

Thrombolysis or Surgery in Patients With Obstructive Mechanical Valve Thrombosis

The Multicenter HATTUSHA Study

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ABSTRACT

BACKGROUND Prosthetic valve thrombosis (PVT) is one of the life-threatening complications of prosthetic heart valve replacement. Due to the lack of randomized controlled trials, the optimal treatment of PVT remains controversial between thrombolytic therapy (TT) and surgery.

OBJECTIVES This study aimed to prospectively evaluate the outcomes of TT and surgery as the first-line treatment strategy in patients with obstructive PVT.

METHODS A total of 158 obstructive PVT patients (women: 103 [65.2%]; median age 49 years [IQR: 39–60 years]) were enrolled in this multicenter observational prospective study. TT was performed using slow (6 hours) and/or ultraslow (25 hours) infusion of low-dose tissue plasminogen activator (t-PA) (25 mg) mostly in repeated sessions. The primary endpoint of the study was 3-month mortality following TT or surgery.

RESULTS The initial management strategy was TT in 83 (52.5%) patients and surgery in 75 (47.5%) cases. The success rate of TT was 90.4% with a median t-PA dose of 59 mg (IQR: 37.5–100 mg). The incidences of outcomes in surgery and TT groups were as follows: minor complications (29 [38.7%] and 7 [8.4%], respectively), major complications (31 [41.3%] and 5 [6%], respectively), and the 3-month mortality rate (14 [18.7%] and 2 [2.4%], respectively).

CONCLUSIONS Low-dose and slow/ultraslow infusion of t-PA were associated with low complications and mortality and high success rates and should be considered as a viable treatment in patients with obstructive PVT. (J Am Coll Cardiol 2022;79:977–989) © 2022 by the American College of Cardiology Foundation.



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ABBREVIATIONS AND ACRONYMS

NYHA = New York Heart Association

PVT = prosthetic valve thrombosis

TEE = transesophageal echocardiography

TT = thrombolytic therapy

TTE = transthoracic echocardiography

UFH = unfractionated heparin

Prosthetic valve thrombosis (PVT) is one of the most serious complications of prosthetic heart valve replacement.¹⁻⁴ Although the major driving force for the generation of PVT is subtherapeutic anticoagulation, the underlying pathophysiological process is complex; besides the conventional predisposing factors, numerous esoteric causes have also been described.⁵ Nevertheless, whatever the cause is, PVT, especially in case of hemodynamic obstruction, requires prompt treatment. The 2 main

treatment options for obstructive PVT include thrombolytic therapy (TT) and surgery.⁵ Because of the paucity of prospectively collected data and the absence of randomized controlled trials, the optimal treatment of PVT remains controversial. Reoperation is still frequently performed with the recommendation of 2 major guidelines for the management of patients with obstructive left sided PVT^{6,7}; however, the reported mortality rates are as high as 18%,⁸ although it varies between developed and under-resourced countries.^{9,10}

SEE PAGE 990

During the last 20 years, TT has become an alternative to surgery as the first-line therapy in patients with thrombosed mechanical valves.⁵⁻⁷ On the basis of 2 major studies regarding management of PVT,^{2,3} low-dose (25 mg) slow (6 hours)/ultraslow (25 hours) infusion of tissue-type plasminogen activator (t-PA) was found to be effective and safe. It begs the question whether the choice of TT vs surgical approach is depending on its rationality in light of the risk-benefit ratio. Because the short-term results of slow/ultraslow infusion of low-dose t-PA in patients with obstructive PVT comparing with surgery are lacking, in this study, we aimed to share our experience regarding the outcomes of TT and surgery in terms of 3-month morbidity and mortality as the initial treatment strategy in patients with obstructive PVT.

METHODS

STUDY POPULATION. This observational prospective study enrolled a total of 158 patients (103 women [65.2%], median age 49 years [IQR: 39-60 years]) who received the diagnosis of obstructive PVT between December 2013 and December 2020 in 8 tertiary centers. Patients with a contraindication to TT, non-obstructive PVT, presence of obstructive pannus formation, end-stage liver disorder, prosthetic valve endocarditis, age <18 years, presence of left atrial thrombus, pregnancy, cardiogenic shock, and

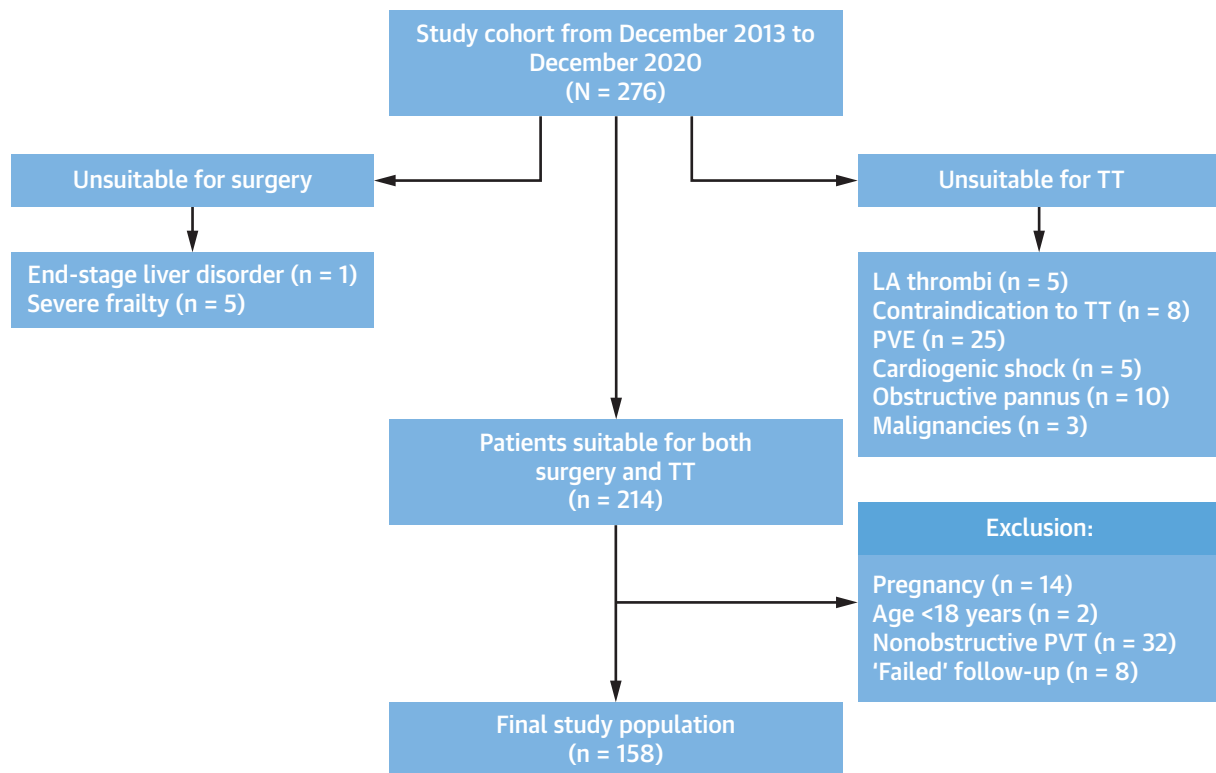
malignancies were excluded from the study. The flowchart for patient selection is summarized in [Figure 1](#).

The heart team (cardiologist, cardiovascular surgeon, and anesthesiologist) reviewed all treatment options, considering the current guidelines and institutional experience. Finally, shared decision making was made with the patient. For centers without adequate experience in redo-valve surgery, TT was opted unless contraindicated. Otherwise, the patient was transferred to the other study centers. In centers where both treatment options were deemed appropriate by the heart team, the clinical judgement of the physician was shared with the patient and a final decision was made. In any case, all patients had to fulfill the criteria for both TT and surgery. A complete blood count and chemistry tests were studied in all patients at the time of admission. The patient demographic characteristics, medical history, elapsed time since valve surgery, type and position of the prosthetic valve, rhythm disorders, New York Heart Association (NYHA) functional class, leading symptoms, and international normalization ratio (INR) values were prospectively entered into a database. This study was conducted in accordance with the principles of the Helsinki Declaration and approved by the Kartal Kosuyolu Heart Training and Research Hospital Institutional Ethics Committee (approval number #2009/11). Written informed consent was obtained from each patient.

ECHOCARDIOGRAPHY. All patients underwent transthoracic echocardiography (TTE) using Vivid 7 Dimension (GE Vingmed Ultrasound AS N-3190) or Philips iE33 (Philips Medical Systems) echocardiography devices, and S5-1 sector array transducer. Following TTE, 2D and real-time 3 dimensional (RT-3D) transesophageal echocardiographic (TEE) studies were performed in all patients by using an X7-2t transducer on an iE33 ultrasound machine (Philips Medical Systems). The presence of obstruction was defined on the basis of Doppler echocardiographic measurements. The cutoff values for these Doppler parameters were defined based on the recent recommendations.^{11,12}

The diagnosis of thrombus, pannus, and vegetation was determined in accordance with previous publications.^{5,13-16} The largest thrombus area was measured by 2D TEE between 0° and 180° angles where there was less interference with acoustic shadowing. In the presence of a single mass the thrombus was traced, otherwise each thrombi was traced separately and the thrombus areas were finally summed-up.^{2,3,16,17} Discrimination between obstructive pathologies such

FIGURE 1 Flow Chart for Patient Selection



The diagnosis of PVT is made by multimodal imaging. Patients suitable for surgery and TT were included in the study. Of these patients, those who were pregnant (n = 14), had nonobstructive PVT (n = 32), were age <18 years (n = 2), and failed follow-up (n = 8) were excluded from the study. LA = left atrium; PVE = prosthetic valve endocarditis; PVT = prosthetic valve thrombosis; TT = thrombolytic therapy.

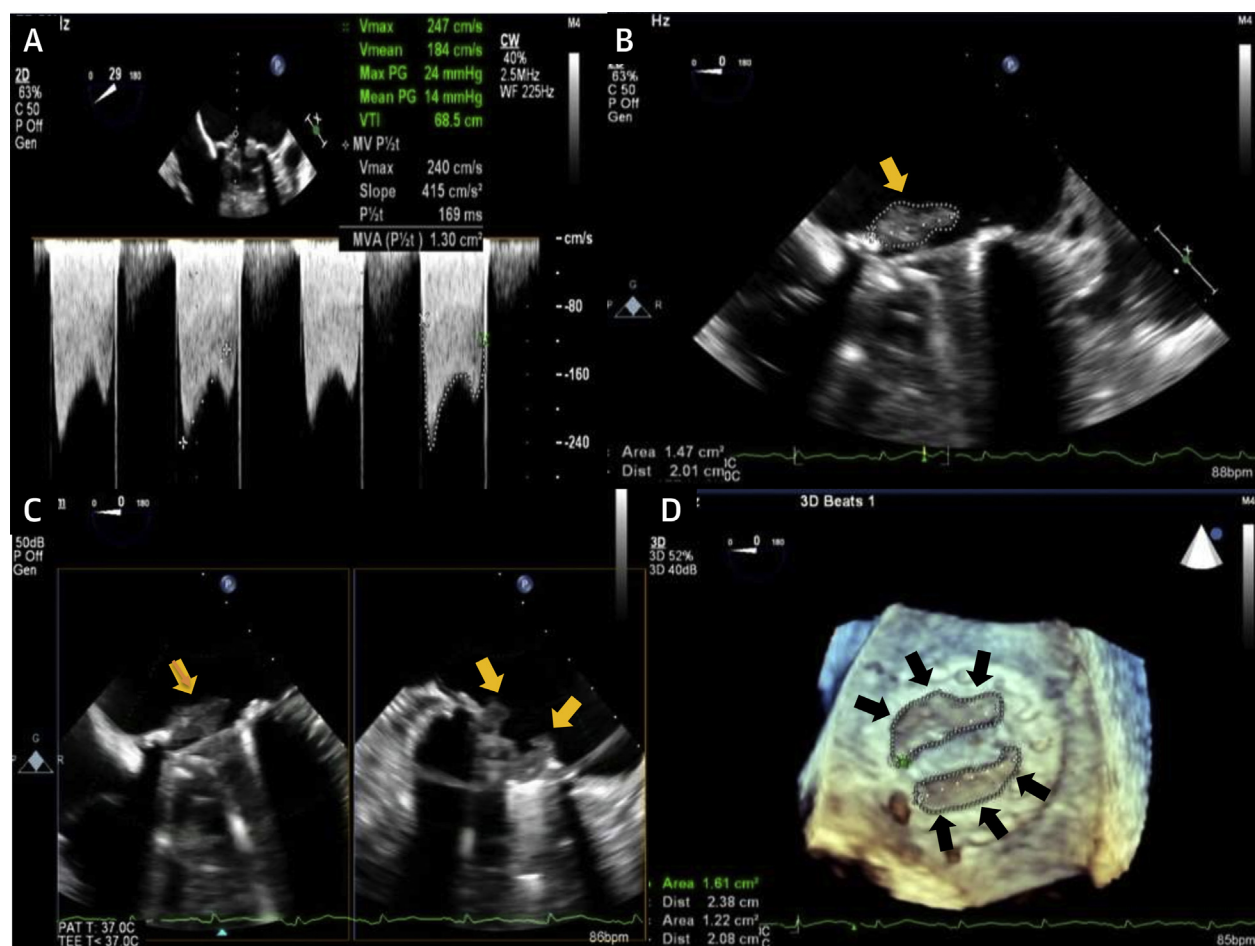
as pannus or thrombus was mainly based on 2D and RT-3D TEE studies in a majority of the patient population. In patients with inconclusive findings, multi-detector computed tomography was performed for the assessment and the differential diagnosis between pannus and thrombus.¹⁵

THE TT REGIMEN. Based on the protocols described in previous reports,^{2,3,17,18} a TT regimen with 6-hour infusion of 25 mg t-PA without a bolus (repeat up to 6 times if needed, maximum total dose of 150 mg) was administered as a first-line therapy to NYHA functional class III-IV patients with obstructive PVT who had no contraindications for TT.¹⁹ All patients underwent serial TTE and TEE examination between each TT session. TT sessions with a low-dose slow-infusion of tPA were repeated until resolution of the obstruction was maintained. Immediate 2D and RT-3D TEE was performed in patients when a partial or complete resolution of the obstruction was observed (Figures 2 and 3). In patients meeting the criteria for complete success and in patients with partial success

and a residual thrombus size <10 mm, TT was halted and anticoagulation with unfractionated heparin (UFH) along with warfarin (until INR reaching to target level) was initiated. TT was continued with low-dose ultraslow infusion of tPA up to 200 mg in patients with partial success with a residual thrombus size ≥10 mm under the guidance of serial TEE examinations between the sessions, according to the protocol described previously.³

In patients with NYHA functional class I-II, a TT regimen with 25-hour infusion of 25 mg t-PA without a bolus (repeat up to 8 times if needed, maximum total dose of 200 mg) was administered as a first-line therapy. Patients underwent serial TTE after each 12 hours, and immediate 2D and RT-3D TEE was performed in patients when a partial or complete resolution of the obstruction was observed. In patients meeting the criteria for complete success and in patients with partial success and a residual thrombus size <10 mm, TT was halted and anticoagulation with UFH and warfarin was initiated. TT was continued with ultraslow infusion of low-dose t-PA up to 200 mg

FIGURE 2 Demonstration of Baseline Echocardiographic Examination of Obstructive Prosthetic Valve Thrombosis



A 2-dimensional transesophageal echocardiography (TEE) image shows an obstructive mitral prosthetic valve thrombus with that the pressure gradient across the mitral valve reached 24 mm Hg (peak)/14 mm Hg (mean) (A) and a total thrombus area of 1.47 cm² (yellow arrows in B and C). Real-time 3-dimensional TEE shows an obstructive mitral prosthetic valve thrombus with a total area of 2.83 cm² (1.61 cm² + 1.22 cm²) (black arrows) (D).

in patients with partial success with a residual thrombus size ≥ 10 mm. Anticoagulation was initiated in these patients after complete or partial success was achieved.

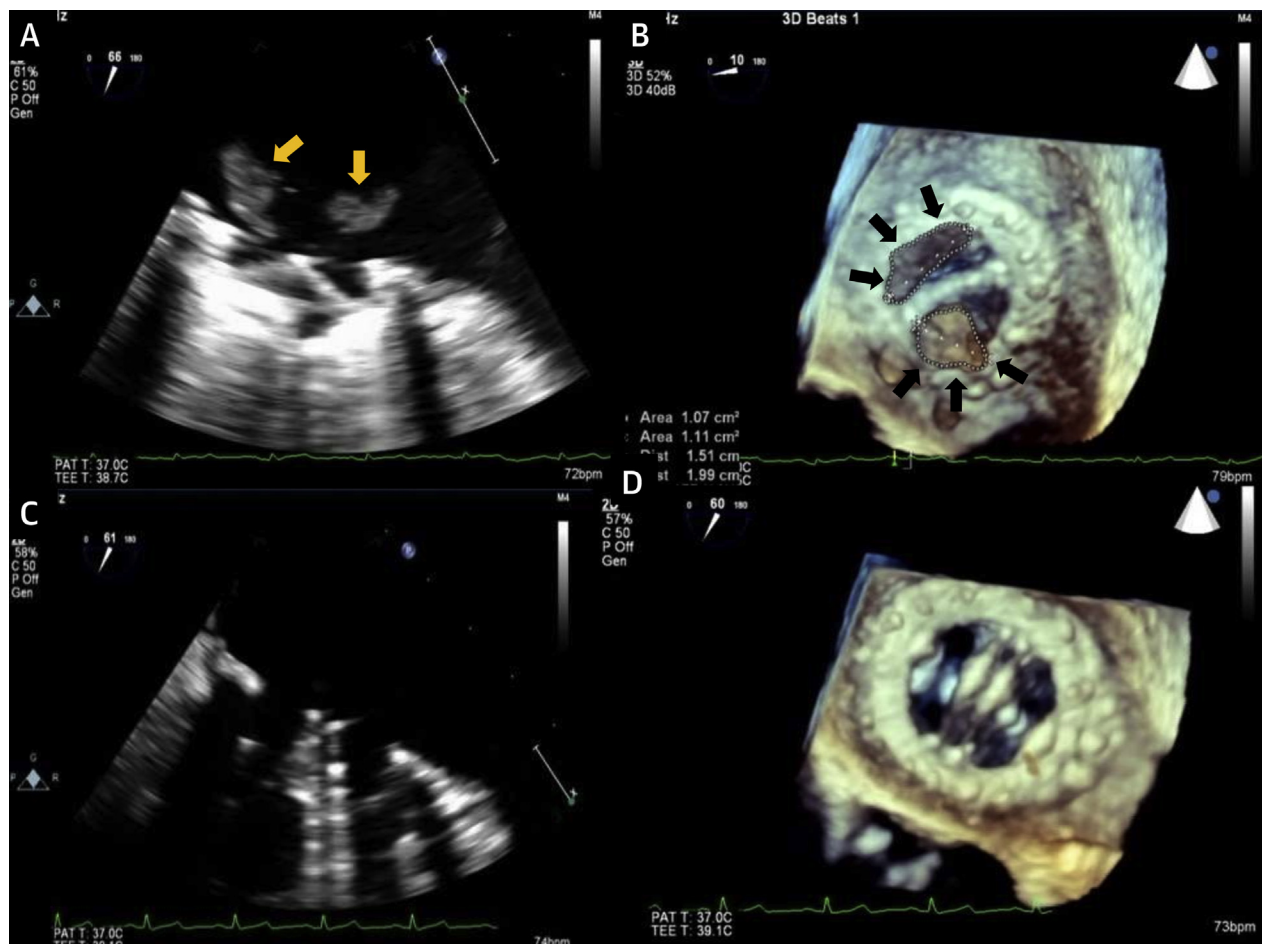
As per previously defined protocols, UFH was not administered in conjunction with t-PA because of safety concerns. UFH infusion, with a target of activated partial thromboplastin time (aPTT) between 1.5 and 2.5 times the control, was started immediately after TT sessions and administered for 6 hours between TT sessions. If a repeated TT session was needed, UFH was interrupted again until aPTT was < 50 seconds.

For patients developing headache, suspicious symptoms of bleeding, or embolism during tPA

infusion, the treatment was interrupted until the patient was comprehensively evaluated with relevant consultations and imaging tools. If a major complication was confirmed, subsequent management was individualized considering both the severity of the complication and the residual valvular obstruction.

In the absence of fatal and nonfatal major adverse events, the following were considered the major criteria for TT success in patients with obstructive PVT: 1) Doppler documentation of the complete improvement in valve hemodynamics; 2) reduction in major diameter and/or area of the thrombus by 75%; and 3) symptomatic improvement. Complete success was defined when all 3 criteria were met, and partial success was defined 2 of 3 criteria were met.^{2,3,17,18}

FIGURE 3 Serial 2D and RT-3D TEE After Each t-PA Session



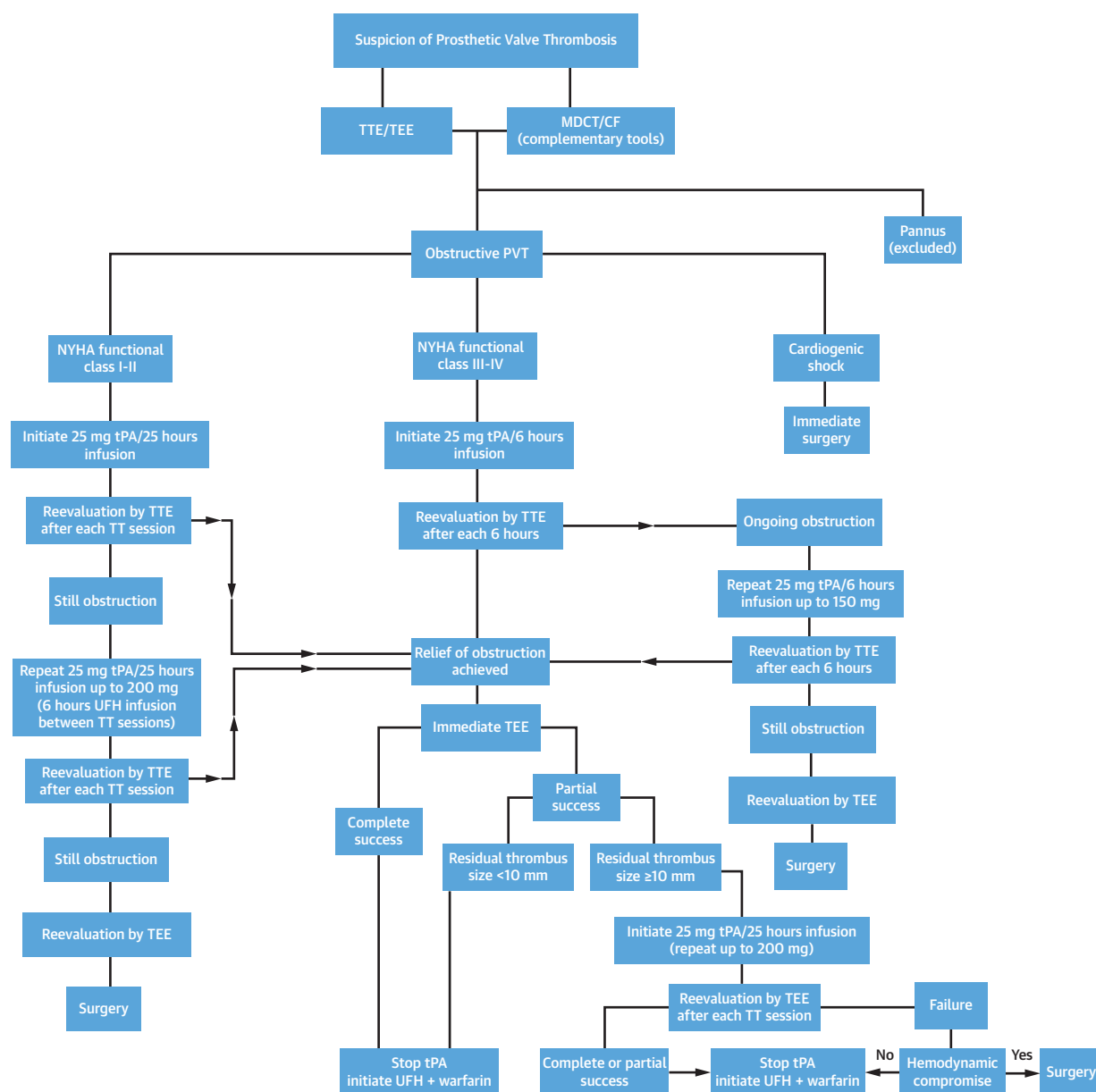
Two-dimensional (2D) and real-time 3-dimensional (RT-3D) transesophageal echocardiography (TEE) imaging shows the size and area of thrombus decreased after first thrombolysis session with a total area of 2.18 cm² (1.07 cm² + 1.11 cm²) (yellow and black arrows) (A and B). 2D and RT-3D TEE imaging shows that the prosthetic valve is normofunctional and complete lysis has been achieved after the second session (C and D).

An overview of the study algorithm was demonstrated in [Figure 4](#).

SURGICAL TECHNIQUE. All patients were operated under general anesthesia and a median sternotomy was utilized. Mediastinal adhesions were opened and cardiac and great vessels were exposed before systemic heparinization. Surgical intervention was performed using a standard cardiopulmonary bypass technique with central cannulation under moderate-degree hypothermia. Myocardial protection was provided with antegrade intermittent or continuous retrograde isothermic blood cardioplegia solution. The previous prosthetic valve was checked and a decision was made for either thrombectomy or valve replacement ([Figure 5](#), [Videos 1](#) and [2](#)).

Thrombectomy was performed to provide an optimal valve function. For replacement, the previously implanted valve and sutures were removed, the valvular annulus was clearly exposed, and interrupted pledgeted sutures were used. Subsequently, hot shot cardioplegia was delivered, and the aortic cross clamp was removed once the heart started beating. Once all parameters were satisfactory, cardiopulmonary bypass was weaned off and the sternum was closed.^{4,10} The patients were followed up for 3 months for any postoperative complications.

DEFINITION OF ENDPOINTS OF THE STUDY. The primary endpoint of the study was 3-month mortality and the secondary endpoint was all major complications that occurred within 3 months after TT or

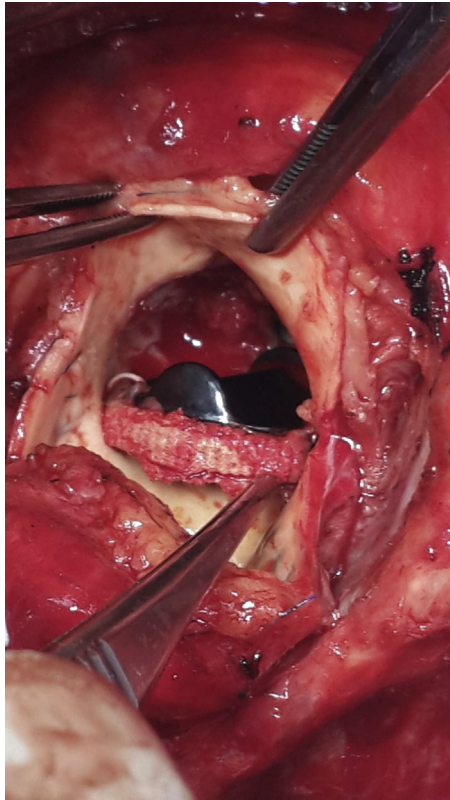
FIGURE 4 Study Algorithm for Patients With Obstructive Prosthetic Valve Thrombosis

CF = cinefluoroscopy; MDCT = multidetector computed tomography; NYHA = New York Heart Association; PVT = prosthetic valve thrombosis; TEE = transesophageal echocardiography; t-PA = tissue-type plasminogen activator; TT = thrombolytic therapy; TTE = transthoracic echocardiography; UFH = unfractionated heparin.

surgery. The major complications included newly developed persistent LV dysfunction, major bleeding, ischemic or hemorrhagic stroke, endocarditis, tamponade requiring revision surgery, sepsis, mediastinitis, acute kidney injury (AKI) requiring renal replacement therapy, catastrophic cardiac injury, a prolonged endotracheal intubation requiring

tracheostomy, coronary or peripheral embolism, and severe paravalvular leak. The minor complications were pneumonia, sternitis, wound infection, minor bleeding, transient ischemic attack, postprocedural developed arrhythmias, presence of left atrial thrombi, and pleural effusion requiring drainage and moderate paravalvular leak.

FIGURE 5 Intraoperative View of Aortic Mechanical Prosthetic Valve



Intraoperative exploration of the mechanical aortic valve demonstrating the obstructive thrombus.

STATISTICAL ANALYSIS. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 19.0. Descriptive statistics were reported as mean $\pm$ SD for continuous variables with normal distribution, median (IQR) for continuous variables without normal distribution, and frequency with percentages for the categorical variables. The cumulative incidence of mortality was calculated with Kaplan-Meier analysis. Due to the observational nature of the study, formal comparative statistics were not performed; hence, *P* values were not reported.

RESULTS

A total of 158 (55 men, 103 women) patients with obstructive PVT were included in the study. The median age was 49 years (IQR: 39-60 years). The initial management strategy was TT in 83 (52.5%) patients (mainly left sided) and surgery in 75 (47.5%)

TABLE 1 Comparison of Baseline Clinical Characteristics Between Study Groups

	Thrombolytic Therapy (n = 83)	Surgery (n = 75)
Age, y	49 (37-58)	49 (39-60)
Sex		
Male	23 (27.7)	32 (42.7)
Female	60 (72.3)	43 (57.3)
BMI, kg/m ²	26.3 (24.3-28.9)	25.5 (24.7-28.7)
ETSVS, mo	35 (10-76)	60 (20-108)
Heart rhythm		
Sinus	46 (55.4)	46 (61.3)
Atrial fibrillation	37 (44.6)	29 (38.7)
NYHA functional class		
I	15 (18.1)	13 (17.3)
II	36 (43.4)	36 (48.0)
III	19 (22.9)	18 (24.0)
IV	13 (15.7)	8 (10.7)
Chief complaint on admission		
Asymptomatic	12 (14.5)	13 (17.3)
Valve obstruction related symptoms	61 (73.5)	55 (73.3)
Embolism related symptoms	10 (12.0)	7 (9.3)
History of		
Stroke	11 (13.3)	8 (10.7)
TIA	6 (7.2)	5 (6.7)
HT	24 (28.9)	25 (33.3)
DM	13 (15.7)	9 (12.0)
CAD	8 (9.6)	7 (9.3)
Asthma/COPD	3 (3.6)	3 (4.0)
Previous PVT	15 (18.1)	19 (25.3)
Thyroid dysfunction	3 (3.6)	2 (2.7)
Smoking	11 (13.3)	10 (13.3)
Family history of thromboembolism	11 (13.4)	3 (4.0)
Drugs		
Warfarin	79 (95.2)	73 (97.3)
Acetylsalicylic acid	19 (22.9)	17 (22.7)
ACE inhibitor	14 (16.9)	20 (26.7)
Angiotensin receptor blocker	2 (2.4)	1 (1.3)
Beta-blocker	49 (59)	41 (54.7)
Digoxin	1 (1.2)	6 (8.0)
CCB	7 (8.4)	5 (6.7)
Amiodarone	2 (2.4)	7 (9.3)
Diuretic	7 (8.4)	9 (12.0)
Statin	7 (8.4)	8 (10.7)
STS score	3.29 (2.18-5.32)	3.45 (1.86-6.07)
EuroSCORE II	9.79 (5.95-16.64)	9.12 (6.11-13.25)
Usual warfarin dose, mg	5 (4.89-6.25)	5 (5-6.25)
Admission INR	1.65 (1.3-2.5)	1.66 (1.34-2.71)
Thrombosed valve location		
MVR	55 (67.1)	63 (86.3)
AVR	18 (22.0)	6 (8.2)
TVR	9 (11.0)	4 (5.5)

Values are median (IQR) or n (%).

AVR = aortic valve replacement; ACE = angiotensin-converting enzyme; BMI = body mass index; CAD = coronary artery disease; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; ETSVS = elapsed time since valve surgery; EuroSCORE II = European System for Cardiac Operative Risk Evaluation II; HT = hypertension; INR = international normalized ratio; PVT = prosthetic valve thrombosis; MVR = mitral valve replacement; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack; TVR = tricuspid valve replacement.

TABLE 2 Baseline Echocardiographic Findings of the Study Groups

	Thrombolytic Therapy (n = 83)	Surgery (n = 75)
2D-thrombus area, cm ²	1.1 (0.9-1.3)	1.1 (0.9-1.4)
2D-mobile thrombus length, cm	1.4 (1.2-1.6)	1.1 (0.75-1.45)
Mitral (n = 119)	55	64
Valve area, cm ²	1.1 (0.9-1.4)	0.95 (0.8-1.25)
Max gradient, mm Hg	28 (25-35)	30 (25-36)
Mean gradient, mm Hg	15 (12-21)	16 (12-23)
Aortic (n = 26)	19	7
Valve area, cm ²	0.65 (0.6-0.72)	0.8 (0.74-0.83)
Max gradient, mm Hg	93 (65-115)	84 (76.5-104.75)
Mean gradient, mm Hg	58 (40-70)	49 (39-65.75)
Tricuspid (n = 13)	9	4
Valve area, cm ²	1.1 (0.77-1.4)	0.78 (0.72-0.88)
Max gradient, mm Hg	23 (20-24.5)	25.5 (19.5-30.75)
Mean gradient, mm Hg	12 (11-14.5)	11.5 (10.25-15.75)
Stuck leaflet	56 (67.5)	60 (80.0)
LV ejection fraction, %	60 (50-60)	60 (50-60)
LV end-diastolic diameter, cm	4.9 (4.6-5.3)	4.8 (4.6-5.1)
LV end-systolic diameter, cm	3.2 (3.0-3.8)	3.1 (3.0-3.5)
LA diameter, cm	4.6 (4.1-4.9)	4.7 (4.5-4.9)
LA spontaneous echo contrast	43 (51.8)	53 (69.3)
Estimated sPAP, mm Hg	35 (30-45)	35 (30-50)
TAPSE, cm	2.1 (1.8-2.3)	2.0 (1.8-2.1)

Values are median (IQR), n, or n (%).
2D = 2-dimensional; LA = left atrium; LV = left ventricle/ventricular; sPAP = systolic pulmonary artery pressure; TAPSE = Tricuspid Annular Plane Systolic Excursion.

cases (n = 13 [17.3%] treated by thrombectomy and n = 62 [82.7%] by valve replacement). The baseline clinical and echocardiographic characteristics and laboratory findings of the groups are demonstrated in **Tables 1, 2, and 3**, respectively.

THROMBOLYTIC SUCCESS AND tPA DOSE AND REGIMEN. The overall success rate of TT was 90.4% with a median TT dose of 59 mg (IQR: 37.5-100 mg). Lytic success could not be obtained in 8 patients either because of development of a major complication (1 coronary embolism, 1 large peripheral embolism, 1 cerebral bleeding, 1 noncerebral bleeding) or unresponsiveness to therapy (4 cases).

In 63 cases, the TT regimen was ultraslow infusion (25 hours) of low-dose (25 mg) t-PA. In 8 cases, the TT regimen was slow infusion (6 hours) of low-dose (25 mg) t-PA. In the remaining 12 cases, the 2 regimens were combined.

COMPLICATIONS. Of 75 patients undergoing surgery, 47 (62.7%) of them experienced 94 complications (12 bleeding, 6 embolism or thrombosis, 76 other events). Of 83 patients undergoing TT, 10 (12%) of them experienced 14 complications (7 bleeding, 5 thrombosis or embolism, 2 other events). Hence, a total of 108 complications occurred. The count of complications for each patient ranged from 1 to 5: 5 in 1

subject, 4 in 6 subjects, 3 in 8 subjects, 2 in 13 subjects, and 1 in 29 subjects. Development of 3 or more complications in a single patient was only observed in the surgery group.

The incidence of total, major, and minor complications of study groups are reported in **Table 4**. Major and minor bleeding event rates were 2.4% and 6% in the TT and 9.3% and 6.7% in the surgery groups, respectively. Besides, total embolic event rates were 2.4% and 5.3% in TT and surgery groups, respectively. The reason for a relatively high overall or major complication rate in the surgery group was the higher rate of surgery-related complications apart from thromboembolism or bleeding. **Table 5** summarizes the distribution of nonembolic and nonhemorrhagic complications of the surgery group. In the TT group, sustained ventricular arrhythmia was detected in 2 patients as the only nonembolic and nonhemorrhagic complication after thrombolysis.

MORTALITY. The 3-month mortality rate (in or out of hospital) was 2.4% in the TT group and 18.7% in the surgery group (**Table 4**). The majority of the deaths occurred during the hospital stay; only 1 patient from each group died within 3 months after being discharged. A Kaplan-Meier analysis shows the 3-month cumulative mortality curves in the surgery and TT groups (**Figure 6**).

When the surgical subgroups were taken into consideration in terms of thrombectomy and valve replacement, the major complication and 3-month mortality rates were found to be 61.5% and 15.4% for thrombectomy and 37.1% and 19.4% for valve replacement, respectively. The median hospital stay was 5 days (IQR: 4-7 days) in the TT group and 9 days (IQR: 5-13 days) in the surgery group (**Table 4**). During the 3-month follow-up period, rethrombosis requiring therapy was observed in 2 (2.4%) patients among the TT group and 5 (6.7%) patients among the surgery group (**Table 4**).

DISCUSSION

The major finding of the current study is that low-dose and prolonged infusion of tPA, as an effective and safe treatment, was associated with low mortality and high success rates in patients with obstructive PVT.

TT has been increasingly used over the last decades; particularly in studies with slow infusion of low-dose t-PA, rates of thrombolysis have revealed favorable clinical outcomes.^{2,3,17-20} Moreover, the PRO-TEE (Prosthetic Valve Thrombolysis-Role of Transesophageal Echocardiography) investigators indicated that a thrombus area <0.8 cm² identified

patients at lower risk for complications from thrombolysis.²¹ We have previously showed that low-dose (25 mg), slow (6 h), and ultraslow (25 h) infusion of t-PA with repetition was associated with successful thrombolysis and reduced the risk of hemorrhage and thromboembolism compared with higher doses or faster infusion of t-PA or streptokinase.^{2,3} Keeping with this, our previous and present data proposed that slow/ultraslow or combined infusion of low-dose t-PA resulted in lower rates of complications and provided mortality-driven benefit. Based on these results, the 2020 American College of Cardiology/American Heart Association guidelines recommend urgent initial treatment with either slow-infusion, low-dose TT or emergency surgery for symptomatic left-sided PVT.⁷ On the other hand, the most recent European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines still prioritize surgery in the management of PVT.⁶ Hence, recommendations of the 2 major guidelines for the management of PVT remain controversial.

SUCCESS RATE OF TT. Caceres-Loriga et al²² previously reported complete success in 85.0% of cases and partial success in 6.0% with TT in their study, with 68 patients during a 6-year period. Moreover, Nagy et al²³ previously reported the results of TT in 62 obstructive PVT cases; complete success was achieved in 73.0% of these cases, and partial success in 21.0%, while the mortality (8.0%) and embolic complication (12.0%) rates of TT were similar to those of previous studies. Recently, 17 studies with clinical outcomes of 756 patients who received TT for treatment of 801 episodes of obstructive PVT were analyzed.²⁴ Complete success was achieved in 81% of patients presenting in NYHA functional classes I/II and 74.0% of patients presenting in NYHA functional class III/IV. The rate of thromboembolism was 14.0%, and the overall 30-day mortality was 8.0%. Indeed, the cumulative success rate of TT in both the Ultraslow PROMETEE (Ultraslow thrombolytic therapy: A novel strategy in the management of PROsthetic MEchanical valve Thrombosis and the prEdictors of outcome) and the TROIA (Comparison of Different TRansesophageal Echocardiography Guided thrOm-bolytic Regimens for prosthetIc vAlve Thrombosis) trials was approximately 90.0%,^{2,3} and the success rate of these TT regimens were substantially higher even in the elderly patient group.¹⁸ In the current study, the overall TT success rate of 90.4% is consistent with the results of 2 major TT studies previously published.^{2,3} Moreover, the present study only includes obstructive PVT, and the combination

TABLE 3 Main Laboratory Findings of the Study Groups

Blood Work-Up Feature	Thrombolytic Therapy (n = 83)	Surgery (n = 75)
Glucose, mg/dL	101 (92-133)	104 (94-116)
Creatinine, mg/dL	0.79 (0.62-1.03)	0.84 (0.69-1.09)
Aspartate aminotransferase, U/L	23 (17-28)	25 (19-30)
Alanine aminotransferase, U/L	19 (14-24)	20 (14-26)
LDH, U/L	342 (259-393)	349 (300-410)
Total bilirubin, mg/dL	0.7 (0.5-1.0)	0.7 (0.5-1.16)
White blood cell count, 10 ⁹ /L	9.1 (7-11)	9.9 (7.4-12.4)
Hemoglobin, g/dL	12.4 (11.0-13.9)	12.3 (10.7-13.7)
Platelet, 10 ⁹ /L	236 (179-306)	242 (192-330)
MPV, fL	8.7 (8.2-9.65)	9.1 (8.2-10.1)
CRP, mg/dL	1.5 (0.53-3.7)	1.69 (0.56-6.71)
ESR, mm/h	20 (13.5-42.5)	25 (9.75-42)

Values are median (IQR).
CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; LDH = lactate dehydrogenase; MPV = mean platelet volume.

of both slow and/or ultraslow regimens has been used for the first time in the current literature.

TREATMENT-RELATED COMPLICATIONS. The overriding concern associated with TT of left-sided PVT includes cerebral thromboembolism and bleeding.^{25,26} A large scaled meta-analysis previously indicated that combined embolic events occurred in 1.6% of surgically treated patients and in 16% of patients who received TT.⁹ In another meta-analysis conducted by Castilho et al,⁸ the incidence of systemic embolism was 12.8% in the TT arm and 4.6% in the surgical treatment arm, whereas the incidence of stroke among the surgery and TT groups was 4.3% and 5.6%, respectively. The low incidence of embolic

TABLE 4 List of Adverse Events in the Study Groups

	Thrombolytic Therapy (n = 83)	Surgery (n = 75)
Hospital stay, d	5 (4-7)	9 (5-13)
Total complications	10 (12.0)	47 (62.7)
Major complications	5 (6.0)	31 (41.3)
Minor complications	7 (8.4)	29 (38.7)
Total embolic complications	2 (2.4)	4 (5.3)
Total bleeding	7 (8.4)	12 (16.0)
Major bleeding	2 (2.4)	7 (9.3)
Cerebral	1 (1.2)	1 (1.3)
Noncerebral	1 (1.2)	6 (8.0)
Minor bleeding	5 (6.0)	5 (6.7)
Rethrombosis requiring therapy	2 (2.4)	5 (6.7)
3-month death	2 (2.4)	14 (18.7)

Values are median (IQR) or n (%). In the first column, the n denotes the number of patients experiencing complications rather than the number of complications that occurred. For instance, "total complications" occurred in 10 cases undergoing thrombolysis and in 47 cases undergoing surgery. Of note, the sum (5 + 31 + 7 + 29 = 72) of the cases experiencing major or minor complications far exceeds the number of cases with total complications (10 + 47 = 57), because both types of complications occurred simultaneously in 15 cases.

TABLE 5 Surgery-Related Complications Apart From Embolism or Bleeding

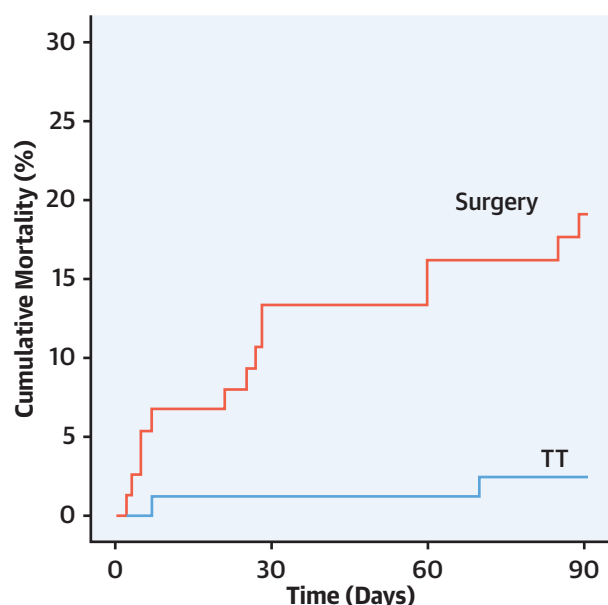
Complications (76 Events)	Surgery Group (n = 75)
Postoperative infection	
Sepsis	3 (4.0)
Endocarditis	2 (2.6)
Mediastinitis	1 (1.3)
Pneumonia	4 (5.3)
Sternotomy	3 (4.0)
Wound infection	7 (9.3)
Newly developed persistent LV dysfunction	6 (8.0)
AKI with a need for renal replacement therapy	12 (16)
Newly developed severe native aortic regurgitation (caused by entrapment of aortic cusp during mitral redo surgery)	3 (4.0)
Atrioventricular groove tear	2 (2.6)
Pericardial effusion with tamponade	6 (8.0)
Tracheostomy after a prolonged endotracheal intubation	1 (1.3)
Pleural effusion requiring hospitalization and drainage	11 (14.6)
Phrenic nerve paralysis	3 (4.0)
Tracheal stenosis requiring intervention	1 (1.3)
Sustained ventricular arrhythmias	1 (1.3)
Paravalvular leak	
Moderate	3 (4.0)
Severe	7 (9.3)

Values are n (%) where n denotes the count of individual events and the (%) denotes the percentage of the count within the surgery group.
AKI = acute kidney injury; LV = left ventricle/ventricular.

events in the present study was consistent with our previous reports.^{2,3} Major bleeding is the most feared complication in both TT and surgery in this patient population and usually has catastrophic consequences.^{1-4,8,9} In several studies and 2 large meta-analyses, the rate of major bleeding in the surgery group was between 0.7% and 18.6%.^{4,8,9,20,27-29} The major bleeding rates were found to be slightly higher in the surgical arm of the present study compared with western data, whereas it was reported to be similar regarding the TT arm. Moreover, intracranial bleeding is observed in only a single case in the TT group.

Surgery is associated with high rate of procedure-related complications apart from embolism or bleeding, which can also be observed in tertiary high-volume centers with an experienced surgical team.²⁹ These nonembolic and nonhemorrhagic complications, including postoperative infection, AKI, tamponade, prolonged endotracheal intubation, tracheal stenosis, multiple organ failure, and arrhythmias, may also compromise surgical success and increase mortality.³⁰ Previously, several investigators demonstrated that the frequency of cardiac complications (persistent LV dysfunction, surgery-related ventricular septal defect, complete atrioventricular block, and tamponade) was 11%-14.0%,^{4,10,29} whereas 3.1%-21.0% of the patients presented with multiple organ dysfunctions^{10,29} and 7.1% experienced AKI, requiring renal replacement therapy.²⁰

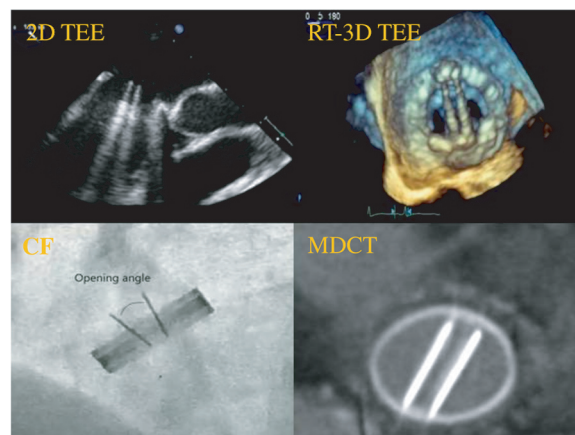
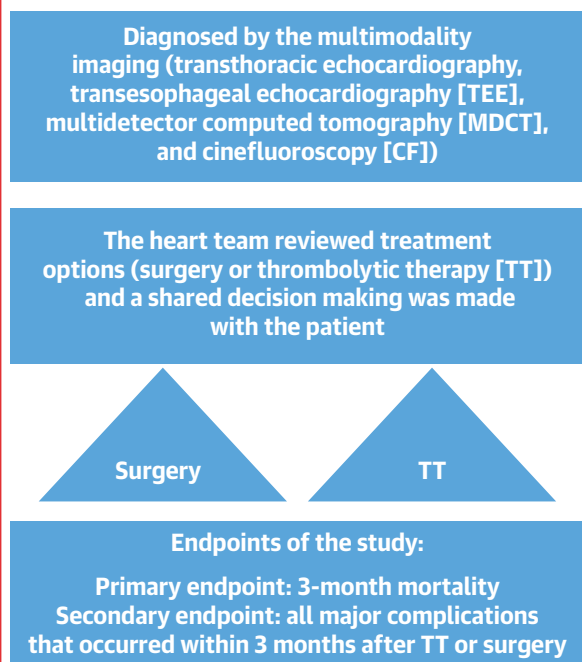
FIGURE 6 Kaplan-Meier Curve for 3-Month Cumulative Mortality



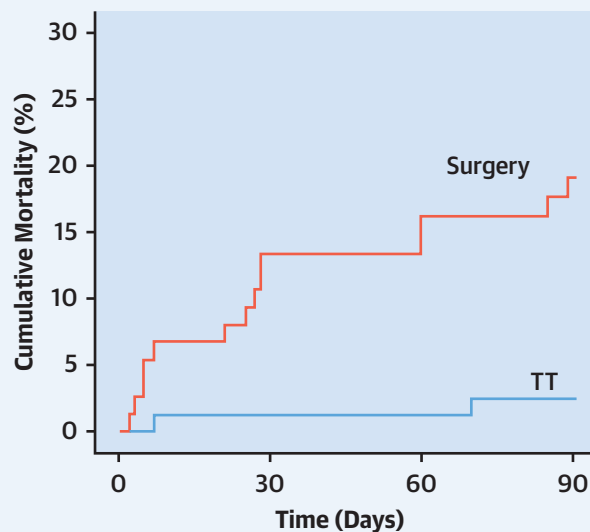
Kaplan-Meier analysis indicates the 3-month cumulative mortality curves in the surgery and TT groups. TT = thrombolytic therapy.

MORTALITY. As expected, over the years, the mortality of prosthetic heart valve surgery has significantly decreased. Recent data showed that the operative mortality is strongly associated with procedural emergency, which doubles the mortality from 10%-15.0% (nonemergency surgery) to 20%-40.0%.^{27,28} Toker et al¹⁰ reported an early mortality rate of 20.6% in 63 patients who underwent reoperations caused by obstructive prosthetic valve dysfunction. However, the etiology of the valve dysfunction was thrombus formation in only 18 (28.6%) patients. They suggested that left ventricular dysfunction was the major determinant of surgical mortality. Besides, Keuleers et al⁴ previously reported perioperative mortality of 11.0% in their study with a limited number of patients (18 of 31 patients were surgical group) with PVT. However, this study only included perioperative mortality and lacked short- or mid-term mortality. In another study authored by Dürreleman et al,²⁸ the operative mortality after PVT was reported as 9.0%. It should be noted that, in this study, approximately one-half of the patients in the surgical group were only treated by

CENTRAL ILLUSTRATION Schematic Representation of the Study Design and Outcomes



Multimodality imaging for the diagnosis of prosthetic valve thrombosis



Kaplan-Meier analysis indicates the 3-month cumulative mortality curves in the surgery and TT groups

Özkan, M. et al. J Am Coll Cardiol. 2022;79(10):977-989.

The diagnosis of prosthetic valve thrombosis was confirmed by multimodality imaging in patients with prosthetic heart valves. Among these patients, those who were suitable for both TT and surgery were included in the study and followed up for 3 months. 2D = 2-dimensional; RT-3D = real time 3-dimensional.

thrombectomy. The outcomes of each treatment strategy for PVT have been evaluated by several meta-analyses and systematic reviews. Previously, Karthikeyan et al⁹ evaluated 690 episodes and 7 PVT studies and reported the mortality rates of surgery and TT as 13.5% and 9%, respectively. Moreover, they recommended urgent surgical intervention to be preferred to TT in experienced centers.⁹ Besides, in a

meta-analysis authored by Castilho et al,⁸ which evaluated 27 studies with 1,107 patients treated by TT and 26 studies with 1,132 patients operated for PHVT, the mortality rate in the TT and surgery groups were 6.6% and 18.1%, respectively. The present study has a relatively high mortality rate among surgically treated patients compared with the published literature. However, the current literature may not reflect

real-world data, because the surgical mortality rates are likely to be higher in developing and under-resourced countries, which may represent most of the world population, whereas TT can be safely administered worldwide when the low-dose treatment protocols are adequately performed¹⁹ (Figure 4). There is limited data and regionally variable evidence for outcomes with surgery and TT in patients with PVT. This observation supports current clinical practice guideline recommendations to engage a multidisciplinary heart team to help guide the choice of management modality for patients with obstructive mechanical PVT (Central Illustration).

STUDY LIMITATIONS. First, although this is a non-randomized observational study; it is still remarkable for its size with both treatment groups. Second, it is difficult to standardize surgical skills, although the re-operations were performed in high-volume centers. Third, more women in the TT group than the surgery group might have led to bias in the findings. Last, only the short-term follow-up data have been included.

CONCLUSIONS

This nonrandomized observational study suggests that prolonged infusions of low-dose TT are associated with low mortality and complication rates, and provide effective treatment in NYHA functional class I-IV patients with obstructive PVT. The combination of 2 regimens—slow and ultraslow infusion of tPA—can be also performed in the same index patient during the clinical course of the disease. Surgery has a high mortality rate even in experienced centers; therefore, TT may be considered as a beneficial treatment strategy in patients with obstructive PVT in the absence of contraindications. Nevertheless, further larger randomized trials are warranted to validate the findings of this study.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: Slowly administered infusions of t-PA are a safe and effective alternative to surgical therapy in selected patients with obstructive mechanical heart valve prostheses.

TRANSLATIONAL OUTLOOK: Multicenter randomized trials with clearly defined inclusion and exclusion criteria would raise the level of evidence available to guide management of patients with obstructive mechanical prosthetic heart valve thrombosis.

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KEY WORDS echocardiography, prosthetic valve thrombosis, surgery, thrombolytic therapy, transesophageal echocardiography

APPENDIX For supplemental videos, please see the online version of this paper.