

# Current and Future Thrombolytic Options for Acute PAO

A review of available plasminogen activators and a description of the novel direct-acting thrombolytic alfimeprase.

BY SEAN P. LYDEN, MD

**P**eripheral arterial atherosclerotic occlusive disease (PAO) occurs in more than 4% of individuals over age 40 and markedly increases in incidence after the age of 70.<sup>1</sup> Most patients with chronic PAO have symptoms such as leg cramping, pain with walking (intermittent claudication), and a very low risk of limb loss.<sup>2</sup> However, up to 20% of patients with chronic PAO will develop acute exacerbation of symptoms known as acute PAO or acute limb ischemia. Acute PAO is usually due to thrombosis of the involved vasculature and is associated with a significant risk of limb loss. Therapy for acute PAO centers on the rapid restoration of arterial patency and blood flow allowing limb preservation.

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Traditional treatment options for acute PAO have been open surgery, such as arterial thrombectomy, endarterectomy, and arterial bypass. Unfortunately, the emergent nature of procedures in this population has been associated with a high rate of complications and death.<sup>3</sup> Suboptimal surgical outcomes in acute PAO have

fueled the proliferation of minimally invasive, catheter-directed procedures, including pharmacologic thrombolysis.

## THROMBOLYSIS

The rationale for pharmacologic thrombolysis is supported by three randomized prospective trials that compared the efficacy of catheter-directed thrombolysis with plasminogen activators to open vascular surgery. The first of these trials was the Rochester series.<sup>3</sup> Ouriel et al randomized 114 patients presenting with acute PAO to catheter-directed thrombolysis with urokinase (Abbott Laboratories, Abbott Park, IL) or surgery. Although simi-

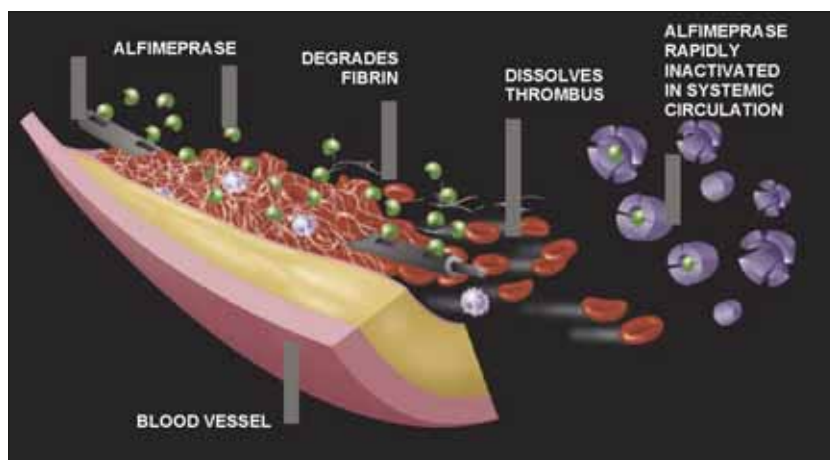


Figure 1. The mechanism of action of alfimeprase. The drug is delivered directly into the thrombus by a catheter. Alfimeprase directly degrades fibrin and dissolves the thrombus. Any alfimeprase that enters the systemic circulation is rapidly bound by  $\alpha_2$  macroglobulin and inactivated.

lar rates of limb salvage were found in both groups, a significantly larger proportion of patients treated with thrombolytics were alive and event free at 1 year (75% vs 52%;  $P=.02$ ).

The Surgery or Thrombolysis for the Ischemic Lower Extremity (STILE) trial evaluated three different acute PAO treatments: catheter-directed urokinase, catheter-directed rtPA (Genentech, Inc., South San Francisco, CA), and open vascular surgery.<sup>4</sup> Although untoward events such as bleeding were more frequent in the thrombolytic groups compared with surgery, amputation and death rates were equivalent. At 1 year, surgery was more effective in limb salvage for native acute PAO (amputations: 0% for surgery vs 10% for lysis;  $P=.0024$ ),<sup>5</sup> whereas thrombolysis was more effective in limb salvage of bypass graft occlusions (amputations: 20% for lysis vs 48% for surgery;  $P=.026$ ).<sup>6</sup>

The Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial compared a recombinant form of urokinase to primary operative intervention in 544 patients.<sup>7</sup> After a mean 1-year follow-up, the rate of amputation-free survival was identical in both groups. Death rates were higher in the surgical cohort (5%) versus the thrombolytic group (0%). In the thrombolytic group, 25.7% of patients alive at 1 year without amputation had only a percutaneous vascular intervention.

The suggestion of equivalent efficacy of thrombolysis compared to surgery with regard to amputation-free survival in the three randomized trials has led to adoption of thrombolysis as the initial treatment modality of choice in many institutions for acute PAO, despite the lack of FDA approval for this indication.

Thrombolysis is used with the goal of opening the vasculature and uncovering the culprit lesions responsible for precipitating the thrombotic occlusions. Oftentimes, an endovascular procedure (eg, balloon angioplasty, atherectomy, and stenting) is required to treat the underlying lesion and minimize the risk of re-occlusion. When open vascular surgical intervention is still required, the procedure can often be performed on an elective basis in an optimized patient, reducing the rates of complication and death.

## MECHANISM OF ACTION OF PLASMINOGEN ACTIVATORS

Currently available thrombolytic agents (ie, streptokinase, urokinase, tPA, rPA, and TNK-tPA) are plasminogen activators that can convert plasminogen to plasmin. Plasmin, in turn, can degrade fibrin in a thrombus and circulating fibrinogen. The plasminogen activator thrombolytic agents, themselves, do not directly degrade thrombus. All of the currently available agents

have varying degrees of fibrin specificity (or the ability to distinguish between circulating and bound plasminogen). Higher fibrin specificity was hoped to lower systemic bleeding complications, but large trials have not shown any difference in bleeding rates.<sup>6</sup>

## LIMITATIONS OF PLASMINOGEN ACTIVATORS

There are many limitations for the use of urokinase, tPA, rPA, and other plasminogen activators for acute PAO. Current thrombolytic agents have needed a mean duration of more than 24 hours to achieve flow in both the STILE and TOPAS trials.<sup>4,7,8</sup> The lag time to re-establish arterial flow excludes patients with imminently threatened limbs and who cannot wait for 24 hours or more to regain limb arterial blood flow. Another limitation of plasminogen activators is that platelet-rich arterial thrombus rich in plasminogen activator inhibitor 1 may be resistant to lysis. Finally, even with localized delivery of a drug, systemic circulation of the drug and generated plasmin occurs, which can create a systemic "lytic state."<sup>9</sup> Circulating plasmin cannot distinguish between physiologic and pathologic thrombus, and distant bleeding can ensue.

Hypofibrinogenemia as a result of fibrinogen degradation by circulating plasmin has been associated with an increased risk of hemorrhage. In fact, 5% to 16% of patients treated with catheter-directed plasminogen activator thrombolysis experience major hemorrhage, whereas 1% to 2% experience intracranial hemorrhage.<sup>3-5</sup>

"Major bleeding . . . [is] the Achilles' heel of currently available thrombolytic agents."

Major bleeding, such as intracranial, retroperitoneal, and gastrointestinal hemorrhagic complications and bleeding at catheter entry sites, along with the amount of time required to restore blood flow, have been the Achilles' heel of currently available thrombolytic agents. Overcoming these disadvantages will only occur with the development of novel agents that do not work through the plasminogen system, that directly degrade fibrin, and that do not generate a systemic lytic state.

## ALFIMEPRASE

Alfimeprase (Nuvelo, Inc., Sunnyvale, CA) is a novel, direct-acting thrombolytic agent that is undergoing evaluation in clinical trials for acute PAO and central venous access device occlusion. Alfimeprase is a metal-

loproteinase produced with recombinant DNA technology and is a genetically modified variant of fibrolase. Fibrolase is an enzyme that proteolytically cleaves the  $\alpha$  and  $\beta$  chains of fibrin(ogen) independent of plasminogen activation to plasmin and directly dissolves thrombi.

**"A key characteristic of alteplase is that it directly degrades fibrin; it does not work by activating plasminogen."**

A key characteristic of alteplase is that it directly degrades fibrin; it does not work by activating plasminogen. Another important aspect is the speed at which the clot is dissolved. Preclinical and clinical testing have demonstrated the ability to lyse large peripheral arterial thrombus and restore blood flow in less than 4 hours, and the ability to lyse smaller catheter-tipped thrombus in as little as 5 minutes.

One might anticipate that the direct degradation of fibrin by alteplase would still generate systemic thrombolysis and continued risk of remote hemorrhage; however, it appears that alteplase is only active at the site of drug delivery. As soon as the drug enters the systemic circulation, apart from an actual thrombus, it becomes bound to  $\alpha_2$  macroglobulin (a protein found in abundance in circulating blood), rendering the drug functionally inactive (Figure 1). Clinically tested alteplase doses were selected so as not to exceed the expected minimum serum  $\alpha_2$  macroglobulin binding capacity. The  $\alpha_2$  macroglobulin/alteplase complex is then cleared by the liver. This mechanism of systemic inactivation and clearance provides a safety mechanism for use. Generation of a systemic "lytic state" seems improbable. Alteplase has the potential to possess an improved safety profile compared to plasminogen activators.

### Clinical Trial Results

The phase 1 trial with alteplase was an open-label, single-dose, dose-escalation study to evaluate the safety, pharmacokinetics, and thrombolytic activity of alteplase in patients with chronic PAO. The study demonstrated no major hemorrhagic events, no significant local or systemic toxicity, no effect on plasma plasminogen and fibrinogen levels, and unanticipated evidence of arterial recanalization in 40% or eight of 20 subjects.<sup>10</sup>

The phase 2 trial in acute PAO (NAPA-1) assessed the safety profile and activity of three different dose levels

(0.1, 0.3, and 0.6 mg/kg) of intrathrombus alteplase. The trial demonstrated the ability of alteplase to rapidly lyse thrombus, rapidly restore arterial blood flow, improve ankle systolic blood pressure, and impact the need for subsequent open vascular surgery. In the phase 2 trial, no major bleeding events were unequivocally attributed to the drug, and no intracranial hemorrhages were reported. Investigators reported thrombolysis rates up to 76% and restoration of arterial flow rates up to 60% at only 4 hours after initiation of therapy. In addition, up to 69% of patients were open vascular surgery-free at 30 days.

A phase 3, multinational, randomized, clinical trial evaluating alteplase versus placebo in patients with Rutherford class I and IIa acute PAO (NAPA-2) is currently enrolling patients. The NAPA-2 trial will hopefully support regulatory approval for alteplase in this indication.

### CONCLUSIONS

Thrombolysis has become the standard initial treatment for acute PAO in threatened but viable limbs in many institutions. Urokinase, tPA, and rPA continue to be used without an FDA approval for this indication (urokinase is currently available but is no longer being produced). Continued development of alteplase holds the potential to revolutionize the treatment of acute PAO by speeding the restoration of arterial flow and minimizing the risk of hemorrhage at remote sites. ■

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