

Recommendations for the Management of Prosthetic Valve Thrombosis

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Prosthetic valve thrombosis (PVT) is a life-threatening disease, for which treatment strategies have been controversial. Herein, existing data on management options are reviewed, and conclusions drawn as to the choice and use of treatment strategies for PVT. The use of transesophageal echocardiography (TEE) allows distinction to be made between obstructive and non-obstructive PVT by the presence or absence of occluder motion limitation. The differentiation of PVT from pannus and vegetation is, however, still limited by TEE. The incidence of PVT has been underestimated by not taking into account a large percentage of non-obstructive PVT. Although the standard treatment for PVT has been surgery, thrombolysis has lower mortality rates, particularly in patients in NYHA functional classes III-IV. The lowest complication rates with thrombolysis have been achieved in patients with non-obstructive PVT. Pregnancy, left atrial appendage thrombi and large PVT are not contraindications to thrombolysis. The

third therapeutic option is anticoagulant therapy. The detrimental effect of anticoagulant treatment in obstructive PVT was shown in a prospective study. Non-obstructive thrombi of >5 mm length have been treated with higher success rates and lower complication rates by thrombolysis than by anticoagulant treatment. In conclusion, all patients with suspected PVT should undergo multiplane TEE. Thrombolysis is the first-line treatment for obstructive PVT, independent of NYHA class and thrombus size if there are no contraindications. Serial TEE studies must be conducted during thrombolysis. Surgery should be reserved for those patients in whom thrombolysis is contraindicated, or has failed. Initial anticoagulant therapy is recommended only for small, non-obstructive PVT if anticoagulation had been subtherapeutic; otherwise, thrombolysis is the treatment of choice if there are no contraindications.

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Recommendations and evidence

It is of utmost importance that recommendations are presented in formats which are easily interpreted. Therefore, recommendations are based on available evidence.

The strength of recommendation (by class), and relevant definition are as follows:

Class I: Evidence and/or general agreement that a given treatment or a diagnostic approach is beneficial, useful, and effective.

Class II: Conflicting evidence and/or divergence of opinions about the usefulness/efficacy of a treatment or a diagnostic measure:

IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

IIb: Usefulness/efficacy is less established by evidence/opinion.

Class III: Evidence or general agreement that the treatment/diagnostic measure is not useful/effective, and in some cases may be harmful.

Likewise, levels of available evidence are as follows:

Level A: At least two randomized trials supporting the recommendation.

Level B: Single randomized trial and/or a meta-analysis of non-randomized studies supporting the recommendation.

Level C: Consensus opinion of experts based on trials and clinical experience.

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To date, for the management of prosthetic valve thrombosis (PVT), no randomized clinical trials have

been conducted, and thus there is no level A evidence. However, many single-center reports, case reports and even one multicenter report (1) are available. These reports provide data which can support class I recommendations, while some conflicting results and opinions will result in Class II recommendations. Furthermore, an attempt has been made to provide a meta-analysis of available data (2).

Introduction

Prosthetic valve thrombosis is a life-threatening disease for which treatment strategies have been controversial. Traditionally, the treatment of choice was surgical, but post-surgical mortality has been as high as 69%, depending on the patients' functional class (NYHA) and the urgency of the operation (3-5). In fact, mortality was about 5% even in NYHA class I-II patients (6). These results led to the introduction of thrombolysis, which was first reported for left-sided valves in 1974 (7). Arguments against thrombolysis in thrombosed left-sided valves include the risk for systemic embolism, bleeding and the potential high recurrence rate. This may be the reason why, even in the latest guidelines, the management of thrombosed mitral and aortic valves has been reserved for patients with a high operative risk (NYHA class III-IV) (8,9). On the other hand, thrombolysis is well accepted for thrombosed valves in the tricuspid and pulmonary positions (8,10).

According to these recommendations, another therapeutic option - anticoagulation therapy starting with intravenous heparin for 48 h and followed by a combination of subcutaneous heparin and warfarin for one to three months - may be considered (9). More recently, a number of reports have been published suggesting a more aggressive and widespread use of thrombolysis (10-15). In the absence of randomized studies, the efficacy and safety of thrombolysis is not unanimously accepted, and therefore indications and contraindications are still not well established. The

goal of these recommendations is to review existing data and to draw conclusions as to the choice and use of treatment strategies for left-sided PVT.

Definitions of PVT

The definition of PVT depends on the diagnostic approach, whether PVT is documented during surgery, autopsy, or non-invasive imaging using transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) or cinefluoroscopy (CF). Multislice computed tomography (CT) may be a powerful additional technique in the near future.

The definition of PVT has been: (i) any obstruction of a prosthesis by non-infective thrombotic material; or (ii) valve-related clotting impairing the function of the valve as diagnosed at operation or autopsy (16). This definition neglects non-obstructive PVT (17,18), while 'prosthetic valve obstruction' (19) or 'stuck prosthetic valve' (14) cover different pathologies (thrombus, pannus, vegetation). TEE allows a more precise definition (20):

prosthetic valve obstruction: limited occluder motion.

obstructive PVT: limited occluder motion by thrombus.

non-obstructive PVT: thrombus, but normal occluder motion.

Diagnosis

Clinical presentation

PVT must be suspected in all patients who are at risk and who present with recent changes in clinical symptoms, initially dyspnea, arrhythmia, pulmonary edema, cardiogenic shock and/or systemic embolism. However, symptoms may progress slowly over months.

On auscultation, prosthetic clicks are muffled or absent, while murmurs of obstruction and/or of regurgitation may be heard and documented early by appropriate sound spectroscopy (21-23). Non-obstructive PVT may cause stroke or peripheral embolism, but may be asymptomatic in almost one-half of the cases (12,16).

Imaging techniques

Any relevant transprosthetic gradient is first assessed using Doppler echocardiography. It should be considered that paravalvular regurgitation, prosthesis-patient mismatch, tachycardia and high stroke volume may increase transvalvular gradients (24). Restricted occluder motion is most rapidly diagnosed by CF (25-28), although this technique cannot add any information with regard to the etiology. By contrast, TEE demonstrates not only a limited occluder motion but

Table I: *Diagnosis of prosthetic valve thrombosis (PVT) by transesophageal echocardiography (TEE).*

Obstructive PVT
- abnormal leaflet motion
- thrombus
- abnormal central regurgitation
- missing
- increased
Non-obstructive PVT
- normal leaflet motion
- thrombus

also the causative mass and the absence or increase of normal transprosthetic regurgitation (12). Coexistent left atrial thrombi may also be seen. Non-obstructive PVT can be diagnosed by multiplane TEE only (29) (Table I). Laboratory findings provide unspecific information only.

Differentiation between obstructive PVT and pannus

Obstructive PVT and pannus may have similar morphology and result in similar functional abnormalities. They coexist in more than 50% of cases (6). Thrombus, however, is more common in patients with inadequate anticoagulation (3,28), or thromboembolic risk factors (mitral position, left ventricular dysfunction, atrial fibrillation, older valve designs, hypercoagulable state, pregnancy) (28,30), early postoperatively (31-33) and if larger and softer masses are detected by TEE (34). Successful lysis is another proof of thrombus versus pannus (35). Partially successful lysis may be consistent with a combination of thrombus and pannus. Intermittent obstruction is more likely to be caused by tissue ingrowth (35,36). The absence of a mass in obstructive PVT suggests pannus, although a thrombus inside the prosthetic valve orifice may also be present.

Differentiation of PVT versus vegetation

Compared with pannus, there are still more similarities between thrombus and vegetation in both obstructive and non-obstructive PVT. The presence of vegetations in suspected infective endocarditis (IE) is supported by fever and other clinical signs of IE. However, fever may accompany PVT (12,37), indicating a link between inflammation and thrombus formation. The presence of perivalvular extension (leak or abscess formation) confirms the suspicion of IE (20).

Limitations of TEE

Although TEE has been accepted as the imaging technique of choice (8) for the diagnosis of PVT, there are three potential limitations: an aortic location; differentiation from pannus and vegetations. In the aortic location, limited leaflet motion and thrombus sometimes cannot be visualized reliably by TEE (38), and therefore CF should be performed in addition if TEE findings are uncertain. Centers with a low mortality with reoperations for prosthetic valve obstruction due to unlimited availability of circulatory support systems recommend only CF for the documentation of occluder malfunction (28). CF may also be used for monitoring thrombolytic therapy (25-27). Severe central aortic regurgitation (as shown with TTE) is a strong indicator of restricted valve motion.

Algorithm for the management of PVT

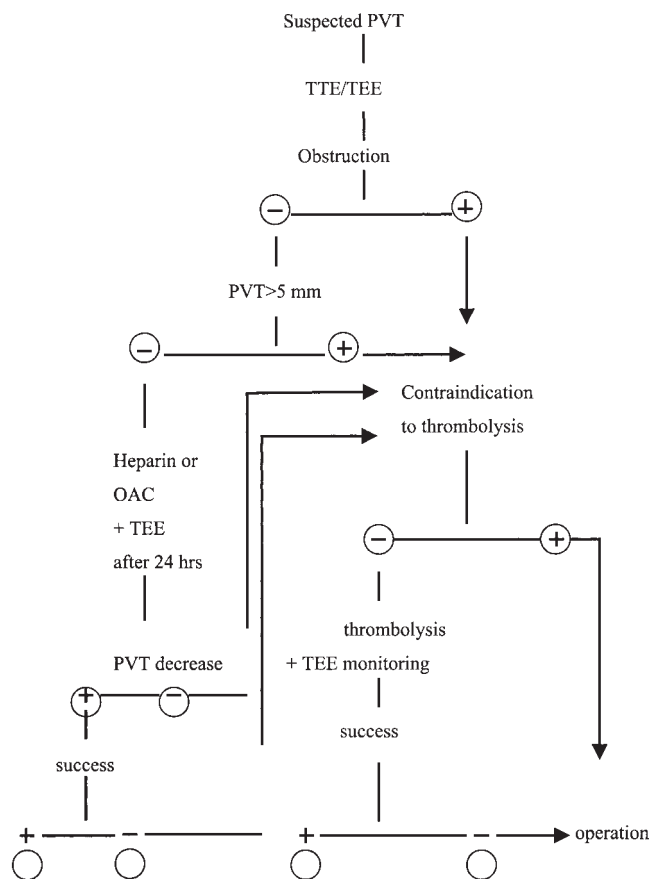


Figure 1: An algorithm for the management of prosthetic valve thrombosis (PVT). OAC: Oral anticoagulant therapy; TEE: Transesophageal echocardiography; TTE: Transthoracic echocardiography.

Epidemiology

The incidence of prosthetic valve-associated thromboembolism despite oral anticoagulation treatment is 1 to 4% per year (39). The true incidence of PVT however is unknown, as data are mostly based on autopsy and intraoperative findings and may not include non-obstructive PVT. It has been reported that 40% of all PVT cases were non-obstructive, and 45% of cases were identified by TEE in asymptomatic patients (12). The indication for TEE in such cases were inadequate anticoagulation, mildly elevated transvalvular gradients and/or early postoperative screening (17,18). A literature search (from 1992 to 1999) revealed an average 10% prevalence of PVT with routine postoperative screening in about 1,000 patients (17,18,31-33). The difficulties of early postoperative anticoagulation and the management of such complications are clearly reflected in these reports (40). Not surprisingly, some of these

Table II: Predictors of thrombolytic success and safety.

Yes	No
NYHA class	Prosthesis type and location
Obstruction	Thrombolytic protocol
Symptom duration	Thrombus size
	Recurrent PVT

authors strongly recommend routine TEE before discharge after valve replacement (31).

Treatment

Surgery

Although in the past the standard treatment for PVT has been surgery, perioperative mortality has been reported to be high, at 43 to 69% (3,4). Mortality was 51% for PVT as opposed to 14% for pannus (5), and much higher in NYHA class IV than in class I-III patients (6). The long-term survival for NYHA class IV patients, particularly with PVT of the aortic prosthesis, was extremely low (3).

Thrombolysis

Thrombolysis for left-sided PVT was introduced in 1974 (7). A review of the English literature containing more than 50 reports with more than 500 cases was presented in a recent meta-analysis (12).

The majority were case reports, whilst the largest studies included 110 (37,41), 127 (42) and 43 (12) cases. The overall success rate was 84%, and the recurrence rate 16%. Systemic embolisms were reported in 9% of cases, and disabling or fatal strokes in only 1.5%; all of the latter occurred in NYHA class III-IV patients. The risk for major bleeding was 3%, and mortality was 5%. In most reports, obstructive and non-obstructive PVT were not distinguished, but the success rate in NYHA class I-II patients tended to be higher (92%) than for NYHA class IV (81%), with no mortality versus 7% ($p = 0.04$). In recurrent PVT, rethrombolysis was performed with a 75% success rate. With recurrent unsuccessful thrombolysis, pannus was a frequent intraoperative finding (12).

When patients operated on between 1974 and 1995 ($n = 235$) were compared to those operated on between 1996 and 2001 ($n = 234$), the success rates were 77 versus 90%, thromboembolism rates 13 versus 4%, mortality 7.5 versus 3.5%, bleeding risk 5 versus 1.4%, and recurrence rates 13 versus 20%. In a large single-center study (1994-2000), the success rate was 86%, while embolism occurred in 9% of patients, bleeding in 2%, death in 5%, and recurrence in 22% (12).

The favorable results with thrombolysis which were

recently documented may be due to the more extended use of multiplane TEE (1,12).

The only multicenter ($n = 14$) PRO-TEE study performed between 1985 and 2001 included 107 patients. The success rate was 85%, while complications occurred in 17.8% of patients and death in 5.6% (1). In the largest single-center study reporting 127 PVT cases between 1978 and 2001, the success rate was 88% (including partial success in 17%), and major bleedings were observed in 5% of patients, embolism in 15%, and death in 12% (42).

Thrombolytic treatment protocols

In most studies, streptokinase (SK) was administered at a dosage traditionally used for pulmonary embolism: a loading dose of 250,000 IU over 30 min, followed by 100,000 IU/h for up to 72 h or until the occurrence of any severe complication (bleeding or stroke) or normalization of valve motion or the disappearance of valve thrombus or a fall of fibrinogen level to zero (9). Short-term, high-dose SK treatment (1,500,000 U in 90 min) was reported in some left-sided PVT cases (43). Urokinase (UK) has often been used as a secondary option after previous SK, with a loading dose of 4,400 U/kg over 30 min, followed by 4,400 U/kg bodyweight per hour. Recombinant tissue plasminogen activator (rt-PA) has been relatively rarely used, mostly in critically ill patients utilizing an accelerated protocol: a bolus of 15 mg followed by 85 mg infused over 90 min (44,45), or 10 mg bolus followed by 50 mg infused over the first hour, and 20/20 mg infusions in the second and third hours (46).

Both SK and rt-PA were more effective than UK (42). A series of two or more fibrinolytic agents was used in one third-of patients in a large single-center study when the first course failed or success was incomplete (42). Long-term thrombolytic treatment in obstructive PVT requires TTE monitoring (every 2-5 h) in all cases, and TEE monitoring is recommended every 24 h.

Predictors of thrombolytic success

The efficacy and safety of thrombolysis may depend on several factors (Table II), including NYHA functional class, obstructive versus non-obstructive PVT, duration of symptoms, type and site of prosthesis, thrombolytic protocol, size of the mass, and initial or recurrent PVT.

In NYHA class IV patients the success rate was lower (79%) than in class I-III patients (91%). All fatalities and all disabling strokes occurred in class IV patients (12).

Non-obstructive PVT represents a special subgroup of patients in which the NYHA functional class is usually low but ischemic stroke is frequent. In one large single-center study, only 11 of 43 patients treated with

Table III: Specific contraindications to thrombolysis.

Yes	No
Large left atrial thrombus	Left atrial appendage or mural thrombus
Ischemic stroke 4 h to 4-6 weeks	Acute ischemic stroke <4 h
Early postoperative period <4 days	Early postoperative period >4-10 days
	Pregnancy

thrombolysis were non-obstructive cases (12).

The reason for the relatively small number of non-obstructive cases reported in the literature (18,29,33) apparently is a recent stroke, a contraindication to thrombolysis. There were no strokes or fatalities as compared to the rate of 5-10% reported for obstructive PVT in the literature.

The supposed duration of PVT of less than 14 days has been considered to increase the success rate (47,48). Others, however, could not identify any relationship between the duration of symptoms and the success of thrombolysis (12,49). The longest period of symptom persistence in an ultimately successful thrombolysis has been reported as 180 days (49).

In a recent report, leaflet immobility and thrombolytic failure were strongly related to symptom duration longer than 21 days. However, lysis appeared to be successful regardless of symptom duration if the leaflets were only hypomobile (50).

Prosthesis type and the time since valve implantation had no influence on thrombolytic success (49). Success was more likely if the thrombus was visualized (12). The choice of thrombolytic agent did not affect the results, but there were more embolic complications with the use of t-PA (45,46,51,52). The efficacy and safety of short-term, high-dose SK administration is controversial (13,43); some authors consider the success rate to be slightly higher in the aortic than in the mitral position (19,52,53), though others could not confirm this observation (37,42).

The predictive role of thrombus size has been controversial. A thrombus area $>0.8 \text{ cm}^2$ as measured by TEE was considered to be predictive for complications, irrespective of NYHA class (1). However, one limitation of this study was its retrospective design and the high proportion of obstructive thrombi (90%) (1) for which the correct measurement of thrombus size is generally not feasible (2).

Non-obstructive PVT, on the other hand, could be successfully and safely thrombolysed, even if the thrombus length was up to 13 mm (12,42).

The results of rethrombolysis after PVT recurrence were comparable to those obtained after the first thrombolysis (12,42).

Contraindications to thrombolysis

In addition to general contraindications for thrombolysis (8), some specific contraindications in patients with left-sided PVT may be considered. These include large PVT, left atrial thrombi, ischemic stroke at presentation and early postoperative period (Table III).

In order to minimize embolic risk, recent guidelines (8,9) and one large review (19) have recommended thrombolysis to be carried out only in the absence of large intracardiac thrombi. The size of obstructive thrombi is difficult to measure as they are sessile and located within the valve orifice, but large mobile thrombi were successfully thrombolysed without subsequent embolism (12).

There is only one case report of a large mobile atrial thrombus treated with low-dose thrombolysis and without embolic consequences (55). Mural thrombi located in the left atrial appendage have been reported with and without embolic complications (13,43,46,47).

Other relative contraindications may be pregnancy, early postoperative period or previous non-hemorrhagic stroke. Seven patients have been reported in the literature who were treated with thrombolysis during pregnancy for PVT, all with success (7,42,52,56,57,58). One of these patients was even in the first trimester, had no complications, and had a normal delivery after nine months' gestation (58).

Early postoperative thrombolysis was reported as soon as four days after valve replacement (31,33,59), without complications. Twenty cases of non-hemorrhagic stroke or transient ischemic attack (TIA) have been treated with thrombolysis, with only one hemorrhagic transformation (12,13,14,44,46,60).

Children can also be treated successfully with thrombolysis for PVT (61).

One potential problem of thrombolysis is the risk of delayed surgery if thrombolysis fails, or if only partial success can be achieved. In critically ill patients, surgery can be performed 2 h after fibrinolytic therapy has been neutralized by protease inhibitors (60). In most cases, however, the partial relief of obstruction leads to a hemodynamic stabilization and hence better surgical outcome (49).

Heparin or oral anticoagulant treatment of PVT

In obstructive PVT, anticoagulant treatment failed in all reports, with an overall mortality rate of 10% (12,14,17,33,38). Although in non-obstructive PVT the success rate is 60%, mortality is similar (9%), and incidences of 7% for stroke and 17% for newly developing valve obstruction have been reported (14,17,18,33,41).

Non-obstructive PVT is a unique entity, in which the patients are clinically stable. Treatment aims to prevent embolism. In addition, almost half of these patients present with or after stroke (12), at which time thrombolysis is generally contraindicated. Therefore, initial anticoagulant treatment is justified (9,33). The success and complication rates are apparently related to thrombus size: for thrombi of <5 mm diameter the success rate was 82%, whilst stroke and TIA rate rates were 4% and 8%, with no deaths. For thrombi of ≥5 mm diameter, the reported success was 61%, while stroke occurred in 23% of patients and death in 38% (17,33).

The duration of treatment with either heparin or oral anticoagulation remains unclear. It seems reasonable to start heparin treatment in non-obstructive PVT if the thrombus size is <5 mm at baseline TEE. If TEE performed after 48 h does not show any increase in mass or obstruction, then heparin may be continued and TEE repeated every two to three days for up to 10 days. If there is progression of the PVT mass, then any further strategies undertaken will depend on the patient's cerebral status. Those who had suffered stroke (as indicated by cerebral CT scans) should undergo surgery, while those who had not, may be switched to thrombolysis. Patients with a small or decreasing brain infarct can be treated for longer with anticoagulants and may be switched to thrombolysis if necessary after six to eight weeks.

Comparison of treatment strategies

Thrombolysis and surgical treatment were directly compared in three studies. In eight cases of obstructive PVT there was complete success without complications with t-PA treatment, but there was one death among 20 NYHA class III-IV patients who underwent surgery (47).

In an intention-to-treat analysis in obstructive PVT, there was no mortality among 19 patients treated with thrombolysis, while five out of 11 surgical patients died (62). In another intention-to-treat analysis of

obstructive PVT and NYHA class IV, the mortality of thrombolysis was 13%, that of surgery 33%, whilst on-treatment basis thrombolysis mortality was 5%, and surgical mortality 30% (12). A review of the literature showed overall mortality among 89 patients in NYHA class IV to be 7% when utilizing thrombolysis (12,41) and ranging from 17 to 54% in operated patients (3-6), whereas in NYHA class I-III patients mortality was about 5% with both treatment modalities (12,37,46,47,51,53).

Only one prospective study was identified which compared all three treatment modalities (Table IV). In this study, thrombolysis was clearly superior to heparin or oral anticoagulant treatment, even in non-obstructive PVT (12).

Recommendations

Class I

All patients with suspected PVT should undergo TTE and multiplane TEE (evidence B).

Thrombolytic therapy is the first-line treatment in all patients with obstructive PVT independently of NYHA class if there are no contraindications (evidence B).

Surgery should be reserved for patients in whom thrombolysis is contraindicated, or has failed (evidence B).

Serial TEE studies should be performed in all patients receiving thrombolytic therapy at least every 24 h (evidence C).

Class IIa

Non-obstructive PVT may be initially treated with unfractionated heparin infusion if the thrombus is small (<5 mm) or the oral anticoagulation was sub-therapeutic to achieve activated partial thromboplastin levels of 2.5- to 3-fold that of control or with low-molecular weight heparin in a weight-adjusted dosage (evidence C).

Serial multiplane TEE should be performed in patients

Table IV: Comparison of treatment results (12).

Treatment	No. of patients	Success (%)	Complications (%)	Death (%)
Lysis				
Obstructive PVT	33	85	12	6
Non-obstructive PVT	11	91	9	0
Heparin				
Obstructive PVT	4	0	0	25
Non-obstructive PVT	18	50	33	0
Surgery				
Obstructive PVT	19	-	10	36
Non-obstructive PVT	2	-	0	0

treated with heparin for non-obstructive PVT after 48 h. After 48 h of heparin treatment, if there is no decrease in thrombus size, then patients should be switched to thrombolysis; otherwise, continuation of heparin together with coumarin is recommended (evidence C). Non-obstructive PVT >5 mm should be treated by thrombolysis (evidence C).

Patients who are critically ill (cardiogenic shock or pulmonary edema) should be treated intravenously with rt-PA immediately according to the accelerated thrombolytic protocol: (100 mg administered as a 10 mg bolus followed by 90 mg infused over 90 min) (evidence C).

Patients at lower risk should be given either low-dose SK (250,000 IU over 30 min followed by 100,000 IU/h for no longer than 72 h, until the disappearance of PVT (as demonstrated by TEE) or fibrinogen drops to zero, respectively) or high-dose streptokinase (500,000 IU over 20 min followed by 1.5×10^6 IU infused over 10 h). Serial thrombolytic protocols may be given to low-risk patients if the first or second agents fail to dissolve the thrombus.

Surgery should be urgently undertaken after administration of fresh-frozen plasma in high-risk patients if the accelerated thrombolytic protocol fails (evidence C).

Concomitant intravenous unfractionated heparin should be administered along with rt-PA therapy to achieve an activated partial thromboplastin level of 1.5- to 2-fold that of control level (evidence C).

Following successful thrombolysis, unfractionated heparin infusion is recommended together with coumarin until the target therapeutic International Normalized Ratio (INR) range (2.5-3.5) is achieved (evidence C). Following successful thrombolysis, 100 mg aspirin should be added to coumarin.

Class IIb

Following successful thrombolysis, low molecular-weight heparin in adjusted dosage is recommended together with coumarin until the therapeutic range of INR (2.5-3.5) is achieved (evidence C).

Class III

It is not recommended to perform thrombolysis in the presence of ischemic stroke as documented by cerebral CT performed after 4 h from the beginning of symptoms.

Thrombolysis in patients with vegetation, early post-operatively (within 4 days following surgery), and in those having large atrial thrombi.

Heparinization in patients with obstructive PVT.

References

1. Tong AT, Roudaut R, Özkan M, et al. Transesophageal echocardiography improves risk assessment of thrombolysis of prosthetic valve thrombosis: Results of the international PRO-TE registry. *J Am Coll Cardiol* 2004;43:77-84
2. Lengyel M. Thrombolysis should be regarded as first-line therapy for prosthetic valve thrombosis in the absence of contraindications (letter). *J Am Coll Cardiol* 2005;45:325
3. Horstkotte D, Burckhardt D. Prosthetic valve thrombosis. *J Heart Valve Dis* 1995;4:141-153
4. Bortolotti U, Milano A, Mossuto E, et al. Early and late outcome after reoperation for prosthetic valve dysfunction: Analysis of 549 patients during a 26-year period. *J Heart Valve Dis* 1994;3:81-87
5. Rizzoli G, Guglielmi C, Toscano G, et al. Reoperations for acute prosthetic thrombosis and pannus: an assessment of rates, relationship and risk. *Eur J Cardiothorac Surg* 1999;16:74-80
6. Deviri E, Sareli P, Wisenbaugh T, Cronje SL. Obstruction of mechanical heart valve prostheses: Clinical aspects and surgical management. *J Am Coll Cardiol* 1991;17:646-650
7. Baille Y, Choffel J, Sicard MP, et al. Traitement thrombolytique des thromboses de prosthese valvulaire (letter). *Nouv Presse Med* 1974;3:1233
8. Bonow RO, Carabello B, deLeon AC, et al. ACC/AHA guidelines for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 1998;32:1486-1588
9. Lengyel M, Fuster V, Keltai M, et al. Guidelines for the management of left-sided prosthetic valve thrombosis: A role for thrombolytic therapy. *J Am Coll Cardiol* 1997;30:1521-1526
10. Alpert JS. The thrombosed prosthetic valve. *J Am Coll Cardiol* 2003;41:659-660
11. Lengyel M, Vándor L. Thrombolysis is the optimal treatment of mitral prosthetic valve thrombosis. *Eur Heart J* 2000;21(Suppl.):266 (abstract)
12. Lengyel M., Vándor L. The role of thrombolysis in the management of left-sided prosthetic valve thrombosis: A study of 85 cases diagnosed by transesophageal echocardiography. *J Heart Valve Dis* 2001;10:636-649
13. Özkan M, Kaymaz C, Kirma C, et al. Intravenous thrombolytic treatment of mechanical prosthetic valve thrombosis: A study using serial transesophageal echocardiography. *J Am Coll Cardiol* 2000;35:1881-1889
14. Shapira Y, Herz I, Vaturi M, et al. Thrombolysis is an effective and safe therapy in stuck bileaflet mitral valves in the absence of high-risk thrombi. *J*

- Am Coll Cardiol 2000;35:1874-1780 [pages]
15. Rinaldi CA, Heppel RM, Chambers JB. Treatment of left-sided prosthetic valve thrombosis: Thrombolysis or surgery? *J Heart Valve Dis* 2002;11:839-843
 16. Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation* 1994;89:635-641
 17. Gueret P, Vignon P, Fournier P, et al. Transesophageal echocardiography for the diagnosis and management of nonobstructive thrombosis of mechanical mitral valve prosthesis. *Circulation* 1995;91:103-110
 18. Lengyel M, Vegh G, Vandor L. Thrombolysis is superior to heparin for non-obstructive mitral mechanical valve thrombosis. *J Heart Valve Dis* 1999;8:167-173
 19. Hurrell DG, Schaff HV, Tajik J. Thrombolytic therapy for obstruction of mechanical prosthetic valves. *Mayo Clin Proc* 1996;71:605-613
 20. Lengyel M. Management of prosthetic valve thrombosis. *J Heart Valve Dis* 2004;13:329-334
 21. Fritzsche D, Eitz T, Grimmig O, et al. Home monitoring of patients after prosthetic valve replacement: A new method of early detection of valve dysfunction. *Z Kardiol* 2004;93:664-670
 22. Horstkotte D. Point-of-care devices to improve long-term prognosis after valve replacement. *J Heart Valve Dis* 2005;14:472-475
 23. Fritzsche D, Eitz T, Minami K, Laczkovics A, Mehlhorn U, Horstkotte D, Körfer R. Digital frequency analysis of valve sound phenomena in patients after prosthetic valve surgery: Its capability for a true home monitoring of valve function. *J Heart Valve Dis* 2005;14:657-663
 24. Rahimtoola SH. The problem of valve prosthesis-patient mismatch. *Circulation* 1978;58:20-24
 25. Montorsi P, Cavoretto D, Repossini A, et al. Valve design characteristics and cinefluoroscopic appearance of five currently available bileaflet prosthetic valves. *Am J Cardiac Imag* 1996;10:29-41
 26. Silber H, Khan SS, Matloff JM, et al. The St. Jude valve. Thrombolysis as the first line of therapy for cardiac valve thrombosis. *Circulation* 1993;87:30-37
 27. Czer LSC, Weiss M, Bateman TM, et al. Fibrinolytic therapy of St. Jude valve thrombosis under guidance of digital cinefluoroscopy. *J Am Coll Cardiol* 1985;5:1244-1249
 28. Piper C, Hering D, Horstkotte D. Prosthetic valve thrombosis: Predisposition and diagnosis. *Eur Heart J* 2001;Suppl.3 (Suppl.Q):Q16-Q22
 29. Gulati M, Furlong K, DeCara J, et al. Thrombolytic therapy of a left-sided prosthetic valve thrombosis without hemodynamic obstruction: A case report. *J Am Soc Echocardiogr* 2001;14:1230-1234
 30. Tiede PJ, Nishimura RA, Gastineau DA, et al. Modern management of prosthetic valve anticoagulation. *Mayo Clin Proc* 1998;73:665-680
 31. Malergue MC, Temkine J, Slama M, et al. Interest de l'échocardiographie transoesophagienne systématique postopératoire précoce des remplacements valvulaires mitraux. *Arch Mal Coeur* 1992;85:1299-1304
 32. Iung B, Cornier B, Dadez E, et al. Small abnormal echos after mitral valve replacement with bileaflet mechanical prostheses: Predisposing factors and effect on thromboembolism. *J Heart Valve Dis* 1993;2:259-266
 33. Bemurat LR, Laffort PR, Deville CJ, et al. Management of nonobstructive thrombosis of prosthetic mitral valve in asymptomatic patients in the early postoperative period: A study in 20 patients. *Echocardiography* 1999;16:339-346
 34. Barbetsas J, Nagueh SF, Pitsavos C, et al. Differentiating thrombus from pannus formation in obstructed mechanical prosthetic valves: An evaluation of clinical, transthoracic and transesophageal echocardiographic parameters. *J Am Coll Cardiol* 1998;32:1410-1417
 35. Hering D, Piper C, Horstkotte D. Management of prosthetic valve thrombosis. *Eur Heart J* 2001;Suppl.3 (Suppl.Q):Q22-Q26
 36. Delgado C, Bonnin O, Garriga JM, et al. Intermittent electromechanical dissociation as an unusual sign of prosthetic valve thrombosis in a patient with prosthetic fibrous ingrowth. *J Am Soc Echocardiogr* 2000;13:685-689
 37. Gupta D, Kothari SS, Bahl VK, et al. Thrombolytic therapy for prosthetic valve thrombosis: Short and long-term results. *Am Heart J* 2000;140:906-916
 38. Habib G, Cornen A, Mesana T, et al. Diagnosis of prosthetic heart valve thrombosis. The respective values of transthoracic and transesophageal Doppler echocardiography. *Eur Heart J* 1993;14:447-455
 39. Salem DN, Stein PD, Al-Ahmad A, Bussey H, Horstkotte D, Miller N, Pauker SG. Antithrombotic therapy in valvular heart disease – native and prosthetic. The Seventh ACCP Conference on Antithrombotic and Thrombolytic therapy. *Chest* 2004;126(Suppl.):457S-482S
 40. Hanania G. Role of heparin in the antithrombotic treatment of valvulopathies. *J Heart Valve Dis* 2004;13:339-343
 41. Roudaut R, Labbe T, Lorient-Roudaut M-R, et al. Mechanical cardiac valve thrombosis. Is fibrinolysis justified? *Circulation* 1992;86(Suppl.II):II8-II15
 42. Roudaut R, Lafitte S, Roudaut M-F, et al. Fibrinolysis of mechanical prosthetic valve throm-

- bosis. A single center study of 127 cases. *J Am Coll Cardiol* 2003;41:653-658
43. Manteiga R, Sonto JC, Altes A, et al. Short-course thrombolysis as the first line of therapy for cardiac valve thrombosis. *J Thorac Cardiovasc Surg* 1998;115:780-784
 44. Sugano T, Fujiwara H, Adachi S, Sugimoto K, Amano J, Suzuki A. Tissue-type plasminogen activator (t-PA) lysis of aortic and mitral valve thrombosis. *J Cardiovasc Surg* 1993;34:259-261
 45. DeNofrio D, Ament AF, Mark JB, George SE. Accelerated TPA for treatment of prosthetic valve thrombosis. *Clin Cardiol* 1996;19:665-668
 46. Renzulli A, Vitale N, Caruso A, et al. Thrombolysis for prosthetic valve thrombosis: Indications and results. *J Heart Valve Dis* 1997;6:212-218
 47. Vitale N, Renzulli A, Cerasuolo F, et al. Prosthetic valve obstruction: Thrombolysis versus operation. *Ann Thorac Surg* 1994;57:365-370
 48. Kurzrok S, Singh AK, Most AS, Williams DO. Thrombolytic therapy for prosthetic cardiac valve thrombosis. *J Am Coll Cardiol* 1987;9:592-598
 49. Koller PT, Aron KV. Thrombolytic therapy of left-sided prosthetic valve thrombosis. *Chest* 1995;108:1683-1689
 50. Montorsi P, Caboretto D, Alimento M, et al. Prosthetic valve thrombosis: Can fluoroscopy predict the efficacy of thrombolytic treatment? *Circulation* 2003;108:II79-II84
 51. Vasan RS, Kaul U, Sanghvi S, et al. Thrombolytic therapy for prosthetic valve thrombosis: A study based on serial Doppler echocardiographic evaluation. *Am Heart J* 1992;123:1575-1580
 52. Munclinger MJ, Patel JJ, Mitha AS. Thrombolysis of thrombosed St. Jude Medical prosthetic valves: Rethrombosis - a sign of tissue ingrowth. *J Thorac Cardiovasc Surg* 1998;115:248-249
 53. Reddy NK, Padmanabhan TNC, Singh S, et al. Thrombolysis in left-sided prosthetic valve occlusion: Immediate and follow-up results. *Ann Thorac Surg* 1994;58:462-471
 54. Birdi I, Angelini GD, Bryan AJ. Thrombolytic therapy for left-sided prosthetic heart valve thrombosis. *J Heart Valve Dis* 1995;4:154-159
 55. Viedt C, Mereles D, Kübler W, Krenzer J. Fibrinolytische Therapie bei Thrombose einer Mitralklappenprothese. *Z Kardiol* 2000;89:698-701
 56. Young E, Shapiro SM, French WJ, Ginzton LE. Use of transesophageal echocardiography during thrombolysis with tissue plasminogen activator of a thrombosed prosthetic mitral valve. *J Am Soc Echocardiogr* 1992;5:153-158
 57. Tissot H, Vergnes C, Rougier P, et al. Fibrinolytic treatment with urokinase and streptokinase for recurrent thrombosis in two valve prostheses for the aortic and mitral valves during pregnancy. *J Gynecol Obstet Biol Reprod Paris* 1991;20:1093-1096
 58. Ambarasan C, Kumar VS, Latchumandhas K, Mullasari AS. Successful thrombolysis of prosthetic mitral valve thrombosis in early pregnancy. *J Heart Valve Dis* 2001;10:393-395
 59. Temkine J, Malergue MC, Berrabha T, Lecompte Y. Thrombose postopératoire asymptomatique d'une valve de Saint-Jude mitrale: Traitement par fibrinolyse au rt-PA. *Arch Mal Coeur* 1991;84:413-417
 60. Witchitz S, Veyrat C, Moisson P, et al. Fibrinolytic treatment of thrombus on prosthetic heart valves. *Br Heart J* 1980;44:545-554
 61. Serpi M, Schmidt KG, Krenz W, et al. Thrombolysis of prosthetic heart valve thrombosis using recombinant tissue plasminogen activator (rt-PA) in infancy and childhood. *Z Kardiol* 2001;90:191-196
 62. Azpitarte J, Sanchez-Ramos J, Urda T, et al. Prosthetic valve thrombosis: Which is the most appropriate initial therapy? *Rev Esp Cardiol* 2001;54:1367-1376