

EDITORIAL COMMENT

Prosthetic Valve Thrombosis

When and How Should We Lyse?*

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With the advent of the Starr-Edwards mechanical mitral and aortic valves in the 1960s, the surgical era of the treatment of cardiac valvular disease began in earnest. Although considered definitive, valve replacement surgery effectively represents an exchange of the pathophysiology of severe valvular dysfunction for the diseases and complications associated with prosthetic valves. These include severe paravalvular leak, endocarditis, severe hemolysis, valvular dehiscence, valve failure, and prosthetic valve thrombosis (PVT).

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The current rate of PVT is estimated to be between 0.03% and 0.13% per patient-year depending on the antithrombotic regimen used and the adherence to therapy (1). The rarity of PVT, its broad spectrum of clinical presentation, and the occasional difficulty in differentiating thrombosis from pannus formation has presented numerous challenges in its diagnosis, management, and systematic study. Previous studies of therapies for PVT have lacked uniformity in definitions of obstruction, treatment success, and diagnostic techniques. Study designs of key reports in the field have included case series (2–4) and retrospective cohorts (5) and have often enrolled patients with both right- and left-sided valvular obstruction. Finally, studies compar-

ing fibrinolysis with surgery have been nonrandomized and thus marked by selection bias (6,7).

As a result, comparing fibrinolytics and fibrinolysis with surgery has been difficult. In the absence of randomized clinical trial data to guide therapeutic strategies for PVT, current guidelines rely on limited data and expert opinion. This has led to a variety of recommendations with regard to the role of surgical valve replacement and systemic fibrinolysis with no class I recommendations being given (8–10). Surgery is recommended as first-line therapy by the European Society of Cardiology regardless of clinical status, whereas the Society of Heart Valve Disease has recommended fibrinolysis as first-line therapy in all cases of PVT in the absence of a contraindication (11). The American College of Chest Physicians (10) recommends thrombolysis as first-line therapy for thrombi <0.8 cm², and the joint American Heart Association and American College of Cardiology guidelines suggest thrombolysis only for stable patients with PVT and incomplete obstruction (9).

It is with this background that the report by Özkan et al. (12) on the TROIA study in this issue of *iJACC* should be considered. The TROIA (Comparison of Different TRansesophageal Echocardiography Guided thrombolytic Regimens for prosthetic Valve Thrombosis) study evaluated a strategy of transesophageal echocardiography (TEE)-guided fibrinolysis with rapid infusion of streptokinase (Group I) versus slow infusion of streptokinase (Group II) versus full-dose tissue plasminogen activator (t-PA) (100 mg) (Group III) versus half dose (50 mg) slow infusion of t-PA (Group IV) versus low dose (25 mg) slow infusion of t-PA (Group V). The investigators should be congratulated for performing a single-center, prospective cohort therapeutic strategy study involving 182

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patients with 220 episodes of PVT from 1993 to 2009, with a key feature of the study being that enrollment in the study arms was nonrandomized and occurred sequentially during the study period. The pre-specified efficacy endpoint was thrombolytic success, defined as the absence of fatal or nonfatal complications and at least 1 of the following criteria: 1) resolution of Doppler gradient and decreased valve area; 2) clinical improvement in symptoms; and 3) reduction $\geq 75\%$ of the area or major diameter of the thrombus. The pre-specified safety endpoints were: 1) all-cause in-hospital mortality; 2) nonfatal major complications (ischemic stroke, intracranial hemorrhage, embolism, bleeding requiring transfusion); and 3) nonfatal minor complications (bleeding without the need for transfusion and transient ischemic attack).

The investigators report successful thrombolysis in 83.2% of cases without a significant difference between thrombolytic protocols (68.8%, 85.4%, 75.0%, 81.5%, and 85.5%, respectively; $p = 0.46$). In multivariate analysis, only a longer time interval since surgery (odds ratio: 1.025; 95% confidence interval: 1.012 to 1.039; $p < 0.001$), and not poor New York Heart Association functional class, position of the thrombosed valve, bileaflet versus monoleaflet valve, mobility of the thrombus, sub-optimal international normalized ratio on admission, or previous aspirin use, was predictive of fibrinolysis failure.

Importantly, the investigators went on to examine complications and report an overall complication rate of 18.6%, including death (14.6%), and nonfatal major (41.5%) and minor (43.9%) complications. Analysis of complication rates by group showed a statistically lower combined complication rate in Group V (10.5%) compared with all other groups (37.5%, 24.4%, 33.3%, 29.6%, and 10.5%, respectively; $p = 0.01$ for Group I vs. Group V, 0.03 for Group II vs. Group V, 0.04 for Group III vs. Group V, and 0.03 for Group IV vs. Group V). Examination of the components of this composite endpoint suggests that the lower complication rate in Group V was driven primarily by a lower mortality rate compared with Groups I (12.5%) and III (16.7%) and lower nonfatal complication rate compared with Groups II (12.12%) and IV (11.1%). Multivariate analysis revealed only a history of transient ischemic attack/stroke and non-Group V status, but not atrial fibrillation, obstructive thrombus, large thrombus, or poor functional capacity as predictors of complications.

Although hampered by possible bias and confounding due to its single-center, nonrandomized, and sequential design, the present study nevertheless represents the largest of its kind to date and provides important data regarding the relative efficacy of multiple thrombolytic regimens in the setting of PVT. Whereas previous studies separately evaluated a variety of thrombolytic agents and regimens, including streptokinase, urokinase, and t-PA, few used either direct or indirect comparison to attempt to identify differences in efficacy and safety based on dosing regimens or varying thrombolytic agents (3,13). As a result, fibrinolytic dosing for thrombolysis in PVT has largely been borrowed from the pulmonary embolism and myocardial infarction literature without critical appraisal. In fact, whereas dosing guidelines for fibrinolysis in pulmonary embolism emphasize that shorter infusion times achieve more rapid clot lysis with lower bleeding rates (14), the results of the present study suggest that lower dose, TEE-guided, repeated, slow administration of a fibrinolytic agent may be equally efficacious with fewer complications.

Given the improvement in safety and preserved efficacy associated with their protocol, Özkan et al. (12) suggest that guidelines regarding the treatment of PVT may need to be updated to reflect the utility of fibrinolysis for all patients, even those who are critically ill. Although administration of slow, low-dose t-PA appears to compare favorably with previous reports of fibrinolytic and surgical treatment of PVT, because the TROIA study did not include a surgical therapy arm, these data should be interpreted as pilot data forming the basis for a clinical trial rather than as definitive proof of the equivalence or superiority of fibrinolysis over surgery in PVT. As such, they are unlikely to significantly change the recommendations of the individual guideline agencies, which have already made widely differing interpretations of the available data.

The recently initiated SAFE-PVT (Surgery Versus Fibrinolytic Therapy for Left-sided Prosthetic Heart Valve Thrombosis) study (NCT01641549) will randomize 150 patients at a single center in India to surgical valve replacement or thrombectomy versus first-line therapy with fibrinolysis with streptokinase or an alternative fibrinolytic agent. Results of this trial are currently expected in 2017 and will include a primary endpoint of in-hospital complete clinical response in the absence of stroke, bleeding, or systemic embolism. The secondary endpoints will be in-hospital and 1 year stroke, bleeding, and systemic embolism.

The findings of this study will be crucial in informing guidelines on the treatment of PVT as the data will begin to address several of the outstanding questions within the PVT therapeutic literature: 1) what are the success and complication rates of contemporary, unselected patients undergoing left-sided surgical thrombectomy or valve replacement for PVT? 2) Is there a difference between fibrinolytic agents with regard to effectiveness and safety in contemporaneously enrolled subjects? 3) What are the long-term (1 year) outcomes

of patients undergoing surgical or fibrinolytic therapy for PVT? Until then, if fibrinolysis is to be used for PVT, the data from the current study suggest that lower dose, TEE-guided repeated, slow administration of a fibrinolytic agent may be the best choice for efficacy and safety.

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REFERENCES

1. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the veterans affairs randomized trial. *J Am Coll Cardiol* 2000;36:1152-8.
2. Cáceres-Lóriga FM, Pérez-López H, Morlans-Hernández K, et al. Thrombolysis as first choice therapy in prosthetic heart valve thrombosis. A study of 68 patients. *J Thromb Thrombolysis* 2006;21:185-90.
3. Roudaut R, Lafitte S, Roudaut MF, et al. Fibrinolysis of mechanical prosthetic valve thrombosis: a single-center study of 127 cases. *J Am Coll Cardiol* 2003;41:653-8.
4. Ozkan 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;35:1881-9.
5. Tong AT, Roudaut R, Ozkan M, et al. Transesophageal echocardiography improves risk assessment of thrombolysis of prosthetic valve thrombosis: results of the international pro-tee registry. *J Am Coll Cardiol* 2004;43:77-84.
6. Lengyel M, Vandor 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;10:636-49.
7. Keuleers S, Herijgers P, Herregods MC, et al. Comparison of thrombolysis versus surgery as a first line therapy for prosthetic heart valve thrombosis. *Am J Cardiol* 2011;107:275-9.
8. Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease: the Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 2007;28:230-68.
9. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused update incorporated into the ACC/AHA 2006 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 (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008;52:e1-142.
10. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schunemann HJ. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:7S-47S.
11. Lengyel M, Horstkotte D, Voller H, Mistiaen WP. Recommendations for the management of prosthetic valve thrombosis. *J Heart Valve Dis* 2005;14:567-75.
12. Ozkan M, Gündüz S, Biteker M, et al. Comparison of different TEE-guided thrombolytic regimens for prosthetic valve thrombosis: the TROIA trial. *J Am Coll Cardiol Img* 2013;6:206-16.
13. Karthikeyan G, Math RS, Mathew N, et al. Accelerated infusion of streptokinase for the treatment of left-sided prosthetic valve thrombosis: a randomized controlled trial. *Circulation* 2009;120:1108-14.
14. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: american college of chest physicians evidence-based clinical practice guidelines. *Chest* 2012;141 2Suppl:e419S-94S.

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