Leading French experts discuss the place of thrombolysis in the modern era.
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The Place of Thrombolysis in the Treatment of Peripheral Arterial Thrombosis

A French multidisciplinary expert panel met to discuss the place of thrombolysis for the treatment of peripheral arterial thrombosis in the modern setting.

BY PATRICK FEUGIER, MD, PhD; ROMARIC LOFFROY, MD, PhD, FCI RSE; JEAN PICQUET, MD, PhD; LUDOVIC BERGER, MD, PhD; ERIC DUCASSE, MD, PhD; AND HERVÉ ROUSSEAU, MD, PhD

Thrombolysis, an established and effective treatment for peripheral arterial thrombosis, has been popular for decades. During thrombolysis, administration of a thrombolytic drug destroys the blood clot. All currently available thrombolytic agents are plasminogen activators; they induce blood clot destruction by converting plasminogen into plasmin, an enzyme that cuts and destroys the fibrin polymer network that unites the thrombus. Because of this lytic action on the fibrin polymer network, thrombolytic agents are also called “fibrinolytic agents.”

ADMINISTRATION ROUTE AND INFUSION METHODS

In the early days of thrombolytic therapy, thrombolytic agents were commonly administered via a central route. Currently, however, this systemic administration route has been abandoned, except for certain specific indications. Today, thrombolytic agents are administered in situ during the arterial revascularization procedure, meaning that the drug is injected close to or directly into the thrombus. This evolution toward a local administration route was driven by improved efficacy, thanks to the increased local intrathrombus fibrinolysis, as well as a reduction in systemic bleeding complications.

There are several recognized methods for thrombolytic delivery: bolusing (lacing), continuous infusion, pulse-spray infusion, stepwise infusion, graded infusion, and enclosed infusion. The method that is most often used today is an intrathrombus high-dose bolus, followed by a medium-dose continuous infusion; it is the least complex protocol, simplifying the overall procedure, and at the same time is highly effective. The bolus method is the delivery of a single, highly concentrated dose of thrombolytic agent throughout the occlusion, in order to saturate the occluded vessel area with the drug. During the continuous infusion, the catheter is connected to a pump, and a constant drug delivery is obtained (see page 10 for an example of a protocol).

THROMBOLYTIC AGENTS

Several thrombolytic agents are currently on the market, including streptokinase, urokinase, alteplase, tenecteplase, and reteplase. The indirect plasminogen activator, streptokinase, was the first agent used for intra-arterial thrombolysis, but its use has been mostly abandoned because of its lesser efficacy and its highly allergenic nature. The use of alteplase, reteplase, and tenecteplase for peripheral artery thrombosis in Europe is not very common, as these agents are not approved for this indication. On the other hand, urokinase is approved for this purpose and is available in most European countries. Moreover, urokinase has been reported to have a better safety profile than alteplase for the treatment of peripheral artery thrombosis.

MONOTHERAPY OR COMBINATION THERAPY WITH A MECHANICAL RECANALIZATION (PHARMACOMECHANICAL THROMBOLYSIS [PMT])?

Mechanical forces can be added to thrombolysis to reduce the therapy duration and improve efficacy on old thrombi. More and more endovascular thrombectomy devices are becoming commercially available, offering a wide variety of mechanical forces, including aspiration, rheolysis, rotational fragmentation, and ultrasounds. An example of a mechanical force frequently associated with thrombolysis in France is an attempt of thrombus aspiration before the start of the thrombolytic infusion. Attempting thrombus aspiration allows the bulk of the thrombus to lessen, thereby reducing treatment duration and the risk of distal embolization. An important downside of endovascular thrombectomy devices, however, is their high cost. Moreover, at the moment, few endovascular
Thrombectomy devices are reimbursed in France and Belgium. A note of caution is warranted for these endovascular thrombectomy instruments, as the safety and efficacy has not been evaluated for all devices in randomized settings.\(^1\)

Thrombolysis can also be added to open surgery techniques to remove the residual thrombus or microemboli in the small arteries and vascular bed (see page 6 and Figure 1 for a proposed algorithm for the selection of the appropriate treatment according to the patient category).\(^6\)

**PROS AND CONS**

**Advantages**

Thrombolysis offers several advantages in comparison to mechanical destruction of the thrombus, using endovascular thrombectomy devices or open surgery.

**Nontraumatic.** A key advantage of thrombolysis is that it does not damage the vessel wall. This is an important characteristic, as vessel injury provokes a thrombogenic endothelial environment, increasing the risk of thrombus recurrence.\(^1\) The absence of vessel trauma is a unique asset of thrombolysis, as vessel damage is commonly reported after use of mechanical endovascular devices as well as open surgery. For example, thromboembolectomy with a Fogarty catheter (Edwards Lifesciences) is known to traumatize the vascular endothelium and induce potential vasospasm.\(^7\)

For the more recent endovascular techniques, damage is frequently reported with arteriovenous fistula in 0% to 5% and vessel perforations in 4.8% to 10% of the cases treated with rotational endovascular devices.\(^8,9\)

Moreover, the radiography-documented positioning of the catheter combined with the non-aggressive nature of the thrombolytic infusion reduces the risk of adverse events encountered when using mechanical thrombus removal therapies, which are rather aggressive and “blind.” The use of thrombolysis has minimal risk of rupture of an underlying aneurysm or dislocation of an endoprosthesis—complications that are reported after thromboembolectomy with a Fogarty catheter.\(^10,11\)

This dissolution of the thrombus without inflicting further damage to the vessel wall allows the interventionist to bring the lesion back to the condition right before thrombosis and visualize the underlying pathology.\(^12\) This permits the concomitant selective correction of the underlying lesion using other endovascular techniques (eg, balloon angioplasty or stents) without extensive vascular trauma, thereby eliminating the threat of rethrombosis.

**Limited invasiveness.** Because thrombolysis is administered via catheter, the invasiveness of the technique is limited to catheter insertion, and the procedure only requires local anesthesia. The fact that the interventionist does not need to (re-)open or deeply anesthetize the patient is especially important for those who have undergone multiple operations or individuals with concomitant pathologies. Less cardiopulmonary adverse events have been reported for thrombolysis than for open surgery, which was associated with better patient survival in the thrombolysis group.\(^13,14\)

Another advantage of the limited invasive nature of thrombolysis is a reduction in wound infections in patients treated with thrombolysis in comparison to open surgery.\(^14\)

**Penetration into the small vessels.** Thrombolytic molecules have the capacity to permeate into the small vessels and vascular bed because of their small size. This is in contrast to open surgery techniques and mechanical endovascular techniques, for which penetration is limited to the diameter of surgical tools and catheters. The complete removal of the thrombus is key not only to restore the blood flow in the main vessel but also to remove the distal flow obstruction and reduce the risk of thrombus recurrence. For this reason, thrombolysis is often added after open surgery/mechanical thrombectomy devices, as it not only removes the residual thrombus in the large arteries but also removes the thrombus or microemboli (that have parted distally after the mechanical intervention) in the small arterioles and vascular bed.\(^15\)

**Disadvantages**

On the other hand, thrombolysis also has some disadvantages.

**Risk of bleeding.** A disadvantage of thrombolysis that is inherent to its mechanism of action is the risk of bleeding. Therefore, a detailed examination of the patient is essential before the start of thrombolytic therapy to enable the exclusion of patients with contraindications to thrombolytic agents. This risk of bleeding depends on the dose of the thrombolytic agent that is being administered and is much less important for a single bolus injection (no significant increase in bleeding complications with a dose up to 500,000 IU urokinase administered as adjuvant to operative lower extremity revascularization\(^16\)) than for a continuous infusion over several days.\(^17\) It is also important to note that the incidence of bleeding today is much lower than the incidence reported for administration via a central route in the literature from the 1980s to the 1990s, thanks to the local, directed infusion of the thrombolytic agent. Recent data from France show an incidence of intracranial bleeding of 0.4% for a protocol of a bolus plus continuous infusion of a medium dose of the thrombolytic agent (Feugier P, Picquet J, et al, unpublished data, 2018).

**Treatment duration.** The thrombolytic treatment dissolves the thrombus gradually, as the activated plasmin eats away
layer after layer of the fibrin network. Therefore, thrombolysis as monotherapy can take several hours or even up to a couple of days (depending on the dose/h of the infused thrombolytic agent and the size of the thrombus), during which close surveillance of the patient is required. It is important to note, however, that although it might take some time before the thrombus is completely dissolved, oxygen and nutrients will be able to pass the partially dissolved occlusion much sooner.

**Most effective on a fresh thrombus.** In order for the thrombolytic agent to break down the fibrin network, it has to be able to penetrate into the thrombus. This penetration is much easier in a fresh thrombus (ideally < 15 days \(^{18}\) but up to 30 days \(^{19}\)) than in a thrombus that is old, established, and has a very organized and hard structure. For the removal of old thrombus, it is best to combine the thrombolytic agent with a mechanical thrombus removal strategy.

**Microembolization.** During thrombolysis, as during mechanical thrombectomy techniques (eg, ballooning an arterial stenosis with fresh clot), it is possible for small parts of the thrombus to break off and part distally, where they block the arterial collateral vessels or small distal vessels (occurs in 1%–15% for catheter-directed thrombolysis and 0%–14% for mechanical thrombectomy).\(^{1,3}\) These microemboli can be very painful for the patient, because they cause an actuation of ischemia that must be managed. However, these distal microemboli can be easily dissolved by further continuation of the thrombolysis.

**Costs.** A disadvantage of thrombolysis from an economic point of view is the cost of the thrombolytic agent itself as well as the necessity of close follow-up on a high- or medium-surveillance unit. The degree of this disadvantage depends on the dose of thrombolytic used and the treatment duration.

**Conclusion.** These advantages and disadvantages underline the importance of patient selection.

### PATIENT SELECTION

**How is the diagnosis of peripheral artery thrombosis made?**

The diagnosis of peripheral artery thrombosis is made using a Doppler echocardiogram, a CT angiography scan, or angiography. Right before the intervention, angiography is performed to determine the precise location, actual length, and morphology of the lesion, as well as the collateral flow, inflow, and distal runoff vessels.

**How are patients with acute limb ischemia classified?**

A classification system was defined by the Society for Vascular Surgery and updated by the TransAtlantic Inter-Society Consensus II guidelines in 2007 for describing the degree of acute limb ischemia (this classification is sometimes also referred to as the *Rutherford classification for acute limb ischemia*—see Table 1).\(^{20}\) The main objective of this categorization is to stratify the acuity of limb ischemia into defined groups for decision-making purposes.

**Which type of patients will benefit from thrombolysis?**

In general, all patients without contraindications can benefit from thrombolysis; however, the severity of the ischemia will determine whether treatment can be thrombolysis as monotherapy or whether it has to be associated with mechanical endovascular thrombectomy or open surgery (combination therapy) (Figure 1).

The selection of the type of therapy that will be most advantageous for the patient is based on the advantages and disadvantages of the therapeutic strategies, as previously mentioned.

Patients who will benefit from catheter-directed thrombolysis have the following characteristics: (1) recent thrombosis (ideally < 15 days\(^{18}\); up to 30 days\(^{19}\)), (2) no sensory-motor deficit (acute limb ischemia category I and IIa) so there is time to intervene, and (3) no

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### TABLE 1. CLASSIFICATION OF ACUTE LIMB ISCHEMIA\(^{20}\)

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>Prognosis of the Limb</th>
<th>Physical Examination</th>
<th>Doppler Signals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensory Loss</td>
<td>Muscle Weakness</td>
</tr>
<tr>
<td>I</td>
<td>Viable</td>
<td>Not immediately threatened</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>II</td>
<td>Threatened</td>
<td></td>
<td>Minimal (toes)</td>
<td>None</td>
</tr>
<tr>
<td>IIa</td>
<td>Marginally</td>
<td>Salvageable with prompt treatment</td>
<td>More than toes, pain at rest</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>IIb</td>
<td>Immediately</td>
<td>Salvageable with immediate treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Irreversible</td>
<td>Major permanent tissue loss</td>
<td>Anesthetic</td>
<td>Paralysis</td>
</tr>
</tbody>
</table>

contraindications for thrombolytic therapy (see paragraph on contraindications).

For the patients with an older thrombus or a sensory-motor deficit (acute limb ischemia category IIb), mechanical endovascular thrombectomy or open surgery is recommended, as the ischemia is very acute and has to be resolved as quickly as possible. Furthermore, we recommend combining these techniques with the administration of a thrombolytic agent (bolus ± continuous infusion) to complete thrombus removal of the entire vascular bed.

Which type of occluded artery can be treated by thrombolysis?

Thrombolysis is a good therapeutic option for all types of vessels, as it has been shown to be effective on native vessels or prosthetic bypass grafts and endoprostheses.

Does the anatomic position of the thrombus play a role?

Thanks to the endovascular approach, avoiding sometimes challenging surgical incisions, thrombolysis can be used to treat thrombi in particularly interesting locations. Therefore, thrombolysis is a particularly interesting solution to retain in the therapeutic arsenal for peripheral arteries (eg, distal arteries of the hand or foot and visceral arteries, including renal and mesenteric arteries).

Which are the most encountered contraindications for thrombolytic therapy?

As a rule, most contraindications to thrombolysis are aimed at minimizing the risk of bleeding; a nonexhaustive list of the absolute and relative contraindications can be found in Table 2. Absolute contraindications to thrombolysis include active or recent internal bleeding, uncontrollable changes in hemostasis, intracranial neoplasm, or recent (within 2 months) cerebrovascular events or craniotomy. Relative contraindications to thrombolysis include recent major surgery, organ biopsy, trauma, gastrointestinal bleeding, pregnancy, postpartum period, uncontrolled hypertension, and diabetic hemorrhagic retinopathy. Within this context, it is important to note that the risk of bleeding strongly depends on the dose of thrombolytic agent infused and the duration of infusion. These contraindications will therefore be more relative for the injection of a bolus of thrombolytic agent versus a continuous infusion during several hours or days. In general, it is key that the prescribing doctor always weighs the risk of bleeding against the benefits of the thrombolytic treatment.

**THROMBOLYTIC PROCEDURE: PRACTICAL STEPS**

1. **Preprocedural Laboratory Investigations**

   Blood work before the start of treatment includes blood count, platelets, a full coagulation profile (prothrombin activity, international normalized ratio), and specific markers for thrombus burden (fibrinogen, D-dimer).

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**Figure 1.** Treatment-decision algorithm for patients with acute limb ischemia.\textsuperscript{1,21} Abbreviation: PMT, pharmacomechanical thrombolysis.
time and/or international normalized ratio, activated partial thromboplastin time \([\text{aPTT}]\), and fibrinogen levels, and renal and hepatic function.

(2) Vascular Access Site

The choice of puncture site should be consistent with lesion location and the patient’s anatomical particularities. For the lower limb, the vascular access site is most commonly retrograde, via the contralateral common femoral artery, allowing access to the contralateral iliac axis or the lower limb by crossover catheterization. In case of distal arterial occlusion, however, anterograde femoral puncture is preferred in a patient in whom homolateral puncture is feasible. It is also possible to consider inserting the catheter for thrombolytic treatment by brachial or popliteal routes, but this remains an exception.

A single arterial wall puncture is needed. We recommend performing this puncture under ultrasonography. Only the anterior arterial wall should be punctured to avoid hematoma or false aneurysms of the posterior wall. After sheath placement, the interventionist secures vascular access by skin fixation.

(3) Angiography

Before revascularization, high-quality diagnostic angiography is performed to assess the inflow and outflow arteries as well as the nature and length of thrombosis.

(4) Guidewire Traversal Test

The guidewire traversal test is an important parameter that, if successful, predicts the positive outcome of catheter-directed thrombolysis. If the thrombus can be crossed with the guidewire, this indicates that the thrombus is recent (fresh) and not yet older and highly organized. Moreover, this test allows the interventionist to create a small channel inside the thrombus to facilitate fibrinolysis.

(5) Thrombolytic Infusion

After guidewire placement, a catheter (preferably a multi-side hole catheter) is inserted into the thrombus, and the thrombolytic therapy can be initiated. It is important to note that the catheter should be positioned in or close to the proximal end of the thrombus, but that one cannot pass the thrombus completely with the catheter, as this would lead to a systemic administration. After the first period of fibrinolysis and according to the results of the angiographic control, the interventionist can advance the catheter further into the thrombus (see [6] Patient Monitoring).

Concomitant administration of anticoagulant therapy?

Treating patients concomitantly with heparin is recommended to prevent pericatheter thrombosis and rethrombosis of the treated vessel. In practice, heparin can be infused via the arterial sheath or via a peripheral venous infusion. As heparin has been shown to increase bleeding complications, it is now standard to use a “subtherapeutic” dose that produces only mild prolongation of the aPTT (see example of a protocol on page 10).

(6) Patient Monitoring

Close medical surveillance of the patient during catheter-directed thrombolysis is essential due to the risk of bleeding complications. Patients need to be monitored carefully in the intensive care unit or the vascular ward. Nurses are key to patient monitoring, as they must closely watch their clinical status. These duties include regular monitoring of the patient’s condition: general well-being, blood pressure, bruises, bleeding at the puncture site, pain, and the appearance of the thrombosed limb. Every 4 hours, a blood analysis has to be performed including blood count, fibrinogen, aPTT, and/or anti-factor Xa assay. The fibrinogen levels of this analysis are used to adapt the urokinase dosage, and the aPTT and/or anti-Xa values are used to adapt the heparin doses. Regular angiographic controls are performed.
in order to follow the dissolution of the thrombus and to allow catheter repositioning if required. The timing of the angiographic controls depends on the protocol and the pathology treated and varies from a repeat angiogram every 4 to 12 hours to a daily angiographic control.

What if the pain increases during the treatment? Sometimes at the beginning of the thrombolytic therapy, the pain intensifies. This increase in pain is generally caused by small parts of the thrombus that are liberated from the dissolving thrombus and distally obstruct small arteries or collateral arteries, thereby causing ischemic pain. This pain is transient, as these small microemboli will dissolve upon further administration of the thrombolytic agent. Pain by itself after fibrinolysis initiation is actually not an argument to stop the fibrinolysis. Administration of the appropriate pain medication is indicated.

(7) Correction of the Underlying Lesion if Applicable

Once the flow is restored, angiography is performed to detect any underlying lesion, allowing for the immediate, appropriate, and selective lesion correction with catheter-based techniques (most commonly angioplasty with or without stenting) or open revascularization.

CONCLUSION

Thrombolysis has several valuable characteristics that offer a benefit in the treatment of patients with peripheral arterial thrombosis. Depending on the severity of the ischemia and the age of the thrombus, thrombolysis will be administered either as monotherapy or in combination with mechanical endovascular thrombectomy techniques or open surgery.

The selective, non-aggressive nature of thrombolysis constitutes a key advantage, because it does not aggravate the underlying vascular pathology and permits for the selective correction of the underlying lesion, thereby minimizing the risk of rethrombosis. Although thrombolysis has a higher risk of bleeding complications compared with open surgery, the risk of cardiopulmonary adverse events is much less important, resulting in an ameliorated survival rate for thrombolysis.

The unique ability of thrombolytics to reach even the smallest vessels explains the value of adding thrombolysis to a mechanical endovascular thrombectomy procedure or open surgery. The further removal of the thrombus in small arteries and the vascular bed improves the clinical outcome and reduces thrombus reocurrence.

In conclusion, we believe that thrombolytic therapy should be a part of the vascular team’s armamentarium in their mission to safely and successfully treat patients with peripheral arterial thrombosis.

EXAMPLE OF A PROTOCOL FOR INTRA-ARTERIAL THROMBOLYSIS

PRE-INTERVENTION PROCEDURES

Patient

Blood work
Serum electrolytes, complete blood count, INR, aPTT*, fibrinogen, creatinine, hepatic function.

Ongoing medical treatments
Stop ongoing treatment with anticoagulants, NSAIDs, ticlopidine, clopidrogrel, ticagrelor, prasugrel, and nephrotoxic medication.

Additional recommendations
Patient needs to be kept on an empty stomach for 8 hours before angiography.

Preparation of the Solutions

UROKINASE
Prepare standard urokinase solution of 50,000 IU/mL in water for injection.

Urokinase solution for the bolus injection of 2,000 IU/kg in 20 minutes
Take the amount of the standard solution (50,000 IU/mL) corresponding to a dose of 2,000 IU/kg.
Dilute with NaCl 0.9% to obtain a total volume of 4 mL.

Urokinase solution for the continuous infusion at 2,000 IU/kg/h for 12 hours of infusion
Take the amount of the standard solution (50,000 IU/mL) corresponding to a dose of 12 X 2,000 IU/kg.
Dilute with NaCl 0.9% to obtain a total volume of 48 mL.

Examples of urokinase dilutions per body weight of the patient:

<table>
<thead>
<tr>
<th>Patient’s weight</th>
<th>IU urokinase</th>
<th>mL urokinase standard solution (50,000 IU/mL)</th>
<th>mL of NaCl 0.9%</th>
<th>IU urokinase = 12 x 2,000 IU/kg</th>
<th>mL urokinase standard solution (50,000 IU/mL)</th>
<th>mL of NaCl 0.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 kg</td>
<td>120,000 IU</td>
<td>2.4 mL</td>
<td>1.6 mL</td>
<td>1,440,000 IU</td>
<td>28.8 mL</td>
<td>19.2 mL</td>
</tr>
<tr>
<td>70 kg</td>
<td>140,000 IU</td>
<td>2.8 mL</td>
<td>1.2 mL</td>
<td>1,680,000 IU</td>
<td>33.6 mL</td>
<td>14.4 mL</td>
</tr>
<tr>
<td>80 kg</td>
<td>160,000 IU</td>
<td>3.2 mL</td>
<td>0.8 mL</td>
<td>1,920,000 IU</td>
<td>38.4 mL</td>
<td>9.6 mL</td>
</tr>
<tr>
<td>90 kg</td>
<td>180,000 IU</td>
<td>3.6 mL</td>
<td>0.4 mL</td>
<td>2,160,000 IU</td>
<td>43.2 mL</td>
<td>4.8 mL</td>
</tr>
<tr>
<td>100 kg</td>
<td>200,000 IU</td>
<td>4 mL</td>
<td>0 mL</td>
<td>2,400,000 IU</td>
<td>48 mL</td>
<td>0 mL</td>
</tr>
</tbody>
</table>

HEPARIN
Heparin continuous infusion at 100 IU/kg/12 hours
Prepare a solution of 100 IU/kg in 48 mL.

START THROMBOLYSIS

Urokinase Bolus
At the moment of the initial arteriography, a urokinase bolus of 2,000 IU/kg in 4 mL is administered in 20 minutes (pump speed of 12 mL/h) via a multiperforated catheter placed into the thrombus.

Continuous Infusion
Start the infusion of urokinase and heparin at the same time.

Urokinase:
Intra-arterial injection via the multiperforated catheter (in thrombus) at a pump speed of 4 mL/hour.

Heparin:
Peripheral IV injection or injection into the arterial catheter sheath at a pump speed of 4 mL/hour.

aPTT* = TCA = temps de céphaline activé
Patient Surveillance

Strict bed rest, do not fold the leg that is being treated, sitting position of 60° if possible. Do not touch the catheter or the bandage.

Every 4 hours: clinical surveillance
- Thrombosed limb: progression of lysis: pain, temperature, mobility, sensitivity/sensibility, color
- Bleeding: at the access site or any other abnormal bleeding (ears, nose, gums, urine, etc)
- Patient's general status: alertness, arterial blood pressure, heartbeat

Every 4 hours: biological surveillance
- Complete blood cell count, INR, aPTT, and fibrinogen.

Every 24 hours: radiological surveillance
- If required, adapt catheter position according to the progression of the thrombolysis.

Note
- In case of temporary ischemic acutization, appropriate pain medication needs to be administered.

Adaptation of the Doses

Revision of the doses
- The doses are reassessed according to the clinical, biological, and radiological results. A new solution of urokinase is prepared in line with this decision.

<table>
<thead>
<tr>
<th>Fibrinogen &gt; 2 g/L</th>
<th>Same dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen between 1–2 g/L</td>
<td>Half the dose and new biological surveillance after 4 hours</td>
</tr>
<tr>
<td>Fibrinogen &lt; 1 g/L</td>
<td>Stop urokinase treatment for 4 hours, new biological analysis after 4 hours After 4 hours, fibrinogen &gt; 2 g/L, restart urokinase at half dose</td>
</tr>
</tbody>
</table>

ADAPTATION OF HEPARIN DOES BASED ON aPTT* (RATIO) LEVELS

| aPTT* ratio between 1 and 1.5 | Increase the dose of heparin by 1,000 IU/12 hours |
| aPTT* ratio between 1.5 and 2 | Keep administering the same dose of heparin |
| aPTT* ratio between 2 and 3 | Lower the heparin dose by 500 IU/12 hours |
| aPTT* ratio between 3 and 4 | Lower the heparin dose by 1,000 IU/12 hours |
| aPTT* ratio > 4 | Stop heparin administration Measure aPTT levels again after 4 hours, and readapt the dose |

Note
- Heparin is co-administered during the whole duration of the thrombolytic treatment at a dose adapted to the aPTT levels.

When interruption of urokinase is required because of clinical and/or biological data:
- Interruption < 12 hours: keep the intra-arterial catheter perfused (eg, with isotonic saline solution)
- Interruption > 12 hours: remove the intra-arterial catheter temporarily

END OF THE THROMBOLYTIC TREATMENT

Timing

- Repermeabilization of the occluded limb
- Biological or clinical complications
- No further radiographic improvement

Note: After the thrombolytic treatment:
- The morning after stopping the thrombolytic therapy: complete biological analysis (complete blood cell count, blood electrolytes, INR, aPTT, and fibrinogen).
- The patient is put on the appropriate anticoagulant medication.

aPTT* = TCA = temps de céphaline activé
Case Reports Illustrating the Application of Expert Consensus

POPLITEAL ARTERY THROMBOSIS COMPLICATING A POPLITEAL ENTRAPMENT WITH DISTAL EMBOLIZATION

By Prof. Patrick Feugier, MD, PhD

DIAGNOSTIC EVALUATION
A 23-year-old man without cardiovascular risk factors presented to the emergency department of our hospital with severe pain in his right foot and leg, which had been persistent for 48 hours. After a few hours of skiing, the patient abruptly felt this pain, associated with a feeling of coldness and paresthesia. This symptomatology and the disappearance of the popliteal and pedal pulses, specifically on the right side, led to the diagnosis of category IIA acute limb ischemia. CT angiography was urgently requested. It confirmed the thrombosis of the retroarticular popliteal artery, multiple thrombi in all arteries of his lower leg, the absence of parietal abnormality on the other arteries, and the presence of an arteriovenous diastasis that was caused by a complementary muscle bundle of the medial gastrocnemius muscle. The initial diagnosis of acute limb ischemia caused by a thrombosis in the popliteal artery related to a complicated popliteal entrapment was maintained (Figure 1).

TREATMENT APPROACH
A fibrinolytic procedure was proposed to the patient, who had no contraindications for this treatment. Access to the artery was conducted by an echo-guided homolateral femoral puncture. A flexible guidewire easily crossed the thrombotic lesion, and a multiperforated 4-F catheter was positioned within the thrombus. A local injection of 100,000 IU of urokinase was immediately administered. Subsequently, in situ fibrinolysis was started at a dosage of 2,500 IU/kg urokinase per hour via an electric syringe pump, which was combined with systemic intravenous heparin administration (100 IU/kg/12 hours). Clinical evaluations were scheduled every hour and biological assessments every 8 hours.

At the 24-hour angiographic control, we observed an almost complete repermeabilization of the popliteal artery. The multiperforated catheter was repositioned to improve urokinase infusion into the arteries of his leg, where several residual thrombi remained. The peripheral pulses were recovered after 48 hours of thrombolysis, and control angiography confirmed complete dissolution of the intra-arterial popliteal and associated crural thrombi (Figure 2). Dynamic maneuvers confirmed the entrapment of the popliteal artery.

One week after the fibrinolytic treatment, we operated on the patient. The intervention consisted of an isolated lift of the entrapment via a posterior access. A control echo-Doppler followed by perioperative angiography confirmed the absence of residual thrombotic popliteal stenosis.

Two-year follow-up showed excellent long-term results, without the need for complementary treatments.

DISCUSSION
The fibrinolytic treatment allowed us the restitutio ad integrum of arterial patency in this case of acute ischemia, without arterial surgical intervention on the lower limb arteries. The targeted intervention on the popliteal entrapment was then able to be carried out in a second procedure in excellent clinical conditions.

Figure 1. Angiography confirmed the popliteal thrombosis, associated with crural embolization.

Figure 2. Control angiography after 48 hours of in situ fibrinolysis.
DIAGNOSTIC EVALUATION
A 75-year-old man presented with acute ischemia in the left foot and calf 4 months after left popliteal artery reconstruction using a synthetic bypass graft for the treatment of a popliteal aneurysm.

TREATMENT APPROACH
The patient was referred for catheter-directed thrombolysis (CDT) because of the risks involved in reoperation, despite warning of the bleeding risks associated with CDT therapy. Prior to the initiation of thrombolysis, coagulation tests were performed and contraindications were eliminated. Selective angiography of the left superficial femoral artery was performed through a 5-F sheath placed into the left common femoral artery via an antegrade approach under local anesthesia and ultrasound guidance. The arteriogram showed complete thrombotic occlusion of the bypass graft without any opacification of the below-the-knee arteries (Figure 1A).

A guidewire was passed through the occluded graft prior to insertion of the thrombolysis catheter. A 4-F multi-side-hole, straight catheter was then placed within the proximal part of the thrombus (Figure 1B), after which a continuous infusion of urokinase was initiated. A dose of 600,000 IU urokinase was infused in 12 hours (50,000 IU/hour). At the start of thrombolysis, 5,000 IU of unfractionated heparin was given intra-arterially. During the thrombolysis, unfractionated heparin (200 IU/hour) was administered through the introducer sheath, with the dose adjusted to activated partial thromboplastin time values to a target of two to three times the reference value. Fibrinogen, activated partial thromboplastin time, hemoglobin, platelets, and creatinine levels were checked continuously according to protocol. Follow-up angiography the next day showed no residual thrombus within the graft (Figure 1C) but did show a high-grade stenosis at the lower popliteal artery anastomosis (Figure 1D), which was successfully treated by placement of a 5- X 19-mm balloon-expandable Herculink stent (Abbott Vascular; Figure 1E). The left peroneal and posterior tibial arteries were patent at the end of the procedure, whereas the anterior tibial artery was chronically occluded. No bleeding complications occurred. No surgery or thrombectomy was needed. The patient was discharged after 2 days without any symptoms. Duplex graft surveillance was performed after thrombolysis according to local protocol. Secondary patency of the bypass graft was maintained at 3-year follow-up.

DISCUSSION
In conclusion, intra-arterial thrombolysis using urokinase is usually a safe and effective therapy for patients with thrombotic occlusion of synthetic lower extremity bypass grafts presenting with acute limb-threatening ischemia, and it allows a high rate of secondary patency, avoiding amputation.
TWO-STEP APPROACH FOR A THROMBOSED POPLITEAL ANEURYSM

By Prof. Jean Picquet, MD, PhD

DIAGNOSTIC EVALUATION

An 85-year-old man without any relevant medical history presented to our hospital with sudden, persistent right lower limb pain. On physical examination, the right foot was cold and livid, without a sensory-motor deficit of the right leg. The patient’s heart rate was regular, both the femoral and the left popliteal pulses were found, and filling of both popliteal regions was present. Rutherford category IIa acute right lower limb ischemia was diagnosed. A CT scan with contrast was performed, demonstrating a thrombosed popliteal artery aneurysm in the right leg and another large popliteal artery aneurysm in the left leg.

TREATMENT APPROACH

After diagnosis, intravenous heparin (200 IU/kg/24 hours) was infused. The patient was subsequently transferred to a hybrid operating room, where initial angiography confirmed the thrombosed aneurysm without patent distal runoff in the right leg (Figure 1). Local in situ thrombolysis was started prior to the surgical procedure in order to revascularize the arterial runoff vessels distal to the aneurysm. Urokinase was administered at 2,500 IU/kg per hour via a multiperforated catheter inserted using contralateral femoral access, with the multiperforated segment of the catheter placed distal to the thrombosed aneurysm. During thrombolytic therapy, the patient remained under close clinical and biological surveillance at the vascular unit. A second round of angiography was performed 24 hours after the start of in situ thrombolysis, showing revascularization of the right lower limb with a patent fibular artery distal to the popliteal aneurysm (Figure 2).

A subsequent operation involved excision of the right leg aneurysm and creation of a saphenous femorodistal bypass. A few weeks later, the aneurysm of the left leg was treated with a similar surgical approach. Three years later, the patient continues to do well.

DISCUSSION

Surgery for thrombosed popliteal aneurysms can have rather disappointing results, with a high rate of secondary amputation, because the distal arterial runoff is usually also thrombosed or inadequate.

In this case report, in situ thrombolysis performed prior to the surgical intervention allowed us to “clean” the arterial runoff and largely facilitated the subsequent surgical procedure. We recommend this approach to be used as a general strategy, except for acute limb ischemia with sensory-motor deficit.

Figure 1. Initial angiography demonstrated a large left popliteal aneurysm and thrombosed arteries distal to the right superficial femoral artery.

Figure 2. Final angiography after intra-arterial thrombolysis showed a large right popliteal aneurysm and patency of the fibular artery.
DIAGNOSTIC EVALUATION
A 57-year-old man with a history of peripheral occlusive disease was referred to our institution for the treatment of right lower extremity claudication. He had bilateral iliac stenting 8 years before his presentation and bilateral femoral artery recanalization and stenting 1 year prior. Duplex scanning indicated that the claudication recurrence was caused by occlusive evolution of the proximal femoral artery and 6-cm-long in-stent hyperplasia.

TREATMENT APPROACH
We decided to manage these lesions endovascularly with access via a left femoral artery sheath and crossover to access the right-side arteries. Initial arteriography via a 45-cm, 6-F sheath positioned in the right common femoral artery confirmed the duplex scan diagnosis. It showed a tight stenosis just below the origin of the femoral artery, proximal and distal in-stent hyperplasia, and nonocclusive mural thrombi into the first part of the popliteal artery (Figure 1). After placing two additional long nitinol stents (6- X 120-mm at the origin of the artery and 6- X 150-mm below the first stent), the femoropopliteal axis was redilated. Control arteriography after the procedure showed that, although the proximal part of the femoral artery was patent, the femoropopliteal axis was thrombosed. More importantly, there was distal embolization in all the below-the-knee (BTK) arteries (Figure 2).

To dissolve the thrombus and emboli, a 5-F straight multipurpose catheter was positioned in the popliteal artery. Urokinase was infused at 1,000 IU/kg per hour, while intra-arterial heparin was concomitantly infused through the introducer sheath at 250 IU/kg per 24 hours. Hematocrit, activated thromboplastin time, and fibrinogen level were measured 4 hours after the start of the thrombolytic treatment. At that moment, the patient had clinically recovered, and the distal part of the tibial artery displayed a normal flow (ankle-brachial index, 1). An angiogram was obtained 6 hours after the initiation of thrombolysis, showing complete resolution of the thrombus and emboli with two patent BTK arteries and a patent plantar arch (Figure 3).

The patient was discharged the same day without hemorrhagic complications or any other adverse events.

DISCUSSION
There are several cases of thrombotic intraprocedural complications that can be challenging to manage. In these instances, an intra-arterial thrombolytic infusion might be an attractive solution. This clinical case illustrates the successful utilization of intra-arterial thrombolytic therapy for the treatment of intraprocedural in situ thrombosis and distal embolization, with a recovery of the femoropopliteal axis and outflow.
THROMBOLYSIS AS ADJUNCT THERAPY TO ANGIOPLASTY AND STENTING FOR CRITICAL LIMB ISCHEMIA

By Prof. Eric Ducasse, MD, PhD

DIAGNOSTIC EVALUATION

An 89-year-old woman presented to our institution with critical limb ischemia involving rest pain and necrosis of the first toe. She was scheduled for angiography and endovascular treatment.

TREATMENT APPROACH

The patient was brought to the operating room and treated under local anesthesia and sedation. A direct puncture was made at the proximal part of the superficial femoral artery (SFA) with a 4-F, 13-cm access sheath (Terumo), and initial angiography was performed.

The initial angiogram showed an occlusion of the distal part of the SFA and the entire popliteal artery, and blood flow resumed in the mid-peroneal artery (Figure 1). Direct recanalization was performed with an 0.018-inch V-18 guidewire (Boston Scientific Corporation) inserted down to the peroneal artery. An initial predilatation was performed with a 2.5- X 8-cm balloon for 1 minute.

Next, the tibioperoneal trunk and the distal part of the popliteal artery were treated with a 3-mm X 4-cm balloon for 1 minute; the mid and proximal parts of the popliteal artery and the distal part of the SFA were treated using a 4-mm X 8-cm balloon.

Control angiography showed a flow-limiting dissection affecting the entire popliteal artery. A long, self-expanding, 5-mm X 8-cm Pulsar-18 nitinol stent (Biotronik) was used to scaffold the reopened artery. After popliteal stenting and a long inflation, the reopened popliteal artery wall showed remaining thrombus extending down to the peroneal artery (Figure 2).

The decision was made to deliver a 600,000-IU bolus of urokinase to induce the destruction of the remaining blood clots and increase the global outflow. After thrombolytic injection for 30 seconds and inflation with 3-mm X 4-cm and 4-mm X 4-cm balloons for 3 minutes each, final control angiography showed good results with satisfactory blood flow and direct connection to the remaining peroneal artery (Figure 3).

DISCUSSION

Adjunct treatment with thrombolysis is frequently used in our current practice for endovascular treatment of below-the-knee arteries. This adjunct therapy may increase the outflow by removing any residual thrombus or microemboli in the small distal or collateral arteries, and subsequently enhance procedural results and clinical follow-up.
CASE REPORT

DIAGNOSTIC EVALUATION

A 55-year-old woman with no particular medical history apart from long-standing arterial hypertension presented to our hospital. Violent lumbar pain led to a CT scan, showing fibromuscular dysplasia lesions in both renal arteries, a non-obstructive dissection on the left side, preocclusive lesions on the right side, and bilateral renal infarction (Figure 1). After a multidisciplinary consultation, the decision was made to revascularize the right renal artery, with the purpose of preserving renal function.

TREATMENT APPROACH

Initial angiography showed extensive fibromuscular dysplasia lesions in both renal arteries, with extension to the intrarenal branches on the right side (Figure 2A). Angioplasty was performed, but immediate control showed residual stenosis and a dissection in the arterial trunk (Figure 2B). Subsequently, two 6- X 18-mm stents were placed with good angiographic results (Figure 2C). The patient returned home after 2 days under antiaggregant treatment.

The patient presented with extreme pain in the right lumbar fossa 5 days after the angioplasty. A CT scan was performed, showing stent thrombosis and almost complete right renal ischemia. The same day, in situ thrombolysis was started (Figure 3).

Arteriography before thrombolysis showed obstruction of the right renal arterial trunk, and after catheterization of this occlusion, only one branch of the intrarenal division was permeable (Figure 4A). After withdrawing the catheter until the ostium of the right renal artery, a 100,000-IU bolus of urokinase was administered, followed by an infusion of 4,000 IU/min urokinase for 4 hours and a subsequent infusion of 1,000 IU/min urokinase for 10 hours with parallel heparin infusion via a long 5-F introducer sheath. Angiographic control at 12 hours showed the permeabilization of all arteries (Figure 4B). The presence of residual stenosis at the ostium of the right renal artery required the placement of another proximal prosthesis.

The postintervention course was simple, with renal function restoration and disappearance of pain. The patient was kept on low-molecular-weight heparin for 3 days, followed by low-dose acetylsalicylic acid and clopidogrel for 2 months.

DISCUSSION

Percutaneous revascularization has proven to be a safe and effective procedure in the treatment of total renal artery occlusion. The indications and technique of local

Figure 1. Presence of bilateral fibromuscular dysplastic lesions in the renal arteries with a dissection at the left side, an irregular stenosis at the right side (arrow), and the presence of segmental infarction in both kidneys (star).

Figure 2. Presence of a preocclusive stenosis of the terminal part of the right renal arterial trunk in combination with distal intrarenal lesions (A). Results after angioplasty, with residual stenosis and a local dissection (B). Placement of two stents, resulting in recovery of a normal diameter (C).
thrombolysis therapy for acute renal artery occlusions are discussed in this case report. The result of treatment depends largely on the time interval between occlusion and the beginning of treatment, but thrombolysis seems to be an effective treatment that may save renal function after up to 24 hours of arterial occlusion.

Figure 3. Conventional CT scan with three-dimensional reconstructions. Presence of an occlusion of the stent in the right kidney and right renal ischemia.

Figure 4. Distal angiography after catheterization of the stent occlusion. Vascular amputation of the retropyllic branch (arrow) with a floating thrombus (A). Repermeabilization of the arteries after 12 hours of thrombolytic treatment (B).
ENDOVASCULAR REVASCULARIZATION OF A RENAL BRANCH ACUTE OCCLUSION IN A THREE-BRANCHED STENT GRAFT

By Prof. Hicham Kobeiter, MD, PhD, and Dr. Vania Tacher, MD, PhD

DIAGNOSTIC EVALUATION
A 64-year-old woman was treated with a branched stent graft (the three branches were positioned into the celiac trunk, the superior mesenteric artery, and the left renal artery) for a thoracoabdominal aneurysm. Three months later, she went into acute renal failure due to an acute left renal branch thrombosis diagnosed with duplex ultrasound.

TREATMENT APPROACH
After intravenous heparin injection, angiography was performed under local anesthesia with a humeral approach. Left renal thrombosis was found via digital subtraction angiography (DSA) (Figure 1). The catheter and guidewire were introduced into the left renal branch and arterial trunk. DSA revealed a fracture of the distal renal branch stent, which was assumed to be the cause of the thrombosis. First, an intrastent dilatation with a 6- X 40-mm balloon was performed to straighten the stent axis. A 6- X 24-mm and a 6- X 16-mm balloon-expandable stent were successfully placed into the fractured stent for alignment. No flow was initially found in the stents, the renal artery, or the renal parenchyma after stent placement.

The flow was completely and immediately recovered in the branch, the stents, the left renal artery, and the renal parenchyma after in situ thrombolysis with a single 100,000-IU bolus of urokinase administered per intervention through a catheter (Figure 2).

Control DSA of all three branches of the endograft confirmed their patency. The patient regained renal function, with moderate renal failure. At follow-up, all three branches remained patent, and the patient did not require dialysis.

DISCUSSION
In this case, successful left renal branch revascularization of a branched endograft was achieved using a thrombolytic agent to resolve the acute thrombosis and stent placement to treat the cause and avoid recurrence.

Figure 1. Initial aortography of the left renal branch level showed a complete occlusion of the left renal branch (arrowhead) and the stents with no nephrogram. The distal stent was fractured (arrow).

Figure 2. At the end of the intervention, final aortography showed the patency of all three branches: the celiac trunk and its branches (arrows), the superior mesenteric artery (arrows), and the left renal artery (arrowhead) (A). It also showed the apparition of a left nephrogram (arrowheads) (B).