Accelerated Infusion of Streptokinase for the Treatment of Left-Sided Prosthetic Valve Thrombosis

A Randomized Controlled Trial

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Background—No large prospective studies have evaluated the efficacy of fibrinolytic therapy for left-sided prosthetic valve thrombosis, yet it remains the first line of treatment in developing countries.

Methods and Results—We performed a randomized controlled trial comparing an accelerated infusion with the conventional infusion of streptokinase in 120 patients with a first episode of left-sided prosthetic valve thrombosis. The primary outcome measure was the occurrence of a complete clinical response, defined as objectively documented complete restoration of valve function in the absence of major complications. The secondary outcome was a composite of death, major bleeding, embolic stroke, or non–central nervous system systemic embolism. Patients were recruited over a 2.5-year period at a single center in India. Complete clinical response occurred in 38 (64.4%) of 59 patients with the accelerated infusion compared with 32 (53.3%) of 60 with the conventional infusion (hazard ratio 1.6, 95% confidence interval 0.9 to 2.5, \( P = 0.055 \)). There was no significant difference in the occurrence of the composite secondary outcome (hazard ratio 1.4, 95% confidence interval 0.5 to 3.5, \( P = 0.50 \)) or major bleeding (hazard ratio 2.2, 95% confidence interval 0.6 to 7.7, \( P = 0.24 \)) with the accelerated infusion. The success rate with fibrinolytic therapy was low overall (59%) and very low in patients in New York Heart Association functional class III/IV (24%).

Conclusions—The large number of patients recruited from a single center underscores the massive burden of prosthetic valve thrombosis in developing countries. Fibrinolytic therapy with streptokinase is less efficacious than previously believed. The accelerated streptokinase infusion is not better than the standard infusion for left-sided prosthetic valve thrombosis. Developing countries urgently need more effective strategies to prevent and treat prosthetic valve thrombosis. (Circulation. 2009;120:1108-1114.)

Key Words: valves ■ prosthesis ■ thrombosis ■ fibrinolysis

Left-sided prosthetic valve thrombosis (PVT) is a potentially devastating complication associated with high morbidity and mortality that is commonly seen in developing countries. In a retrospective analysis from a large tertiary-care hospital in India, left-sided PVT occurred in 6.1% of patients within 6 months of valve replacement,\(^1\) a rate far higher than that seen in developed countries (0.3 to 1.3 per 100 patient-years).\(^2\) Guidelines differ on whether surgery or fibrinolytic therapy should be the treatment of choice in patients presenting with left-sided PVT,\(^3\)\(^-\)\(^7\) but because of the limited availability and high cost of surgery, fibrinolytic therapy has become the first-line treatment in much of the developing world.\(^8\)\(^-\)\(^13\) The first-generation fibrinolytic agents, streptokinase and urokinase, are widely available, inexpensive, and easy to administer but are associated with high rates of bleeding and thromboembolic complications.\(^4\) Moreover, improvement in hemodynamics may not occur until 24 to 48 hours after commencement of fibrinolytic drug infusions.\(^4\) A delayed response to treatment and prolonged exposure to the fibrinolytic agent may further increase the risk of complications.

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Currently used regimens of fibrinolysis for treatment of PVT have been adapted from those used for the treatment of pulmonary thromboembolism.\(^4\) Because patients with obstructive left-sided PVT are often hemodynamically compromised, specifically designed treatment protocols to accelerate
valve opening may improve clinical outcomes. We hypothesized that an accelerated protocol that consisted of an initial high-dose infusion of streptokinase, followed if necessary by a regular low-dose infusion, would expedite fibrinolysis and restore valve function more rapidly than the conventional protocol, thereby limiting total exposure to the drug and reducing complications. We performed a prospective, randomized trial to compare the efficacy and safety of accelerated infusion of streptokinase with the conventional slow-infusion regimen.

Methods
This was a randomized controlled trial to examine the efficacy and safety of an accelerated infusion of streptokinase compared with the conventional infusion of streptokinase in patients with a mechanical heart valve who presented with a first episode of objectively confirmed left-sided PVT. Eligible patients were recruited from the emergency and outpatient departments of the All India Institute of Medical Sciences, New Delhi. The diagnosis of PVT was suspected clinically in patients who presented with symptoms attributable to valve dysfunction (dyspnea, angina, congestive failure) of less than 2 weeks duration, with or without muffled valve sounds on auscultation. Definitive diagnosis required the documentation of new onset of hypomobile or immobile valve leaflets on fluoroscopy,14 with or without elevated transvalvular gradients on Doppler echocardiography. Patients with mechanical valves undergo periodic fluoroscopic and echocardiographic examinations during routine follow-up visits, and previous records were consulted to confirm new onset of valve dysfunction before therapy was instituted. Patients with recurrent PVT and those with a contraindication to fibrinolytic therapy were excluded from participation. Contraindications to fibrinolytic therapy included any previous intracranial hemorrhage, ischemic stroke within the last 3 months, presence of a left atrial thrombus on transthoracic echocardiography, and pregnancy. All patients gave informed consent, and the study protocol was approved by the institute’s Ethics Committee.

Randomization
Patients were randomized in blocks of 10 by use of consecutively numbered opaque, sealed envelopes that contained the treatment allocation. An independent study statistician (M.K.) prepared the study envelopes using a computer-generated randomization sequence that remained concealed to patients and healthcare providers throughout the study. Envelopes were opened only after the diagnosis of PVT was objectively confirmed and the patient had provided written informed consent to participate in the study. Once the seal was broken, the patient was considered irrevocably randomized.

Study Interventions
Patients were randomized to receive either the accelerated or the conventional infusion of streptokinase. Patients in the accelerated infusion group received 1.5 million units (MU) of streptokinase over 1 hour. Transthoracic echocardiography and fluoroscopic evaluation were performed 60 to 90 minutes after completion of the initial infusion of 1.5 MU of streptokinase. In patients without complete valve opening (defined below), streptokinase infusion was continued at a rate of 0.1 MU/h. Those randomized to the conventional infusion received 0.25 MU of streptokinase over 30 minutes followed by a 0.1-MU/h infusion. Infusions of streptokinase were continued for up to 72 to 96 hours at the discretion of the treating physician. Response to therapy in both groups was monitored by transthoracic echocardiography and fluoroscopy, performed at 8- to 12-hour intervals. In all patients, treatment with unfractionated heparin was initiated 4 to 6 hours after cessation of the streptokinase infusion as a bridging therapy until stable therapeutic international normalized ratio levels were achieved. Infusions were stopped if there was clinical suspicion of cerebral embolism or major bleeding and were resumed only after these conditions were ruled out by appropriate investigation.

Outcomes
The primary outcome was the occurrence of a complete clinical response, defined as complete restoration of valve function in the absence of death, major bleeding, or embolic stroke. The key secondary outcome was a composite of death, major bleeding, embolic stroke, or non–central nervous system systemic embolic event. Patients were monitored for adverse events until they were discharged from the hospital.

Complete restoration of valve function consisted of (1) restoration of normal leaflet motion on fluoroscopy and (2) normalization of transvalvular pressure gradients on Doppler echocardiography (mitral mean diastolic gradient <6 mm Hg and end-diastolic gradient <2 mm Hg and aortic peak gradient <30 mm Hg). Fibrinolytic therapy was considered to have failed if transvalvular gradients were reduced by less than 50% from baseline, with persistent leaflet abnormality on fluoroscopy, or if a complication resulted in death, irrespective of whether valve function was restored. Partial response was defined as improvement in transvalvular gradients >50% from baseline but without complete normalization of leaflet motion on fluoroscopy.

Major bleeding was defined as bleeding that was intracranial, required transfusion, or led to surgical exploration. Other bleeding episodes were considered minor. Embolic stroke was defined as any focal neurologic deficit that lasted >24 hours with brain imaging suggestive of a primary ischemic origin. All patients with a suspected ischemic stroke or intracranial hemorrhage underwent brain imaging. The diagnosis of non–central nervous system systemic embolism was made clinically (loss of arterial pulse or evidence of end-organ ischemia) and confirmed by Doppler studies when appropriate. Outcomes were assessed by the patients’ treating physicians, who were aware of treatment assignment.

Statistical Analysis
Sample Size
From our previous experience,11 we expected that the primary outcome would occur in 73% of patients who received the conventional infusion of streptokinase. We estimated that 58 patients would be required in each arm to detect a 30% difference in treatment efficacy with 80% power at a 2-sided α-level of 0.05, with an anticipated crossover rate of 5% from the accelerated- to the standard-infusion arm. One planned interim analysis was performed at the end of 1 year,15 with the α-level set at 0.001 for stopping the trial, using the rule of Peto.16 The difference in the response rates between the 2 arms in this analysis (16 of 20 with the accelerated infusion and 10 of 20 with the standard infusion, P=0.047) did not support termination of the trial.13

Analysis
All analyses were performed according to the intention-to-treat principle. Baseline characteristics are reported as means (SD) and proportions. Kaplan–Meier curves were constructed for the time to complete response for the 2 treatment groups, and hazard ratios (HRs) were calculated using Cox regression. Because of the small number of patients and the potential for imbalance of key prognostic variables between the groups, we also performed an adjusted analysis with inclusion of the following prespecified baseline variables in the Cox model: Randomized treatment allocation (accelerated or conventional infusion), functional class (New York Heart Association [NYHA] class I/II versus class III/IV), time after valve replacement (≤12 months versus >12 months after valve replacement), position of thrombosed valve (aortic or mitral), and cardiac rhythm at presentation (sinus rhythm or atrial fibrillation). HRs were also calculated for the composite outcome and its individual components. The 2-sample t test or χ² test was used to compare other treatment and outcome variables between the 2 groups as appropriate. We performed 1 prespecified subgroup analysis according to baseline functional class (NYHA I/II versus III/IV). All
Table 1. Baseline Characteristics of Included Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Accelerated Infusion (n=60)</th>
<th>Conventional Infusion (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>34 (10)</td>
<td>31 (10)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>24 (40)</td>
<td>29 (48)</td>
</tr>
<tr>
<td>Affected valve, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral</td>
<td>41 (68)</td>
<td>38 (63)</td>
</tr>
<tr>
<td>Aortic</td>
<td>14 (23)</td>
<td>16 (27)</td>
</tr>
<tr>
<td>Both</td>
<td>5 (9)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>20 (33)</td>
<td>19 (32)</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>11 (19)</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Class II</td>
<td>35 (59)</td>
<td>24 (40)</td>
</tr>
<tr>
<td>Class III</td>
<td>6 (10)</td>
<td>17 (28)</td>
</tr>
<tr>
<td>Class IV</td>
<td>7 (12)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>(n of MVRs)</td>
<td>30 (65)</td>
<td>30 (68)</td>
</tr>
<tr>
<td>Time from valve replacement, mo, median (IQR)</td>
<td>24 (8–58)</td>
<td>26 (11–48)</td>
</tr>
</tbody>
</table>

MVR indicates mitral valve replacements; IQR, interquartile range.

*Two patients randomized to the accelerated infusion of streptokinase did not receive treatment. One patient withdrew consent for fibrinolytic therapy, was treated with an infusion of unfractionated heparin, and was followed up until discharge; however, the results of repeat fluoroscopy or echocardiography before discharge were not available for this patient. This patient is therefore not included in the analysis. The second patient did not receive streptokinase because of a very high international normalized ratio due to liver dysfunction. This patient died of cardiogenic shock before any treatment could be instituted and is included in the intention-to-treat analysis.

P values were 2-sided, and P<0.05 was considered statistically significant. Analyses were performed with SPSS version 16 (SPSS Inc, Chicago, Ill).

Results

Between November 2004 and March 2007, we randomized 120 patients (60 to either group) from among 125 who presented with a first episode of left-sided PVT. Reasons for exclusion were initiation of treatment before randomization could occur (3 patients) or physician preference for 1 of the study treatments. Two patients randomized to the accelerated regimen did not receive therapy. One patient died before any treatment could be instituted and was included in the intention-to-treat analysis. The other patient withdrew consent for fibrinolytic therapy. The results of repeat fluoroscopy or echocardiography before discharge were not available for this patient, and this patient is therefore not included in the analysis. The key baseline characteristics of the study patients are presented in Table 1. All patients had bileaflet mechanical valves (St Jude Medical, St Paul, Minn) and showed new-onset, abnormal leaflet mobility on fluoroscopy at the time of presentation. A larger proportion of patients were in better functional class in the accelerated infusion group than in the conventional infusion group (NYHA class I/II, 78% versus 60%, respectively). Other variables were similarly distributed between the 2 groups.

Efficacy of Accelerated Streptokinase Infusion

There was no significant difference between the accelerated infusion protocol and the conventional infusion protocol in producing a complete clinical response (38 [64.4%] of 59 versus 32 [53.3%] of 60, respectively; HR 1.6, 95% confidence interval [CI] 0.9 to 2.5, P=0.055). Six additional patients (3 in either group) had complete restoration of valve function but sustained a major complication. More than one fourth of the patients who received the accelerated infusion (15 of 58; 26%) achieved a complete response with the initial 1-hour infusion of 1.5 MU of streptokinase. Among those who received the allocated therapy, significantly more patients in this group than in the conventional infusion group also had a complete response within 12 hours (24 of 58 versus 7 of 60; P<0.001). There was, however, no difference in the total dose of streptokinase or duration of infusion between the 2 treatment groups (Table 2).

No patient underwent urgent valve replacement during the index admission. Patients who failed to respond to fibrinolytic therapy and those who had an incomplete response were scheduled for early elective surgery. They were stabilized on decongestive therapy before discharge and maintained on a higher than usual international normalized ratio until the time of surgery.

Safety of Accelerated Streptokinase Infusion

The secondary composite of death, major bleeding, embolic stroke, or non–central nervous system systemic embolism occurred in 20 (16.7%) of the 120 patients. There was no statistically significant difference between the 2 treatment protocols in the rate of embolic stroke (3 [5.0%] of 60 patients in the accelerated infusion group versus 3 [5.0%] of 60 patients in the conventional infusion group; HR 1.0, 95% CI 0.1 to 10.0, P=0.99). Of the 6 patients with systemic embolism, 5 were women, and 3 were in functional class V. The other patient was a 97-year-old man in class II who developed a first episode of right-sided PVT; 1 hour after starting an accelerated infusion of 1.5 MU of streptokinase, he developed a large pericardial effusion and was treated with an infusion of unfractionated heparin, and was followed up until discharge; however, the results of repeat fluoroscopy or echocardiography before discharge were not available for this patient.

Table 2. Dose and Duration of Streptokinase Infusion in the 2 Treatment Groups*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Accelerated Infusion (n=58)</th>
<th>Conventional Infusion (n=60)</th>
<th>P for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) dose of streptokinase, MU</td>
<td>5.1 (3.7)</td>
<td>5.4 (3.3)</td>
<td>0.65</td>
</tr>
<tr>
<td>Mean (SD) duration of streptokinase infusion, h</td>
<td>40.5 (40.9)</td>
<td>52.7 (34.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Complete response with ≤12 h of streptokinase infusion, n (%)</td>
<td>24 (40)</td>
<td>7 (12)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Analysis among patients who received allocated treatment.

Table 3. Adverse Events With Treatment

<table>
<thead>
<tr>
<th>Outcome, n (%)</th>
<th>Accelerated Infusion (n=60)</th>
<th>Conventional Infusion (n=60)</th>
<th>Unadjusted HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, major bleeding, or non-CNS embolism</td>
<td>11 (18)</td>
<td>9 (15)</td>
<td>1.4 (0.5–3.5)</td>
<td>0.50</td>
</tr>
<tr>
<td>Death</td>
<td>5 (8)</td>
<td>4 (7)</td>
<td>1.3 (0.3–5.2)</td>
<td>0.71</td>
</tr>
<tr>
<td>Embolic stroke or non-CNS embolic event</td>
<td>4 (7)</td>
<td>2* (3)</td>
<td>2.7 (0.5–14.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>7 (12)</td>
<td>4 (7)</td>
<td>2.2 (0.6–7.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>4 (7)</td>
<td>1 (2)</td>
<td>4.5 (0.5–43.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Other major bleeding</td>
<td>3 (5)</td>
<td>3 (5)</td>
<td>1.4 (0.3–7.0)</td>
<td>0.69</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>8 (13)</td>
<td>5 (8)</td>
<td>2.1 (0.7–6.5)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

CNS indicates central nervous system.

Values are n (%).

*One patient had coronary embolism.
groups in the composite secondary outcome (HR 1.4, 95% CI 0.5 to 3.5, \( P = 0.50 \)) or any of the individual components of the composite; however, there were numerically more major bleeds, particularly intracranial bleeds, and more embolic strokes with the accelerated infusion (Table 3). There was a trend toward an increase in minor bleeding.

**Adjusted Analyses and Subgroup Effects**

The adjusted HR for achieving a complete clinical response with the accelerated infusion was 1.4 (95% CI 0.9 to 2.4, \( P = 0.15 \); Figure). The only independent predictor of the primary outcome was better functional class (NYHA class I/II) at the time of presentation (Table 4). The efficacy of the accelerated infusion did not differ between patients in NYHA class I/II (HR 1.4, 95% CI 0.8 to 2.3) and class III/IV (HR 1.0, 95% CI 0.3 to 2.3; \( P \) for interaction 0.66). Overall, however, patients in NYHA class III/IV fared very poorly with fibrinolytic therapy, with only 24% of patients showing a complete response and 24% experiencing major adverse events (Table 5). Patients in NYHA class III/IV had a better complete response rate, but therapy was nevertheless associated with a high rate of major adverse events (Table 5).

**Discussion**

The present study represents the largest prospective experience and the first randomized controlled trial of fibrinolytic therapy for left-sided PVT. Our major findings are 3-fold. First, we found no evidence that an accelerated infusion of streptokinase was better than the conventional slow infusion for the treatment of a first episode of left-sided PVT. The clinical response was more rapid in patients who received an

**Table 5. Outcomes With Fibrinolytic Therapy by Functional Class**

<table>
<thead>
<tr>
<th>Functional Class</th>
<th>Accelerated Infusion (n=59)</th>
<th>Conventional Infusion (n=60)</th>
<th>Total (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class I/II</td>
<td>Complete clinical response, n (%)</td>
<td>35/46 (76)</td>
<td>26/36 (72)</td>
</tr>
<tr>
<td></td>
<td>Death, major bleeding, embolic stroke, non-CNS embolism, n (%)*</td>
<td>8/46 (17)</td>
<td>3/36 (8)</td>
</tr>
<tr>
<td>NYHA class III/IV</td>
<td>Complete clinical response, n (%)</td>
<td>3/13 (23)</td>
<td>6/24 (25)</td>
</tr>
<tr>
<td></td>
<td>Death, major bleeding, embolic stroke, non-CNS embolism, n (%)*</td>
<td>3/13 (23)</td>
<td>6/24 (25)</td>
</tr>
</tbody>
</table>

CNS indicates central nervous system.

*The difference was mainly due to a higher incidence of intracranial hemorrhage (4 vs 1) and death (3 vs 0) in the accelerated fibrinolytic therapy group compared with the conventional infusion group.
accelerated infusion of streptokinase, but the data indicated a potential for increased bleeding, including intracranial bleeding. Second, the overall rates of complete success with fibrinolytic therapy were substantially lower than reported previously. This reduction in the response rate reduced the power of this study to detect small but potentially relevant differences between the 2 fibrinolytic strategies, and therefore, these may be considered pilot data. Third, the present study, conducted at a single center over a 2.5-year period, highlights the huge burden of PVT in developing countries.

**Efficacy of Accelerated Fibrinolysis**

A high initial dose of streptokinase is used routinely in patients with acute ST-elevation myocardial infarction and has also been used successfully in patients with massive pulmonary embolism.17,18 The use of an accelerated fibrinolytic infusion in patients with left-sided PVT is attractive owing to the potential for rapid restoration of valve function, although clinicians have been concerned that this could increase the risk of embolization to the brain. Despite achieving more rapid lysis, we found no benefit of accelerated fibrinolytic infusion and a concerning increase in bleeding and embolization. As seen with fibrinolytic therapy for acute myocardial infarction, similar doses of a fibrinolytic agent may be associated with a greater tendency to cause intracranial bleeding if given in an accelerated fashion.19

Only 2 uncontrolled retrospective studies involving a combined total of 33 patients have previously evaluated an accelerated protocol of fibrinolysis with streptokinase for left-sided PVT. The reported complete response rates in those studies were 59% and 53%, respectively, although in the second trial, the complete response rate increased to 80% after a second dose of streptokinase.11 The response rate in the present study of only 26% (15 of 58) after the initial bolus dose of 1.5 MU of streptokinase was much lower than that seen in those studies.

**Efficacy of Fibrinolytic Therapy for PVT**

The overall response rate of 59% (70 of 119) with fibrinolytic therapy observed in the present study was substantially lower than that reported in the literature. These poor results occurred despite the fact that patients were treated at a tertiary-care center with a great deal of experience in diagnosing and managing PVT. Outcomes at smaller centers are likely to be worse. Consensus statements on the treatment of PVT and recent systematic reviews, however, suggest that the success rate with fibrinolytic therapy is at least 80%.3,6,20,21 On the basis of this high success rate, the American College of Cardiology/American Heart Association and American College of Chest Physicians guidelines recommend fibrinolytic therapy as first-line treatment for patients in good functional class with low thrombus burden and in all other patients if they are considered to be at high risk for surgery.3,5,7 Some others recommend fibrinolytic therapy as first-line therapy for all patients with left-sided PVT.7 Published reports of the efficacy of fibrinolytic therapy for left-sided PVT, however, are based on retrospective studies and case series, which are subject to positive publication bias and potentially overestimate the success rates with fibrinolytic therapy.

It is possible that a high prevalence of antibodies against streptokinase may have led to the low response rates. We did not measure anti streptokinase antibodies in the patients in the present study. However, several observations argue against such a possibility. First, previous retrospective analyses from our own hospital and from other developing countries have shown much higher response rates with streptokinase. Second, we excluded patients who had had a previous episode of PVT, thereby excluding prior exposure to streptokinase. Finally, studies from South Asia have previously shown that reperfusion rates after fibrinolytic therapy with streptokinase for acute myocardial infarction were not influenced by high anti-streptokinase antibody titers.22,23

The relatively low success rate in the present study occurred despite the inclusion of a high proportion of patients in NYHA functional class I/II (69%), who are more likely to achieve a complete response than patients in NYHA class III/IV. Even among patients in NYHA class I/II, fibrinolytic therapy was successful only in three fourths of patients and was associated with a significant risk of major adverse events, including embolic stroke and intracranial hemorrhage. On the other hand, surgery invariably restores valve function, with low mortality rates (4% to 5%) in patients in NYHA classes I through III, and is associated with a very low risk of embolic stroke or intracranial hemorrhage (<1%).24,25 Collectively, these data suggest that patients in good functional class may be offered surgery as first-line therapy, particularly if transesophageal echocardiography shows a large thrombus burden.6,26 Another potential therapeutic option in these patients is anticoagulant therapy. Anticoagulant therapy was found to be inferior to fibrinolysis with streptokinase in 1 small, nonrandomized study (n=20), but these results cannot be considered definitive.27

Less than one fourth of the patients who presented in NYHA class III/IV responded to fibrinolytic therapy, and a similar proportion experienced major adverse events. Surgery for patients in NYHA class IV in 2 surgical series was associated with a mortality rate of 17.5% and 24%, respectively.24,25 Thus, contrary to current recommendations,3,5,7 fibrinolytic therapy may not be a reasonable alternative to surgery for these patients.

**Burden of PVT in Developing Countries**

Accurate data on the incidence of left-sided PVT in developing countries are lacking, but our experience suggests that there is a massive burden of disease. Approximately 50 patients, all operated on at our center, presented with PVT annually during the course of this study. The median time from valve replacement was 24 months. Because approximately 500 valve replacement procedures are performed annually at this center,24 this translates to a 10% incidence of PVT. The latter estimate is consistent with a rate of 6.1% in the first 6 months after valve replacement reported in a retrospective study and much higher than the 0.3 to 1.3 per 100 patient-years reported in developed countries.2 The majority of patients presenting with PVT are reported to have subtherapeutic international normalized ratio values at presentation.20 In the present study, 72% (79/110) of the patients had inadequate anticoagulation at presentation. This observation highlights the urgent need to
develop, test, and implement strategies to improve the quality of oral anticoagulation in resource-poor countries.

**Study Limitations**

Despite being the largest prospective study to date, because of the lower than expected response rates, the present study was underpowered to detect a modest but still worthwhile benefit with the accelerated compared to the conventional infusion of fibrinolytic therapy. We did not perform routine transesophageal echocardiography to assess thrombus size. Although we analyzed patients by functional class, which correlates well with thrombus size, transesophageal echocardiography may have helped to refine our evaluation of efficacy. Another potential limitation of the present study is that outcome assessors were not blinded to treatment assignment.

**Conclusions**

The results of our randomized controlled trial provide no evidence for a benefit of an accelerated fibrinolytic infusion compared with a conventional infusion for patients with left-sided PVT and demonstrate a substantially lower success rate with fibrinolytic therapy than reported previously. These results should prompt the reevaluation of existing guidelines that recommend the routine use of fibrinolytic therapy in patients with left-sided PVT and should lead to the initiation of collaborative randomized trials involving larger numbers of patients to determine optimal treatment. The massive burden of PVT in the developing world underscores the urgent need for strategies to improve the quality of anticoagulation. New oral anticoagulants such as the thrombin and Xa antagonists, which do not require routine laboratory monitoring, may be candidates for evaluation as alternatives to vitamin K antagonists in patients with mechanical heart valves.

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**Disclosures**

None.

**References**


CLINICAL PERSPECTIVE

Left-sided prosthetic valve thrombosis is frequently seen in developing countries and is most often treated with prolonged infusions of streptokinase. Treatment is often associated with a high rate of serious embolic and bleeding complications. In a single-center randomized controlled trial, we compared an accelerated infusion of streptokinase with the standard prolonged infusion in 120 patients presenting with a first episode of left-sided prosthetic valve thrombosis, in the belief that the accelerated regimen may expedite valve opening and reduce the rate of complications. The primary outcome was the occurrence of a complete clinical response, defined as complete restoration of valve function in the absence of major complications. The secondary outcome was a composite of death, major bleeding, embolic stroke, or non–central nervous system systemic embolism. We were unable to demonstrate a statistically significant difference in the occurrence of the primary or secondary outcomes between the treatment and control groups. This was because of the loss in power that resulted from an unexpectedly low response rate (59%) with streptokinase. In particular, the subgroup of patients in New York Heart Association class III/IV responded very poorly. This is in contrast to previous retrospective series that suggested overall response rates in excess of 80%. These results, derived from the only large prospective study of patients with prosthetic valve thrombosis, call into question the current practice of offering fibrinolysis as first-line therapy. In addition, the large number of patients recruited over a relatively short period of time from a single center in India highlights the huge burden of prosthetic valve thrombosis in developing countries.
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