JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 8, NO. 10, 2015
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2015.06.009

EDITORIAL COMMENT

Catheter-Directed Thrombolysis for Pulmonary Embolism

Where Do We Stand?*

Akhilesh K. Sista, MD,† Clive Kearon, MB, PhD‡

There have been 2 main treatments for acute pulmonary embolism (PE)—anticoagulant therapy alone or systemic thrombolytic therapy. Although systemic thrombolytic therapy is effective at preventing deaths from PE, it markedly increases bleeding, including intracranial and fatal bleeding (1). The recent PEITHO (Pulmonary Embolism Thrombolysis Study) (2), which compared tenecteplase with placebo in 1,000 PE patients without hypotension but with right ventricular dysfunction, found no clear net benefit from systemic thrombolytic therapy; the reduction in cardiovascular collapse (odds ratio: 0.30) was offset by the increase in major bleeding (odds ratio: 5.2). Consequently, systemic thrombolytic therapy is usually reserved for PE patients with hypotension (3). The ability to actively remove thrombus in patients with acute PE without increasing bleeding would be an important advance. Catheter-based therapy has that potential.

Catheter-directed thrombolysis (CDT) was initially developed for treatment of arterial, dialysis graft, and deep vein thromboses (leg or arm). When used to treat acute PE, a wire is usually passed through the embolus, followed by placement of a multiside hole infusion catheter through which a thrombolytic drug is infused over 12 to 24 h (4). The delivery of the drug directly into the thrombus is expected to be as effective as systemic therapy but to cause less bleeding because a much lower dose of the drug is used. If more rapid thrombus removal is required, such as in a decompensating patient, fragmentation, balloon maceration, and aspiration may be used as adjunct to CDT or instead of it (i.e., in patients with a high risk of bleeding). These mechanical techniques, however, are avoided in stable patients because they may cause pulmonary artery injury. The addition of an ultrasound-emitting wire to a multiside hole infusion catheter is thought to accelerate thrombolysis by ultrasonically disrupting thrombus (5). Although this approach has been used to treat arterial and deep venous thromboses for about 10 years, there is uncertainty that the addition of ultrasound emission increases the efficacy of CDT (6). Based partly on the findings of the SEATTLE II (A Prospective, Single-Arm Multi-Center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism) study, which is reported in this issue of *JACC: Cardiovascular Interventions*, ultrasound-assisted CDT is now approved by the U.S. Food and Drug Administration for treatment of acute PE (7).

SEE PAGE 1382

SEATTLE II is a single-arm prospective cohort study in which 150 patients with lobar artery or more central PE (31 with and 119 without hypotension) were treated with ultrasound-assisted CDT using a standardized protocol (7). Tissue plasminogen activator was infused into each treated lung at a rate of 1 mg/h, to a total dose of 24 mg (over 12 h for bilateral lung infusions), and no additional mechanical maneuvers were used to disrupt or aspirate thrombus. When computed tomography pulmonary angiography was repeated after 48 h, the right ventricular to left ventricular ratio was decreased by 27% and thrombus burden was reduced

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the †Division of Interventional Radiology, Department of Radiology, Weill Cornell Medical College, New York, New York; and the ‡Department of Medicine, Thrombosis and Atherosclerosis Research Institute, McMaster University, Hamilton, Ontario, Canada. Drs. Sista and Kearon have reported that they have no relationships relevant to the contents of this paper to disclose.

by 30%. Pulmonary artery pressure also decreased by 27% between the start to the end of CDT. These 3 improvements were each highly statistically significant. There were 17 episodes of major bleeding in 15 patients (10%): one was associated with hypotension; all required transfusion; none was intracranial; and none was fatal. Strengths of the SEATTLE II study include its prospective design, inclusion of 150 patients, high patient retention, involvement of many clinical centers, standardized treatment protocol, and rigorous reporting. Limitations include that there was no comparison group (neither anticoagulation alone nor systemic thrombolytic therapy), short-term surrogate outcomes were used to assess efficacy, and that long-term outcomes such as quality of life or exercise capacity were not assessed. SEATTLE II also did not assess whether ultrasound-assisted CDT was more effective than standard CDT.

So, how effective and safe is CDT? The short-term improvements in right ventricular dimensions, thrombus burden, and pulmonary hypertension in SEATTLE II are consistent with the improvement in right ventricular dimension with ultrasound-facilitated CDT in 35 patients in the ULTIMA (Ultrasound Accelerated Thrombolysis of Pulmonary Embolism) study (8). In ULTIMA, there was almost no improvement in this outcome at 24 h in the 35 patients who were randomized to anticoagulant therapy alone, and the difference between the CDT and anticoagulant therapy alone groups was highly statistically significant. A recently published prospective registry of 101 patients with acute PE (PERFECT [Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis]) (9) reported similar efficacy of CDT, with or without ultrasound-assisted thrombolysis, to ULTIMA and SEATTLE. There was no major bleeding in this registry, although follow-up may not have been as standardized as the follow-up for the SEATTLE II and ULTIMA studies. The improvements in imaging and pulmonary artery pressure with ultrasound-assisted CDT in SEATTLE II and ULTIMA also appear to be at least as marked as the short-term improvements in these outcomes with systemic thrombolytic therapy (10). Therefore, based mostly on indirect comparisons of short-term surrogate outcomes, CDT appears to be effective compared with anticoagulant therapy alone and probably is as effective as systemic thrombolytic therapy, which uses much higher dose of the thrombolytic drug. The frequency of major bleeding in SEATTLE II, however, suggests that CDT may be associated with substantially more bleeding than anticoagulation alone. Although it is encouraging that there were no intracranial bleeds in the 150 patients in SEATTLE II, the upper boundary of the 95% confidence interval on this estimate is 2.4%. Although it seems likely that there is a lower risk of nonprocedural bleeding with CDT than with systemic thrombolytic therapy, this remains uncertain.

What then is the role of CDT in patients with PE? We think that current evidence suggests that CDT is preferred to systemic thrombolytic therapy in patients with acute PE who require active thrombus removal and have risk factors for bleeding. We suggest that venous puncture for CDT should always be ultrasound-guided and that the total dose of thrombolytic drug should be kept to a minimum in patients with a high risk of bleeding (3). If there is need for active thrombus removal in patients with a very high risk of bleeding, it may be necessary to use catheter-based therapy without thrombolytic drug or to use surgical embolectomy. We are not ready to encourage use of CDT in preference to anticoagulation alone in stable patients with acute PE and right ventricular dysfunction. We suggest that there is a need for evidence that the short- and long-term benefits of CDT outweigh the associated risk of bleeding before CDT can be recommended for such patients. We encourage randomized trials that compare CDT with systemic thrombolytic therapy in unstable patients with PE and compare CDT with anticoagulation alone in stable patients who have large PE and right ventricular dysfunction. Evidence from such studies would place the role of CDT for PE on a firmer footing.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Clive Kearon, Juravinski Hospital, Room A3-73, 711 Concession Street, Hamilton, Ontario L8V 1C3, Canada. E-mail: kearonc@mcmaster.ca.

REFERENCES

1. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA 2014;311:2414–21.

2. Meyer G, Vicaut E, Danays T, et al., for the PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402–11.

3. Konstantinides SV, Torbicki A, Agnelli G, et al., for the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35:3033–69, 3069a–k.

4. Kuo WT. Endovascular therapy for acute pulmonary embolism. J Vasc Interv Radiol 2012;23:167–79.e164, quiz 179.

5. Braaten JV, Goss RA, Francis CW. Ultrasound reversibly disaggregates fibrin fibers. Thromb Haemost 1997;78:1063–8.

6. Engelberger RP, Spirk D, Willenberg T, et al. Ultrasound-assisted versus conventional catheter-directed thrombolysis for acute iliofemoral deep vein thrombosis. Circ Cardiovasc Interv 2015;8: piie002027.

7. Piazza G, Hohlfelder B, Jaff MR, et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: The SEATTLE II study. J Am Coll Cardiol Intv 2015;8:1382–92.

8. Kucher N, Boekstegers P, Muller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014;129:479–86.

9. Kuo WT, Banerjee A, Kim PS, et al. Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT): initial results from a prospective multicenter registry. Chest 2015 Apr 9 [E-pub ahead of print].

10. Dong B, Jirong Y, Wang Q, Wu T. Thrombolytic treatment for pulmonary embolism. Cochrane Database Syst Rev 2006;(2): CD004437.

KEY WORDS catheter-directed, endovsacular therapy, pulmonary embolism, thrombolysis, treatment