

Guidelines for Management of Left-Sided Prosthetic Valve Thrombosis: A Role for Thrombolytic Therapy

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Objectives. We sought to form a consensus recommendation for management of prosthetic valve thrombosis (PVT) from previous case and uncontrolled reports from a consensus of international specialists.

Background. PVT and thromboembolism relate to inadequate anticoagulation and valve type and location. PVT is suspected by history (dyspnea) and auscultation (muffled valve sounds or new murmurs) and confirmed by Doppler echocardiography showing a marked valve gradient.

Methods. A consensus conference was held to recommend management of left-sided PVT.

Results. Transesophageal Doppler echocardiography is used to visualize abnormal leaflet motion and the size, location and mobility of thrombus. Thrombolysis is used for high risk surgical candidates with left-sided PVT (New York Heart Association functional class III or IV) because cerebral thromboembolism may occur in 12% of patients. Duration of thrombolysis depends on resolution of pressure gradients and valve areas to near

normal by Doppler echocardiography performed every few hours. Lysis is stopped after 72 or 24 h if there is no hemodynamic improvement (operation indicated). Heparin infusion with frequent measurement of activated partial thromboplastin time (aPTT) begins when aPTT is more than twice control levels and can be converted to warfarin (international normalized ratio [INR] 2.5 to 3.5) plus aspirin (81 to 100 mg/day). Patients in functional class I or II have lower surgical mortality, and those with large immobile thrombi on the prosthetic valve or left atrium have responded to endogenous lysis with combined subcutaneous heparin every 12 h (aPTT 55 to 80 s) plus warfarin (INR 2.5 to 3.5) for 1 to 6 months. Operation is advised for nonresponders or patients with mobile thrombi.

Conclusions. Thrombolysis, followed by heparin, warfarin and aspirin, is advised for high risk surgical candidates with left-sided PVT.

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Inadequate anticoagulation in patients with mechanical heart valves can result in a significant incidence of thromboembolism. The incidence of prosthetic valve thrombosis (PVT) and total thromboembolism (thrombolism with permanent deficit or transient ischemia) during warfarin (Coumadin) therapy is

dependent on valve type and location and especially adequacy of anticoagulation and averages 0.2% and 1.8%/patient-year, respectively (1). The incidence of PVT may be as high as 13% in year 1 or 20% overall in patients with tricuspid valve prostheses and 0.2% to 6%/patient-year in those with aortic or mitral valve prostheses (2,3). Operation has been the traditional treatment for PVT. However, reported operative mortality rates range between 0% and 69%, largely depending on clinical functional class (3-5). Fibrinolytic therapy is an alternative to surgical treatment (3,6-15) and is considered the treatment of choice for tricuspid PVT (16,17). However, because of the high risk of cerebral thromboembolism during thrombolysis for left-sided PVT, its use is reserved for high risk surgical candidates (4,18-23); the use of thrombolysis in low risk patients remains controversial. A search of at least 200 published reports of left-sided prosthetic valve thrombolysis showed an 82% initial success rate, an overall thromboembolism rate of 12%, and a stroke rate of 5% to 10%, with 6% death, 5% major bleeding episodes and 11% recurrent throm-

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Abbreviations and Acronyms

aPTT	=	activated partial thromboplastin time
CT	=	computed tomographic
INR	=	international normalized ratio
LA	=	left atrial
PVT	=	prosthetic valve thrombosis
rt-PA	=	recombinant tissue-type plasminogen activator
SK	=	streptokinase
TEE	=	transesophageal Doppler echocardiography (echocardiographic)
TIA	=	transient ischemic attack
UK	=	urokinase

bosis (3-6,9-15,18-35). The larger studies are summarized in Table 1.

Thus, there is a need to define indications and management guidelines for thrombolytic therapy with left-sided PVT on the basis of benefit and risk of thrombolytic and antithrombotic therapy that takes into account the functional class of the patient, left ventricular function and overall operative risk. Optimal antithrombotic treatment to prevent thromboembolic complications also needs definition. Transesophageal Doppler echocardiography (TEE) has recently been reported to be the diagnostic technique of choice for selecting and monitoring candidates for safe and efficacious thrombolytic treatment of mitral PVT (9,11,12,25-28,36,37). Some investigators use cinefluoroscopy (14). A consensus conference was therefore convened to formalize practical guidelines for the management of left-sided aortic and mitral PVT.

Diagnosis of Left-Sided PVT

Clinical presentation of patients with left-sided PVT: definition of groups. *Group 1* includes patients with clinically silent PVT diagnosed by TEE performed for some other clinical reason. *Group 2* includes patients with PVT and stroke or TIA or peripheral systemic embolism. *Group 3* includes patients with hemodynamic symptoms and evidence of valve

obstruction (most common). *Group 4* includes patients with both systemic embolism and hemodynamic evidence of valve obstruction. Patients in Group 1 or 2 have usually mild symptoms related to PVT (New York Heart Association functional class I or II). They may have other causes of cardiac symptoms, such as left ventricular dysfunction, tricuspid regurgitation or atrial fibrillation with uncontrolled ventricular rate. Patients in Groups 3 and 4 are usually more symptomatic (functional class III or IV, critically ill) (3,8,14).

Diagnostic approach and tests for PVT. Clinical evaluation includes history for type, severity and duration of symptoms; auscultation; electrocardiogram; and chest radiograph. Signs and symptoms of infective endocarditis should be sought. Previous adequacy of anticoagulation should be defined.

The auscultatory findings of muffled prosthetic valve sounds or murmurs can be of great value; however, auscultation may be unreliable if the obstruction is partial, as with a bileaflet valve or in the presence of another normally functioning prosthesis (15).

Cinefluoroscopy assesses restriction of leaflet motion and opening and closing angles, complements TEE and is limited to radiopaque disc or bileaflet valves (14,24).

TEE may visualize restricted prosthetic valve leaflet motion. It images thrombus on the atrial but rarely on ventricular surface of mitral prosthetic valves (3). An eccentric and narrow mitral inflow jet by color Doppler echocardiography raises suspicion of partial valve obstruction.

Measurement of Doppler echocardiographic hemodynamic variables is essential for assessment of obstructive PVT by measurement of gradients and valve area (8,11,13,19,20). A flow-dependent Doppler gradient is insufficient for diagnosis, unless the gradient is very high. A Doppler gradient may significantly overestimate the hemodynamic situation in the aortic position, particularly with small prostheses and with St. Jude valves (38). There is a significant variety of normal gradient and area values even within the same valve type and size (39). To avoid misinterpretation of patient or prosthesis hemodynamic variables, most investigators now recommend baseline postoperative/predischarge/Doppler measurements

Table 1. Thrombolytic Treatment for Thrombosed Left-Sided Prosthetic Valves

Report Date (ref no.)	No. of Pts	No. of Episodes	Site AV/MV	TE or Stroke	Reop	Death	
						Lysis	Postop
1988 (21)	58	62	23/39	11	14	6	4
1992 (3)	63	74	33/41*	11	11	9	2
1993 (14)	12	12	9/3†	0	0	0	0
1994 (8)	38	44	5/40‡	0	0§	5	0
1994 (12)	8	8	1/7	1	0	0	0
Total	179	200	71/130	23 (12%)	25	20 + 6 = 26	

*Immediate efficacy better for aortic valve (AV) (85%) than for mitral valve (MV) (63%). †All St. Jude (bileaflet) valves; diagnosis and follow-up primarily by cinefluoroscopy. ‡One episode involved both aortic and mitral valves, 43/45 bileaflet valves. §Patients could not afford reoperation. ||Four of five patients presented with shock and one with pulmonary edema; all five failed to respond to thrombolysis. Postop = postoperative; Pts = patients; ref = reference; Reop = reoperation; TE = thromboembolism.

(40,41). Increased gradients may be caused by other hemodynamic factors unrelated to prosthetic valve malfunction, such as tachycardia, residual subaortic septal hypertrophy or high cardiac output, such as may be caused by anemia.

TEE is recognized by many as the technique of choice for visualizing not just prosthetic valve leaflet motion abnormalities (which may be more difficult in the aortic position) but also for determining the etiology (38-41). Size, location and mobility of the thrombus can be visualized. In addition, TEE can detect thrombi in the body or appendage of the left atrium. Monoplane TEE has a much lower diagnostic accuracy than biplane or multiplane TEE. Fluoroscopy in the proper projection may be considered for initial screening of mechanical bileaflet valve motion (3,14,24).

Laboratory studies. Current and previous prothrombin times (measured as international normalized ratios [INRs]) may provide important clues to the diagnosis of PVT. In the febrile patient, blood cultures should be drawn. A complete blood count, including platelet count, activated partial thromboplastin time (aPTT) and fibrinogen and D-dimer levels should be determined as baseline values for possible subsequent heparin or fibrinolytic therapy. Because the patient may need urgent operation, additional baseline studies should be obtained. In patients with stroke, TIAs or history of cerebral events, magnetic resonance imaging or a computed tomographic (CT) of the brain can effectively differentiate between hemorrhagic and ischemic stroke and also helps to rule out nonvascular lesions. Absence of blood on early magnetic resonance imaging or CT is important information supporting the diagnosis of ischemic stroke in patients with a stroke syndrome (42).

Indications for Thrombolysis

Thrombolytic treatment of left-sided PVT has been accepted for critically ill patients in functional class III or IV in whom surgical intervention carries high risk or in patients with contraindication to operation (18). The reasoning against thrombolysis in patients in functional class I or II is based on the relatively low surgical mortality in this group as opposed to the embolic risk of 12% to 17% caused by thrombolysis (3,15,18,43). Reports of thrombolytic treatment in 32 patients presenting in functional class I or II show an 88% success rate, 3% (1 patient) major stroke rate and zero mortality (3,9,11,13-15,26,27), whereas the lowest surgical mortality rate in a similar group has been reported as 5%. The experience with heparin treatment of nonobstructive PVT has been reported in 19 cases (9,27) with a 63% success rate, 2 cases of minor cerebral embolism and 1 case (5%) of fatal stroke. An alternative approach used successfully by some investigators in functional class I or II patients with a large amount of thrombus takes advantage of the different antithrombotic actions of heparin and warfarin and their enhancement of longer term endogenous lysis. The use of subcutaneous heparin (every 12 h, aPTT 55 to 80 s) plus warfarin (INR 2.5 to 3.5)

Table 2. Contraindications to Thrombolysis

Absolute contraindications	
	Active internal bleeding
	History of hemorrhagic stroke
	Recent cranial trauma or neoplasm
	Blood pressure >200/120 mm Hg
	Diabetic hemorrhagic retinopathy
Relative contraindications	
	Recent (within 10 days) gastrointestinal bleeding
	Recent (within 10 days) puncture of noncompressible vessels
	Recent (within 2 mo) nonhemorrhagic stroke
	Infective endocarditis
	Uncontrolled severe hypertension
	Large thrombus in left atrium or on prosthesis
	Recent (within 2 wk) major operation or trauma
	Known bleeding diathesis
	Previous exposure to streptokinase or APSAC (contraindication to reuse any streptokinase-containing agent)

APSAC = anistreplase (anisoylated plasminogen streptokinase activator complex).

for ~3 months usually dissolves moderate amounts of residual thrombosis.

Patients with mitral or aortic PVT documented by TEE with Doppler flow obstruction and functional class III or IV symptoms should be treated with fibrinolysis if the surgical risk is high and there is no contraindication. Surgical therapy is an alternative for patients in functional class III or IV not at high surgical risk. In addition, obstruction due to endocarditis with abscess formation and usually very large thrombi with obstruction or mobile masses are indications for operation. The benefit and risk of the many factors of the individual patient must be balanced against the expertise and experience at each center to arrive at a decision for thrombolysis or operation (4).

Nonobstructive PVT in patients presenting in functional class I or II (Groups 1 and 2) may be treated with intravenous heparin by continuous infusion for 48 h. If patients remain hemodynamically stable and thrombus is not dissolved (not unusual), intravenous infusion can be converted to subcutaneous injection (overlap infusion for 2 h after injection, average dose from five studies is 17,000 U subcutaneously every 12 h) (44) and combined with warfarin (INR 2.5 to 3.5) for 1 to 3 months on an outpatient basis to allow endogenous thrombolysis. Combined warfarin and subcutaneous heparin are especially helpful for consistent antithrombotic therapy in the patient with a variable INR. Initial experience suggests a very low risk for bleeding. With complete or nearly complete resolution of thrombus, the need for operation may be avoided. Valve types (all may thrombose) or the suspected duration of valve thrombosis does not influence the choice of, or indications for, treatment (3,8,12,14,21).

Contraindications to Thrombolysis

Contraindications to thrombolysis are shown in Table 2. Pregnancy is generally considered a relative contraindication. However, when there is great danger to the patient, the

advantages and disadvantages of fibrinolysis should be considered. There have been at least four reported cases (3,15,29) in which fibrinolysis was successfully used during pregnancy, with no harm to the fetus.

Left-sided intracardiac thrombus has previously been considered a relative contraindication to thrombolysis. Patients with large thrombotic material attached to the prosthetic valve or in the left atrium are probably at increased risk of major embolism and stroke when treated with thrombolytic therapy (30). Although a few reports of successful thrombolysis of left atrial (LA) clots have been published (43,45), a large LA thrombus should be ruled out by TEE before the start of thrombolytic treatment. Early postoperative (at least by the tenth postoperative day) successful thrombolysis has also been reported (27,34,43) with no contraindications in a small number of cases. However, adequate and prolonged anticoagulation with heparin and then warfarin for 3 to 6 months for large, nonobstructive thrombi will usually lead to dissolution by endogenous thrombolysis, as seen by Doppler echocardiographic follow-up of individual patients with valvular or LA thrombi by the authors (M.L., V.F., J.S., J.C.).

Thrombolytic Agent, Dosage Duration and Monitoring of Treatment

Streptokinase (SK) and urokinase (UK) have been the most commonly used fibrinolytic agents; there was no statistically significant difference in their success rates (18). Patients with known allergy to SK or those who have been exposed previously to SK should be given UK (43). The recommended dosage of SK is a 250,000-U bolus given in 30 min, followed by an infusion of 100,000 U/h. UK is given as in pulmonary embolism: 4,400 U/kg per h (43). The use of recombinant tissue-type plasminogen activator (rt-PA) has also been reported in doses used in the treatment of pulmonary embolism, but it is more costly, and no advantage of rt-PA for valve thrombosis has been demonstrated over SK or UK. Indeed, rt-PA may increase risk; two fatal strokes and one additional death occurred in 21 patients treated for PVT with rt-PA (3,12,26,30,31,46). However, superior results of rt-PA compared with those for SK in patients with acute stroke are discussed later.

Duration of administration of thrombolytic agents depends on the achievement of an improved hemodynamic effect or the disappearance of thrombus. In obstructive PVT, Doppler echocardiographic (performed every 2 to 3 h) is recommended for hemodynamic monitoring. Thrombolytic infusion should be stopped when values of pressure gradient and valve area return to normal or near normal. If there is no normal baseline value for a given patient and the result is equivocal, repeat TEE is recommended. In nonobstructive cases, TEE is the only technique that is useful for monitoring treatment. TEE should be performed at 24 h and if thrombus is still present, should be repeated at 48 and at 72 h if necessary. Duration of thrombolytic treatment has varied between 2 and 120 h (13,21). The

administration of lytic agent should be stopped if there is no hemodynamic improvement at 24 h or after 72 h, even without complete hemodynamic recovery. If D-dimer and aPTT do not increase, and fibrinogen does not decrease at 24 h of lytic treatment (failure to document a lytic state), the infusion can be discontinued. If SK was used, UK may be tried because antibodies to SK may have prevented its action.

In case of unsuccessful thrombolysis, operation is indicated and can be performed 24 h after the discontinuation of the infusion (34) or 2 h after fibrinolytic activity has been neutralized by protease inhibitors (15).

Management of Complications

Low rates of thromboembolism are reported for lysis of bileaflet valves (Table 1).

Peripheral embolism. Thrombolytic and then antithrombotic therapy should be continued, irrespective of the hemodynamic results, to dissolve the peripheral embolus. Severe peripheral embolism with persistent symptoms despite lysis should be treated by embolectomy.

Cerebral embolism. The efficacy of early thrombolytic treatment of acute stroke for improvement at 3 months has been established for patients not receiving anticoagulant therapy, with no bleeding and no or only minor early signs of infarction on the initial CT scan. They are treated with short-term (1 h) rt-PA therapy within 3 h of onset (47). Treatment <6 h from onset targeted another specific group with moderate to severe hemispheric stroke (48-50). Two large randomized trials of intravenous SK treating most patients >3 h after onset of stroke were stopped early because of unacceptable rates of intracranial hemorrhage (51,52). Another trial showed no significant benefit for combined fatality and severe disability at 6 months (53).

Thrombolytic treatment should be discontinued if neurologic symptoms of stroke develop. A CT scan of the brain should be urgently obtained to rule out hemorrhage. If the stroke is nonhemorrhagic, anticoagulant treatment may be administered. If the second CT scan performed 36 to 48 h after the stroke still rules out brain hemorrhage, operation may be performed 72 h after the stroke.

Bleeding. Minor bleeding is anticipated at puncture or incision sites. If bleeding occurs, local pressure should be applied to control it. Severe internal bleeding involving intracranial, gastrointestinal, genitourinary, retroperitoneal or previous puncture sites can occur and result in fatalities. If major bleeding occurs, the thrombolytic infusion should be immediately terminated. If necessary, bleeding can be reversed with fresh-frozen plasma or more rapidly with prothrombin complex concentrate containing Factor VII and blood loss managed with appropriate replacement therapy.

Anticoagulant treatment. During thrombolytic treatment, adjuvant anticoagulant therapy is not recommended. Administration of warfarin should be discontinued during thrombolysis. There is usually no need to reverse its effect by vitamin K. At the end of thrombolytic therapy, treatment with heparin by

continuous infusion is recommended to prevent recurrent thrombosis. Heparin treatment without a loading dose should begin when the aPTT has decreased to less than twice the normal control (or baseline) value. Heparin dosage is considered adequate if the aPTT is 1.5 to 2 times normal (55 to 80 s). The average dosage to achieve this effect is 20,000 to 40,000 U/24 h. The initial heparin dosage is usually 1,300 U/h (54). Because of rapidly changing levels of fibrinogen and heparin binding proteins over the first 24 to 48 h after stopping thrombolysis, the aPTT should be checked four times every 6 h and three times every 8 h, then daily. Conversion to oral anticoagulant treatment is performed in the usual manner, by starting warfarin simultaneously with heparin (55).

Management of patients after successful thrombolytic treatment. Anticoagulation is targeted to an INR of 2.5 to 3.5 according to the standard recommendations (56), and the addition of aspirin (81 to 100 mg daily) is strongly recommended (57). Close follow-up of anticoagulant control is necessary, along with clinical assessment and Doppler echocardiography on an individual basis. Doppler echocardiography should be performed at least monthly during the first 6 months, then every 6 months.

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