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Μαλκότς Μπελκίς
Ειδικευόμενη Καρδιολογίας
Πανεπιστημιακή Καρδιολογική Κλινική,ΠΓΝΑ
Διευθυντής: Καθ. Τζιακάς Δημήτριος
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Investigation

ombolysis or Surgery in ents With Obstructive hanical Valve Thrombosis: The Multicenter TTUSHA Study

Özkan MD [a, b], Sabahattin Gündüz MD [a], Ahmet Güner MD [c], Macit Kalçık MD [d]
Ozan Gürsoy MD [e], Begüm Uygur MD [c], Nurşen Keleş MD [f], Hasan Kaya MD [g], Alev Kılıçgedik MD [a]
Bayam MD [a], Semih Kalkan MD [a], Mehmet Ali Astarcıoğlu MD [h], Süleyman Karakoyun MD [i]
t Yesin MD [i], Duygu İnan MD [f], Ali Fedakar MD [j], Sabit Sarıkaya MD [j], Mehmet Aksüt MD [j]
nan MD [k], Cevdet Uğur Koçoğulları MD [l]

Προοπτική μελέτη παρατήρησης

This study aimed to prospectively evaluate the outcomes of **TT**-*low-dose (25 mg) slow (6 hours)/ultraslow (25 hours) infusion of tissue-type plasminogen activator (t-PA)*- and **surgery** as the first-line treatment strategy in patients with obstructive PVT

Diagnosed by the multimodality imaging (transthoracic echocardiography, transesophageal echocardiography [TEE], multidetector computed tomography [MDCT], and cinefluoroscopy [CF])

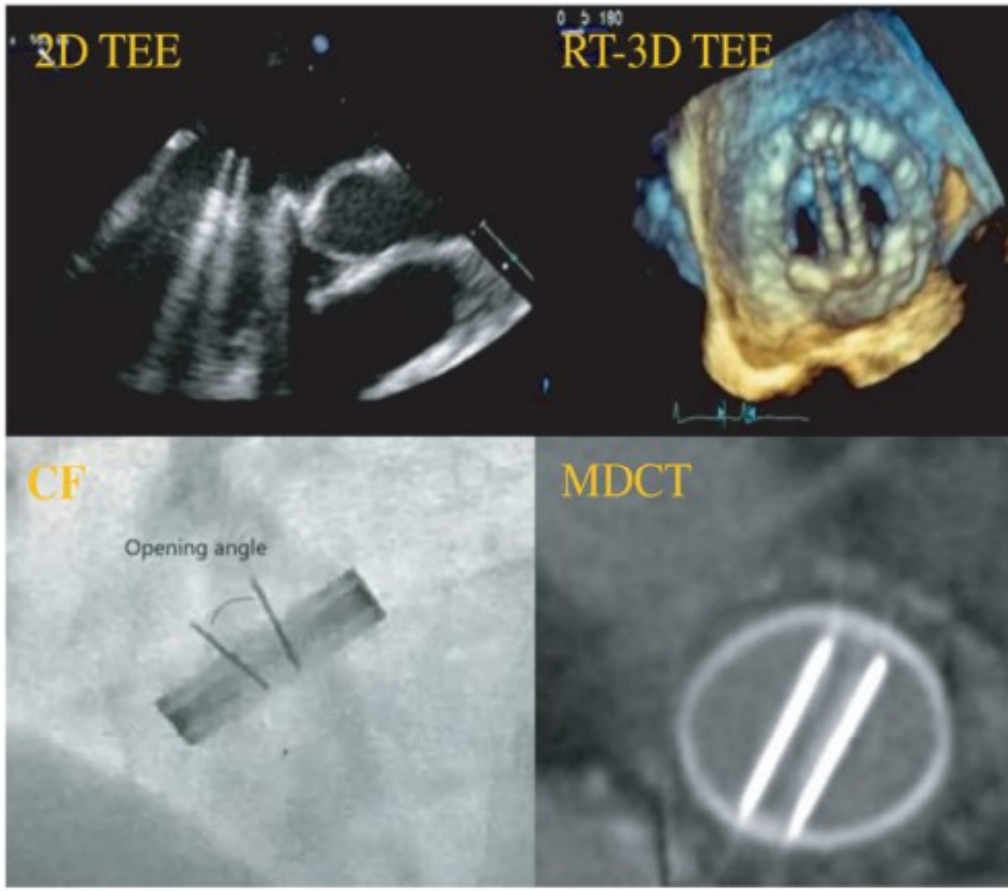
The heart team reviewed treatment options (surgery or thrombolytic therapy [TT]) and a shared decision making was made with the patient

Surgery

TT

Endpoints of the study:

Primary endpoint: 3-month mortality
Secondary endpoint: all major complications that occurred within 3 months after TT or surgery



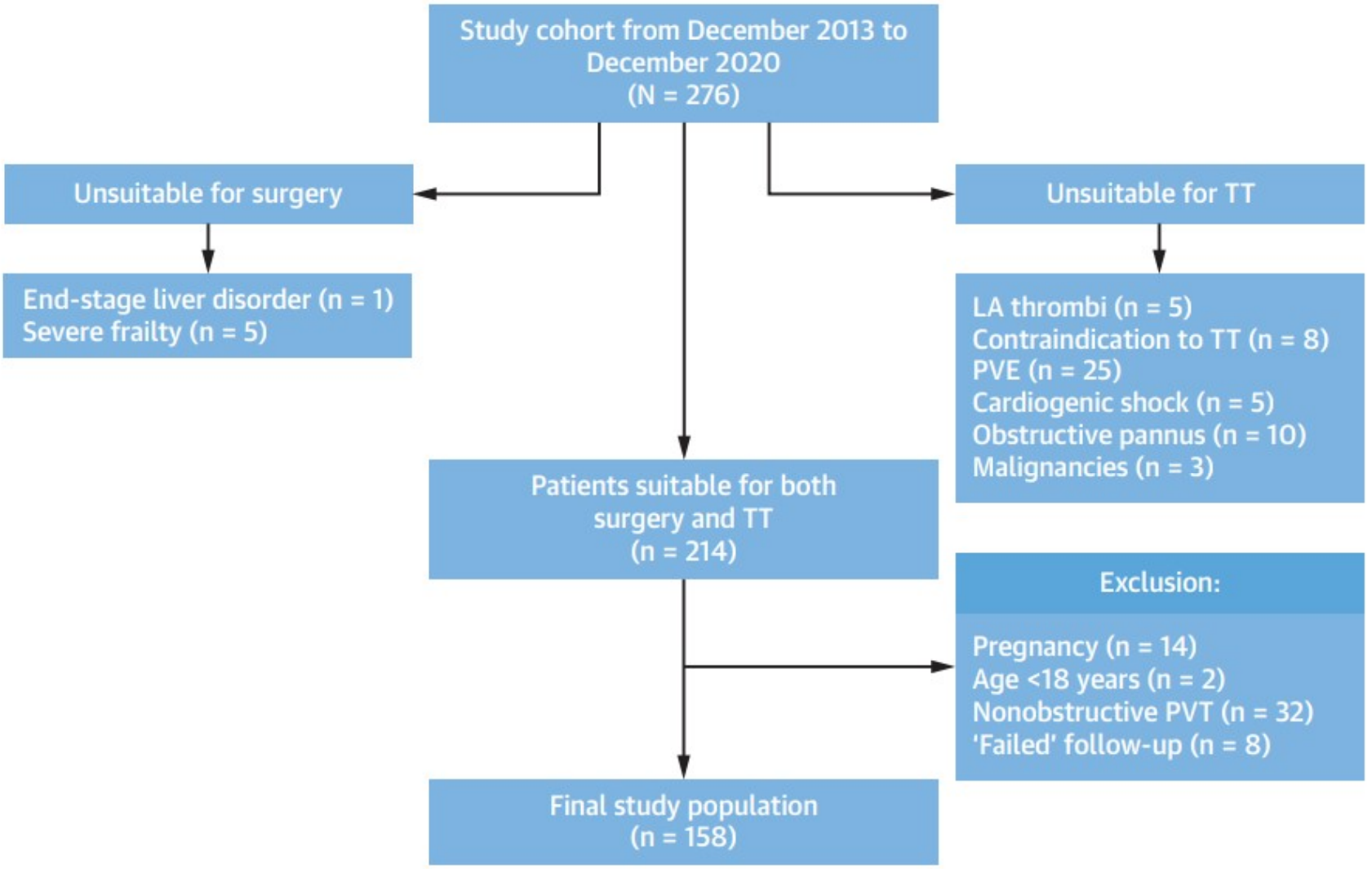
ΜΕΘΟΔΟΙ

158 patients (103 women [65.2%], median age 49 years [IQR: 39-60 years])

December 2013 - December 2020 in 8 tertiary centers

Patients with a contraindication to TT, nonobstructive 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

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.

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.

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, f/L	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).

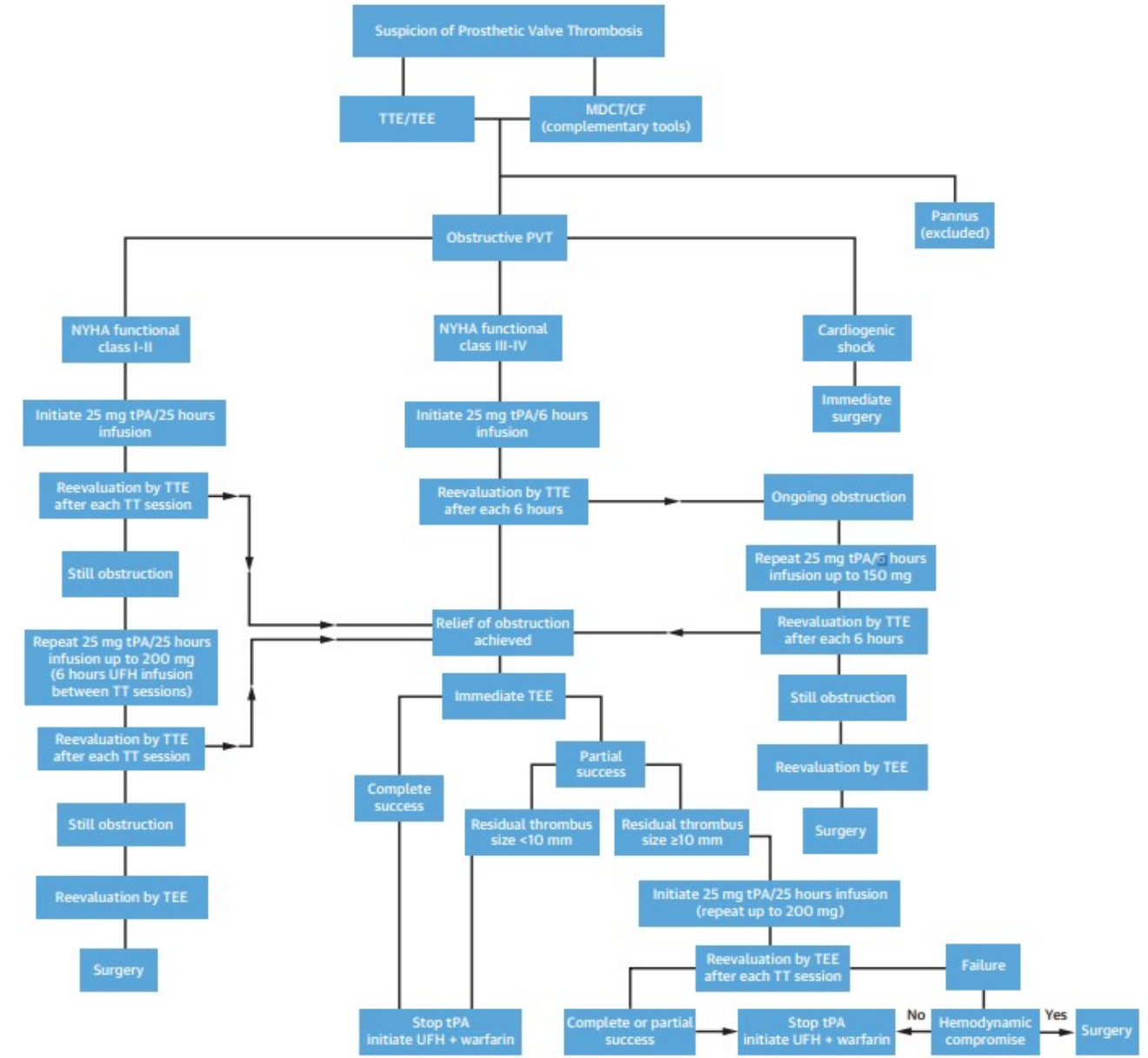
CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; LDH = lactate dehydrogenase; MPV = mean platelet volume.

THE TT REGIMEN

6-hour infusion of 25 mg t-PA without a bolus (repeat up to 6 times if needed, maximum total dose of 150 mg) ➡ NYHA III-IV

25-hour infusion of 25 mg t-PA without a bolus (repeat up to 8 times if needed, maximum total dose of 200 mg) ➡ NYHA I-II

FIGURE 4 Study Algorithm for Patients With Obstructive Prosthetic Valve Thrombosis

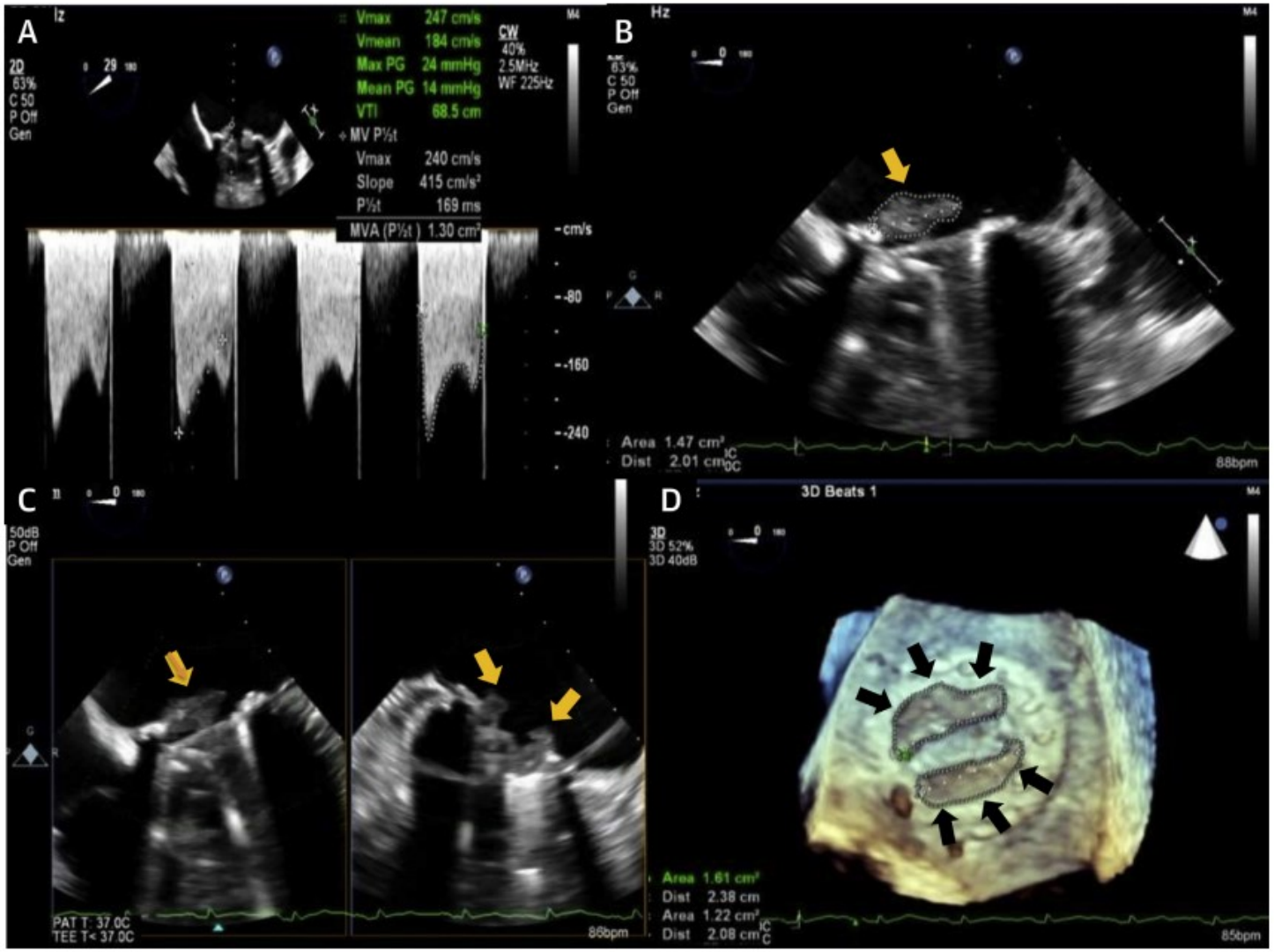


CF = cinefluoroscopy; MDCT = multidetector computed tomography; NYHA = New York Heart Association; PVT = prosthetic valve thrombosis; TEE = transesophageal echocardiography; t-PA = tissue-type plasminogen activator; TT = thrombolytic therapy; TTE = transthoracic echocardiography; UFH = unfractionated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

SURGICAL TECHNIQUE

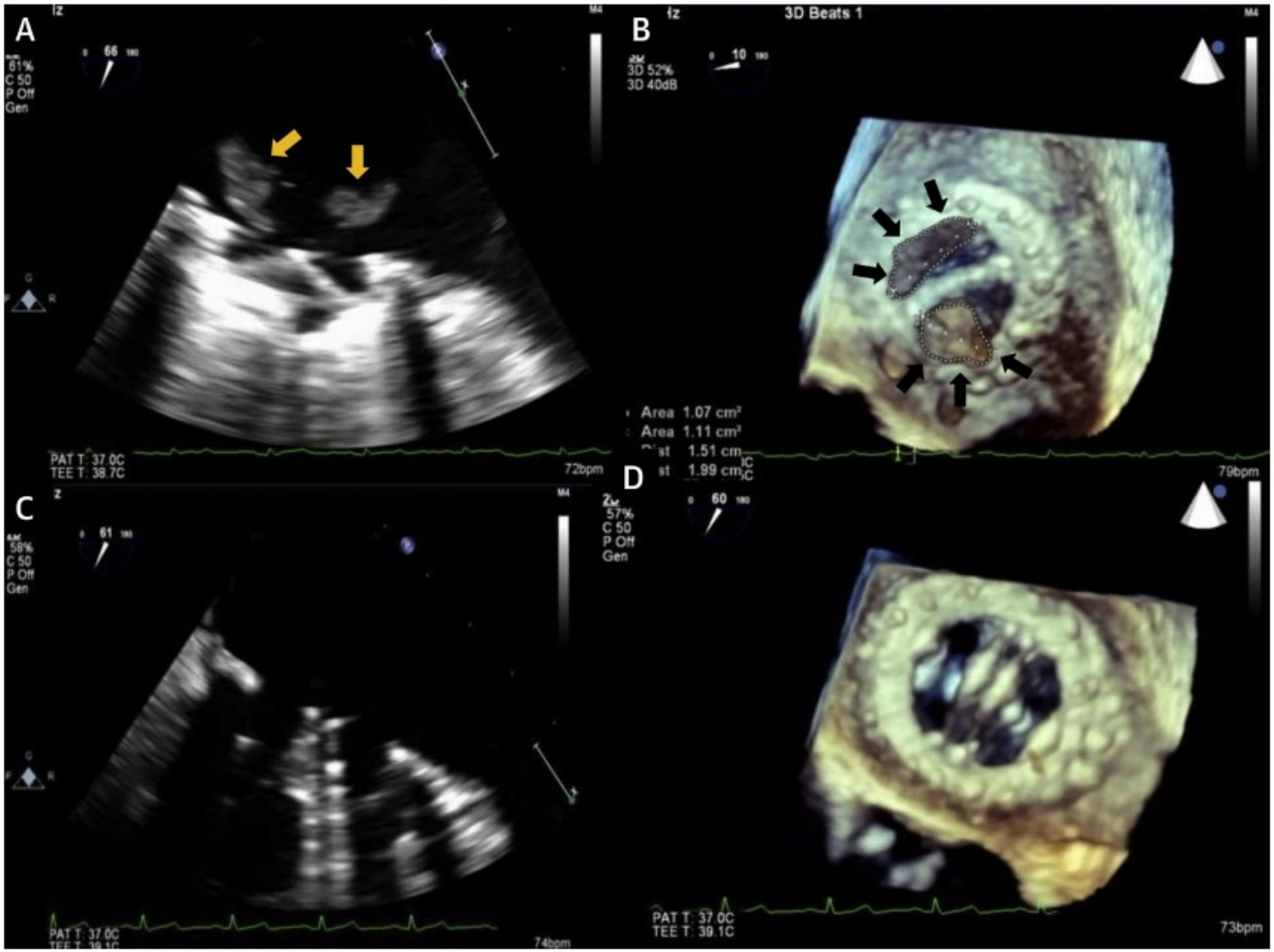
Thrombectomy or valve replacement

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 cm^2 **(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 cm^2 (1.61 cm^2 + 1.22 cm^2) **(black arrows) (D).**

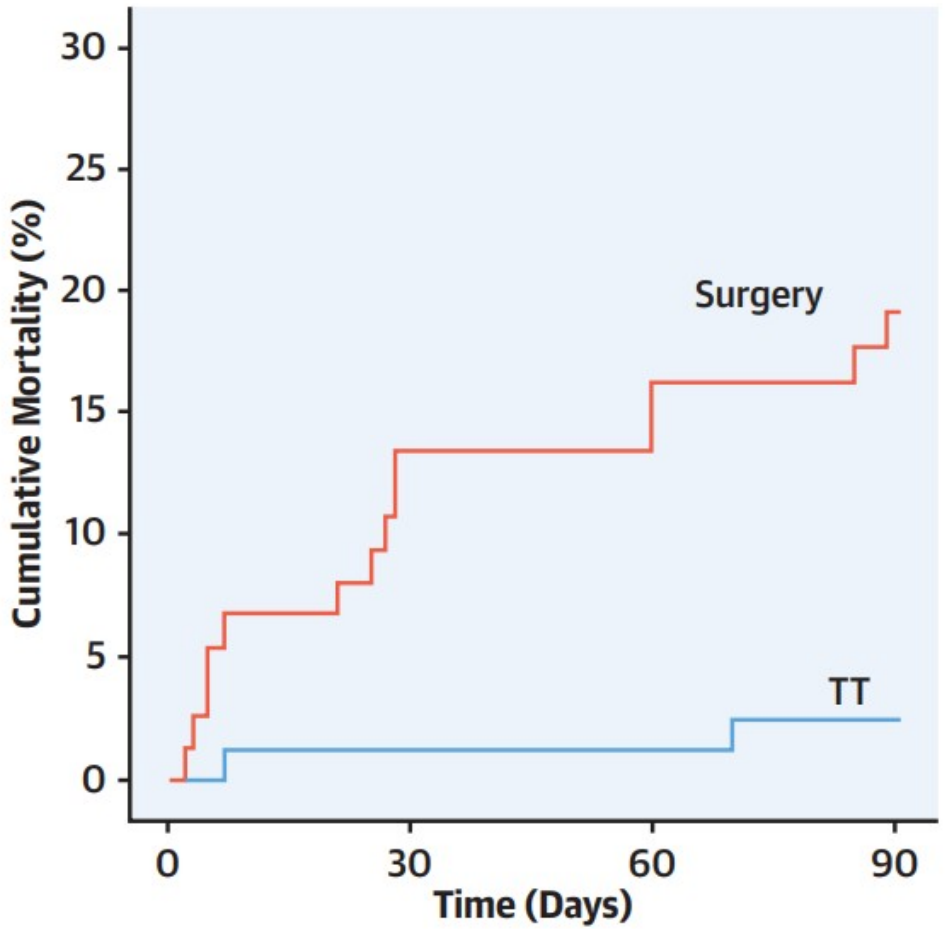
FIGURE 3 Serial 2D and RT-3D TEE After Each t-PA Session



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 cm^2 (1.07 cm^2 + 1.11 cm^2) **(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).**

RESULTS-PRIMARY ENDPOINT

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.

The 3-month mortality rate
out of hospital) was 2.4% in
group and 18.7% in the surg
group

MAJOR COMPLICATIONS-SECONDARY ENDPOINTS

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.

LE 5 Surgery-Related Complications Apart From Embolism or Bleeding

Complications (76 Events)	Surgery Group (n = 75)
perative infection	
sis	3 (4.0)
docarditis	2 (2.6)
diastinitis	1 (1.3)
eumonia	4 (5.3)
rnitis	3 (4.0)
und infection	7 (9.3)
y developed persistent LV dysfunction	6 (8.0)
ith a need for renal replacement therapy	12 (16)
y developed severe native aortic regurgitation (caused by entrapment of aortic cusp during mitral redo surgery)	3 (4.0)
ventricular groove tear	2 (2.6)
ardial effusion with tamponade	6 (8.0)
eostomy after a prolonged endotracheal intubation	1 (1.3)
al effusion requiring hospitalization and drainage	11 (14.6)
ic nerve paralysis	3 (4.0)
eal stenosis requiring intervention	1 (1.3)
ined ventricular arrhythmias	1 (1.3)
alvular leak	
derate	3 (4.0)
ere	7 (9.3)

s are n (%) where n denotes the count of individual events and the (%) denotes the percentage of the count the surgery group.

= acute kidney injury; LV = left ventricle/ventricular.

In the TT group, sustained ventricular arrhythmia was detected in 2 patients a the only nonembolic and nonhemorrhagic complication after thrombolysis.

CONCLUSIONS

- 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
- Surgery has a high mortality rate even in experienced centers
- TT may be considered as a beneficial treatment strategy in patients with obstructive PVT in the absence of contraindications
- Larger randomized trials are warranted to validate the findings of this study

STUDY LIMITATIONS

- nonrandomized observational study
- Difficulty in standardizing surgical skills
- more women in the TT group than the surgery group might have led to bias in the findings
- only the short-term follow-up data have been included

ΕΥΧΑΡΙΣΤΩ!