails comparing thrombolytic therapy and surgery. We aimed to study the outcomes of prosthetic valve thrombosis treated with fibrinolytic therapy or surgery and to study the recurrence of prosthetic valve thrombosis episodes on follow-up.

We conducted a retrospective and prospective observational study in our institute from 2010-22.

A total of 65 patients with confirmed left or right-sided prosthetic valve thrombosis were included. Patients received Streptokinase Alteplase, and Urokinase as a fibrinolytic drug. Patients with contraindication to fibrinolysis underwent redo surgery. Primary endpoint was considered as occurrence of complete response . The secondary endpoint was combined outcome of major bleed, embolism, death and recurrence of PVT.

Mean age of presentation was 43.55± 12 yrs and females were more common(60%). PVT was most common in the mitral position(72.3%) followed by aortic

position(23.07%).St.Jude medical was most common valve involved(70.8%).Most of the patients were in NYHA FC III(40%) followed by FC-IV(33.85%).27 patients were treated with Streptokinase, 22 with Alteplase, 3 with Urokinase and 13 underwent redo-surgery. Complete success was seen in 79.24%, thromboembolism in 21%, bleeding in 3.8%, and death in 11.3% among the fibrinolytic therapy group. Among the redo surgery group, there were no death and no major complications. 15 patients in fibrinolytic therapy group and 2 in the redo-surgery group developed recurrence of PVT.

Fibrinolysis can be used in patients of Prosthetic valve thrombosis with NYHA FC III-IV who are at increased risk of redo surgery or when surgery is not available as a treatment option. Fibrinolysis is a safer option in patients with recurrent prosthetic valve thrombosis.

1.INTRODUCTION

Valve replacement with mechanical or bioprosthetic valve is a treatment option for patients with valvular heart disease. These patients are at risk of prosthetic valve dysfunction due to primary valve failure, endocarditis, thrombosis, thromboembolism and hemolytic anemia [1,2].Prosthetic valve thrombosis (PVT) is a serious complication with significant morbidity, and is potentially fatal. PVT has an incidence from 0.1% to 6% per patient-year of left sided valves and up to 20% for Tricuspid valves [3] In a retrospective study from India, left-sided PVT was seen in 6.1% of patients within 6 months of valve replacement[4]. The risk of PVT depends on valve type, anticoagulation status, valve position, and presence of prothrombotic states such as pregnancy, atrial fibrillation, and ventricular dysfunction. The most common cause is inadequate anticoagulation. Incidence of thromboembolism is 1-2% per year even with the use of oral anticoagulation and the risk is considerably higher without oral anticoagulation [1,5]. Studies have shown that thromboembolism involving PVT is more in the mitral position compared to the aortic position. Acute obstruction can lead to heart failure or cardiogenic shock or can be an insidious process with acute thrombus on pannus formation. Emergency surgery has been considered a traditional treatment. There is no clear consensus regarding the optimal management of left-sided prosthetic valve thrombosis, and even the available major guidelines differ in their recommendations [6][7]. There is a general

agreement that surgery is better for patients with a higher thrombus burden and more severe New York Heart Association (NYHA) class. There is little randomized data and limited prospective data comparing the efficacy of fibrinolytic therapy (FT) and emergency surgical valve replacement (SVR). However, emergency surgery is not feasible in many centers, especially in the developing world where fibrinolytic therapy is commonly used for treating PVT.

This study was conducted to study the outcomes of PVT treated with fibrinolytics or surgery.

SCOPE OF THE STUDY

There are no definitive guidelines on the management of Prosthetic valve thrombosis. This study was done to study the outcomes of patients treated with fibrinolytics or surgery and about recurrence. There are only few studies that compared fibrinolytic therapy and surgery. No studies are available about the recurrence of Prosthetic valve thrombosis and their treatment.

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2 AIMS AND OBJECTIVES

AIM OF THE STUDY-

To study the outcome in patients with prosthetic valve thrombosis treated with thrombolytics VS surgery

OBJECTIVES

- Primary outcome- complete restoration of valve function.
- Secondary outcome- death, thromboembolism, major bleeding, recurrence of PVT.

3 LITERATURE REVIEW

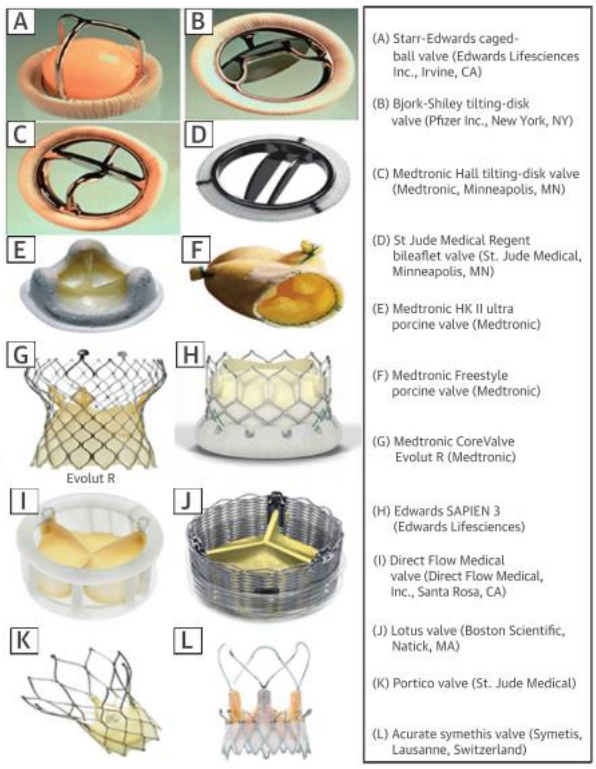
Valvular heart disease affects more than 100 million people worldwide. It is associated with significant morbidity and mortality. In the last 5 decades, the epidemiology of valvular heart disease had changed with marked reduction in incidence of Rheumatic heart disease and increase in incidence of degenerative valve disease [8]. With the aging population and life span increase, the prevalence of degenerative valve diseases is set to increase.

Surgical valve replacement is the current standard treatment of valvular heart disease in low- intermediate risk patients [9]. However, in the last decade, the development of transcatheter valve implantation now offers alternative to surgery in patients at high surgical risk. Transcatheter valve implantation for aortic stenosis and mitral regurgitation are currently established treatment option for patients with intermediate to high surgical risk.

Two different types of heart valves are available – mechanical and bioprosthetic valves. Mechanical heart valves (MHV) are more durable and highly thrombogenic requiring lifelong oral anticoagulation (OAC). Bioprosthetic heart valves (BHV) are less thrombogenic compared to MHV, but also are less durable. BHV are made of porcine or bovine pericardium and mounted on frame or stent and covered by fabric which serves as sewing ring [10]. All the transcatheter aortic and mitral Prosthetic valves consist of a

porcine or bovine pericardial tissue trileaflet mounted on a self-expandable or balloon-expandable metallic frame.

Figure 1- Surgical and Transcatheter Prosthetic Heart Valve Examples



MECHANICAL HEART VALVES-

Caged Ball valve

Starr–Edwards Ball Valve Prosthesis

The poppet is made of silicone rubber, Stellite alloy cage, and Teflon/polypropylene cloth sewing ring. The aortic cage is formed by 3 arches made of titanium located at 120 ° intervals around the sewing ring.

The ball-cage valve is more thrombogenic and has less favorable hemodynamic performance characteristics than either bileaflet or tilting disk valves.

Tilting Disk Prostheses

Medtronic–Hall Mechanical Heart Valve

It is constructed from single piece of titanium alloy without bends or welds. The round central disk is made from tungsten impregnated graphite with a pyrolytic carbon coating and has a central hole that allows the disk to be retained by a curved central guide strut that is part of the housing. Aortic prostheses are available in sizes from 20–31 mm. Mitral prostheses are available in sizes from 23–33 mm.

TTK Chitra valve

TTK Chitra Heart Valve Prosthesis is one of the extensively researched, tested and clinically evaluated device in India [11] . It was developed at Sree Chitra Tirunal Institute for medical sciences and technology. It consists of 3 components. A frame carved out of a single block of Chrome Cobalt Alloy. Central disk or occlude made from the superbly biocompatible Ultra High Molecular Weight Polyethylene (UHMW-PE) and a sewing ring made of 100% polyester fabric.

Bileaflet Prostheses –

Two pyrolytic semicircular leaflets or disks with a slit-like central orifice between the two leaflets and two larger semicircular orifices laterally. The opening angle of the leaflets relative to the annulus plane is 75 to 90 degrees. Size 19-31 are available for aortic and 23-31 for mitral position. Examples of bileaflet prosthesis include St Judes Medical Regent valve, Carbomedics heart valve, Medtronic and On-X valve.

On-X valve- It is constructed completely of pyrolytic carbon. The lack of silicon doping in the valve's carbon construction decreases its Thrombogenicity and a tall flared inlet increases orifice area and decreases the ability of retained valve tissue to interfere with valve opening and closing. The design of the valve's pivots also allows the valve to wash itself. Aortic valves are available in sizes from 19–29 mm, and mitral valves are available in sizes from 23–33 mm.

STENTED BIOPROSTHETIC VALVE-

Valve consists of three biological leaflets made from a porcine aortic valve or bovine pericardium. The leaflets are mounted on a metal or polymeric stented ring, and they open to a circular orifice in systole. Treated with glutaraldehyde to reduce antigenicity and also anti-calcifying agents. Examples include Carpentier Edwards, St.Jude Trifecta and Hancock II.

STENTLESS BIOPROSTHETIC VALVE-

They were developed to address hemodynamic issues related to stent and sewing ring. They are made of porcine tissue and can be used only in aortic position.

TRANSCATHETER VALVES-

It consists of bovine or porcine pericardial tissue mounted on balloon expandable or self-expandable metal frame. Examples of balloon expandable valves include- Edwards Sapien XT and Sapien 3 and for self-expanding valve include Evolute R and Evolute Pro.

Prosthetic valve thrombosis is a rare but serious complication of prosthetic valve replacement. It has varied clinical presentation depending on the amount of valve obstruction. Diagnosis is often difficult and requires a high index of suspicion. Transthoracic echocardiography (TTE), Transesophageal echocardiography (TEE), cine fluoroscopy are the available diagnostic tools to diagnose PVT. Though surgery is the preferred treatment in obstructive PVT, fibrinolytic therapy (FT) is an available option. The various treatment options offered for PVT are primarily based on the presence of obstruction of the valve orifice, by location of the valve (right or left sided), and clinical mode of presentation. Therefore, treatment of left sided PVT can be different from right-sided PVT or non-obstructive PVT.

INCIDENCE OF PVT-

Rate of PVT are highly variable and underestimate the true incidence as valve imaging is not performed routinely and even if performed may be suboptimal. Risk of PVT is higher for MHV compared to BHV implanted in mitral compared to aortic position and higher in right sided than left sided prosthetic valve [12]. The rate of prosthetic valve thrombosis with MHV ranges from 0.1-5.7% with higher rates observed in early post operative period and in mitral and tricuspid position in association with subtherapeutic anticoagulation. In a retrospective study from India, left sided PVT occurred in 6.1% of patients within 6 months of valve replacement [13]. The annual rate of prosthetic valve thrombosis with BHV is 0.3% [6]. Thy type of BHV appears to influence the risk of thrombosis with stented porcine valves having higher risk than stent less valves. Risk of PVT appears to be higher in the first 3 months after implantation and inadequate anticoagulation acts as an independent predictor of thrombosis [14]. Incidence of PVT after Transcatheter aortic valve replacement (TAVR) is uncertain. No cases were reported in PARTNER trial. Latib et al reported 26 cases(0.61%) of PVT among 4266 patients undergoing TAVR within a median of 121 days after implantation[15].The risk of PVT after TAVR is highest in first 3 months of implantation and decreases thereafter to match that of general population.

MECHANISM OF PVT-

PVT is a multifactorial phenomenon. Based on Virchow's triad- 3 main factors predispose to thrombosis. These include surface, hemodynamics and hemostasis related factors.

Surface factors- Artificial surface leads to rapid surface adsorption of proteins such as fibrinogen and fibronectin and these in turn lead to platelet adhesion and activation. Adsorbed fibrinogen is replaced by components of contact system which generate more thrombin resulting in formation of fibrin-platelet on prosthetic surface. It take approximately 3 months for this fibrin coat to be replaced by neointimal cells and endothelization[16].

Hemodynamic factors- These include patients cardiovascular hemodynamics and also hemodynamic characteristic of prosthetic valve. Turbulence across the valve leads to neointimal injury and produces low shear stress that increases blood coagulability. Low cardiac output state lead to hypercoagulability by reducing the washout of activated clotting factors[17]. Regional turbulence may disrupt the laminar flow and lead to prothrombotic state.

Hemostatic factors- Hypercoagulability is a less frequent mechanism in PVT , But may be an important contributor in high risk patients. Acquired causes can be due to chronic kidney disease, anemia, smoking ad obesity. Local tissue injury during valve implantation may expose the tissue factor to blood thereby leading to activation of extrinsic pathway[18].

PVT is a subacute or chronic process rather than acute phenomenon. Several studies have suggested that thrombosis occurs in conjunction with other mechanism of valve dysfunction such as pannus ingrowth, vegetation, or structural degeneration. Pannus is fibrotic in nature and is generally unaffected by anticoagulation.

CLINICAL PRESENTATION-

Patients with PVT may present with progressive dyspnea and signs of heart failure such as orthopnea and pulmonary edema. Severe cases may present in cardiogenic shock requiring ionotropic support and mechanical ventilation. Few patients may present with systemic embolization. Alternatively, PVT can be an incidental finding at the time of echocardiographic follow up[16].PVT may or may not be associated with subsequent thromboembolism. Arterial thromboembolism may manifest with signs an symptoms related to arterial territory occluded by embolus resulting in stroke, transient ischemic attack, limb ischemia, acute mesenteric ischemia or acute kidney injury[19]. Right sided thromboembolism may result in pulmonary embolism, or paradoxical systemic embolism in patients with septal defects or patent foramen ovale. In a study by Labit et al, PVT after TAVR most commonly presented as progressive dyspnea with elevated transvalvular gradient and thickened leaflets or thrombotic apposition of leaflets[15].

IMAGING-

TRANSTHORACIC ECHOCARDIOGRAPHY-

Regardless of the anatomic location of prosthetic valve, Transthoracic echocardiography (TTE) is the first line imaging test for the diagnosis of PVT. Acoustic shadowing caused by the prosthetic valve may limit the visualization of thrombus.. Lin et al. described 4 independent predictors of MHV thrombosis: increased transvalvular gradient (aortic Pmax >50 mm Hg ,mitral Pmean >10 mm Hg); presence of an occlusive mobile mass on the prosthetic valve; and an international normalized ratio (INR) <2.5[20]. For mitral prosthetic valve mean gradient >6mmHg and effective orifice area <1.3cm2 is suggestive of PVT and >8mmHg is indicative of PVT. For aortic valve mean gradient >30mmHg is suggestive and gradient >50mmHg in the absence of other causes is indicative of aortic PVT. Factors associated with BHV thrombosis include >50% increase in transvalvular gradient from baseline within 5 years, paroxysmal Atrial fibrillation, subtherapeutic INR , Abnormal thick cusp and abnormal cusp mobility[21].

TRANSESOPHAGEAL ECHOCARDIOGRAPHY-

TEE should always be performed if images on TTE are suboptimal or there is a strong clinical suspicion of PVT.TEE can offer vital information that guide treatment. Fibrous pannus must be differentiated from thrombus. Pannus formation is more commonly seen on the aortic valve compared to mitral position. Indirect signs of PVT by TEE are usually the non visualization of the physiological prosthetic

device regurgitation, the visualization of central regurgitation, and left atrial spontaneous contrasts in echocardiography.PRO -TEE registry suggest that a thrombus with size >0.8cm2 and previous history of cerebrovascular accident as a significant factor for anticipation of risk of thrombolysis [22]. TEE can be difficult to perform in patients with NYHA FC-IV or critically ill patient who are not on mechanical ventilation.

FLUOROSCOPY-

For MHV, Valve mobility can be assessed using fluoroscopy, which allows accurate prosthesis opening and closing angle measurements. Fluoroscopy is not suitable for BHV, and TTK Chitra valves as these are radiolucent. This method is also not helpful in differentiating pannus from thrombus.

TREATMENT OF PVT-

PVT is a life-threatening condition, and prompt treatment is necessary. Treatment options for PVT include anticoagulation, Thrombolytics, and surgery. Prosthetic device type doesn't impact treatment option, and treatment option depends on prosthetic valve position, size of thrombus, and patient's hemodynamic condition.

NON-OBSTRUCTIVE PVT-

For non-obstructive thrombi >5mm, surgery may be indicated in case of failure of medical treatment(heparin), particularly in the presence of large, mobile, and pedunculated thrombi. Medical management is preferred for small (<5mm) non-obstructive thrombi.

OBSTRUCTIVE PVT-

Obstructive PVT requires aggressive treatment in the form of surgery or fibrinolysis as anticoagulant therapy only is inadequate. There are no randomized control trials comparing fibrinolysis and surgery. The Society of Heart Valve Disease (2005) recommends that the first choice be thrombolysis in all cases of PVT unless such treatment is contraindicated. The American College of Chest Physicians (2012) recommends that the main criterion in the therapeutic decision should be the size of a thrombus. The European Society of Cardiology (2017) proposes surgery as the initial treatment, regardless of clinical status and the thrombus size. The American Heart Association and American College of Cardiology (AHA/ACC) (2017) in the last updated guideline recommend as an indication class I-B, the urgent initial treatment with either slow-infusion low-dose fibrinolytic therapy or emergency surgery in patients with a left-sided mechanical PVT presenting with symptoms of valve obstruction. AHA in the recent Valvular heart disease guidelines 2020, gives IB recommendation for urgent initial treatment with a low dose, slow infusion fibrinolytic drug or emergency surgery for patients with left-sided prosthetic valve thrombosis.

RIGHT SIDED OBSTRUCTIVE PVT-

Mechanical valves are rarely implanted in the right heart because of their high thrombogenicity. Fibrinolysis should be considered in tricuspid or pulmonary valve thrombosis [23].surgery can be considered in case of failed fibrinolysis.

LEFT-SIDED OBSTRUCTIVE PVT-

Obstructive left-sided PVT was considered an indication for surgery. Recent advances in surgery, anesthesia and perioperative care have improved prognosis. According to a recent study, mortality was 4% for patients with NYHA class I- III, whereas it reached 17.5% in patients with NYHA class IV symptoms. In a study by Lengyel et al., fibrinolysis was efficacious in 82% cases with 10% mortality and 12.5 % risk of systemic emboli [24].

FIBRINOLYTIC REGIMENS-

There is no definite consensus regarding the best fibrinolytic regimen. In patients with hemodynamic instability, ‘‘rescue’’ fibrinolysis should be preferred, using a ‘‘short protocol’’ consisting of either:

a) recombinant tissue plasminogen activator (rtPA) 10 mg bolus + 90 mg in 90 mins, or
b) streptokinase 1 500 000 U in 60 mins without heparin.

In hemodynamically stable patients, a long protocol is often preferred using either:

a) urokinase 4500 U/kg/h over a 12 h period, or 2000 U/kg/h + heparin over 24 h,
b) streptokinase 500 000 IU in 20 mins followed by 1 500 000 IU for 10 h without heparin
c) rtPA 10 mg bolus, 50 mg during the first hour, 20 mg during the second hour and 20 mg during the third hour [25].

4 MATERIALS AND METHOD

METHODOLOGY

STUDY DESIGN- Retrospective and prospective observational study

Study setting- Department of Cardiology, Sree Chitra Tirunal Institute of Medical Sciences and Technology (SCTIMST), Trivandrum

INCLUSION CRITERIA- Patients aged>18 years and admitted to SCTIMST with Prosthetic valve thrombosis from 2010-2022 wee included.

EXCLUSION CRITERIA- Patients who underwent thrombolysis in outside hospital and patients who had infective endocarditis or sepsis at presentation were excluded.

Consecutive patients admitted with PVT between 2010- 2022 were included retrospectively and prospectively.Retrospective data was collected from the hospital medical records. The study was conducted at Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), a tertiary care cardiac center located in South India.

The demographic data like age, sex, position of prosthetic valve (PV), duration from initial surgery, the prothrombin time (PT) and international ratio (INR), the liver and renal function parameters, the echocardiographic parameters including the valve

gradients and the estimated pulmonary arterial pressure, and the NYHA class of the patients was collected. The effectiveness of the FT was assessed with echocardiographic evidence of normalization of valve gradient and fluoroscopic visualization of the leaflet movements if the discs were radiopaque. When the valve leaflet was not fluoroscopically visible as with the TTK-Chitra valve, Starr Edward valve- transthoracic or transesophageal echocardiogram was used to confirm the impairment and normalization of leaflet movement.

Echo criteria for diagnosing PVT:

By Philips HD 7/IE 33 echo machine two-dimensional and Doppler

echocardiographic studies were done; the system has 5.0 and 8Mhz transducers (2-dimensional echocardiography), and 5 MHz transducers for pulsed and continuous wave Doppler. A thorough 2-D echocardiographic examination was performed to view the prosthesis in many cross-sectional views. Continuous wave Doppler mode was used to measure the flow across the prosthetic valves. Peak pressure gradients were obtained from peak velocities by modified Bernoulli equation: P=4 xV2; mean pressure gradients were obtained with the software in the echo machine. Pressure half-time method was used to calculate the effective mitral orifice area.

Table 1-Echocardiographic criteria to diagnose mitral prosthetic valve obstruction:

	Normal	Possible	Significant
Peak Velocity	<1.9	1.9-2.5	≥2.5
Mean gradient(mmHg)	≤5	6-10	>10
VTImv/VTI LVO	<2.2	2.2-2.5	>2.5
EOA(cm2)	≥2	1-2	<1
PHT(ms)	<130	130-200	>200

Table 2 - Echocardiographic criteria to diagnose aortic prosthetic valve obstruction

	Normal	**Possible**	**Significant**
Peak velocity	<3	3-4	>4
Mean gradient	<20	20-35	>35
EOA(cm^2)	>1.2	1.2-0.8	<0.8
Contour of jet	Triangular early peaking	Triangular to indeterminate	Rounded symmetrical
AT (ms)	<80	80-100	>100

Fluoroscopic criteria for diagnosing PVT-

Persistent restriction of leaflet(s) motion with a calculated opening angle greater than the mean value (_2SD) obtained in a reference group of patients with normally functioning valves of the same type. Opening and closing angles were defined as the distance between the 2 leaflets in the fully open and closed position.

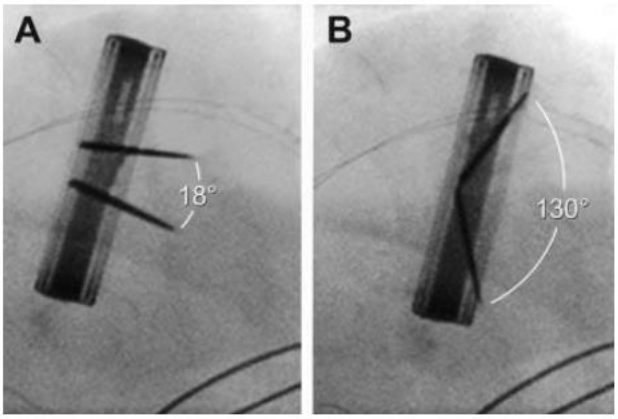


Figure 2- opening and closing angle measurement by fluoroscopy

THROMBOLYTIC REGIMEN-

Fibrinolytic regimen was administered as per the available drug at the time of admission. Streptokinase and Urokinase were administered as 2.5lakh IU bolus over 30-60 minutes followed by infusion of 1 lakh IU/hour for 24-72 hours depending on 2D echo observation of valve gradients. Alteplase was administered as 25 mg over 4-6 hours with echocardiographic monitoring of valve gradients. If valve gradients were still elevated and fluoroscopy showed restricted valve movements, patient were given an additional dose. After the infusion, patients were started on heparin infusion with monitoring of Activated partial thromboplastin time and OAC was started. Heparin was continued till INR was in the therapeutic range. All the patients received Aspirin at the time of discharge and OAC drug.

Follow-up data, echocardiographic details were collected from electronic medical records.

DEFINITION-

Complete success- Defined as complete restoration of valve function.

Partial success- Defined as incomplete restoration of valve function (reduction in mean transvalvular gradients $\geq$ 50% from baseline, but without normalization of fluoroscopic leaflet motion.

Failure- Defined as death or absence of hemodynamic response after 24hr of fibrinolysis.

Complications-Embolic, major and minor bleed, death, recurrence

STATISTICAL ANALYSIS

Continuous variables as mean, standard deviation and percentage. Median and inter-quartile range were used for skewed data. Categorical data are compared using the χ^2 test. Qualitative data was compared using chisqure test, Fisher Exact test . Quantitative date was compared using Independent t test . Analysis was performed using SPSS statistical software.

ETHICAL JUSTIFICATION-

This study was approved by the Institutional ethics committee.

5 RESULTS

From 2010 -2022, 65 patients admitted to SCTIMST with PVT were studied. Of these three patients were treated with heparin and were excluded from the final analysis. The baseline characteristics of the study are as follows.

Table 3- Baseline characteristics of patients with PVT

	n (%)
Total no.of patients (n)	65
Age(yrs.) mean ± SD	43.55 ± 12.87
Gender	
Male	26(40%)
Female	39(60%)
Etiology of VHD	
Rheumatic	61(93.8%)
Bicuspid aortic valve	2(3.1%)
CCTGA	1(1.5%)
Dysplastic TV	1(1.5%)
Valve position	
Mitral	47(72.3%)
Aortic	15(23.07%)
Tricuspid	1(1.53%)
DVR	2(3.1%)

The mean age of the patient admitted with PVT was 43.5 years. As the prevalence of RHD is more common in women, the same was found in our study, with 39(60%) of the patients being female and 26(40%) being male (figure 1).

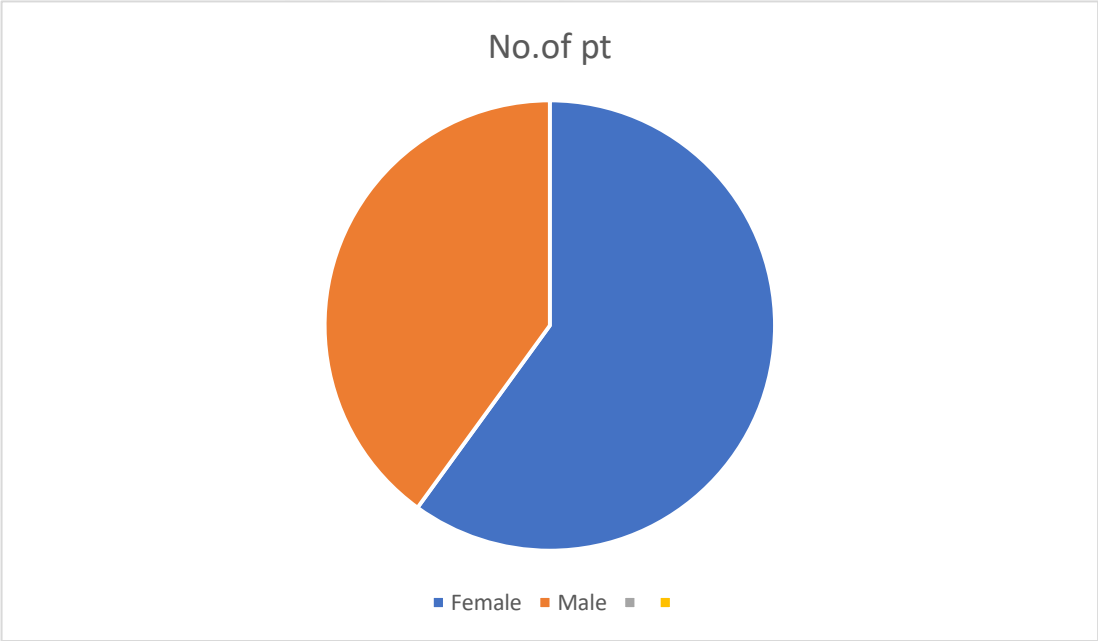


Figure 3- Gender distribution among the patients with prosthetic valve thrombosis

Rheumatic heart disease is the most common cause of valvular heart disease in our country. 61(93.8%) patients with PVT had RHD as the most common cause of valvular heart disease, followed by Bicuspid aortic valve (BAV) in 2(3.1%) and

1(1.5%) each with Congenitally corrected Transposition of Great arteries(CC-TGA) and Dysplastic Tricuspid valve.

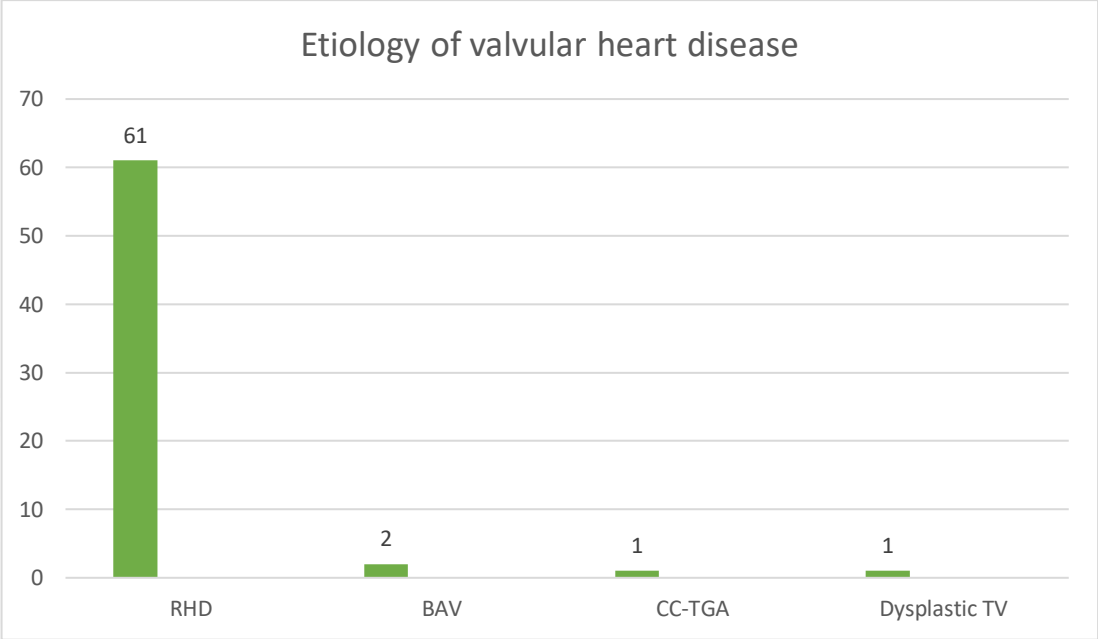


Figure 4- Etiology of valvular heart disease

The Mitral valve is the most common valve involved in RHD. Among the 65 patients admitted with PVT, 47(72.3%) patients had prosthetic valve replacement done in the mitral position, 15 (23.07%) in the aortic position, and 2 (3.1%) in both aortic and

mitral and 1(1.5%) in Tricuspid position. Mitral valve was involved in both the patients with DVR.

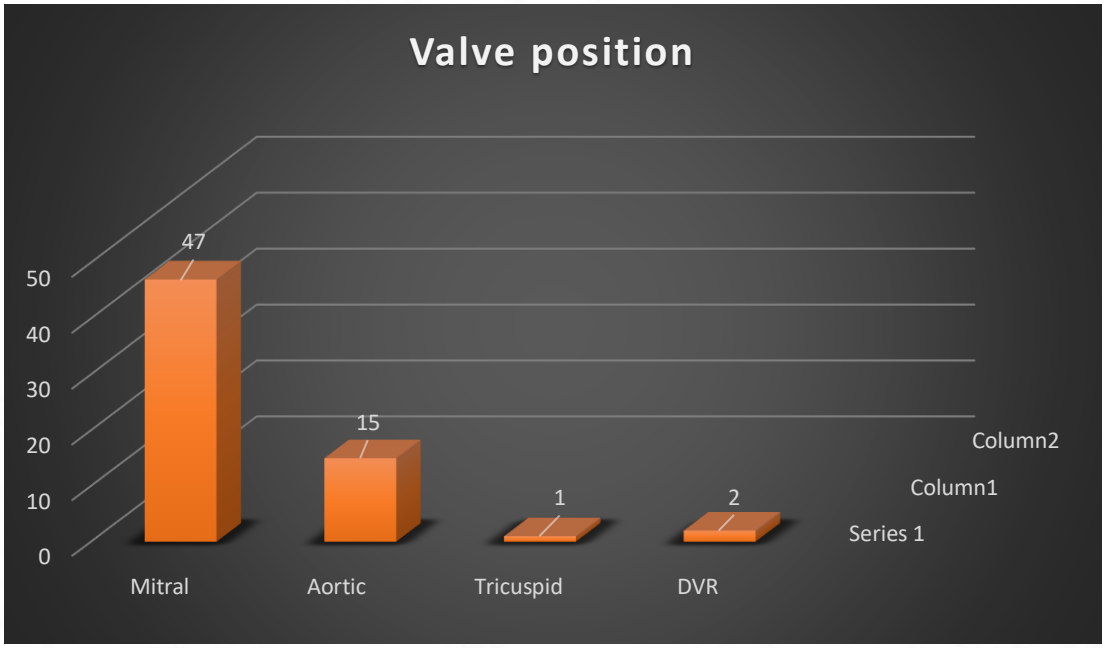


Figure 5- Position of prosthetic valve

As St. Jude's medical (SJM) valve was the most commonly used valve, the majority of our patients, 46(70.8%,) had the SJM valve replaced in either aortic or mitral position, followed by the Chitra prosthetic valve (CHPV) found in 13(20%).

The median presentation duration with PVT was 48 months, ranging from 3 to 108 months.

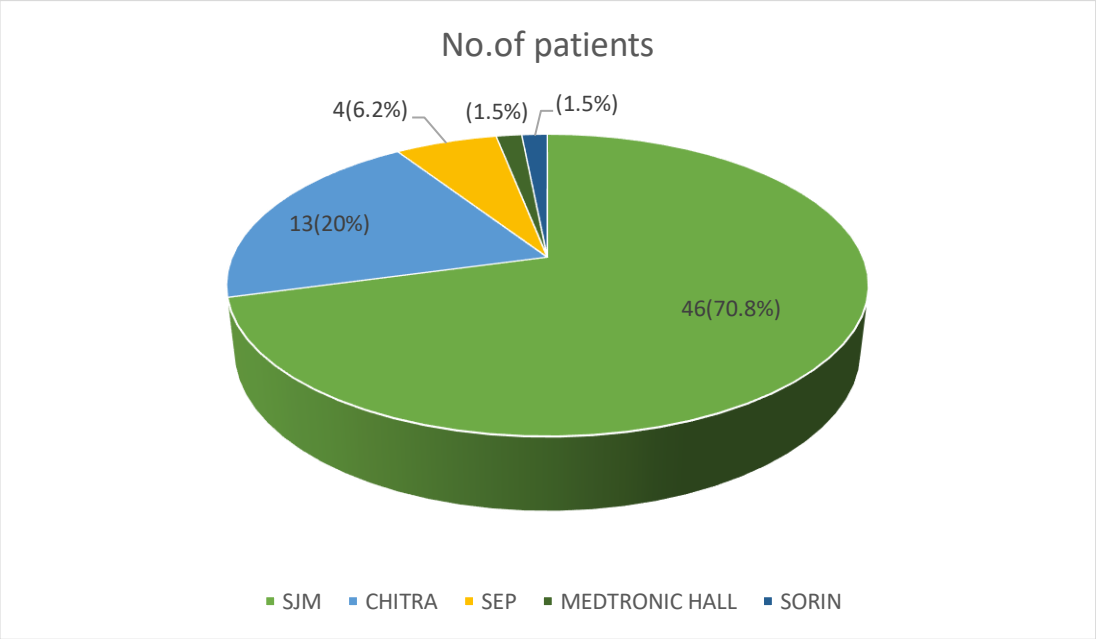


Figure 6- Figure showing different valves replaced

	n(%)

Table 4 –

Dyspnea	64(98.5%)
Orthopnea	34 (52.3%)
PND	2 (3.1%)
Syncope/presyncope	3 (4.6%)
Palpitation	10 (15.4%)
Chest pain	4(6.2%)
NYHA	
FC-II	17(26.15%)
FC-III	26(40%)
FC-IV	22(33.85%)
Pulmonary edema	31(47.7%)
Cardiogenic shock	6 (9.2%)
Heart rhythm	
Sinus	46(70.8%)
Atrial fibrillation	18(27.7%)
CHB	1 (1.5%)

Clinical characteristics of patients with PVT

The most common presenting symptoms in patients with PVT were Dyspnea(98.5%)and orthopnea (52.3%). Few patients also presented with palpitation and chest pain. Most of the patients were in NYHA FC-III followed by NYHA FC-IV with 47.7% having pulmonary edema and 9.2% having cardiogenic shock requiring ionotropic support.

Atrial fibrillation is an additional risk factor for PVT and was found in 27.7% of the patients, while 70.8% were in Sinus rhythm at the time of presentation. Only one patient had a complete heart block, which recovered to sinus rhythm after thrombolysis.

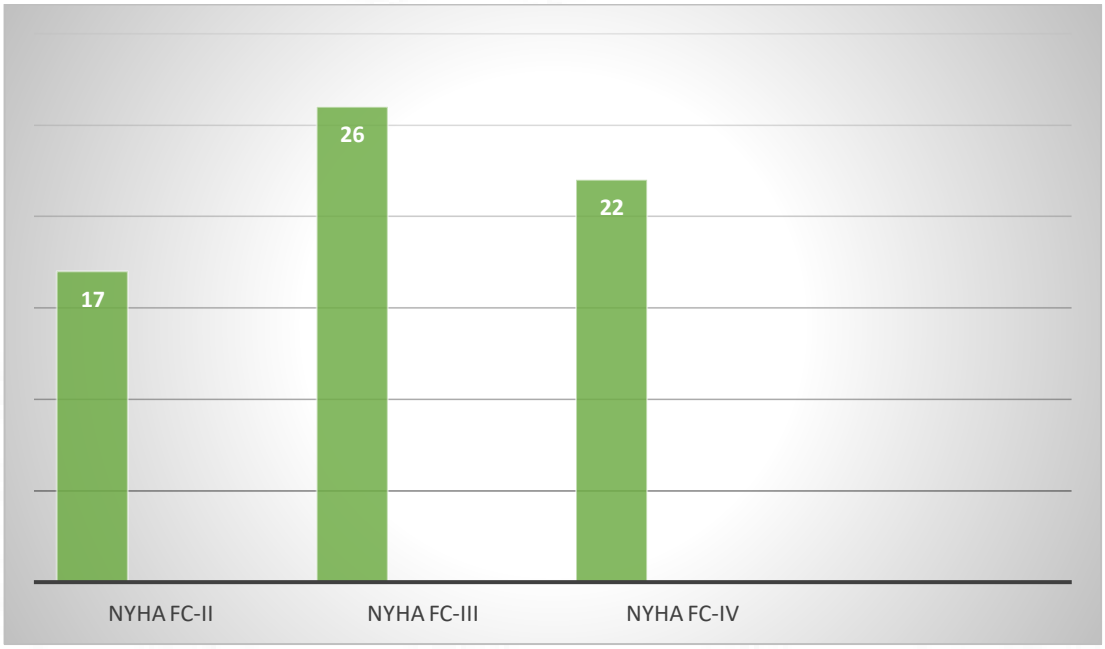


Figure 7- Figure showing patients with NYHA FC

Table 5- Echo and Fluoroscopic characteristics of patients with PVT

	n(%)
Echo characteristics	
Ejection Fraction (Mean ± SD)	59.37 ± 10.31
Estimated PASP (Mean ± SD)	53.73 ± 5.5
Stuck valve seen	24 (36.9%)
Not seen	37 (56.9%)

Fluoroscopy done	47
1 leaflet partial stuck	3 (6.3%)
2 leaflet partial stuck	4 (8.5%)
1 leaflet complete stuck	5 (10.6%)
2 leaflet complete stuck	22 (46.8%)
1 partial and 1 complete	13 (27.6%)
Probnp	3000 (IQR-6016)(82-35000)

All the patients with PVT underwent echocardiography either bedside or in an echo lab, depending on the clinical status. The majority of the patients had an average Left ventricular ejection fraction with a mean of 59.37% and an estimated Pulmonary artery systolic pressure(PASP) of 53.73 mmHg indicating severe Pulmonary hypertension due to PVT.

Fluoroscopy was done in a total of 47 patients. As majority had SJM valve, a bileaflet valve, both leaflets were completely stuck in 22(46.8%) while 13(27.6%) had one leaflet partially and completely stuck.

Table 6- Treatment details of patients with PVT

	n (%)
Adherence to OAC	
Adherent	48 (73.8%)
Nonadherent	12 (18.5%)
Discontinued	5 (7.7%)
Aspirin	
Yes	38 (58.5%)
No	27 (41.5%)
Oral anticoagulant	
Warfarin	32 (49.2%)
Acenocoumarol	33 (50.8%)
INR according to valve position	
Mitral INR>3.0	36(72.0%)
Mitral INR<3.0	14(28.0%)
Aortic INR >2.5	10(71.42%)
Aortic INR<2.5	4(28.58%)

All the patients with prosthetic valve replacement were on oral anticoagulation(OAC) with either warfarin or Acenocoumarol, but only 58.5% were on oral Aspirin therapy before PVT. 73.8% of the patients adhered to the OAC drugs with INR monitoring, with 36(72%) patients with mitral valve having INR in the therapeutic range and 14(28%) having subtherapeutic INR levels. Among the patients with

prosthetic valve in aortic position, the majority(71.42%) were in therapeutic range, with only 4(28.58%) having subtherapeutic INR levels.

Table 7- Treatment details of patients with PVT

	n (%)
Treatment type	
Fibrinolytic	52 (80%)
Surgery	13 (15.4%)
Heparin	3 (4.6%)
Thrombolytic drug (no.of patients)	
Streptokinase	27 (53.82%)
Alteplase	22(42.3%)
Urokinase	3(3.88%)

Of the 65 patients admitted with PVT, 52(80%) were treated with thrombolytic drugs, 3 patients (4.6%) were treated with heparin. Of these 3 patients, one had a small thrombus with only minimal elevation of mean and peak prosthetic valve gradients, while 2 patient's relatives did not consent for thrombolysis. 13 (15.4%) patients underwent redo surgery for PVT. Of these 9 patients had contraindication for

thrombolysis, while 2 patients with partial success with thrombolysis underwent redo surgery. One patient with a Prosthetic valve in Tricuspid position who had successful thrombolysis underwent redo surgery with a bioprosthetic valve.

Table 8- Treatment details of patients with PVT treated with Streptokinase

STREPTOKINASE	**n (%)**
No.of patients	27
Bolus dose (IU) (Mean ± SD)	248000.70 ± 93290.76
Duration of bolus dose(Min) (Mean ± SD)	28.6 ± 9.4
Infusion (IU) (Mean ± SD)	102678.6 ± 30686.0
Duration of maintenance (HRS) (Mean ± SD)	23 ± 12.5
Success- Complete	19 (70.37%)
Partial	5 (18.51%)
Failure	4 (14.81%)
Complications	
Bleeding	0
Embolism	5 (18.51%)
Rash	1 (3.70%)
Death	3 (11.11%)
Required 2nd drug	1

In our study, patients who underwent thrombolysis were treated with one of the available thrombolytic drugs. Till 2016, the majority of the patients were treated with Streptokinase (STK), as it was most commonly available and economically affordable. Overall, 27 patients were treated with Streptokinase. The most common regimen followed was 2.5 lakh IU as a bolus followed by infusion with echocardiographic monitoring of mean and peak gradients. The infusion was stopped once echocardiography showed normalization of prosthetic valve gradients and fluoroscopy showed restoration of valve movements. A mean of 2.48 lakh IU was administered over 28.6 minutes, followed by an infusion of 102678.6 IU over the duration of 23hours. 19(70.37%) patients had complete success with complete restoration of valve movements and normalization of prosthetic valve gradients. 5 (18.51%) patients had partial success and 4(14.81%) had a failure of thrombolysis.

Of the 5 patients who had partial success, 2 underwent Mitral valve replacement (MVR), while 3 patients had partial restriction of valve leaflets and were kept on medical follow-up. On medical follow-up these 3 patients had normal prosthetic valve gradients and were asymptomatic.

Of the 4 patients with a failure of thrombolysis, 3 died, and one was advised Valve replacement.

Embolism was the most common complication associated with Thrombolysis with STK. Of the 5 patients, 3 had lower limb embolism, and 2 had embolism to the brain. None of them required additional treatment and were managed with anticoagulation.

One patient receiving a bolus dose of STK developed a generalized rash and was treated with Urokinase.

Table- 9 Treatment details of patients treated with Alteplase

ALTEPLASE	n(%)
No.of patients	22
Dose (MG) (Mean ± SD)	23.25 ± 8.7
Duration of infusion (hrs) (Mean ± SD)	4.6 ± 2.94
No.of patients receiving addl. Dose	4
Success- Complete Partial Failure	18 (81.81%) 3 (13.63 %) 1 (4.54%)
Complications Bleeding Embolism Death	 1 6 3
Required 2nd drug	0

Twenty two patients were treated with Alteplase. The average dose was 23.25, mg administered over 4.6hrs. Of these 22 patients four, 4 patients needed an additional dose. Complete success was seen in majority of patient 18(81.81%). 3 (13.36%) patients had partial success of which one underwent MVR and 2 are on medical

follow up with normal Prosthetic valve gradients. one patient had failure of thrombolysis and died.

There were two additional deaths in the patients treated with Alteplase after complete restoration of valve function. These two patients died of sepsis and septic shock.

Most common complication was peripheral embolism to lower limb seen in all 6 patients, with one requiring surgical intervention in view of critical limb ischemia. One patient had Intracranial bleed requiring Emergency craniectomy.

Table 10- Treatment details of patients treated with Urokinase

UROKINASE	**n(%)**
No.of patients	3
Bolus dose (IU)	2,50,000
Duration of bolus dose (Min) (Mean ± SD)	19.1 ± 16.5
Infusion dose (IU) (Mean ± SD)	1,75,000 ± 1,06,066
Duration of infusion (HRS)	18
Success- Complete	3(100%)
Partial	0
Failure	0
Complications	
Bleeding	1
Embolism	0
Rash	0
Death	0

Only 3 patients underwent treatment with Urokinase. The mean dose of Urokinase administered was 2.5 lakh IU administered over 19 Minutes, followed by an infusion of 1.75 lakh IU over 18 hours. All three patients had complete restoration of valve function, with one having gum bleeding and no major complications.

Table 11- Characteristics of patients who underwent Redo surgery for prosthetic

		n(%)
No. of patients		13
NYHA FC	I-II	3
	III-IV	10
Valve involved	MV	11 (84.61%)
	AV	1 (7.70%)
	TV	1(7.70%)
Contraindication for thrombolysis		8
	Prior ICH	4 (50.0%)
	Recent CVA	1 (12.5%)
	Large thrombus	3 (37.5%)
Valve change	CHVP	6 (46.2%)
	SJM	4 (30.8%)
	PM	3 (23%)
Complications	Acute liver injury	2

A total of 13 patients underwent Redo surgery for PVT. Of these, 3 underwent redo surgery after thrombolysis. Eight patients had contraindication for thrombolysis in the form of Prior ICH(50%), recent CVA(12.5%), and Large thrombus(37.5%).

In 6 patients, the valve was replaced with a Chitra valve, while 4 patients were replaced with SJM valve. One patient with a prosthetic valve in a Tricuspid position who had complete success with Alteplase underwent replacement with a bioprosthetic valve. Two patients with age >65 yrs underwent replacement with a Bioprosthetic valve.

Only two patients had post-operative Acute liver failure and were managed medically. None of the patients who underwent redo surgery for PVT developed any complications seen with Thrombolysis.

Table 12 - Comparison of fibrinolytic success depending on NYHA Functional class

Fibrinolytic success	NYHA II	NYHA III	NYHA IV
Complete	12 (85.71%)	19 (79.16%)	11 (64.72%)
Partial	2(14.28%)	2(8.33%)	4 (23.52%)
Failure	0	3(12.5%)	2 (11.76%)

P-0.43

When Fibrinolytic success was compared among different NYHA functional class, it was seen that majority of patients had complete success among different NYHA functional class. It was statistically insignificant. This table shows that Fibrinolysis is effective irrespective of the NYHA functional class of the patient.

Table 13- Comparison of Fibrinolytic success depending on Fibrinolytic drug

Fibrinolytic success	STK	ALTEPLASE
COMPLETE	19(70.37%)	18(81.81%)
PARTIAL	5(18.51%)	3(13.63%)
FAILURE	4 (14.81)	1 (4.54%)

p-0.44

When Fibrinolytic success was compared among STK and Alteplase, majority had complete success but was statistically insignificant between the groups.

Table 14- Comparison of mitral and aortic gradients before and after thrombolysis

	Pre thrombolysis mean±SD	**Post thrombolysis mean**±SD	**p**
Mitral Mean gradient(mmHg)	24.49 ± 9.28	5.05 ± 2.66	<0.001
Peak gradient	39.73 ± 11.68	11.30 ± 4.31	<0.001
Aortic Mean gradient	58.38 ± 16.50	14.54 ± 9.13	0.001
Peak gradient	129.00 ± 29.51	27.46 ± 19.59	0.001

The mean and peak mitral prosthetic valve gradient prior to thrombolysis was 24.49 mmHg and 39.73 mmHg respectively and 5.05mmHg ad 11.30 mmHg after thrombolysis respectively. Among the patients with PVT in the aortic position, mean and peak gradients prior to thrombolysis was 58.38mmHg and 129mmHg respectively and 14.54mmHg and 27.46mmHg after thrombolysis. Reduction in the mean and peak gradients after thrombolysis was statistically significant in both mitral and aortic position.

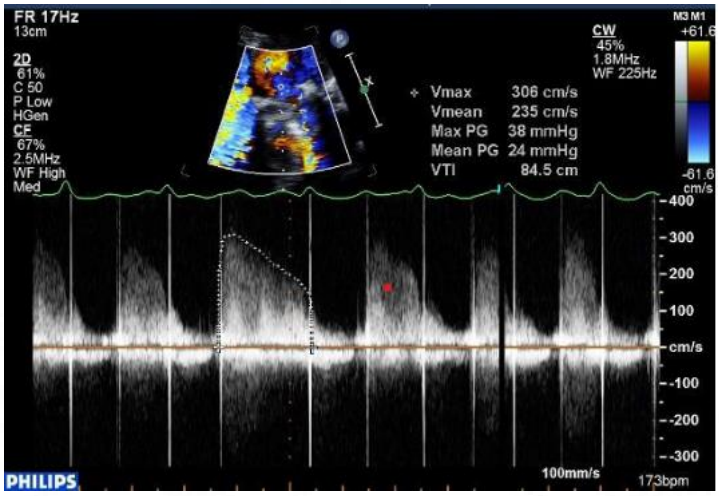


Figure 9- showing elevated prosthetic valve gradient on continuous wave doppler

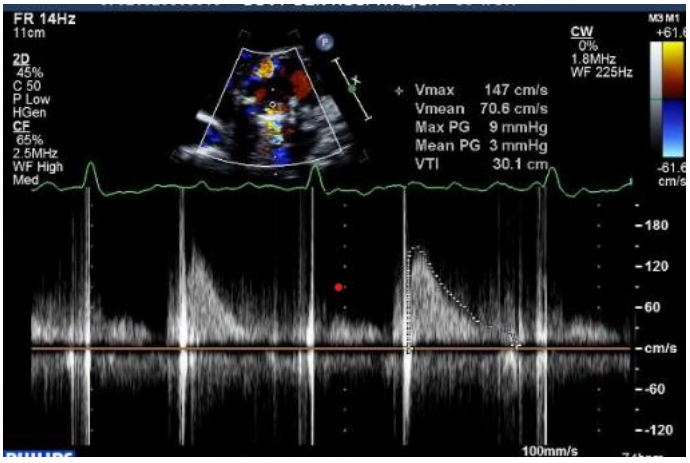


Figure 10 -showing decrease in prosthetic valve gradients following thrombolysis.

Table 15- outcome comparison between Fibrinolytic group and redo surgery

	Fibrinolytic	Redo surgery	p
Primary outcome complete success	42 (79.24%)	13(100%)	0.005
Secondary outcome	24 (45.28%)	2(15.3%)	0.03
Thromboembolism	11 (21.11%)	0	
Bleeding	2 (3.84%)	0	
Recurrence	15 (28.88%)	2 (15.3%)	0.32
Death	6 (11.3%)	0	

The primary outcome of complete success was seen in 42 (79.24%) patients treated with fibrinolytic drugs while all the patients with redo surgery had complete restoration of valve function and was statistically significant.

The composite secondary outcome was seen in 45.28% of patients treated with fibrinolytics compared to 15.3% of the patients with redo surgery and was statistically significant. Among the secondary outcomes, recurrence was seen in 28.88% of the patients in fibrinolytic group and 2 patients (15.3%) in the redo-surgery group.

Table 16- Follow-up details of patient with PVT treated with Fibrinolytics or redo surgery

	Fibrinolytic	**Redo surgery**
F/U Duration(median) months	48 (IQR 70.5) (1-120)	18 (IQR-45) (2-132)
Available	41	11
Lost to follow up	2	2
Recurrence	15	2
Death during rec.PVT	5	1

Of the 47 patients of PVT treated with fibrinolytic, 41 patients were available for follow-up over a median duration of 48 months with a range of 1-120 months. Among the 13 patients who underwent redo surgery for PVT, 11 patients were available for follow-up over a median duration of 18 months with a range of 2- 132 months.

There were a total of 15 recurrence episodes of PVT among the patients previously treated with Fibrinolytics, while only two patients who underwent redo surgery developed recurrence of PVT on follow-up.

Table 17- Comparison between CHPV and other valves

	CHVP	Other valves
No.Of pt	13	52
Treatment type		
Thrombolytic	9	43
Surgery	4	6
Complete success	9(100%)	33(76.7%)
Death	1	6
Recurrence	2	13

p-0.74

The above table shows a comparison among patients with CHPV and other valves. Of the 13 patients with CHPV, complete success was seen in all 9(100%) patients treated with fibrinolytic drugs with only 2 patients developing recurrent PVT , while only 33(76.7%) patients with other valves had complete success with fibrinolysis and more number of recurrent PVT indicating that CHPV has a lesser risk of thrombosis compared to all other valves, but was statistically insignificant .

Table 18- Details of patient with recurrence of PVT on follow-up

	Fibrinolytic	Redo surgery
No.of Patients	15	2
No.of recurrence		
1	12(80%)	2(100%)
≥2	3 (20%)	
Valve involved		
Mitral	9(60%)	2 (100%)
Aortic	6(40%)	
Valve type		
SJM	13(86.6%)	2(100%)
CHVP	2(13.4%)	
NYHA Class		
II	4(26.66%)	1 (50%)
III	7 (46.66%)	1 (50%)
IV	4(26.66%)	
Treatment type		
FT	12	1
SX	2	1
Heparin	1	

Streptokinase Alteplase Urokinase	2 6 3	1
Death	5	1

On follow-up, 15 patients who received Fibrinolytics for 1st episode of PVT developed recurrent PVT. Of these 12 (80%) patients had only 1 recurrence while 3 patients had >2 episodes of PVT.SJM valve was most commonly associated with recurrence of PVT, while CHPV was seen in only two patients. Mitral valve was involved in 60% of patients with recurrent PVT, and the aortic valve was seen in 40% of cases.

Of these 15 patients, 12 were treated with fibrinolytic drugs. Alteplase was the most common drug used during the recurrent PVT, while Streptokinase and Urokinase were used in 3 and 2 patients, respectively.

There were 5 deaths in the recurrent PVT group treated with fibrinolytic drugs. Of these 2 patients were brought in cardiac arrest requiring resuscitation, while 3 patients developed sepsis and septic shock and succumbed.

Among the redo-surgery group, 2 patients initially replaced with SJM for PVT developed recurrence. One patient was treated with a fibrinolytic drug, while another was brought in cardiogenic shock and died before the fibrinolytic drug was administered.

6 DISCUSSION

Prosthetic valve thrombosis is a serial complication of mechanical valve replacement and requires a high degree of suspicion when a patient with valve replacement presents with symptoms and signs of heart failure. Decision on optimal treatment is challenging as there are no randomized control trials for the management of PVT. Current guidelines are based on observational studies and expert opinions. A study by Lengyel et al [24] in 1997 formed the basis for guidelines for the management of Left sided PVT. It recommended thrombolytics for right-sided PVT and in patients with left-sided PVT, thrombolytics were considered for patients with NYHA FC-III-IV or those who had high surgical risk. In patients with NYHA FC-II, surgery was the treatment of choice.2020 ACC/AHA guidelines [26] for management of valvular heart disease give IB recommendation for treatment with low dose thrombolysis or emergency surgery for mechanical PVT. High surgical mortality rates associated with redo surgery led to the wide use of fibrinolytic due to low cost, ease of administration, and lower mortality rates than surgery. In our study, 80% of patients underwent treatment with thrombolytics, and only 15% underwent redo surgery.

In our study, PVT was most commonly seen in women (60%) and was similar to other studies conducted in India. In a study by Purushotama et al. [27], women constituted 51.8% of the total cases. As RHD is more common in women and undergoes valve replacement surgery, PVT was seen as more common among women. Mitral valve prosthesis, compared to aortic valve was most commonly involved in PVT (75% vs 23%). This was similar to Patil S, et al. [28], which

showed that the mitral valve was more commonly involved than the aortic valve(71.5% vs 19.5% respectively). Dyspnea and orthopnea were the most common presenting symptoms indicating pulmonary venous hypertension due to PVT. A higher number of patients presented with NYHA FC-III and IV symptoms (77.85%) followed by FC-II. This was, in contrast, to study by Patil S, et al[28] in which NYHA FC-II and III were major presentations while NYHA FC-IV was seen in only 9.1%. Atrial fibrillation was seen in 27.7% of the patients which could be an additional risk factor for the development of PVT. A significant proportion of the patients in this had the INR within or above the target range, with 73.8% adhering to OAC drugs and yet suffering from PVT. About 72% of patients with PVT in mitral or aortic position had INR in the supratherapeutic range. In multiple studies consisting of a total 1005 patients, Huang et al. [29] observed that 61% had an adequate INR. It has been described that transient and rapid fluctuations in the intensity of anticoagulation can trigger thrombus formation[30] in patients with PV.PVT most often presents acutely with fresh thrombus but can also present as a subacute or chronic phenomenon. A study by Barbetseas J, et al. have shown a high prevalence of fibrous pannus formation (present between 45–75% of cases), and that is was also associated with a risk of thrombosis[31].SJM was the most common valve (70.8%) involved in PVT in our study. This was comparable to a study by Purushotama et al[27]and Patil S,et al[28] where SJM and Medtronic were the most common involved mechanical prosthetic valves.

Anticoagulation with heparin must be started immediately once diagnosis of PVT is made, but definitive therapy requires either fibrinolytic drugs or surgery. Fibrinolytic

therapy is an effective treatment option for PVT; however, there is no head-to-head comparison between different regimens, with most studies limited to a single-center study. In our research Streptokinase, Alteplase and Urokinase were the fibrinolytic drugs used. About 53.82% of patients received Streptokinase from 2010- 2016 and were replaced by Alteplase after 2016. The reason could be ease of availability of Streptokinase and lower cost compared to Alteplase. Patients in our study received bolus dose of 2.48 Lakh IU followed by infusion of 1 lakh IU over varying duration depending on the normalization of pressure gradients on echocardiography. Ganesan Karthikeyan et al [32] in 2009 conducted a randomized control trial comparing an accelerated infusion and the conventional infusion of Streptokinase in 120 patients with a first episode of left-sided prosthetic valve thrombosis. There was no significant difference in secondary outcomes between slow infusion and accelerated infusion of Streptokinase. Complete success with Streptokinase was seen in 70.37 % patients in our study. Mortality in this group was 11%. Consensus statements on the treatment of PHVT and recent systematic reviews have shown that success rate with fibrinolytic therapy is at least 80% [33,34]. Sharma et al [35] in a study on 48 patients, used Streptokinase and reported 81% success and 8% mortality. This was almost comparable with our study. In a study of Shahid Abbas et al [36], a total of 84 patients underwent thrombolysis with Streptokinase, and mortality was 21.4% which was higher compared to our study. Embolism was seen in 5 patients treated with Streptokinase with 3 patients having embolism to the lower limb and 2 patients having embolism involving cranial vessels. Embolism and stroke were observed in 11% and 7.4% of the patient thrombolysed with Streptokinase which was higher compared to the study by Purushotama et al [27].

From 2016, the fibrinolytic drug of choice was changed over to Alteplase in our center, probably due to better results seen with low dose, slow infusion regimen. A total of 22 patients were treated with Alteplase with a mean dose of 23 mg over 4.6 hours. 81.81 % had complete success, while mortality was seen in 13.63 %, with one death due to failed thrombolysis and two deaths due to sepsis. Peripheral embolism was seen in 6 patients (27.27%) and One Intracranial bleed In the TROIA study, 220 PVT episodes were studied comparing 5 different fibrinolytic drug regimens. Low dose, slow infusion of t-PA (25 mg dose over 6 hours) was associated with no mortality and low over all complications[37]. With respect to thrombolysis-induced cerebral bleeds or embolic phenomenon, studies carried out in high-risk groups in left-sided PVT have shown satisfactory safety outcomes as most of the thromboembolic events did not cause any serious consequences.

Urokinase was used in 3 patients, and all had complete success, with only one patient having minor gum bleeding. There were no embolic or strokes seen. Being a very small sample, it is difficult to comment on the complications and safety of Urokinase. Feng Huan et al [38] studied 23 patients with PVT receiving Urokinase. Complete success was seen in 69%, and mortality was 13%. Two patients had mild hematuria, and one patient had a severe cerebral hemorrhage and died.

A total of 13 patients underwent redo surgery for PVT. Of these 10 directly underwent redo surgery. 9 patients had contraindication for thrombolysis. Of the remaining three patients, 2 underwent redo surgery after thrombolysis was done and leaflets were still immobile and one patient with mechanical prosthesis underwent bioprosthetic valve replacement after thrombolysis. Only 2 patients had Acute liver injury that was managed medically. None of the patients had stroke or embolism. On follow up 11 patients were available and 2 developed repeat PVT. In a multicenter HATTUSHA study [39] , a total of 75 patients underwent redo surgery for PVT of which 86% were in mitral position.62.7% of patients had complications (12 had bleeding and 6 had thromboembolism, and others had minor complications). Three-month mortality was 18.7%. There were no major complications in our study and no mortality in the surgical group. During 3-month follow up, 6.7% of the patients who underwent redo surgery in this study had a recurrence of PVT. The overall 30-day mortality rate with surgery is 10% to 15%, with a lower mortality rate of <5% in patients with NYHA class I or II symptoms [40].

Only few studies compared the transvalvular pressure gradient before and after thrombolysis [27]. It was observed that thrombolytic therapy improved the pressure gradient after thrombolysis. Same was found in our study. There was a significant reduction in mean and peak gradients after thrombolysis. This evidence favors non-invasive thrombolytic therapy as a first-line treatment option irrespective of obstruction and functional class in the absence of contraindication.

Recurrence of PVT was seen in 15 patients and 2 patients who were treated with fibrinolytics and surgery respectively. Again, mitral prosthesis was the most commonly involved. Majority of the cases had SJM valve.12 patients were treated with fibrinolytics, with Alteplase being most common followed by Streptokinase and Urokinase. There were no embolism or bleeding complications seen. This shows that Fibrinolysis can be effective in repeat PVT without any major increase in the risk of complications in those previously treated with fibrinolysis. There were 5 deaths of which 3 were brought with cardiac arrest and 2 died of sepsis and septic shock. There were only 2 recurrences among the Surgical group, and one was treated with fibrinolysis as risk with redo surgery is high. There are no studies about recurrence of PVT and treatment. Our study shows that fibrinolysis can be safely administered in the recurrence of PVT.

LIMITATIONS OF STUDY-

- Single center
- Observational study
- Small surgical group

STRENGTHS OF STUDY-

- Studied different fibrinolytic drugs.
- Recurrence of PVT and treatment studied.

7 SUMMARY

- We studied 65 patients admitted with Prosthetic valve thrombosis.
- Mean age of presentation was 43.55 years.
- Women constituted about 60% and males 40%.
- Rheumatic heart disease was the most common etiology of valvular heart disease with 61(93.8%) followed by a bicuspid aortic valve (3.1%).
- St.Jude's medical valve was most involved in 46(70.8%)
- PVT most commonly involved mitral prosthetic valve (72.3%).
- Dyspnea (98.5%) and orthopnea (52.3%) were the most common clinical symptoms.
- The majority of the patients were in NYHA FC-III (40%) followed by FC-IV (33.85%). 9.2% of patients presented in cardiogenic shock.
- Among the patients admitted with PVT, 48(73.8%) were adherent to OAC and only 58.5% were on Aspirin.
- 72% of patients with mitral PVT had INR in the therapeutic range, while 71.42% of patients with PVT in aortic position had INR in the therapeutic range.
- 52 patients received fibrinolytic therapy and 13 patients underwent redo-surgery for PVT.
- 27 patients (53.82%) received Streptokinase and complete success was seen in 70.37% . 5 patients had an embolism, and 3 patients died.

- 22 patients (42.3%) received Alteplase, and complete success was seen in 81.81%, while 6 patients had an embolism and 3 died. Only 1 patient had an intracranial bleed.
- 3 patients received Urokinase, and complete success was seen in all three patients.
- 13 patients underwent redo surgery for PVT.
- 10 patients were in NYHA FC-III-IV.
- 8 patients had contraindication for thrombolysis.
- There were no deaths and major complications in the redo surgery group.
- There was no significant difference of fibrinolytic success among different NYHA FC.
- There was no difference of fibrinolytic success between Streptokinase and Alteplase.
- Primary and secondary outcomes occurred more in the Fibrinolytic group compared to the surgical group.
- On follow up 15 patients had a recurrence of PVT in the fibrinolytic group. SJM was most common involved valve (86.6%).
- 12 patients with recurrent PVT were treated with Fibrinolytic drugs.
- There were 5 deaths in the recurrent PVT group of which 3 were brought in cardiac arrest, while 2 patients died of sepsis and septic shock.
- Two patients who underwent redo surgery for PVT presented with recurrent PVT and one underwent fibrinolytic therapy and one patient presented in cardiac arrest and died.

8 CONCLUSION

- Fibrinolysis was able to restore complete valve function in the majority of patients irrespective of NYHA FC but was associated with complications and recurrences.
- Fibrinolysis can be used in patients with Prosthetic valve thrombosis with NYHA FC III-IV who are at increased risk of redo surgery or when surgery is not available as a treatment option.
- Fibrinolysis is a safer option in patients with recurrent prosthetic valve thrombosis.

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ANNEXURES

List of publications from Thesis
Curriculum Vitae
Appendices
APPENDIX A – ETHICS COMMITTEE APPROVAL
APPENDIX B – SUPPLEMENTARY TABLES
APPENDIX C - PUBLICATIONS
APPENDIX D – PLAGIARISM CHECK REPORT

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेंद्रम - 695 011, केरल, भारत
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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1624/DECEMBER-2020 16.12.2020

Dr. Nitin Naik
DM Cardiology
Department of Cardiology
SCTIMST

Dear Dr. Nitin Naik,

Thank you for submitting documents related to your proposal titled "**STUDY OF THE OUTCOMES IN PATIENTS WITH PROSTHETIC VALVE THROMBOSIS** (IEC/1624)" to the IEC for review.

The following documents were reviewed:

1. Checklist
2. Full proposal
3. IEC Application Form
4. Covering letter addressed to the Chairman, IEC, SCTIMST dated 07.07.2020 forwarded by HOD
5. Proforma
6. TAC Approval Letter
7. Patient Information Sheet in English
8. Patient Information Sheet in Malayalam
9. Consent Form in English
10. Consent Form in Malayalam
11. CV of Dr. Nitin Naik with TSMCMC registration number
12. CV of Dr. Bijulal S with TCMC registration number
13. CV of Dr. Sanjay G with TCMC registration number
14. Covering letter addressed to the Chairman, IEC, SCTIMST dated 07.07.2020 forwarded by HOD

The following members of the Students Sub-Committee of the Institutional Ethics Committee participated in the discussions held online on Dec 9, 2020 at the offices and residences of the members

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
5.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
6.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision
The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

PAPERS PUBLISHED

1. Ramachandran P, Naik N, Jayaram AA, Rao MS. Takotsubo cardiomyopathy: A hype or a hypo?. Heart India. 2017 Apr 1;5(2):102.
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Study of outcomes in PVT.1

by Nitin Naik

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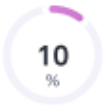

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