**Echocardiography**

# Transesophageal Echocardiography Improves Risk Assessment of Thrombolysis of Prosthetic Valve Thrombosis: Results of the International PRO-TEE Registry

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**OBJECTIVES**      The goal of this study was to evaluate whether quantitation of thrombus burden with transesophageal echocardiography (TEE) can help risk-stratify patients undergoing thrombolysis of prosthetic valve thrombosis (PVT).

**BACKGROUND**
**METHODS**      Thrombolytic therapy of PVT has an unpredictable risk of embolization and complications. An international registry of patients with suspected PVT undergoing two-dimensional/Doppler and TEE before thrombolysis was established. All TEE studies were reviewed and quantitated by a single observer blinded to all data.

**RESULTS**      From 1985 to 2001, 107 patients (71 females; age 24 to 86 years) from 14 centers (6 in the U.S.) were identified. The majority of cases involved the mitral valve (79 mitral, 13 aortic, and 15 tricuspid). Hemodynamic success rate was achieved in 85% and was similar across valves. Overall complications were observed in 17.8%, and death in 5.6%. Predictors of complications were: New York Heart Association (NYHA) functional class, presence of shock, sinus tachycardia, hypotension, previous history of stroke, thrombus extension beyond the valve ring, and thrombus area. Multivariate analysis demonstrated that two variables were independent predictors of complications: thrombus area by TEE (odds ratio [OR] 2.41 per 1 cm$^2$ increment, 95% confidence interval [CI] 1.12 to 5.19) and prior history of stroke (OR 4.55, 95% CI 1.35 to 15.38). A thrombus area <0.8 cm$^2$ identified patients at lower risk for complications from thrombolysis, irrespective of NYHA functional class.

**CONCLUSIONS**      In PVT, the thrombus size imaged with TEE is a significant independent predictor of outcome. Transesophageal echocardiography can identify low-risk groups for thrombolysis irrespective of symptom severity and is therefore recommended in the management of prosthetic valve thrombosis.   (J Am Coll Cardiol 2004;43:77–84) © 2004 by the American College of Cardiology Foundation

Prosthetic valve thrombosis (PVT) is an infrequent but potentially life-threatening complication, with a reported incidence of 0.5% to 8% of left-sided valves and up to 20% of tricuspid valves (1–3). Although re-operation has been the traditional treatment for PVT, it is associated with significant morbidity and mortality, particularly in very symptomatic individuals (4–7). Since the first report of Luluaga et al. (8), intravenous thrombolytic therapy has emerged as an alternative to re-operation. The potential risk

of cerebral thromboembolism, however, has limited its use in left-sided PVT. Case reports and case series have varied widely in the rate of success and, particularly, in the morbidity and mortality associated with thrombolysis (9–20). Accordingly, recommendations for thrombolysis in left-sided PVT have varied from first-line therapy (10,12,21) to poor operative candidates or patients who refuse surgery (4,9,14,22).

Transesophageal echocardiography (TEE) is currently the test of choice for evaluating the mechanism of prosthetic valve obstruction (23) and allows the quantitation of thrombus burden (24,25). Whether TEE is helpful in identifying structural or functional parameters that can risk-stratify patients undergoing thrombolysis has not been previously investigated. In the present study, we sought to explore the role of TEE, in addition to clinical and echocardiographic parameters, in predicting the safety and

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**Abbreviations and Acronyms**
BP    = blood pressure
CI     = confidence interval
NYHA = New York Heart Association
OR   = odds ratio
PVT  = prosthetic valve thrombosis
TEE  = transesophageal echocardiography

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efficacy of thrombolysis of PVT and to assess the thrombus burden beyond which complications are increased with thrombolysis.

## METHODS

**Patient population.** An international registry of patients with suspected PVT undergoing two-dimensional/Doppler and TEE before thrombolysis was established. Major national and international echocardiography laboratories were contacted for this purpose. Inclusion criteria included all the following: 1) suspected prosthetic valve thrombosis with the presence of prosthetic valvular obstruction by Doppler echocardiography or thrombus formation on the valve by TEE with or without obstruction; 2) availability of TEE before thrombolysis; and 3) subsequent treatment with thrombolysis.

A detailed questionnaire to the participating centers captured the following: patient characteristics (age, gender, date of valve implantation, model, size, and position), clinical presentation (symptoms including New York Heart Association [NYHA] functional class, embolic phenomena, angina, symptom duration, and anticoagulation status), history of hypertension, diabetes, coronary artery disease, and peripheral vascular disease. Transthoracic two-dimensional and Doppler examination reports were also requested including valvular gradients before and within one to two weeks after thrombolysis, the treatment protocol used, clinical outcome, and complications. All centers were asked to provide tapes of the TEE studies performed before thrombolysis for review and quantitation.

**Echocardiographic analysis.** All TEE tapes were sent to the echocardiography laboratory at Baylor College of Medicine and were reviewed and quantitated by a single observer (A.T.) blinded to all clinical data and outcomes. The size of the mass on the prosthetic valve was quantitated (largest length and area of the mass from any TEE view). The mass was also evaluated for mobility, extension beyond the valve ring onto adjacent structures (atrial wall, aorta), and ultrasound intensity (soft or dense), as previously described (24). Inter- and intra-observer variability in evaluating mass characteristics was performed on a randomly selected subgroup of patients.

**Definition of outcome.** Both hemodynamic and clinical outcome were assessed within one week and up to two weeks after thrombolysis. "Complete hemodynamic success" was defined as return of the transvalvular gradient to

normal range for the particular prosthesis (26), whereas "partial hemodynamic success" was defined as partial improvement in gradient without complete normalization. "Clinical success" was defined as hemodynamic success without clinical complications, because instances of major complications in the presence of hemodynamic success could occur.

Recorded complications of thrombolytic therapy included death, intracranial bleed, stroke, transient cerebral ischemic attacks, peripheral embolic events, coronary emboli, and bleeding requiring transfusions. All central nervous system complications were documented by neurological examination and evaluated with computed tomography.

**Statistical analysis.** Results are shown as mean ± SD. The chi-square test was used for the comparison of discrete variables. The Student $t$ test and Wilcoxon rank-sum two-sample test were used, respectively, for continuous variables that were (blood pressure (BP), heart rate, and gradients) and were not (other variables) normally distributed. Kruskal-Wallis analysis of variance on ranks was used to compare outcomes among ≥3 groups because variables were not normally distributed. If analysis of variance demonstrated significance, Dunn's multiple comparison procedure was performed. Logistic regression analysis was used to assess the strength of associations of various factors with clinical success, complications, and embolic risk. Linear correlation between intra- and inter-observer measurements of thrombus area was performed with Pearson's product moment correlation. The receiver operating characteristic curve of thrombus mass size for predicting complications was plotted. The best cut-off was defined as the one providing high sensitivity with a moderate specificity for events, as is desirable clinically. Statistical significance was set at $p < 0.05$. SAS System for Windows 8.0 was used for analysis.

## RESULTS

**Patient population.** Fifty-five national and international centers were contacted, of which 14 had cases that fulfilled study entry criteria (Appendix). At the participating centers, there were a total of 107 cases (Table 1) from 1985 to 2001 with suspected PVT in which a TEE was performed before thrombolysis. In some centers, thrombolysis was the first-line therapy regardless of TEE findings such as size or mobility of the thrombus (two centers including 38 patients), whereas in others, thrombolysis was not standard therapy; selected patients included those who had contraindications to surgery, were poor surgical candidates, or refused surgery. The majority of patients were in NYHA class III to IV (63.5%); 5% were asymptomatic, with the diagnosis being made through routine echocardiography.

**Thrombolytic treatment.** The thrombolytic agents used are listed in Table 1. Streptokinase was given as a slow infusion over 12 to 48 h, with occasional extension to 72 to 120 h. Urokinase was given as slow infusion over 6 to 48 h.

**Table 1.** Clinical Characteristics of the 107 Patients With Prosthetic Valve Thrombosis

| | |
|---|---|
| Age (yrs) | 54.2 ± 15.8 (24–86) |
| Gender (male/female) | 36/71 |
| Median time since valve replacement (days) | 33 (0.25–288) |
| Valve | |
|   Mitral | 79 (73.8) |
|   Aortic | 13 (12.2) |
|   Tricuspid | 15 (14.0) |
| Type of prosthetic valve | |
|   Bileaflet | 83 (77.6) |
|   Tilting disc | 23 (21.5) |
|   Porcine | 1 (0.9) |
| Median duration of symptoms (days) | 7 (0.125–270) |
|   <7 days | 59 (55.1) |
| On anticoagulation | 99 (93.4) |
| INR on admission ≥2.5 | 33 (32.4) |
| Aspirin use | 78 (75%) |
| Atrial fibrillation | 41 (39.4) |
| Systolic blood pressure on presentation (mm Hg) | 119.5 ± 18.9 |
| Heart rate on presentation (beats/min) | 91.7 ± 21.3 |
| NYHA class on presentation | |
|   I | 14 (13.1) |
|   II | 25 (23.4) |
|   III | 49 (45.8) |
|   IV | 19 (17.7) |
| Presenting symptoms | |
|   Dyspnea | 98 (91.1) |
|   Shock | 3 (2.8) |
|   Angina | 6 (15.1) |
|   Cardiac arrest | 1 (0.94) |
|   Cerebrovascular accident | 12 (11.3) |
|   Peripheral emboli | 5 (4.7) |
|   Asymptomatic | 5 (4.7) |
| Previous condition | |
|   Stroke | 26 (24.3) |
|   Emboli | 11 (11.2) |
|   Hypertension | 19 (19.6) |
|   Diabetes | 16 (16.3) |
|   Coronary artery disease | 18 (18.4) |
|   Peripheral vascular disease | 8 (8.3) |
| Thrombolytic used | |
|   Streptokinase | 58 (54.7) |
|   Urokinase | 18 (17.0) |
|   Tissue plasminogen activator | 31 (28.9) |
| Second agent required | 25 (23.8) |

Data shown as n (% of patients with reported data), mean ± SD or median (range) where appropriate.
INR = international normalized ratio; NYHA = New York Heart Association.

Recombinant tissue plasminogen activator was administered as 10 mg bolus followed by 90 mg infusion over 2 to 6 h. Intravenous heparin infusion was usually resumed after the completion of thrombolysis. Allergic reaction to streptokinase occurred in three patients requiring switching to urokinase.

**Echocardiographic characteristics of PVT and relationship to clinical presentation.** The TEEs were performed with either multiplane (81.3%) or biplane (15%) probes; monoplane was used in only four patients, all of whom had thrombus visualized. A definite mass on the prosthesis was seen in 86.0% (Table 2); the largest thrombus area was 14.7 cm². The inability to visualize a mass on an obstructed

valve is usually associated with a small thrombus or pannus affecting the hinge of the prosthesis (24) and was encountered similarly for aortic and mitral valves (15.4% and 13.9%, respectively). Overall, the prosthetic gradient was elevated before thrombolysis compared with normal values (Table 2). Thrombus burden, in general, was largest for mitral valves. Thrombi without significant hemodynamic obstruction were observed in 14 patients. In general, these were smaller than those with hemodynamic obstruction, especially for the mitral position, and were more often mobile. Non-obstructive thrombi were also less likely to be associated with the presence of NYHA class IV (0% vs. 20.4%, p ≤ 0.0001) and more likely to be associated with a history of prior stroke (57.1% vs. 20.5%, p = 0.004) and presentation with a stroke (71.4% vs. 2.2%, p < 0.0001).

Inter- and intra-observer variability in mass evaluation was performed in 14 randomly selected patients (10 mitral, 3 aortic, and 1 tricuspid). The mean maximal mass area was 1.21 cm², with a range of 0 to 4.94 cm². Intra- and inter-observer concordance in classifying echo density of the mass was 93%. The intra- and inter-observer mean difference in area was 0.04 ± 0.03 cm² and 0.12 ± 0.16 cm², respectively. Excellent linear correlations were observed for intra- and inter-observer measurements of mass area (r = 0.97 and 0.95, respectively).

**Predictors of success of thrombolytic therapy.** HEMODYNAMIC SUCCESS. After thrombolytic therapy, a significant decrease in gradient was seen (Table 2). Complete hemodynamic success was achieved in 76.3% of the 93 obstructed valves and was similar among different valves and lytic agents (Table 3). Partial hemodynamic success was infrequently seen (8.6%). Clinical and hemodynamic variables did not influence the rate of hemodynamic success. An obstructive soft mass by TEE (n = 59) was associated with a very high degree of hemodynamic success (91.5%). Although hemodynamic success was lower when a dense mass was seen (n = 20, p = 0.053), it was still high (75%). In the 14 cases with obstruction but without obvious mass, hemodynamic success was also high (85.7%). Using logistic regression analysis that considered a number of variables (age, gender, presenting systolic pressure and heart rate, NYHA functional class, prior history of stroke, thrombus area, the echodensity and mobility of the mass), a soft mass by TEE was the single predictor of hemodynamic success, p = 0.029. Of the 14 patients with hemodynamic failure, nine were referred for surgery within two to 13 days after thrombolysis. At surgery, four patients were found to have pannus with thrombus, one patient had entrapment of chordae, and four had obstructive thrombi. There were no postoperative deaths. The remaining five patients without hemodynamic improvement did not undergo surgery because of complications (n = 2) or poor clinical status.

CLINICAL SUCCESS. Clinical success was achieved in 73.8% and was best for tricuspid prostheses (Table 3). Clinical

**Table 2.** TEE and Doppler Findings in the 107 Patients With Prosthetic Valve Thrombosis

| | Aortic (n = 13)† | Mitral (n = 79)† | Tricuspid (n = 15)† | p Value |
|---|---|---|---|---|
| Thrombus characteristic at TEE | | | | |
| Mass visualized on valve | 11 (84.6) | 68 (86.1) | 13 (86.7) | NS |
| Non-obstructive thrombus | 2 (15.4) | 12 (15.2) | 0 | NS |
| Thrombus area (cm$^2$) | 0.45 ± 0.07 | 0.39 ± 0.28 | | NS |
| Mobility (%) | 2 (100) | 9 (81.8) | | NS |
| Obstructive thrombus | 11 (84.6) | 67 (84.8) | 15 (100) | NS |
| Thrombus area (cm$^2$) | 0.68 ± 0.54 | 1.13 ± 2.06 | 0.77 ± 0.71 | NS |
| Mobility (%) | 6 (66.7) | 26 (45.6) | 10 (66.7) | NS |
| Extension beyond valve (%) | 1 (7.7) | 11 (13.9) | 4 (26.7) | NS |
| >Moderate regurgitation (%) | 3 (23.1) | 8 (10.1) | 7 (46.7) | 0.002 |
| Soft ultrasound density of mass | 4 (30.8) | 50 (63.3) | 12 (80.0) | 0.008 |
| Prosthetic valve gradients | | | | |
| Mean gradient pre-lytic all valves (mm Hg) | 40.1 ± 18.2 | 13.4 ± 7.5 | 11.8 ± 3.11 | < 0.0001* |
| Mean gradient post-lytic all valves (mm Hg) | 24.8 ± 23.4 | 4.7 ± 2.5 | 3.7 ± 1.5 | |
| Mean gradient pre-lytic bileaflet (mm Hg) | 41.9 ± 21.6 | 13.1 ± 7.5 | 11.9 ± 3.2 | < 0.0001* |
| Mean gradient post-lytic bileaflet (mm Hg) | 26.2 ± 29.2 | 4.7 ± 2.6 | 3.7 ± 1.7 | |
| Mean gradient pre-lytic tilting disc (mm Hg) | 37.2 ± 12.6 | 14.8 ± 7.6 | 11.0 ± 2.8 | < 0.0001* |
| Mean gradient post-lytic tilting disc (mm Hg) | 22.6 ± 11.8 | 4.9 ± 1.9 | 3.5 ± 0.7 | |

*Prethrombolysis vs. postthrombolysis gradients for each valve location and type; †numbers denote all valves in that position.
NS = not significant; TEE = transesophageal echocardiography.

success was associated with smaller thrombi (0.60 ± 0.60 cm$^2$ vs. 1.91 ± 2.95 cm$^2$, p = 0.027), lower incidence of prior stroke (16.5% vs. 46.4%, p = 0.0015), and higher diastolic BP at presentation (72.7 ± 9.1 mm Hg vs. 65.6 ± 14.7 mm Hg, p = 0.0078). Presentation with shock was associated with clinical failure (10.7% vs. 0%, p = 0.0032), mostly from clinical complications. Less severe NYHA functional class had a trend toward higher clinical success rate (Table 4). In a logistic regression analysis model, after adjusting for age, gender, and presenting BP, smaller thrombus area by TEE (odds ratio [OR] 0.41/cm$^2$, 95% confidence interval [CI] [0.20 to 0.82]) and lack of prior history of stroke (OR 0.29, 95% CI [0.10 to 0.86]) were independent variables associated with clinical success.

**Predictors of complications of thrombolytic therapy.** Complications within the first week of thrombolysis occurred in 19 (17.8%) patients (Table 5); 18 in mitral valves and one in an aortic valve (coronary emboli). No apparent clinical complications occurred in the tricuspid valve group, although lung perfusion or computed tomography scans were not performed to document subclinical pulmonary embolism. The left-sided embolic complication rate was 14%. The major complication rate, combining end points of death, stroke, myocardial infarction, cerebral bleeding, and peripheral emboli requiring intervention was 9.3%. Six patients (5.6%) died within the first week after thrombolysis, all of whom had major complications before death. All deaths were in the mitral valve group.

All clinical and echocardiographic parameters (Tables 1 and 2) were analyzed as possible predictors of complications. Univariate predictors of all complications are listed in Table 6. Patients with a previous stroke (range 0.5 to 240 months, median 6.0) had a higher incidence of complications. However, in the few patients presenting with acute non-hemorrhagic stroke (n = 12), there was no increase in complication or death rates (8.3% and 0%, respectively). In

**Table 3.** Early Outcome of Thrombolytic Therapy

| | Overall (n = 107) | Aortic (n = 13)† | Mitral (n = 79)† | Tricuspid (n = 15)† | p Value |
|---|---|---|---|---|---|
| Any hemodynamic success (%)* | 79 (85.0) | 8 (72.7) | 56 (83.6) | 15 (100) | NS |
| Complete hemodynamic success (%)* | 71 (76.3) | 7 (63.6) | 50 (74.6) | 14 (93.3) | NS |
| Partial hemodynamic success (%)* | 8 (8.6) | 1 (9) | 6 (8.9) | 1 (6.7) | NS |
| Clinical success (%) | 79 (73.8) | 9 (69.2) | 55 (69.6) | 15 (100) | 0.04 |
| Obstructive thrombus (%) | | 7 (63.6) | 46 (68.7) | | NS |
| Non-obstructive thrombus (%) | | 2 (100) | 9 (75.0) | | NS |
| Any complication (%) | 19 (17.8) | 1 (7.7) | 18 (22.8) | 0 (0) | 0.06 |
| Obstructive thrombus (%) | | 1 (9.1) | 16 (23.8) | | NS |
| Non-obstructive thrombus (%) | | 0 (0) | 2 (16.7) | | NS |
| Death (%) | 6 (5.6) | 0 (0) | 6 (7.6) | 0 (0) | NS |
| Repeat valve surgery (%) | 9 (8.4) | 2 (15.4) | 7 (8.9) | 0 (0) | NS |

*Includes only patients with obstructive thrombus (overall = 93; aortic = 11; mitral = 67; tricuspid = 15); †numbers denote all valves in that position.
NS = not significant.

**Table 4.** Outcome of Thrombolytic Therapy According to NYHA Class at Presentation

| NYHA Class | n | Thrombus Area (cm²)* | Hemodynamic Success (%) | Clinical Success (%) | Any Complication (%) | Embolic Complication (%)† | Death (%) |
|---|---|---|---|---|---|---|---|
| Class I | 14 | 0.51 ± 0.36 (0–1) | 92.9 | 71.4 | 21.4 | 15.4 | 0 |
| Class II | 25 | 0.61 ± 0.71 (0–3) | 88.0 | 80.0 | 8.0 | 4.2 | 0 |
| Class III | 49 | 0.86 ± 1.06 (0–6.5) | 85.7 | 77.6 | 14.3 | 14.3 | 8.2 |
| Class IV | 19 | 1.89 ± 3.4 (0.1–14.7) | 84.2 | 57.9 | 36.8 | 29.4 | 10.5 |

*Analysis of variance (ANOVA) p = 0.04; class IV vs. others p < 0.05; †ANOVA p = 0.075.
NYHA = New York Heart Association.

these patients, the thrombus size was small (0.45 ± 0.24 cm²). Thrombus size in patients with complications averaged 2.41 ± 3.48 cm², while in patients without complications it was 0.63 ± 0.60 cm² (p = 0.039). Using receiver operating characteristic curve analysis, the best cut-off of thrombus size for predicting complications was 0.8 cm² (sensitivity 79%, specificity 68%). Figure 1 shows the relation of complication rate and death rate with increasing thrombus area. The 0.8 cm² cut-off was applicable to both mitral and aortic valves as well as bileaflet or tilting disc valves (complication rate of small vs. large thrombi: mitral, 8.5% vs. 43.8%; aortic, 0% vs. 25%; tilting disc, 6.7% vs. 14.3%; bileaflet, 7.3% vs. 48.3%). In a logistic regression analysis model, after adjusting for age, gender, and NYHA functional class, two variables were independent predictors of complications: larger thrombus area by TEE and prior history of stroke (Fig. 2). An increase of 1 cm² in thrombus size was associated with a 2.4-fold increase in complication rate (OR 2.41/cm², 95% CI 1.12 to 5.19), and a prior history of stroke was associated with a 4.5-fold increase in complication rate (OR 4.55, 95% CI 1.35 to 15.38). The history of stroke was most relevant for complications in patients with large thrombi. In patients with prior history of stroke and small thrombus <0.8 cm² (n = 12), there were no complications or death. On the other hand, in patients with large thrombus ≥0.8 cm² and prior history of stroke (n = 14), the complication rate was 78.6%. In patients with large thrombus ≥0.8 cm² but no prior history of stroke (n = 29), the complication rate was 13.8%.

Thrombus area was a predictor of outcome, irrespective of functional class (Fig. 3). Patients with NYHA class I to II and small thrombus area had the best outcome, with no complications or death. Patients with functional class III to

**Table 5.** Complications of Thrombolytic Therapy of Prosthetic Valve Thrombosis in 107 Patients

| Type of Complication | n (%) |
|---|---|
| Peripheral emboli | 4 (3.7) |
| Central nervous system bleeding | 2 (1.9) |
| Stroke | 3 (2.8) |
| Transient ischemic attack | 3 (2.8) |
| Coronary emboli | 3 (2.8) |
| Bleeding requiring transfusion | 4 (3.7) |
| Death | 6 (5.6) |
| All embolic complications | 15 (14.0) |
| Any complication | 19 (17.8) |

IV and small thrombi had a lower complication rate (10.8%) and death rate (5.4%) than patients with larger thrombi of similar functional class.

There was no difference between patients with aortic or mitral PVT with regard to duration of symptoms, presenting BP or heart rate, success rate, or complications. As the majority of complications occurred in mitral valves, the mitral valve group was analyzed separately. As expected, similar univariate predictors of complications were seen. In a multivariate logistic model, the same independent predictors of complications emerged: thrombus size by TEE (OR 2.76/cm², 95% CI 1.23 to 6.22) and prior history of stroke (OR 4.62, 95% CI 1.37 to 15.59).

## DISCUSSION

The present study is the first to evaluate whether TEE can help predict the success of thrombolysis and improve risk stratification of patients undergoing thrombolysis for PVT. Thrombus size determined by TEE was a significant determinant of clinical outcome and complications, irrespective of functional class. This prognostic power of imaging was additive to that of clinical parameters, namely previous stroke.

**Thrombolysis of PVT: hemodynamic vs. clinical success.** Thrombolysis of PVT has emerged as an alternative to surgery by circumventing the risks of re-operation (4) but carries inherent complications. In recent reviews (15,27) and in a series of 110 patients by Gupta et al. (18), hemodynamic improvement was seen in the majority (>70%) of cases, with a complication rate of 12% to 24%, and a death rate of 6% to 10%. In the study by Gupta et al. (18), atrial fibrillation was reported as a risk for embolic complication. However, only 16.4% of cases underwent TEE before thrombolysis, thus precluding the evaluation of whether thrombus burden impacts clinical outcome.

The availability of TEE in this international registry allows for the first time the examination of the role of thrombus characteristics in the outcome of thrombolysis. The rate of hemodynamic success and complications, similar to previously published reports without TEE imaging, supports that this registry is quite representative of patients undergoing thrombolysis. Thrombus burden was found to be an independent predictor of clinical success, in addition to a history of stroke. The history of stroke, however, appeared to be relevant and additive in predicting poor

**Table 6.** Univariate Predictors of Any Complication After Thrombolysis

| Parameters | Complication (n = 19) | No Complication (n = 88) | p Value |
|---|---|---|---|
| Clinical parameters | | | |
| Previous history of stroke | 57.9% | 17.1% | 0.0002 |
| Presence of shock | 15.8% | 0% | 0.0002 |
| NYHA class IV at presentation | 36.8% | 13.6% | 0.016 |
| Systolic blood pressure (mm Hg) | 110 ± 22.8 | 121.9 ± 17.1 | 0.016 |
| Heart rate (beats/min) | 101.6 ± 19.1 | 88.3 ± 21.2 | 0.035 |
| Echocardiographic parameters | | | |
| Thrombus size $\geq 0.8$ cm$^2$ | 78.9% | 31.8% | 0.0001 |
| Extension of thrombus beyond valve | 36.8% | 10.2% | 0.003 |
| Soft ultrasound density of mass | 94.4% | 66.2% | 0.017 |

NYHA = New York Heart Association.

outcome only when thrombus size was large. One possible explanation is that patients with prior history of stroke are at increased risk and sicker clinically to start with. Thrombolysis of a large thrombus with a higher potential for embolization lead to worse outcome in this setting. On the other hand, nonobstructive small thrombi were more likely to be associated with presentation with a stroke, before thrombolysis. Although the number of patients with small nonobstructive thrombi presenting with stroke is relatively small to allow firm conclusions about safety, they appear to have low complication rate with thrombolysis, similar to the whole cohort of patients with small thrombi.

Using receiver operating characteristic analysis, the best cut-off of thrombus area for predicting complications was 0.8 cm$^2$, with the risk of complications increasing significantly with larger thrombus burden. Of interest is the discrepancy between determinants of hemodynamic and clinical success. Whereas a larger thrombus was associated with clinical complications, the alleviation of obstruction was independent of thrombus burden.
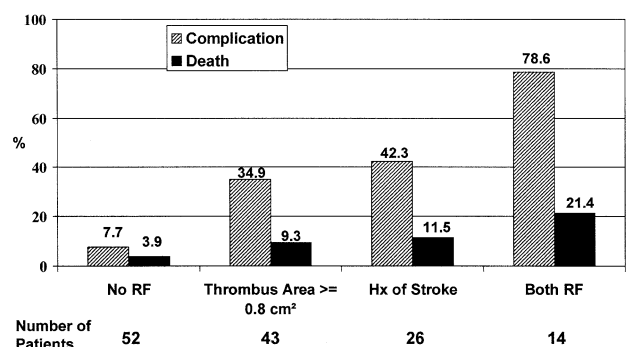
**Severity of clinical presentation, thrombus burden, and clinical outcome.** Patients presenting with symptoms of advanced heart failure in the setting of PVT have a worse clinical outcome, irrespective of treatment modality (9,13).
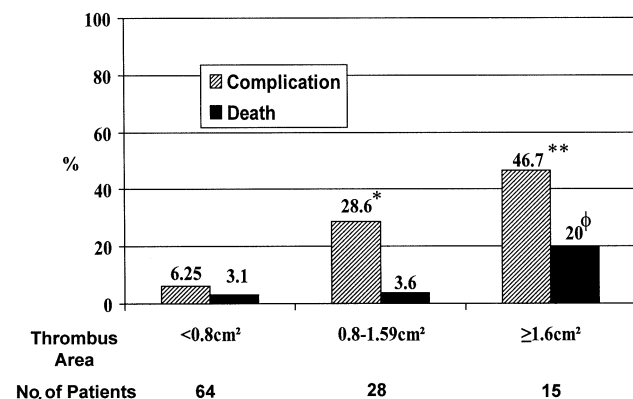
Whereas the reported mortality with thrombolysis is very low (0%) in minimally symptomatic patients (27), it is significantly higher in patients with functional class III and IV (11.9% and 13%, respectively). Patients with cardiogenic shock appear to fare even worse. The present series, the largest to evaluate outcome of patients with advanced symptoms and known thrombus burden, demonstrates that patients with severe heart failure indeed have poor outcome, and yet have similar hemodynamic success compared with those with lesser symptoms. The worse clinical outcome was observed in patients with large thrombi, irrespective of severity of symptoms (Fig. 3). Thus, the observed higher complication and death rate in hemodynamically compromised patients is likely due to a combination of the severity of the clinical condition and, importantly, the size of the thrombus.

**Thrombolysis versus surgery for PVT: identifying a low-risk group for thrombolysis.** The optimal therapy for PVT is still debated. In the absence of randomized trials, the choice of thrombolysis versus surgery is driven by a historical comparison of the respective risks in similar patient subsets (4,7,12,22,28–30). Surgical mortality of valve re-operation has been related to the severity of clinical presentation—similar to thrombolysis, but, in addition, to other risks such as ventricular dysfunction and renal failure (30). Whereas in patients with NYHA class I to III surgical mortality can be low (4.7%) (4), those with functional class



**Figure 1.** Relationship of thrombus area by transesophageal echocardiography to overall complication rate and death rate. *p = 0.003; **p < 0.0001 versus thrombus area <0.8 cm$^2$; $^\phi$p = 0.016 and p = 0.07 versus thrombus area <0.8 cm$^2$ and 0.8 to 1.59 cm$^2$, respectively.



**Figure 2.** Incidence of complication rate and death rate according to the presence or absence of the two risk factors (RF) of thrombus area $\geq 0.8$ cm$^2$ and previous stroke.
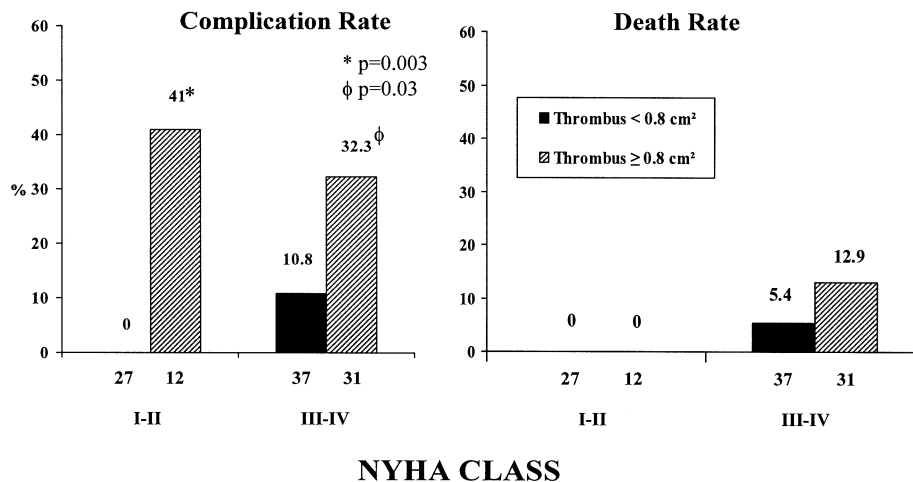
**Figure 3.** Complication rate and death rate in patients grouped according to New York Heart Association (NYHA) functional class and thrombus size.

IV symptoms or shock have a high mortality (17% to 41%), particularly if surgery is urgent (7).

In 1998, the American College of Cardiology/American Heart Association valve disease guidelines (31) reserved thrombolysis for patients in NYHA class III and IV who presented a high surgical risk or had contraindications to surgery, and for patients with "small clot" and NYHA class I to II who fail treatment with heparin. There were no available data to define what constituted a small clot. The present investigation validates these recommendations and further refines them by providing the threshold of thrombus burden ($0.8\ cm^2$) beyond which complications with thrombolysis increase. Patients in functional class I to II and a small thrombus $<0.8\ cm^2$ have essentially no or minimal complications with thrombolysis. In contrast, patients in functional class I to II and larger thrombi have a high complication rate and should undergo surgery unless there are contraindications. The present study also shows the importance of quantitating thrombus burden even in patients with functional class III to IV. In this subgroup with historically high surgical mortality, a small thrombus by TEE identifies patients with relatively low complication and death rates and who, therefore, may benefit from thrombolysis as first-line therapy. Considering that some patients in this registry have received thrombolytic therapy because of poor surgical risk gives more credence to these recommendations. On the other hand, patients in functional class III to IV with larger thrombi need assessment of total surgical risk. Repeat surgery is generally indicated unless the surgical risk is higher than that of thrombolysis. Further confirmation of these recommendations requires a prospective randomized trial of surgery versus thrombolytic therapy for PVT.

**Study limitations.** Because of its retrospective design, our study may be subject to selection bias. However, the success and complication rates observed are similar to those reported in thrombolytic series without TEE. Thrombolysis

was used as first-line therapy in some centers irrespective of high-risk TEE findings, whereas, in others, it was reserved for those too unstable for surgery. This different approach may actually have helped assess the risk of different size thrombi, including large ones, as most patients were not excluded based on TEE findings. The majority of valves undergoing thrombolysis were bileaflet mechanical prostheses in the mitral position, and, therefore, the current findings are most applicable to this valve type and position. Finally, the thrombolytic regimens used were different among centers. Although firm conclusions as to the most effective and safest protocol could not be ascertained, the efficacy of thrombolysis with different agents appears to be similar.

**Conclusions.** In prosthetic valve thrombosis, the size of thrombus is a significant independent predictor of outcome. Transesophageal echocardiography is, therefore, recommended in the management of PVT because it can identify low-risk groups for thrombolysis, irrespective of severity of symptoms, in whom thrombolysis may be used as first-line therapy.

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## APPENDIX

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