

# Rush Hemophilia & Thrombophilia Center

## Thrombotic Complication related to a central venous access device

### Central venous access device

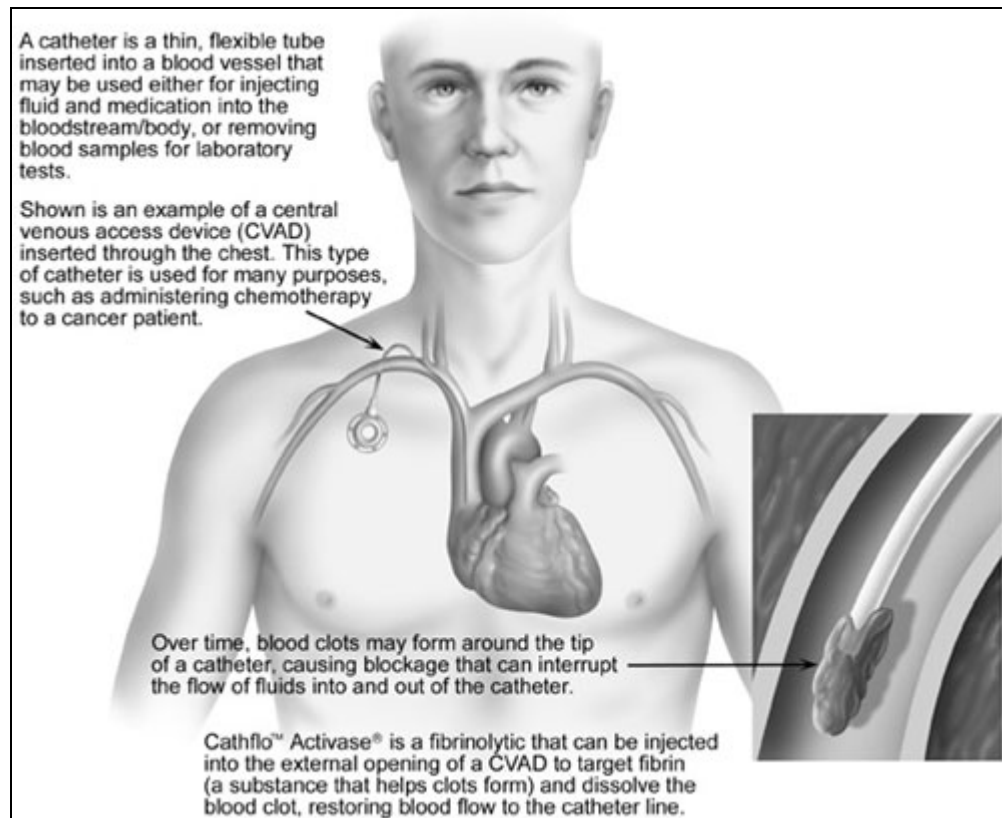
Central venous access device, or CVAD, is a broad term that includes many types of catheters (thin, flexible hollow tubes) that are inserted into and positioned within a vein in the body to deliver therapies to the bloodstream or withdraw blood for testing. CVADs are used to provide life-saving medications and critical treatment, such as chemotherapy for cancer patients, supplements for patients at risk for malnutrition who cannot receive nutrients via the digestive tract, and antibiotics for patients with severe infections.

An estimated 5 million CVADs are placed each year in the U.S., and this number is increasing as the population ages.

### Types of Central venous access device

Varying types of CVAD are used for different conditions and therapies. There are two general types of CVADs: catheters and ports. Catheters have one end positioned outside the body, while ports are surgically placed under the skin and require a special needle for access. With both catheters and ports, the opposite end of the tubing is positioned within the large vein near the heart. The most common CVADs include:

1. Peripherally inserted central catheters (PICCs)--inserted into one of the peripheral veins in the upper arm
2. Nontunneled percutaneous central venous catheters--inserted into the subclavian vein (in the chest) or jugular vein (in the neck)
3. Tunneled central venous catheters--inserted into the subclavian vein or jugular vein; subcutaneous tissue grows into the polyester fiber cuff surrounding and therefore stabilizing the catheter
4. Implanted ports--inserted into the subclavian vein or jugular vein and attached to a fluid reservoir placed in a surgically created subcutaneous pocket on the upper chest, or into an arm vein with a peripheral port pocket



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### **Thrombotic Complication related to a central venous access device**

#### **Complication associated with Central venous access devices**

Occlusions are a common complication associated with CVADs. It is estimated that 25 percent of all CVADs become occluded and that 60 percent of these occlusions are caused by thrombosis, the formation of a blood clot. When CVADs become occluded, many complications can occur, including the inability to inject or infuse solutions and/or the inability to withdraw blood.

Occlusions are generally classified as:

1. **Thrombotic:** A blood clot, or thrombus, typically develops over time when fibrin, a naturally occurring substance that promotes blood coagulation, builds up near or around the tip of the CVAD.
2. **Mechanical:** These occlusions occur when the tube is pinched (which is often observed when a CVAD catheter is placed between the rib and the collarbone), when the catheter tip moves into a smaller vein or when the tube becomes blocked against the vessel wall.
3. **Precipitate:** Precipitate occlusions may occur when two or more incompatible drugs or nutritional interact and the resulting sediment remains in the CVAD, often causing disruption of fluid transmission. Nutritional may also leave a waxy buildup of lipids on the CVAD catheter wall.

While thrombotic occlusions develop over time, mechanical and precipitate occlusions typically form spontaneously.

#### **Treatment of thrombotic complication associated with central venous access devices**

Thrombolytic agents administered in low doses have been shown to be effective in restoration of function to CVADs. However, since the thrombolytic urokinase (Abbokinase®) was withdrawn from the marketplace upon the recommendation of the U.S. Food and Drug Administration (FDA) in December 1998, there have been no approved pharmaceutical alternatives available for use in clearing thrombotic occlusions.

Genentech, Inc.'s thrombolytic Cathflo™ Activase® targets fibrin to dissolve the thrombus and restore function to the CVAD. In September 2001, the FDA approved Cathflo Activase for restoring function to CVADs as assessed by the ability to withdraw blood. In clinical trials, the most serious adverse events reported after treatment were sepsis, gastrointestinal bleeding and venous thrombosis.

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#### **Frequently Asked Questions about central venous access devices.**

Q:

What is a central venous access device?

A:

A central venous access device, or CVAD, is a broad term that includes many types of catheters (thin, flexible hollow tubes) that are inserted into and positioned within a vein in the body to deliver therapies into the bloodstream or withdraw blood for testing. It is estimated that 5 million central venous access devices are placed each year in the U.S.

Q:

What types of patients require CVADs?

A:

CVADs are placed in many different types of patients, including:

1. Cancer patients who require frequent administration of chemotherapy agents or blood withdraws
2. Patients with severe infections who require administration of antibiotics
3. Patients who have digestive problems and need to receive nutritional fluids on a regular basis
4. Any critically ill patient who requires frequent blood withdrawal or medication administration

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Q:

How is a CVAD inserted?

A:

The tube is surgically inserted into a vein in the arm or chest, depending on the CVAD's intended use and the length of time it is expected to remain in the body. It is then threaded through the vein until it reaches the superior vena cava, which carries blood from the person's upper body, including the upper trunk, head, neck and arms, into the heart.

Q:

What are the most common complications associated with CVADs?

A:

Complications of CVAD include occlusions or blockages preventing withdrawal of blood or administration of fluid. A kink in the tube, the buildup of sediment or precipitate in the line, or the most common reason, the formation of a blood clot, can cause these complications.

Q:

What is available to treat blockages in CVADs?

A:

If the CVAD becomes blocked due to a kink in the line, it may require surgical replacement. When a blood clot blocks the flow of fluids through the catheter, a clot-busting agent may be administered to dissolve the clot without the need for surgery.

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#### **Cathflo™ Activase® (Alteplase)**

##### Full Prescribing Information

##### Restoring Function to Central Venous Access Devices as Assessed by the Ability to Withdraw Blood

Cathflo Activase is a recombinant form of a naturally-occurring enzyme produced by the body known as tissue plasminogen activator, or t-PA. In September 2000, Genentech, Inc., filed a Supplemental Biologic Licensing Application (sBLA) with the U.S. Food and Drug Administration (FDA) for Cathflo Activase in restoring function to central venous access devices (CVADs). There are currently no other pharmaceutical agents marketed for this indication.

Central venous access device, or CVAD, is a broad term that includes many types of catheters (thin, flexible hollow tubes) that are inserted into and positioned within a vein in the body to deliver therapies to the bloodstream or withdraw blood for testing. It is estimated that 5 million CVADs are placed each year in the U.S., and occlusions are a common complication. It is estimated that up to 25 percent of all CVADs become occluded and that 60 percent of those occlusions are caused by thrombosis, the formation of a blood clot.

Cathflo Activase is a thrombolytic that works by targeting fibrin (the substance that causes blood to clot), dissolving the thrombus (blood clot) and restoring function to the CVAD.

Cathflo Activase is currently marketed in a different dosing regimen under the trade name Activase® (Alteplase, recombinant) for the treatment of acute myocardial infarction (AMI), acute ischemic stroke within three hours of symptom onset, and acute massive pulmonary embolism. The FDA for the treatment of AMI in November 1987 first licensed Activase for marketing.

#### **Clinical Trials**

Genentech, Inc., studied Cathflo Activase in two Phase III clinical trials assessing the safety and efficacy of the product for use in clearing occluded CVADs. The trials in the COOL (Cardiovascular thrombolytic to Open Occluded Lines) program included the COOL efficacy trial and the COOL-2 safety trial.

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Cathflo Activase was instilled as a 2 mg bolus injection directly into the lumen opening (tube that carries fluid through a CVAD catheter directly to the vein) of a CVAD. If function was not restored after the first administration, a second 2-mg dose was given after 30-minute or 120-minute dwell times.

#### **Safety**

The COOL-2 trial, a Phase IIIb, single arm, open-label study, enrolled 995 pediatric (2yr + <10kg) and adult patients with CVAD occlusion present for any duration to determine the safety of Cathflo Activase for restoring function to CVADs occluded due to a blood clot.

COOL-2 demonstrated that Cathflo Activase has an acceptable safety profile with a dwell time of 30 minutes or 120 minutes per dose up to two doses, and reconfirmed the product's efficacy, restoring CVAD function to 85 percent of patients after up to two doses. Trial results were reported at the annual meeting of the Society of Vascular Surgery in June 2001. COOL-2 data has been accepted for publication in the Journal of Clinical Oncology (JCO).

While bleeding is a known risk when using lytic agents at high doses to treat blood clots in heart attacks or stroke, Genentech has concluded from data collected during the trials that there is a significant decrease in bleeding risk when Cathflo Activase is used at very low doses for the restoration of function in a CVAD. There were no reports of intracranial hemorrhage or pulmonary emboli in the Cathflo Activase clinical trials. In clinical trials, the most serious adverse events reported after treatment were sepsis, gastrointestinal bleeding and venous thrombosis.

#### **Efficacy**

The COOL efficacy trial, a Phase III, six-month, randomized, placebo-controlled, double-blind study, enrolled 150 patients with CVAD occlusion up to 24 hours in duration. In this study, Cathflo Activase or placebo was instilled directly into the lumen opening, for a dwell time of 120 minutes. Patients with CVADs that remained occluded after an initial dose of Cathflo Activase or placebo were administered a 2mg dose of Cathflo Activase as either a first dose (for the placebo group) or follow-up dose (treatment group). Study results demonstrated that after just one dose of Cathflo Activase, 67 percent of the patients' CVADs were functional, compared to 16 percent restored in the placebo group. A total of 88 percent of Cathflo Activase patients treated with either a double-dose or single-dose had restored CVAD function. COOL efficacy data was presented at the International Symposium on Endovascular Therapy in Miami Beach, Florida, January 2001 and published in the August issue of the Journal of Vascular and Interventional Radiology.

#### **Past and Current Treatment Options**

The thrombolytic urokinase was previously used for CVAD clearance until the FDA recommended its removal from the marketplace in December 1998 due to inconsistencies in the manufacturing process at Abbott Laboratories. Current treatments include invasive techniques such as surgically removing and replacing the CVAD, which can be an uncomfortable, expensive and potentially risky procedure for patients. But it can be even more dangerous and uncomfortable for patients if CVADs remain occluded, which can prevent proper administration of needed fluids and medications or require that patients undergo multiple needle sticks to withdraw blood samples.

Approved by the U.S. Food and Drug Administration in September 2001, Cathflo Activase restores function of the CVAD without the need for invasive surgery. A convenient 2-mg single-patient-use vial will enable simple dosing and administration.

Revised March 2, 2005

Information taken from Genentech, Inc. at <http://www.gene.com/gene/products/information/cardiovascular/cathflo-activase/>