# Systemic thrombolytics for DVT were more effective than local treatment or placebo, but adverse events were more frequent

Schweizer J, Kirch W, Koch R, et al. **Short- and long-term results after thrombolytic treatment of deep venous thrombosis.** J Am Coll Cardiol. 2000 Oct;36:1336-43.

## QUESTION

In patients with deep venous thrombosis (DVT) who are treated with compression stockings and anticoagulants (heparin initially and then oral agents for 1 year), does local treatment (tissue plasmsinogen activator [t-PA] or low-dose urokinase) or systemic treatment (high-dose urokinase or streptokinase) prevent the post-thrombotic syndrome (PTS)?

## DESIGN

Randomized {allocation concealed*}†, blinded (outcome assessors),* controlled trial with 1-year follow-up.

## SETTING

A university hospital in Germany.

## PATIENTS

250 patients (mean age 40 y, 58% men) with recent acute pelvic or leg DVT. Exclusion criteria were pulmonary embolism; DVT at only 1 level; DVT for > 9 days; previous DVT in the same leg; thrombosis in the calf veins only; gastrointestinal or urogenital bleeding; inflammatory bowel disease; acute pancreatitis; recent surgery or cerebral trauma; intramuscular injections within the previous 10 days; arterial hypertension; diabetes mellitus; history of cerebral disease, cancer, or renal failure; hemorrhagic diathesis; pregnancy or lactation; or recent delivery. Follow-up was 96%.

## INTERVENTION

50 patients were allocated to each of the 5 treatment groups (2 local, 2 systematic, and 1 control). Active treatment groups received local or systematic thrombolytic agents for 4 to 7 days plus heparin, compression stockings, and oral anticoagulants for 1 year. Local treatments were t-PA (alteplase, 20 mg) or urokinase, 100 000 IU infused directly into a dorsal pedal vein over 4 hours. Systemic treatments were urokinase, 5 million IU infused over 4 hours, or streptokinase, 3 million IU infused over 6 hours, plus pretreatment with hydrocortisone, ranitidine, and clemastine. 1 placebo group was also studied.

## MAIN OUTCOME MEASURES

Number of closed-vein segments and degree of the PTS (from no to serious symptoms).

## MAIN RESULTS

The proportion of closed segments was lower in the systemic groups than in the local groups or placebo group (26% for systemic urokinase and 27% for streptokinase vs 36% for each of t-PA and local urokinase and 48% for placebo, $P < 0.001$). The degree of the PTS was less in the systemic groups than in the control group ($P < 0.001$). More patients in the systemic groups had major bleeding complications or pulmonary embolism than in the local or placebo groups (16% for systemic urokinase and 20% for streptokinase vs 2% for local urokinase, 4% for local t-PA, and 0% for placebo; $P \leq 0.05$ for all systemic groups compared with local and placebo groups).

## CONCLUSION

Systemic thrombolytic agents (streptokinase or urokinase) for deep venous thrombosis were associated with a lower risk for closed-vein segments and a less serious degree of the post-thrombotic syndrome than were placebo or local treatment (urokinase or tissue plasminogen activator), although the rate of serious adverse events was higher.

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*For correspondence: Dr. J. Schweizer, Klinik Chemnitz gGmbH, Krankenhaus Küchenwald, Klinik für Innere Medizin I, Bürgerstrasse 2, D-09113 Chemnitz, Germany. FAX 49-0371-333-42567.* ■

*See Glossary.

†Information supplied by author.

## COMMENTARY

The consequences of acute DVT include pulmonary embolism, recurrent DVT, and chronic venous insufficiency. Schweizer and colleagues asked whether thrombolytic therapy restores venous function, prevents venous insufficiency symptoms, and normalizes venographic appearance. Elaborate steps were taken to measure outcomes in an unbiased fashion. Repeated venograms were done and interpreted independently by radiologists blinded to treatment status. Simple and reproducible indices of clinical and venographic venous insufficiency were applied. Venous function was assessed by Doppler and B-mode ultrasonography. The 5 treatment groups included local and systemic thrombolysis, different thrombolytic agents, and standard care with conventional anticoagulation. All patients wore custom-fitted graded compression stockings, which were examined for wear and refitted every 3 months.

The patient population was relatively young and highly selected in an effort to gather patients with a first episode of DVT who could tolerate thrombolysis. 12 patients, who were evenly distributed amongst the groups and were relatively noncompliant with compressive treatment, missed the 12-month evaluation. The results of the study were mixed. In the 200 patients treated with thrombolytic agents, there were 12 major bleeds, none of which were fatal or involved the central nervous system, and 9 pulmonary emboli. A decrease was seen in the percentage of closed venous segments in the systemic groups, but cleared veins do not necessarily mean restored venous function. The follow-up interval was too brief to compare rates of venous ulcer formation. Several comparisons were done, which increased the chance of finding statistical but not clinical differences among the groups.

The study shows that thrombolysis has hemodynamic benefits but increases risk for bleeding and embolization from untethered clots. The authors cautiously suggest using systemic thrombolysis for limb-threatening DVT. For the young patient, I cautiously agree.

*Daniel M. Becker, MD, MPH*
*University of Virginia Medical Center*
*Charlottesville, Virginia, USA*