

# Resolution of Left Atrial Thrombus after 6 Months of Anticoagulation in Candidates for Percutaneous Transvenous Mitral Commissurotomy

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**Background:** Resolution of left atrial thrombus after long-term oral anticoagulation enhances safe percutaneous transvenous mitral commissurotomy (PTMC); however, the short-term benefit has not been defined.

**Objectives:** To estimate the resolution rate of left atrial thrombus among PTMC candidates after 6 months of oral anticoagulation and to determine its main predictors.

**Design:** Prospective cohort.

**Setting:** Community-based university medical center.

**Patients:** 219 PTMC candidates with thrombus demonstrated by multiplane transesophageal echocardiographic studies.

**Measurements:** The primary outcome was the status of the thrombus at the first 6-month follow-up; secondary measures were bleeding or thromboembolic complications.

**Results:** Among 219 PTMC candidates with left atrial thrombus (mean age [±SD], 39.6 ± 7.4 years [range, 19 to 62 years]), complete resolution of thrombus, with an overall disappearance rate of

24.2% (95% CI, 18.5% to 29.9%), was demonstrated in 53 patients who subsequently underwent successful PTMC. In another 166 patients, the thrombus size was reduced by 24% ( $P < 0.001$ ). No thrombus resolution was observed in the 27 patients with a left atrial body thrombus. Eighteen patients had minor bleeding. The significant predictors of thrombus resolution were a New York Heart Association class of 2 or less, a left atrial appendage thrombus size of 1.6 cm<sup>2</sup> or less, a left atrial spontaneous echocardiographic contrast grade of 1 or less, and an international normalized ratio (INR) of at least 2.5. Patients with all of these predictors had a 94.4% chance of complete thrombus resolution (CI, 84.4% to 98.1%).

**Conclusions:** After 6 months of oral anticoagulation, the left atrial thrombus disappeared in about a quarter of PTMC candidates so they could safely undergo PTMC. Less clinical severity, lower grading of the left atrial spontaneous echocardiographic contrast, a smaller thrombus, and a higher INR level predict thrombus resolution.

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Percutaneous transvenous mitral commissurotomy (PTMC) is a successful alternative to surgical treatment for mitral stenosis when regurgitation and valvular calcifications are limited (1–4). The presence of a left atrial thrombus is a contraindication for this procedure because of the risk for embolism (1–3). Under some conditions, complete resolution of the thrombus can be achieved with long-term oral anticoagulation, which in turn allows safe PTMC (5–11). In a preliminary study with 75 patients, the size of the thrombus and the severity of left atrial spontaneous echocardiographic contrast were significantly related to thrombus resolution (10). Using a larger sample (11), we devised a model based on the New York Heart Association (NYHA) classification system (12) and the original thrombus size to predict thrombus disappearance after 6 to 34 months of follow-up. However, the short-term effect of oral anticoagulation on a thrombus at specified times is much more clinically important. We therefore estimated the disappearance rate of left atrial thrombi among PTMC candidates treated with 6 months of oral anticoagulation and determined the significant predictors of that rate.

## METHODS

### Study Participants

Between 1 August 1996 and 1 February 2002, candidates for PTMC who had symptomatic (12) severe mitral

stenosis (that is, a mitral valve area  $\leq 1.0$  cm<sup>2</sup>, a total echocardiographic score for the mitral valve of  $\leq 11$ , and a mitral regurgitation score of  $\leq 2+$ ) (13) were consecutively recruited at a university referral hospital in northeastern Thailand. The patients underwent both transthoracic and multiplane transesophageal echocardiographic studies before PTMC; those with a thrombus formed the cohort. We excluded patients who had received an oral anticoagulant for more than 72 hours before study entry, who were pregnant, or who had a contraindication to transesophageal echocardiography.

### Echocardiographic Method

Standard transthoracic and multiplane transesophageal echocardiography (14) were performed using a 2.5- or 3.5-MHz color Doppler system and a 5.0-MHz multiplane transducer (Hewlett-Packard Imaging System Sonos 1000 and, since August 1999, Sonos 5500, Hewlett-Packard, Andover, Massachusetts). Within 24 hours of the transthoracic echocardiographic study, echocardiographers who were blinded to those findings performed transesophageal echocardiography. The diagnosis of thrombus, the severity of left atrial spontaneous echocardiographic contrast (15), and the echocardiographic measurements have been described elsewhere (10, 11). The maximal area of the thrombus was measured by planimetry using the built-in software. When more than 2 thrombi were identified, we analyzed each independently.

**Context**

Patients with a left atrial thrombus cannot have percutaneous transvenous mitral commissurotomy for mitral stenosis because of the embolic risk.

**Contribution**

This prospective study from a university medical center showed that oral anticoagulation for 6 months resolved the atrial thrombus in 24% of 219 patients with mitral stenosis. These patients subsequently had successful percutaneous transvenous mitral commissurotomy. Eighteen of the 219 patients had minor bleeding during anticoagulation.

**Implications**

In patients with atrial thrombus and mitral stenosis who do not need immediate surgery, a 6-month trial of oral anticoagulation might increase the number eligible for percutaneous transvenous mitral commissurotomy.

—The Editors

We recorded the transthoracic and transesophageal echocardiographic studies on VHS videotapes for determination and verification of a thrombus, left atrial spontaneous echocardiographic contrast, maximal area, and mobility of the thrombus. Three echocardiographers independently performed all echocardiographic measurements and then resolved discrepancies by consensus.

**Management of the Patients**

At enrollment, we recorded the NYHA functional class, the elapsed time between first symptoms and the first

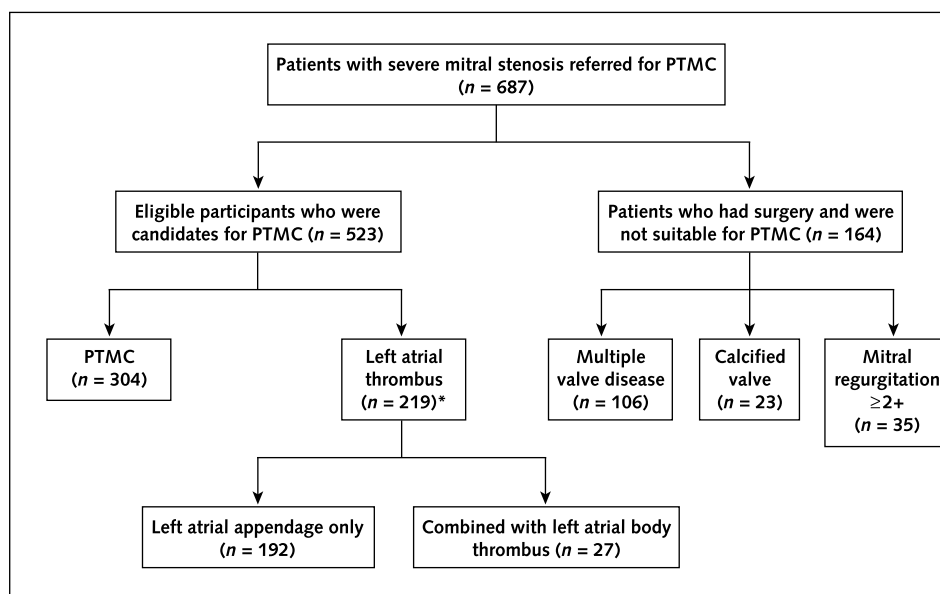
echocardiographic study, history of systemic embolism, and the presence of hemoptysis and syncope. All bleeding and thromboembolic events during follow-up were recorded, including the international normalized ratio (INR) value the day the event occurred. Each patient provided written informed consent, and our institutional ethics committee approved the research protocol.

After we identified the presence of thrombi, all patients began taking oral anticoagulants to maintain an INR between 2.0 and 3.0 (16, 17), beginning with weekly adjustments for the first 2 weeks and then changing to monthly adjustments. The presence and size of thrombi were studied by using results from both transthoracic and transesophageal echocardiographic studies at the first 6-month follow-up. Patients with complete thrombus resolution underwent PTMC. All patients received follow-up care at our hospital. We followed patients with potential adverse effects by mail and telephone.

**Statistical Analysis**

The rates of thrombus resolution after the first 6 months and the corresponding 95% CIs were estimated on the basis of a binomial distribution. For patients whose thrombus persisted, we calculated the relative reduction in size over the first 6 months and the CI based on a normal distribution and tested whether the mean change was zero by using the paired *t*-test. A univariate logistic regression was used to assess the effects of selected factors on thrombus resolution. Continuous variables were categorized by tertiles. Patients were ranked according to the scores of the corresponding variable, then divided into 3 equal groups, which allowed assessment of linearity. In relation to the INR, in patients who had 6 available measurements, the

Figure. Patients that formed the study cohort.



The asterisk indicates that these 219 participants were recruited between August 1996 and February 2002, and all instances of left atrial thrombus occurred in the left atrial appendage. PTMC = percutaneous transvenous mitral commissurotomy.

mean for each patient was used for all analyses. (The 2 highest tertiles of some variables were combined because no outcomes occurred in either.) Possible confounding and interaction effects were investigated through modeling.

The initial model contained clinically important variables and those with a *P* value of 0.2 or less in the univariate analysis, namely, 3 continuous variables (the time elapsed from the first symptoms, the initial thrombus area, and the mean INR at 6 months); 2 dichotomous variables (the NYHA functional class and the left atrial spontaneous echocardiographic contrast); and the interaction term of the NYHA functional class and the initial thrombus area. The assumption of linearity was assessed for each continuous variable by plotting the log odds against the categories of each. Thrombus area and the INR departed from linearity and were therefore dichotomized on the basis of univariate analysis and the restricted cubic spline functions (18). Backward elimination was used for variable selection, according to Kleinbaum and colleagues (19). Model adequacy and goodness of fit were tested according to Hosmer and Lemeshow (20). Predicted probabilities of left atrial thrombus resolution by all possible combinations of significant predictors were then estimated from the final model. A probability of 0.05 was set for statistical significance. All analyses were done by using Stata (Stata Corp., College Station, Texas).

## RESULTS

### Patient Characteristics

Of 687 consecutive patients with severe mitral stenosis, 523 were candidates for PTMC. Of these, 219 patients between 19 and 62 years of age (mean age [ $\pm$ SD],  $39.6 \pm 7.4$  years) who had left atrial thrombus demonstrated by transesophageal echocardiography formed the study cohort (Figure). All patients underwent the first 6-month follow-up echocardiography.

### Effect of Anticoagulant Therapy

Complete disappearance of thrombus was documented in 53 patients at the first 6-month follow-up, with an overall disappearance rate of 24.2% (95% CI, 18.5% to 29.9%), and all of these patients underwent successful and uneventful PTMC. Among the 166 patients whose thrombus persisted, the mean area was reduced from the baseline by approximately 24% ( $P < 0.001$ ). None of the 27 patients with a thrombus in the left atrial body had thrombus resolution, nor did thrombi in an appendage resolve, although they were reduced approximately 6% from the baseline. Table 1 shows the percentage of left atrial thrombus resolution at 6 months for selected factors.

### Factors Affecting Thrombus Resolution

The final model using multiple logistic regression suggested that the factors significantly associated with thrombus resolution were NYHA functional class 1 or 2, a small left atrial appendage thrombus less than  $1.6 \text{ cm}^2$  at the first

**Table 1. Percentage of Left Atrial Thrombus Resolution at the Sixth Month of Follow-up**

Factors	Patients, n	Left Atrial Thrombus Resolution, %
Age*		
19 to 37 y	79	22.8
38 to 42 y	73	30.1
43 to 62 y	67	19.4
Sex		
Male	59	28.8
Female	160	22.5
Duration*		
6 to 26 mo	76	42.1
27 to 44 mo	72	18.1
45 to 120 mo	71	11.3
Occurrence of previous cerebral embolism		
Yes	61	26.2
No	158	23.4
Presence of hemoptysis		
Yes	51	15.7
No	168	26.8
New York Heart Association functional class		
1 or 2	115	40.9
3 or 4	104	5.8
Presence of atrial fibrillation		
Yes	150	20.7
No	69	31.9
Mitral valve area*		
0.40 to 0.70 $\text{cm}^2$	82	7.3
0.71 to 0.82 $\text{cm}^2$	64	25.0
0.83 to 1.16 $\text{cm}^2$	73	42.5
Mitral valve score		
<7	56	44.6
7	71	26.8
>7	92	9.8
Left atrial size*		
3.12 to 3.96 cm	73	23.3
3.97 to 4.96 cm	75	28.0
4.97 to 6.41 cm	71	21.1
Tricuspid regurgitation pressure gradient*		
14 to 31 mm Hg	73	41.1
32 to 43 mm Hg	75	25.3
44 to 80 mm Hg	71	5.6
Width of thrombus†		
0.40 to 1.06 cm	74	60.8
1.07 to 8.40 cm	145	5.5
Length of thrombus*		
0.01 to 1.15 cm	73	52.1
1.16 to 1.96 cm	73	19.2
1.97 to 11.4 cm	73	1.4
Area of thrombus†		
0.47 to 1.59 $\text{cm}^2$	73	58.9
1.60 to 12.5 $\text{cm}^2$	146	6.9
Mobility of thrombus		
Fixed	192	27.4
Mobile	27	29.6
Left atrial spontaneous echocardiographic contrast		
Grade 1	36	69.4
Grade $\geq 2$	183	15.3
Mean international normalized ratio (6 mo-period)*		
2.20 to 2.49	73	2.7
2.50 to 2.59	73	30.1
2.60 to 3.10	73	39.7

\* Categorization based on tertile.

† Categorization based on tertile in which the 2 highest tertiles were combined because no outcomes occurred in either.

Table 2. Predicted Probabilities of Left Atrial Thrombus Resolution at the Sixth Month of Follow-up\*

Predictors				Predicted Probabilities (95% CI)
NYHA Class $\leq 2$	Area of Left Atrial Thrombus $< 1.6 \text{ cm}^2$ at Baseline	Left Atrial Spontaneous Echocardiographic Contrast $\leq$ Grade 1	Mean INR $\geq 2.5$ over a 6-Month Period	
No	No	No	No	0.002 (0.000–0.012)
Yes	No	No	No	0.013 (0.003–0.059)
No	Yes	No	No	0.035 (0.008–0.149)
No	No	Yes	No	0.013 (0.002–0.074)
No	No	No	Yes	0.022 (0.006–0.071)
Yes	Yes	No	No	0.19 (0.056–0.479)
Yes	No	Yes	No	0.079 (0.018–0.286)
Yes	No	No	Yes	0.124 (0.058–0.246)
No	Yes	Yes	No	0.194 (0.046–0.547)
No	Yes	No	Yes	0.284 (0.116–0.546)
No	No	Yes	Yes	0.127 (0.032–0.389)
No	Yes	Yes	Yes	0.725 (0.389–0.916)
Yes	No	Yes	Yes	0.483 (0.234–0.741)
Yes	Yes	No	Yes	0.718 (0.547–0.844)
Yes	Yes	Yes	No	0.608 (0.277–0.862)
Yes	Yes	Yes	Yes	0.944 (0.844–0.981)

\* Determined by all possible combinations of significant predictors. INR = international normalized ratio; NYHA = New York Heart Association.

study, a left atrial spontaneous echocardiographic contrast of grade 1 or less, and an INR of 2.5 or more (Table 2). Patients with all of these predictors had a 94.4% (CI, 84.4% to 98.1%) chance of complete thrombus resolution. This model fit the data satisfactorily ( $P > 0.2$  [Hosmer–Lemeshow statistic]).

#### Intensity of Oral Anticoagulation and Its Adverse Effects

During the 6-month study, INR was measured monthly in all 219 patients. Among the total 1314 INR measurements, the mean ( $\pm$ SD) and median (range) were  $2.53 \pm 0.39$  and 2.52 (range, 1.72 to 3.92), respectively. The percentage of patients whose INR was between 2 and 3 (using 219 as the denominator for each of the 6 months) was 95.0%, 84.5%, 71.7%, 79.0%, 82.2%, and 73.5%, respectively, while the percentage of patients with an INR greater than 3 was 2.7%, 7.8%, 18.7%, 13.2%, 10.5%, and 19.6%, respectively. The INR of 217 of the patients (99.1%) was between 2 and 3 for at least 50% of the follow-up period.

During follow-up, none of the patients had major bleeding. Eighteen had minor bleeding, 12 of whom had an INR of less than 2.5 and 6 of whom had an INR of 3.6 or more the day the event occurred. There were 61 systemic embolic events (2.1 per 100 patient-months) before study entry. After oral anticoagulation was started, only 1 patient (whose INR was 1.8 the day the event occurred and averaged 2.1) developed a transient ischemic attack.

#### DISCUSSION

Percutaneous transvenous mitral commissurotomy is accepted as a safe and effective alternative to surgery because it produces good, immediate hemodynamic outcomes; has a low complication rate; and permits sustained hemodynamic and clinical improvement of mitral stenosis

(1–4). The presence of a thrombus contraindicates PTMC, making open surgical commissurotomy the only treatment option.

The waiting time for surgical correction of severe mitral stenosis at our hospital is between 9 and 16 months. During that time, patients are given oral anticoagulation to prevent thromboembolic events. Although resolution of thrombus after long-term oral anticoagulation has been documented (5–11), the clinically important effect of short-term anticoagulation has been less clearly defined.

The tertile of the mean INR suggests that among patients whose mean INR was less than 2.5, only 2 of 73 (2.7%) had thrombus resolution. In fact, no thrombus resolution occurred among patients whose mean INR in the first 6 months was less than 2.44 (26.5% of patients [58 of 219]) or among those whose thrombus area was greater than  $2.11 \text{ cm}^2$  (51.1% of patients [112 of 219]). These factors caused departure from linearity in the logistic regression model so that categorization was necessary.

Because categorizing continuous variables can invalidate results, all of these analyses were categorized in a summary of INRs, based on cutoffs suggested by restricted cubic spline functions (18). The categorization incorporated the findings from the univariate analysis (that is, the odds ratios were similar in the 2 highest tertiles; data not shown). The same approach was used for the adjusted thrombus area, and qualitatively the conclusion was the same.

Since we had only 53 events, overfitting the model was a real possibility. We therefore limited the number of variables in the initial model to 6. We could then follow the model coefficients and their CIs while fitting the model.

According to previous research (5–11) and for patient convenience, we selected the first 6 months after beginning

oral anticoagulation for evaluating a short-term effect and considering the greatest clinical importance. Any earlier would have been impractical, and any later would have increased the risk for systemic embolism.

The NYHA functional class and the thrombus area have been shown to be significant, independent predictors (10, 11) for resolution of thrombus before prescription of oral anticoagulation. The present study underscores the effect of initial thrombus area on thrombus resolution and the need to maintain an INR of 2.5 or more to enhance thrombus resolution after oral anticoagulant therapy is begun. A randomized, controlled trial to determine the most appropriate cutoff point of INR should prove promising.

This prospective series is, to our knowledge, the first and the largest demonstrating the short-term effect of anticoagulation on successful resolution of left atrial thrombus. Such an outcome would be enhanced in patients with less clinical severity, a small left atrial appendage thrombus, left atrial spontaneous echocardiographic contrast of grade 1 or lower, a high INR, or any combination of these factors.

Our study has important clinical implications. First, not all PTMC candidates with thrombus need immediate surgery, and second, nearly 25% of those on surgical waiting lists can safely undergo PTMC by the sixth month of follow-up if their thrombus completely disappeared after oral anticoagulation. These might be practical guidelines for clinical assessment and proper management for cardiologists, general practitioners, internists, and cardiac surgeons caring for patients with mitral stenosis.

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