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Comparison of Different TEE-Guided Thrombolytic Regimens for Prosthetic Valve Thrombosis

The TROIA Trial

Mehmet Özkan, MD,* Sabahattin Gündüz, MD,* Murat Biteker, MD,* Mehmet Ali Astarcioglu, MD,* Cihan Çevik, MD,† Evren Kaynak, MD,‡ Mustafa Yıldız, MD, PHD,* Emrah Oğuz, MD,* Ahmet Çağrı Aykan, MD,* Emre Ertürk, MD,* Yusuf Karavelioğlu, MD,* Tayyar Gökdeniz, MD,* Hasan Kaya, MD,* Ozan Mustafa Gürsoy, MD,* Beytullah Çakal, MD,* Süleyman Karakoyun, MD,* Nilüfer Duran, MD,* Nihal Özdemir, MD*

Istanbul, Turkey; and Houston, Texas

OBJECTIVES The aim of this prospective study was to identify the most effective and safest regimen among different thrombolytic treatment strategies.

BACKGROUND The best treatment strategies for prosthetic valve thrombosis have been controversial.

METHODS Transesophageal echocardiography–guided thrombolytic treatment was administered to 182 consecutive patients with prosthetic valve thrombosis in 220 different episodes (156 women; mean age, 43.2 ± 13.06 years) between 1993 and 2009 at a single center. These regimens chronologically included rapid (Group I), slow (Group II) streptokinase, high-dose (100 mg) tissue plasminogen activator (t-PA) (Group III), a half-dose (50 mg) and slow infusion (6 h) of t-PA without bolus (Group IV), and a low dose (25 mg) and slow infusion (6 h) of t-PA without bolus (Group V). The endpoints were thrombolytic success, in-hospital mortality, and nonfatal complication rates.

RESULTS The overall success rate in the whole series was 83.2%; it did not differ significantly among Groups I through V (68.8%, 85.4%, 75%, 81.5%, and 85.5%, respectively; $p = 0.46$). The overall complication rate in the whole series was 18.6%. Although the overall complication rate was similar among Groups I through IV (37.5%, 24.4 %, 33.3%, and 29.6%, respectively; $p > 0.05$ for each comparison), it was significantly lower in Group V (10.5%, $p < 0.05$ for each). The combined rates of mortality and nonfatal major complications were also lower in Group V than in the other groups, with all differences significant except for comparison of Groups IV and V. By multivariate analysis, the predictors of combined mortality plus nonfatal major complications were any thrombolytic therapy regimen other than Group V (odds ratios for Groups I through IV: 8.2, 3.8, 8.1, and 4.1, respectively; $p < 0.05$ for each) and a history of stroke/transient ischemic attack (odds ratio: 3.5, $p = 0.011$). In addition, there was no mortality in Group V.

CONCLUSIONS Low-dose slow infusion of t-PA repeated as needed without a bolus provides effective and safe thrombolysis in patients with prosthetic valve thrombosis. (Comparison of Different TRansesophageal Echocardiography Guided thrOmbolytic Regimens for prosthetIc vAlve Thrombosis; NCT01451320) (J Am Coll Cardiol Img 2013;6:206–16) © 2013 by the American College of Cardiology Foundation

From the *Department of Cardiology, Kosuyolu Kartal Heart Training and Research Hospital, Istanbul, Turkey; †Division of Adult Cardiology, Texas Heart Institute at St. Luke's Episcopal Hospital, Baylor College of Medicine, Houston, Texas; and the ‡Division of Adult Cardiology, The University of Texas Health Science Center, Houston, Texas. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Prosthetic valve thrombosis (PVT) is a serious complication with high mortality and morbidity (1). The PVT incidence was reported to be 0.03% in bioprosthetic valves (2), 0.5% to 8% in mechanical valves in the mitral and aortic positions, and as high as 20% in mechanical tricuspid valves (3). The best treatment of PVT is controversial, although surgery (4–8), anticoagulation (4,9), and thrombolysis (9–22) options have been available.

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In the most recent American College of Cardiology/American Heart Association guidelines (23), surgery is recommended for patients in New York Heart Association (NYHA) functional classes III and IV unless surgery is high risk (functional class IIA). Thrombolysis is given a NYHA functional class IIA indication in patients with right-sided valve thrombosis and a NYHA functional class IIB indication in patients with a left-sided but small thrombus. The European Society of Cardiology guidelines (24) also emphasize surgery for critically ill patients (NYHA functional class IC) and restrict thrombolysis to patients with high surgical risk and/or right-sided valve thrombosis. Moreover, the use of fibrinolytic therapy with a nonobstructive thrombus was also discouraged because of the increased risk of bleeding and embolization. On the other hand, the Society for Heart Valve Disease (25) clearly states that thrombolysis is the first-line treatment for obstructive PVT, independent of NYHA functional class and thrombus size. The American College of Chest Physicians guidelines recommend thrombolysis for small thrombi and surgery for larger ones (26). Cáceres-Lóriga et al. (11), Lengyel et al. (9), Shapira et al. (12), and Alpert (13) emphasized the role of thrombolysis.

Despite the improvement in mortality within the past decade, surgical management of PVT has been associated with a significant death risk for 40 years. Therefore, establishment of a more effective strategy to treat PVT is crucial, especially in the developing countries where this condition is prevalent. Currently, there is no agreement on the type, dose, and route of administration of thrombolytic agents. In this study, thrombolysis was used as first-line therapy, and we prospectively analyzed our 16-year experience in which 5 different thrombolytic regimens were used for the treatment of PVT in chronological order, in an effort to identify the most effective and safest regimen.

METHODS

Rationale of the study methods. This single-center study was not a randomized, controlled study comparing thrombolytic therapy (TT) with surgery for the treatment of PVT. The sporadic and catastrophic nature of PVT historically has not allowed a large-scale, randomized, controlled clinical trial to be conducted on this entity. Because previous reports demonstrated that surgery was associated with high mortality (average 20%) and this finding was similar to our institution's surgery outcomes for the treatment of PVT between 1996 and 2005 (8), we did not intend to randomize patients to a cardiac surgery group; therefore, such a comparison was not performed. TT and surgery were not considered as alternative treatment options; instead, they were considered as complementary treatments. Hence, TT was the first treatment option for virtually all patients with PVT at our institution, and since the first patient was enrolled in this study, surgery was only performed in the patients who had a major contraindication to TT or in those in whom thrombolysis failed. Despite the improvements in anesthesia and perioperative care, in-hospital mortality of surgery for the treatment of obstructive PVT was 17% at our institution (between 2006 and 2011, 64 patients with PVT who had a contraindication to TT or in whom TT failed underwent surgery; 11 of these patients died after the surgery) and 11% in a recent study from Belgium (27). These findings necessitate a nonsurgical therapy; in particular, thrombolysis with new TT protocols for the treatment of PVT.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
INR = international normalization ratio
NYHA = New York Heart Association
OR = odds ratio
PVT = prosthetic valve thrombosis
SKZ = streptokinase
TEE = transesophageal echocardiography
t-PA = tissue plasminogen activator
TT = thrombolytic therapy
TTE = transthoracic echocardiography
TIA = transient ischemic attack

The rationale for the different TT regimens and, in particular, the reasons for switching from one to another were as follows. Throughout this study, we constantly evaluated the outcomes of the patients after each course of TT. When a particular regimen was applied to 4 patients, an official data evaluation meeting was held by the physicians involved in the care of these patients. The TT regimen was continued for the next 4 patients if the complication rate was favorable compared with the previous regimen. The TT regimen was discontinued and a new regimen was started when it resulted in a complication rate similar to that of the previous regimen. Our first TT protocol (Group I) was stopped because the major complication rates were similar to those of surgery. Thus, we intended to

use potentially safer regimens by reducing the dose of TT and/or increasing the infusion duration of the same dose to achieve a reduced complication rate in each subsequent group. Therefore, the regimens described were used as the first treatment option in all patients who presented with PVT in chronological order. A new thrombolytic protocol was used in the next therapy period. Finally, the groups in which the complication rates increased rapidly during the earlier course of treatment retained a relatively small number of patients due to termination of that protocol.

We hypothesized that the most serious complication of TT (bleeding) could be diagnosed early, and the TT infusion could be stopped immediately with a low-dose, slow-infusion protocol.

Similarly, we did not use concomitant heparin anticoagulation with TT due to the potential increased risk of bleeding.

Patient population and enrollment. The study was approved by the local ethics board, and the patients were enrolled after providing informed consent. A total of 182 consecutive in-hospital patients with 220 episodes of mechanical PVT between 1993 and 2009 were included in the study. A PVT episode refers to the entire treatment period of a patient who is admitted to the hospital with a PVT and includes all TT infusions per thrombolytic regimen whether or not each infusion was successful. If the same patient was readmitted at a different time with rethrombosis of the prosthetic heart valve, this was considered a separate PVT episode.

The exclusion criteria were as follows: patients with a contraindication (Table 1) to thrombolytic treatment, patients with asymptomatic nonobstructive PVT without a history of recent thromboembolism and with a thrombus diameter of <10 mm, patients with prosthetic valve obstruction who had no thrombus/mass/pannus on transesophageal echocardiography (TEE), and normal prosthetic valve leaflet motion on fluoroscopy considered patient-prosthesis mismatch, and were excluded from the study.

The inclusion criteria were as follows: all patients with obstructive PVT, patients with nonobstructive PVT with recent systemic thromboembolism, patients with asymptomatic nonobstructive PVT with a thrombus diameter of at least 10 mm, and PVT patients with ischemic stroke were included only if they were stable by neuroradiological assessment after 3 weeks of anticoagulation (patients without hemorrhagic conversion and/or severe disability).

The patient demographic characteristics, medical history, date of the surgery, type and make of the prosthetic valve, rhythm disorders, aspirin use, NYHA functional class, primary symptoms, and international normalization ratio (INR) values at the time of admission were prospectively entered into a database.

Echocardiography. The diagnosis of PVT was verified each time by TEE when a patient was admitted with thromboembolism or a persistently low INR (at least 2 measurements) for the preceding consecutive 3 months and when transthoracic echocardiography documented prosthetic valve dysfunction or thrombus. If these criteria were unmet, we did not perform TEE unless there was a suspicion of PVT on transthoracic echocardiography or a clinical history of recent thromboembolism. There was no patient with a shorter duration of low INR in our study. The diagnostic criteria used in our study were published previously (10). All patients underwent transthoracic echocardiography and TEE before and within an hour after the thrombolysis sessions. The cross-sectional area and the largest diameter of the thrombus were measured on TEE. Thrombus was visualized in all patients with echo-

Table 1. Contraindications of Thrombolytic Therapy

Absolute Contraindication	Relative Contraindication	No Contraindication
Left atrial thrombus	Active peptic ulcer	Isolated left atrial appendage thrombus
Recent (<3 weeks) ischemic stroke	Blood pressure >180/110 mm Hg	Acute (<4 h) or previous (>3 weeks) ischemic stroke*
Hemorrhagic stroke	INR 2–3†	INR <2
Early (<4 days) post-operative period	Recent (<4 wk) internal bleed	Late (>4 days) post-operative period
Traumatic accident <4 weeks	Previous SKZ therapy (5 days to 2 yrs)	Pregnancy
Bleeding diathesis‡	Recent CPR	
Intracranial mass	Infective endocarditis	
Active internal bleed	Hemorrhagic retinopathy	
Aortic dissection	Pericarditis	

*Patients with hemorrhagic conversion of cerebral infarction on the neuroradiological study were not included. †INR levels represent the samples obtained at the time that the thrombolytic treatment decision was made. Thrombolytic agents were administered to the patients with an INR between 2 and 3 when the clinical setting was appropriate to avoid treatment delays. ‡Patients with acquired/congenital bleeding diathesis or an INR >3.
CPR = cardiopulmonary resuscitation; INR = international normalized ratio; SKZ = streptokinase.

cardiography. Patients with prosthetic valve obstruction who had no thrombus/mass/pannus on TEE and normal prosthetic valve leaflet motion on fluoroscopy were considered a "patient-prosthesis mismatch." These patients were excluded from the study and did not receive TT. Patients with indeterminate prosthetic valve mass (i.e., thrombus or pannus unclear) were included in the study (21 episodes), and they received TT per protocol until they received the maximal thrombolytic dose.

Thrombolytic therapy. TT was administered as a first-line therapy to patients with obstructive thrombus and those with nonobstructive thrombus but a history of recent thromboembolism or a thrombus diameter of ≥10 mm. The patients who presented with ischemic stroke (21 episodes) were included only if they were stable by neuroradiological assessment after 3 weeks of anticoagulation. The PVT episodes were divided into 5 groups according to the TT regimen used. In fact, there was no predetermined time period for each therapy protocol, and each TT regimen was used in chronological order, and simultaneous use of ≥2 regimens in the same period or in the same PVT episode did not occur.

1. Years 1993 through 1997: 3-h infusion of 1.5 million units of streptokinase (SKZ) (16 patients, 16 episodes), repeat once 24 h later if needed (maximum total dose: 3 million units).
2. Years 1997 through 2001: 24-h infusion of 1.5 million units of SKZ (41 patients, 41 episodes), repeat once 24 h later if needed (maximum total dose 3 million units).
3. Years 2001 through 2002: 5-h infusion of 90 mg t-PA after a 10-mg bolus (10 patients, 12 episodes), repeat once 24 h later if needed (maximum total dose 200 mg).
4. Years 2002 through 2005: 6-h infusion of 50 mg t-PA without a bolus (27 patients, 27 episodes), repeat once 24 h later up to 3 times if needed (maximum total dose 150 mg).
5. Years 2005 through 2009: 6-h infusion of 25 mg t-PA without a bolus (108 patients, 124 episodes), repeat once 24 h later up to 6 times if needed (maximum total dose 150 mg).

Anticoagulation with intravenous unfractionated heparin was withheld during thrombolytic agent infusion. Heparin, 70-U/kg bolus and 1,000-U/h infusion with a target activated partial thromboplastin time between 1.5 and 2.5 times the control, was started immediately after infusion of the thrombolytic agent. If repeat thrombolytic agent infusion was needed, heparin was withheld until the activated partial thromboplastin time was <50 s. After thrombolytic success, warfarin was restarted while the patient was on intravenous heparin.

Criteria for thrombolytic success

Obstructive thrombus (in the absence of fatal or nonfatal major complications):

1) Doppler documentation of the resolution of increased gradient and decreased valve area.
2) Clinical improvement in symptoms.
3) Reduction by ≥75% in major diameter and/or area of the thrombus.

Complete success was defined when all 3 criteria were met and partial success was defined as <3.

Nonobstructive thrombus (in the absence of fatal or nonfatal major complications):

1. Complete success: ≥75% reduction in thrombus area and/or length.
2. Partial success: 50% to 75% reduction in thrombus area and/or length.

For this study, partial and complete success rates were combined.

Definition of complications

1. All-cause in-hospital mortality.
2. Nonfatal major complications: ischemic stroke, intracranial hemorrhage, embolism (coronary or peripheral), bleeding requiring transfusion.
3. Nonfatal minor complications: bleeding without need for transfusion, transient ischemic attack (TIA).

Statistical analysis. Statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois). All analyses were done based on episodes. Descriptive statistics are reported as mean, SD, median, minimum and maximum values for continuous variables, and as frequency with percentages for the categorical variables. Group comparisons for continuous variables were tested using the Mann-Whitney *U* test because the data distributions were not normal. Comparisons of categorical variables were evaluated by the chi-square test using the Monte-Carlo method. Significance level was accepted as $p < 0.05$ in all statistical analyses. The Bonferroni correction was applied to significance level α for multiple comparisons. Appropriate univariate predictors for success and complications (covariates: TT groups, age, sex, atrial fibrillation, NYHA functional class, history of

stroke/TIA, obstruction, thrombus area, and elapsed time since valve surgery) were entered into multiple logistic regression analyses. The cutoff values were estimated by receiver-operating characteristic curve analysis.

RESULTS

Baseline characteristics. This series of 220 episodes in 182 patients included 156 women (70.9%) and 64 men (29.1%). The average age was 43.2 ± 13.1 years (median 44 years; range 17 to 82 years). A subtherapeutic INR was present on admission in 175 episodes (79.5%). The most common symptom was dyspnea (72.3%). The prevalence of a poor functional capacity (NYHA functional class III/IV) was quite high (41.4%). Patients had atrial fibrillation in 56.6% of the PVT episodes. There was a history of a stroke/TIA in 40.9% of the episodes (stroke in 15% and TIA in 25.9%). The prevalence of hypertension was 13.6%, 6.4% for diabetes, and 25.7% for previous aspirin use. The most common valve type was the St. Jude Medical (St. Jude Medical Inc., St. Paul, Minnesota) bileaflet valve (80 episodes) with the mitral position being the most common thrombus site (185 episodes). There were no differences among the groups in terms of baseline characteristics including sex, age, elapsed time since valve surgery, heart rhythm, functional capacity, history of stroke or TIA, previous aspirin use, clinical presentation, thrombosed valve position, and echocardiographic findings on admission (Table 2).

Table 2. Comparison of Baseline Characteristics Among Groups

	Group I (n = 16)		Group II (n = 41)		Group III (n = 12)		Group IV (n = 27)		Group V (n = 124)		p Value
	N	%	n	%	n	%	N	%	n	%	
Demographic characteristics/ medical history											
Sex, female/male	6/10	37.5/62.5	29/12	70.7/29.3	8/4	66.7/33.3	19/8	70.4/29.6	94/30	75.8/24.2	0.06
Age, yrs	39.2 ± 9.7		41.3 ± 12.2		42.2 ± 8.6		42.6 ± 11		44.6 ± 14.4		0.37
ETSVS, months	48.2 ± 60.3		26 ± 25.7		39.6 ± 29.4		33.3 ± 44.1		23.6 ± 22		0.05
Hypertension	4	25	8	19.5	1	8.3	2	7.4	15	12.1	N/A
Diabetes mellitus	1	6.3	6	14.6	0	0	0	0	7	5.6	N/A
Atrial fibrillation	8	50	21	51.2	6	50	14	51.9	61	49.2	0.97
NYHA functional class I–II/III–IV	9/7	56.3/43.8	24/17	58.5/41.5	7/5	58.3/41.7	15/12	55.6/44.4	74/50	59.7/40.3	0.99
Stroke or TIA*	7	43.8	17	41.5	5	41.7	10	37	51	41.1	0.99
Aspirin use	3	18.8	10	24.4	2	16.7	6	22.2	29	23.4	N/A
Clinical presentation											
Dyspnea/HF	11	68.8	25	61	8	66.7	20	74.1	95	76.6	0.39
Stroke	2	12.5	5	12.2	1	8.3	2	7.4	11	8.9	N/A
Loss of valve sound	1	6.3	3	7.3	1	8.3	1	3.7	3	2.4	N/A
Angina/ACS	1	6.3	2	4.9	1	8.3	2	7.4	6	4.8	N/A
Limb ischemia	1	6.3	2	4.9	0	0	1	3.7	1	0.8	N/A
Asymptomatic	0	0	4	9.8	1	8.3	1	3.7	8	6.5	N/A
Thrombosed valve											
Mitral	12	75	35	85.4	9	75	23	85.2	105	84.7	0.78
Aortic	3	18.7	6	14.6	1	8.3	2	7.4	9	7.3	N/A
Tricuspid	0	0	0	0	2	16.7	2	7.4	10	8.1	N/A
Mitral + aortic	1	6.3	0	0	0	0	0	0	0	0	N/A
Echocardiographic features											
OT/NOT	9/7	56.3/43.8	20/21	48.8/51.2	6/6	50/50	14/13	51.9/48.1	56/68	45.2/54.8	0.91
Monoleaflet/bileaflet†	7/8‡	46.7/53.3	21/19	52.5/47.5	1/5	16.7/83.3	2/20	9.1/90.9	9/82	9.9/90.1	N/A†
Mobile THR	6	42.9	19	50	4	36.4	11	40.7	59	47.6	0.89
THR area, cm^2	1.17 ± 0.57		1.05 ± 0.46		1.37 ± 0.5		1.15 ± 0.52		1.12 ± 0.57		0.49

Values are mean ± SD. *The majority of patients had a TIA (25.9%), and 15% had stroke. †Due to the reduced number of monoleaflet valve replacements in recent years, the number of monoleaflet PVT episodes was relatively low in the chronologically latest treatment groups (Groups IV and V). For this reason, monoleaflet/bileaflet valve numbers were not compared among groups. ‡Data regarding the valve type in 1 episode in Group I were missing.
ACS = acute coronary syndrome; HF = heart failure; ETSVS = elapsed time since valve surgery; N/A = not applicable (p value was not calculated due to the low number of events); NOT = nonobstructive thrombus; NYHA = New York Heart Association; OT = obstructive thrombus; PVT = prosthetic valve thrombosis; THR = thrombus; TIA = transient ischemic attack.

Echocardiographic results. In mitral and tricuspid obstructive PVT episodes (n = 93), the mean valve area was 1.08 ± 0.3 cm^2 (median 1.09 cm^2; range 0.5 to 1.7 cm^2); and the average peak and mean gradients were 29.9 ± 12.4 mm Hg (median 29 mm Hg; range 10 to 70 mm Hg) and 16.6 ± 8.6 mm Hg (median 17 mm Hg; range 3 to 45 mm Hg), respectively. In aortic obstructive PVT episodes (n = 12), the mean valve area was 1.02 ± 0.3 cm^2 (median 0.98 cm^2; range 0.6 to 1.3 cm^2), and the average peak and mean gradients were 83.2 ± 13.8 mm Hg (median 84 mm Hg; range 70 to 105 mm Hg) and 52.6 ± 8 mm Hg (median 53; range 42 to 65 mm Hg), respectively.

In nonobstructive mitral and tricuspid PVT episodes (n = 106), the mean valve area was 2.4 ± 0.5 cm^2 (median 2.4 cm^2; range 1.75 to 3.5 cm^2), and the average peak and mean gradients were 14.7 ± 7 mm Hg (median 15 mm Hg; range 6 to 40 mm Hg) and 6.6 ± 4 mm Hg (median 6 mm Hg; range 2 to 25 mm Hg), respectively. In aortic nonobstructive PVT episodes (n = 9), the mean valve area was 2.2 ± 0.4 cm^2 (median 2.2 cm^2; range 1.9 to 2.6 cm^2), and the average peak and mean gradients were 38 ± 10 mm Hg (median 37 mm Hg; range 31 to 55 mm Hg) and 20.7 ± 4 mm Hg (median 21 mm Hg; range 17 to 27 mm Hg), respectively.

The PVT was obstructive in 105 episodes (47.7%) and nonobstructive in 115 (52.3%). The number of obstructive episodes did not differ among Groups I through V (56.3% vs. 48.8%, 50.0%, 51.9%, and 45.2%, respectively; p = 0.91). The thrombus area could be measured in 185 episodes (85.5%) and showed no significant difference among Groups I through V (mean 1.17 cm^2 [median 1.15 cm^2]; mean 1.05 cm^2 [median 0.95 cm^2]; 1.37 cm^2 [median 1.4 cm^2]; 1.15 [median 1.1 cm^2]; 1.12 cm^2 [median 1.0 cm^2] cm^2, respectively; p = 0.49).

Determinants of treatment success. A successful result was obtained in 83.2% of the episodes. The success rate was not different among Groups I through V (68.8%, 85.4%, 75.0%, 81.5%, and 85.5%, respectively; p = 0.46). The average doses of TT agents per PVT episode used were 2.06 ± 0.75 (median 1.5) million units SKZ in Group I, 2.12 ± 0.75 (median 1.5) million units SKZ in Group II, 123.33 ± 41.41 (median 100) mg t-PA in Group III, 66.11 ± 27.19 (median 50) mg t-PA in Group IV, and 55.85 ± 32.53 (median 50) mg t-PA in Group V. A similar success rate was obtained with the lowest t-PA dose in Group V.

The success rate did not appear to be affected by obstructive thrombus, poor NYHA functional class, history of stroke/TIA, atrial fibrillation, the position of thrombosed valve, bileaflet or monoleaflet valve, mobility of thrombus, history of hypertension or diabetes, suboptimal INR value on admission, and previous aspirin use (Table 3). A shorter time interval since valve surgery and/or female sex were associated with a higher likelihood of success (21.8 ± 21.5 months vs. 58.0 ± 49.4 months, p < 0.001; 87.2% vs. 73.4%, p = 0.01, respectively). By multivariate analysis, the only independent predictor of an unsuccessful result was a longer time interval since valve surgery (odds ratio [OR]: 1.025; 95% confidence interval [CI]: 1.012 to 1.039; p < 0.001).

Predictors of complications. Complications occurred in 41 episodes (18.6%) and included death (n = 6, 14.6%) and nonfatal major (n = 17, 41.5%) and minor (n = 18, 43.9%) complications. Intracranial hemorrhage occurred in 7 patients (2 died, nonfatal in 5), gastrointestinal hemorrhage in 3, gum bleed in 4, nosebleed in 4, hemoptysis in 1, vaginal hemorrhage in 1, ischemic stroke in 7 (4 died, 3 nonfatal in 4), TIA in 8, acute myocardial infarction in 3, and peripheral embolism in 3.

The number of complications, mortality, nonfatal major complications, minor complications, and the combined rate of mortality plus nonfatal major complications in each group are reported in Table 4. The overall complication rate was significantly lower in Group V (10.5%, p < 0.05 for each comparison) compared with all other groups; it did not differ among Groups I through IV (37.5%, 24.4%, 33.3%, and 29.6%, respectively; p > 0.05 for each

Table 3. Comparison of Success Rates Among Specific Subsets*

	Success, %	p Value
Female/male	87.2/73.4	0.01
INR effective/ineffective	77.8/84.6	0.28
Hypertension, no/yes	83.2/83.3	0.98
Diabetes mellitus, no/yes	82.5/92.9	0.32
Atrial fibrillation/sinus rhythm	80.9/85.4	0.37
NYHA functional class I–II/III–IV	86/79.1	0.18
Stroke/TIA, no/yes	86.1/78.9	0.16
Aspirin use, no/yes	82.9/83.2	0.86
THR site: mitral/aortic/tricuspid	83.2/85.7/78.6	0.86
NOT/OT	87/79	0.12
Monoleaflet/bileaflet	82.5/81.3	0.87
Mobile/fixed thrombus	83.5/82.8	0.90
Age, yrs, successful/failed cases	43 ± 13.7/43.9 ± 9.2	0.56
THR area, cm^2, successful/failed cases	1.11 ± 0.55/1.17 ± 0.43	0.18
ETSVS, months, successful/failed cases	21.8 ± 21.5/58 ± 49.4	<0.001

*Plus/minus values are mean ± SD.
Abbreviations as in Tables 1 and 2.

Table 4. Prevalence of Complications and Death Among Groups

	Complications									
	Total		Death		Nonfatal Major		Minor		Combined	
Group	N	%	N	%	n	%	n	%	n	%
I	6	37.5	2	12.5	2	12.5	2	12.5	4	25
II	10	24.4	1	2.4	5	12.2	4	9.8	6	14.6
III	4	33.3	2	16.7	1	8.3	1	8.3	3	25
IV	8	29.6	1	3.7	3	11.1	4	14.8	4	14.8
V	13	10.5	0	0	6	4.8	7	5.6	6	4.8
Total	41	19.2	6	2.8	17	7.9	18	8.5	23	10.8
p value*	0.01 for Group I vs. Group V, 0.03 for Group II vs. Group V, 0.04 for Group III vs. Group V, 0.03 for Group IV vs. Group V, NS for other comparisons		0.01 for Group I vs. Group V, 0.01 for Group III vs. Group V, NS for other comparisons		NS for all comparisons		NS for all comparisons		0.02 for Group I vs. Group V, 0.04 for Group II vs. Group V, 0.03 for Group III vs. Group V, NS for other comparisons†	

*Only significant p values are shown; $p > 0.05$ for all other comparisons. †The p value is 0.08 for Groups IV and V.

comparison). This difference was primarily driven by the absence of mortality in Group V (0%) compared with Groups I (12.5%) and III (16.7%), and lower nonfatal major complications in Group V (4.84%) compared with Groups II (12.12%) and IV (11.1%). The combined number of deaths and nonfatal major complications was lower in Group V compared with other groups and was significant for all comparisons except for Groups IV and V.

The combined rate of mortality and nonfatal major complications was higher in patients with previous stroke/TIA (16.7% vs. 6.2%, $p = 0.01$) and male sex (18.8% vs. 7.1%, $p = 0.01$). Age, sex, obstructive thrombus, thrombus cross-sectional area, atrial fibrillation, poor functional capacity (NYHA functional class III/IV), prosthetic valve type or position, mobility of thrombus, and history of hypertension or diabetes were not significant predictors of complications (Table 5). By multivariate analysis, the independent predictors of combined mortality plus nonfatal major complications were any TT regimen other than Group V (ORs for Groups I through IV: 8.21 [95% CI: 1.80 to 37.43], 3.78 [95% CI: 1.05 to 13.61], 8.12 [95% CI: 1.54 to 42.68], 4.13 [95% CI; 1.00 to 16.99], respectively; $p < 0.05$ for each) and a history of stroke/TIA (OR: 3.47 [95% CI: 1.32 to 9.11]; $p = 0.01$).

Table 5. Comparison of Combined Complication Rates Among Specific Subsets

	Combined Complication, %	p Value
Female/male	7.1/18.8	0.01
INR, effective/ineffective	4.4/12	0.14
Hypertension, no/yes	10.5/10	0.93
Diabetes, no/yes	10.7/7.1	1.00
Atrial fibrillation/sinus rhythm	11.8/9.1	0.51
NYHA functional class I–II/III–IV	7.8/14.3	0.12
Stroke/TIA, no/yes	6.2/16.7	0.01
Aspirin use, no/yes	10/12	0.69
THR site: mitral/aortic	10.3/19	0.23
NOT/OT	7.8/13.3	0.18
Monoleaflet/bileaflet	15/11.2	0.52
Mobile/fixed THR	9.1/11.3	0.6
Age, yrs, complicated/uncomplicated cases	44.5 ± 8.9/43.1 ± 13.5	0.51
THR area, cm^2, complicated/uncomplicated cases	1.18 ± 0.4/1.11 ± 0.6	0.25

Values are % or mean ± SD.
Abbreviations as in Tables 1 and 2.

DISCUSSION

The aim of this study was to identify a thrombolytic regimen that could provide successful and safe PVT resolution. Systemic embolization and intracranial hemorrhage have been the Achilles' heel of the TT in PVT. In this single-center series, which is the largest cohort published to date, we developed a strategy of slow, repeated infusions of low-dose t-PA based on our previous experience with SKZ and higher doses of t-PA over the years. We hypothesized that successive low dose (25 mg) and slow infusion (6 h) of t-PA would induce thrombolysis and limit the risk of hemorrhage and embolization. The results of our study indicate that although the success rate for thrombolysis was similar among Groups I through V, the Group V regimen was superior to the other 4 regimens because it was associated with reduced complications and mortality (Fig. 1).

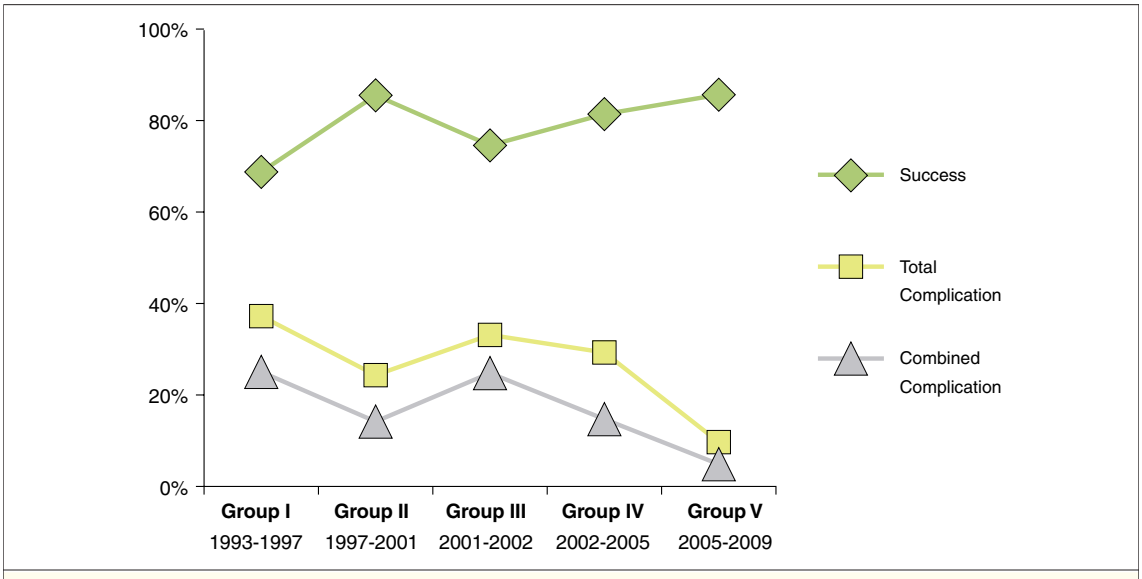

Figure 1. Thrombolytic Success and Complication Rates Among the Study Groups and Years

The line graph showing each of the 5 time periods and the study groups on the horizontal axis and percentage of outcomes on the vertical axis with 3 lines displayed in 3 colors. A nonsignificant trend toward an increase in success and significant decline in total and combined complications is apparent.

Thrombolytic success. The overall success rate (85.9%) in our study is well within the range of previous publications, although there has been no uniformity of treatment regimens or definition of success (10,11,14–18,27,28). Moreover, the success rates were similar in the 5 groups.

Although the success rate after the initial dose of a thrombolytic agent was lower in Group V, at the end of the repeated doses of a thrombolytic agent, an increased success rate could be achieved without the cost of increased complications. More than 1 t-PA infusion was necessary in 75 episodes and >3 in 21 episodes in Group V. Increasing possibility of success with repeated administration of thrombolytic agents under TEE guidance was noted in our previous publication (10). In Groups I through IV, >1 TT infusion was performed in 6, 17, 4, and 8 episodes, respectively.

In the overall series, the only multivariate predictor of decreased success was a longer time interval since valvular surgery. It was reported that the time interval between valve surgery and PVT episode had no significant effect on success (16,18). Our results, on the other hand, indicate that a longer time interval is associated with reduced thrombolytic success, perhaps due to the higher incidence of pannus in this group. Pannus formation may not be easily differentiated from thrombus but obviously will not respond to thrombolytic drugs. The increased success rate in women was considered a coincidental finding because multivariate analysis did not demonstrate sex as an independent predictor of success.

Complications. The overall complication rate of 18% in our series is close to previously published results (11,16,17,20). The mortality rate of 2.8% compares favorably with the 5% to 30% mortality rates of surgical series (5–8). Although there was no surgery arm in our study, low-dose, slow-infusion TT seems to be safer than surgery based on the mortality rates of surgery among similar cases at our institution and the published data. In addition, nonfatal complication rates also favor TT over surgery. The lowest surgical mortality rate to date among these patients was reported by Keuleers et al. (27). Although these authors reported an 11% death rate for the surgical treatment of PVT, the nonfatal complications including post-operative infection, sepsis, need for a permanent pacemaker, and ventricular septal defect increased the combined (death + nonfatal) complication rate to 33% in this study. In our study, patients in Group V had a combined (death + major + minor) complication rate of 10.5%. However, PVT patients who underwent surgery usually had severe symptoms, were hemodynamically unstable with obstructive/large thrombi, and experienced TT failure, which, in turn, might have contributed to increased mortality rate.

Low-dose, slow t-PA infusion in Group V was associated with a lower complication rate mainly due to a lower incidence of mortality and nonfatal major complications. Moreover, the severity of such events was less in Group V. For example, intracranial hemorrhage in Group I resulted in severely disabling neurological deficits, whereas less significant residual deficits were noted in Group V. Lower doses, slower infusions, and the 24-h interval between repeat TT sessions probably allowed earlier identification of complications.

Rapid thrombolysis is associated with increased embolic risk, especially in the presence of large thrombi. This has been reported by our group (10,19) and in the multicenter PRO-TEE (Prosthetic Valve Thrombolysis–Role of Transesophageal Echocardiography) study (15). In the latter study, the embolic risk increased when the thrombus area was >0.8 cm^2. Similarly, we calculated the cutoff value of the thrombus size that predicted embolic complications. Thrombi >0.9 cm^2 were associated with increased major and minor embolic events in our study (sensitivity, 80.0%; specificity, 45.1%; area under the curve, 0.64; $p = 0.02$). In each group, the embolic event rate in patients with thrombi >0.9 cm^2 was 37.5%, 15.0%, 20.0%, 0.0%, and 8.2%; respectively (p value: not applicable secondary to the small number of events). Group IV was also a slow-infusion regimen like Group V, which may explain the low rates of embolism in the 2 groups even in patients with large thrombi. This may be related to more gradual lysis of thrombi in slow-infusion groups compared with rapid destruction after rapid administration and/or higher doses of thrombolytic agents.

In the overall series, the multivariate predictors of favorable outcomes in terms of combined mortality plus nonfatal major complications were only the Group V TT regimen and the absence of a stroke/TIA history. In other words, atrial fibrillation, obstructive thrombus, larger thrombus, and poor functional capacity, the so-called predictors of poor outcome in TT of PVT, did not seem to predict the combined endpoint in this large cohort of PVT patients. Thus, we conclude that TT is safe in PVT patients, and administration of a lower dose (25 mg) and prolonged (6 h) infusion of t-PA further increase the safety, even in more seriously ill patients. This may call for a change in guideline recommendations. Critically ill patients with cardiogenic shock and/or pulmonary edema have extremely high surgical risk and appear to benefit from high-dose t-PA (21,22). In our series, there were 13 critically ill patients. Eight (1 with cardiogenic shock, 7 with pulmonary edema) of 13 patients were in Group V, 6 had a successful outcome (29), and other 2 underwent surgery because of TT failure. One patient with pulmonary edema in Group I had a stroke; 2 patients with pulmonary edema in Group II had successful lyses without complications, but another patient with pulmonary edema underwent surgery due to TT failure. One patient with cardiogenic shock in Group III died. It appears that the low-dose, prolonged infusion regimen may help these critically ill patients. However, there may be individual circumstances that preclude prolonged TT in patients with such advanced comorbidities and presentations (19).

Study limitations. Although our study was a single-center, nonrandomized, observational study, it is still remarkable for its size and the fact that a large number of patients were treated in consistent fashion at a single center.

The medical treatment strategies other than thrombolytic agents for the patients with PVT have not changed in the past 2 decades. Therefore, it is unlikely that the background treatments for these patients have altered our outcomes over time. However, the residual confounding effect due to changes in general patient care cannot be ruled out.

Our study was still not a head-to-head comparison of TT with surgery for the treatment of PVT. Furthermore, almost 50% of the patients in any of the study groups had a nonobstructive PVT. In general, these are smaller thrombi and usually less symptomatic and have a better prognosis with either surgery or TT. Some of the groups in this study had uneven numbers of patients. The frequencies of complications in Groups II and V more likely represent the associated TT regimen, whereas the frequency of complications in Groups I, III, and IV may be less robust because of the relatively small number of patients included in these groups. These limitations are important to keep in mind before applying our conclusions to the current practice.

CONCLUSIONS

In this largest cohort of PVT patients published to date, slow infusion of 25 mg t-PA without a bolus appears to be the safest thrombolytic regimen with lower complication and mortality rates for PVT with no loss of effectiveness compared with higher doses or rapid infusions of SKZ or t-PA.

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Reprint requests and correspondence: Dr. Mehmet Özkan, Department of Cardiology, Koşuyolu Kartal Heart Training and Research Hospital, Denizer Caddesi, Cevizli-Kartal, Turkey, Istanbul, Istanbul 34846, Turkey. *E-mail: memoozkan1@gmail.com.*

REFERENCES

1. Edmunds LH Jr., Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. Ad hoc liaison committee for standardizing definitions of prosthetic heart valve morbidity of The American Association for Thoracic Surgery and The Society of Thoracic Surgeons. J Thorac Cardiovasc Surg 1996;112:708–11.
2. Grunkemeier GL, Rahimtoola SH. Artificial heart valves. Annu Rev Med 1990;41:251–63.
3. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation 1994;89:635–41.
4. Laplace G, Lafitte S, Labeque JN, et al. Clinical significance early thrombosis after prosthetic mitral valve replacement: a postoperative monocentric study of 680 patients. J Am Coll Cardiol 2004;43:1283–90.
5. Ozkokeli M, Sensoz Y, Ates M, Ekinci A, Akcar M, Yekeler I. Surgical treatment of prosthetic valve thrombosis-short and long-term results. Int Heart J 2005;46:105–11.
6. Toker ME, Eren E, Balkanay M, et al. Multivariate analysis for operative mortality in prosthetic valve dysfunction due to pannus and thrombus formation. Int Heart J 2006;47:237–45.
7. Deviri E, Sareli P, Wisenbaugh T, Cronje SL. Obstruction of mechanical heart valve prostheses: clinical aspects and surgical management. J Am Coll Cardiol 1991;17:646–50.
8. Durrleman N, Pellerin M, Bouchard D, et al. Prosthetic valve thrombosis: twenty year-experience at the Montreal Heart Institute. J Thorac Cardiovasc Surg 2004;127:1388–92.
9. Lengyel M, Vegh G, Vandor L. Thrombolysis is superior to heparin for non-obstructive mitral mechanical valve thrombosis. J Heart Valve Dis 1999;8:167–73.
10. Özkan M, Kaymaz C, Kırma C, et al. Intravenous thrombolytic treatment of mechanical prosthetic valve thrombosis: a study using serial transesophageal echocardiography. J Am Coll Cardiol 2000;35:1881–9.
11. Cáceres-Lóriga FM, Pérez-López H, Morlans-Hernández K, et al. Thrombolysis as first choice therapy in prosthetic heart valve thrombosis. A study of 68 patients. J Thromb Thrombolysis 2006;21:185–90.
12. Shapira Y, Vaturi M, Sagie A. Obstructive left-sided prosthetic valve thrombosis. Acute Card Care 2009;11:160–8.
13. Alpert JS. The thrombosed prosthetic valve: current recommendations based on evidence from the literature. J Am Coll Cardiol 2003;41:659–60.
14. Karthikeyan G, Math RS, Mathew N, et al. Accelerated infusion of streptokinase for the treatment of left-sided prosthetic valve thrombosis: a randomized controlled trial. Circulation 2009;120:1108–14.
15. Tong AT, Roudaut R, Ozkan M, et al. Prosthetic Valve Thrombolysis-Role of Transesophageal Echocardiography (PRO-TEE) Registry Investigators; transesophageal echocardiography improves risk assessment of thrombolysis of prosthetic valve thrombosis: results of the international PRO-TEE registry. J Am Coll Cardiol 2004;43:77–84.
16. Roudaut R, Lafitte S, Roudaut MF, et al. Fibrinolysis of mechanical prosthetic valve thrombosis: a single center study of 127 cases. J Am Coll Cardiol 2003;41:653–8.
17. Gupta D, Kothari SS, Gahl VK, et al. Thrombolytic therapy for prosthetic valve thrombosis: short- and long-term results. Am Heart J 2000;140:906–16.
18. Koller PT, Arom KV. Thrombolytic therapy of left sided prosthetic valve thrombosis. Chest 1995;108:1683–9.
19. Biteker M, Duran NE, Gündüz S, et al. Thrombolysis of an acute prosthetic mitral valve thrombosis presented with cardiogenic shock under the guidance of continuous transoesophageal monitoring. Eur J Echocardiogr 2009;10:468–70.
20. Nagy A, Denes M, Lengyel M. Predictors of the outcome of thrombolytic therapy in prosthetic mitral valve thrombosis: a study of 62 events. J Heart Valve Dis 2009;18:268–75.
21. Renzulli A, Vitale N, Caruso A, et al. Thrombolysis of prosthetic valve thrombosis: indications and results. J Heart Valve Dis 1997;6:212–8.
22. Denofrio D, Ament AF, Mark JB, George SF. Accelerated TPA for treatment of prosthetic valve thrombosis. Clin Cardiol 1996;19:665–8.
23. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e1–142.
24. Vahanian A, Baumgartner H, Bax J, et al., Task Force on the Management of Valvular Hearth Disease of the European Society of Cardiology; ESC Committee for Practice Guidelines. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J 2007;28:230–68.

25. Lengyel M, Horstkotte D, Voller H, Mistiaen WP. Working group infection, thrombosis, embolism and bleeding of the society for heart valve disease. Recommendations for the management of prosthetic valve thrombosis. J Heart Valve Dis 2005; 14:567–75.
26. Salem DN, O'Gara PT, Madias C, Pauker SG, American College of Chest Physicians. Valvular and structural heart disease: American College of Chest Physicians Evidence-Based Practice Guidelines (8th Edition). Chest 2008;133:593–629.
27. Keuleers S, Herijgers P, Herregods MC, et al. Comparison of thrombolysis versus surgery as a first line therapy for prosthetic heart valve thrombosis. Am J Cardiol 2011;107:275–9.
28. Cevik C, Izgi C, Dechyapirom W, Nugent K. Treatment of prosthetic valve thrombosis: rationale for a prospective randomized clinical trial. J Heart Valve Dis 2010;19:161–70.
29. Ozkan M, Biteker M, Duran NE, Yildiz M. Images in cardiovascular medicine. Huge prosthetic mitral valve thrombosis in a pregnant woman. Circulation 2009;120:e151–2.

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