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INVITED COMMENTARY

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The publication of a randomized controlled trial in the vascular arena is rare. The publication of a trial with negative results is rarer. Han and colleagues should be applauded for an honest portrayal of the use of alfimeprase in the setting of acute limb ischemia (ALI). Alfimeprase, a novel recombinant variant of fibrolase, displayed promising results in preclinical and pilot studies. In contrast to available thrombolytic agents, alfimeprase is a direct fibrinolytic enzyme and has no effect on plasminogen. In addition, any drug that escapes into the general circulation is quickly degraded by α_2-macroglobulin which is ubiquitous in plasma. These properties have the potential to overcome limitations that exist with current therapies: the duration of therapy and the risk of bleeding. A rapidly-acting, direct fibrinolytic without systemic plasminogen activation and plasma neutralization seem like ideal characteristics for a thrombolytic agent. In this report, data from two essentially blinded, placebo-controlled, randomized controlled trials evaluating alfimeprase for ALI are reported. Alas, alfimeprase showed no greater effectiveness than placebo in ALI patients with mostly femoral/popliteal thrombus in native arteries. In fact, the rates of distal embolization and amputation in the treatment groups were troubling.

Trial design is a critical component in the analyses of any pharmaceutical agent. The primary endpoint of "avoidance of open vascular surgery at 30 days" may not be a realistic endpoint in patients with ALI. Thrombolysis may be the only therapy required for patients with an embolus in an otherwise normal arterial tree. However, most patients reported in these trials developed ALI from thrombosis in the setting of extensive atherosclerotic occlusive disease. The dissolution of thrombus uncovers a culprit lesion which may require a limited surgical procedure for durable patency. Time to patency, cost, resource utilization, and grading of the extent of open surgery are surrogate endpoints that can be used for ALI trials and would likely favor alfimeprase in future studies. Amputation-free survival is perhaps the best global endpoint, but one that requires a large sample size. The inclusion of a placebo group is difficult since acceptable results are obtained with thrombolysis in patients that are often ill-prepared to withstand major limb revascularization. In fact, the surprising "effectiveness" of intrathrombus placebo leads to the alternative conclusion that percutaneous mechanical thrombectomy devices utilizing rheolysis may be clinically beneficial in most cases of ALI. The compelling preclinical data on alfimeprase did not translate into clinical efficacy. Enhanced dosing and delivery strategies may salvage alfimeprase. I agree with the authors that further study is warranted.