*CASE REPORT*

# Catheter-Directed Thrombolysis with Direct Intra-Catheter Administration of Argatroban and Alteplase for Extensive Deep Vein Thrombosis in a Patient with Heparin-Induced Thrombocytopenia

**Jonathan H Sin, Debbie C Yen**

Department of Pharmacy, Massachusetts General Hospital, Boston, MA, USA

## ABSTRACT

Catheter-directed thrombolysis (CDT) has emerged as a potential management option for proximal deep vein thrombosis (DVT). Low-dose alteplase with concomitant heparin have traditionally been used in this setting. Patients with heparin-induced thrombocytopenia (HIT) undergoing CDT pose a challenge since heparin would be contraindicated. Robust evidence regarding use of direct thrombin inhibitors (DTI) in these scenarios is lacking. Additionally, there are even fewer data regarding direct intra-catheter DTI administration at the target site during CDT. We describe the case of a 61-year-old female who developed HIT and an extensive right iliofemoral DVT with distal involvement. After obtaining access via the popliteal vein, argatroban 0.8 mcg/kg/min was infused through the venous sheath with a goal aPTT of 40-50 seconds, while intra-catheter alteplase was infused at 1 mg/hr. Post-operatively, both infusions continued for 8 and 18 hours, respectively. Repeat venography showed clot resolution and patency from the common femoral down to the peroneal vein. Residual clot burdens and stenosis were still noted in the lower inferior vena cava and common iliac vein, prompting suction thrombectomy and balloon angioplasty. Argatroban was transitioned back to being infused intravenously. No bleeding complications occurred and an argatroban-to-warfarin bridge was subsequently completed. To our knowledge, this is the first case report to describe direct intra-catheter administration of both argatroban and alteplase during CDT for a patient with HIT who developed an extensive iliofemoral DVT with distal involvement. If clinicians are to opt for direct intra-catheter argatroban administration, we advise individualizing pharmacotherapy with close monitoring of coagulation parameters.

**Key words:** Argatroban, tissue plasminogen activator, heparin-induced thrombocytopenia, catheter-directed thrombolysis, endovascular procedures

**Correspondence:**
Jonathan H Sin, PharmD, BCPS,
Department of Pharmacy, Massachusetts General Hospital, 55 Fruit Street, GRB-005, Boston, MA, 02114, USA.
E-mail: jsin@mgh.harvard.edu

**Access this article online**

**Website:** www.jbclinpharm.org

**Quick Response Code:**

## INTRODUCTION

Proximal deep vein thrombosis (DVT) has traditionally been treated with medical therapy in patients without contraindications to systemic anticoagulation. In recent years, catheter-directed thrombolysis (CDT) has emerged as a potential interventional management option, which allows for the direct intra-thrombus administration of pharmacologic agents. Current clinical practice guidelines state CDT is a reasonable therapy in certain clinical settings, such as acute iliofemoral DVT associated with impending limb-threatening thrombosis, provided the patient has a low risk of bleeding complications and good expected functional status.[1-3]

CDT involves direct intra-thrombus administration of weight-based recombinant tissue plasminogen activator (rtPA); alteplase is recommended at a rate of 0.01 mg/kg/hr, not to exceed 1 mg/hr.[4] Proposed advantages of CDT include the ability to achieve high intra-thrombus concentrations of drug, lower overall exposure to thrombolytic doses as compared to systemic thrombolysis, and decreased risk of developing post-thrombotic syndrome (PTS) and venous ulceration. Interventionalists also have the option of implementing adjunctive mechanical therapy during the procedure to further enhance clot dissolution and/or removal.[5-7] An anticoagulant agent, typically unfractionated heparin (UFH), is often administered concomitantly. Depending on each institution's CDT protocol, UFH may be given intravenously or via direct intra-catheter infusion at the target site. Unfortunately, if a patient has confirmed or suspected heparin-induced thrombocytopenia (HIT), an alternative non-heparin anticoagulant may have to be considered.

Currently, the clinical evidence investigating the use of direct thrombin inhibitors (DTI) during CDT for acute proximal DVT is not well-defined. Furthermore, there is even less efficacy and safety data regarding the direct administration of DTIs at the target site during CDT, as well as a lack of formal dosing recommendations in this scenario. Herein, we present the case of a patient with HIT and an extensive iliofemoral DVT treated with CDT using direct intra-catheter administration of both argatroban and alteplase.

## CASE REPORT

A 61-year-old female with a history of hypertension, hyperlipidemia, and acute cholecystitis was admitted after an incidental finding of a right renal mass with inferior vena cava (IVC) invasion. She underwent a right radical nephrectomy and IVC tumor thrombectomy and was discharged 6 days later on prophylactic subcutaneous enoxaparin 40 mg daily. Her platelet count upon discharge was 277 x $10^3$/µL. After 16 days of prophylactic enoxaparin, she began experiencing pain and swelling in her right lower extremity, which extended from her calf to her thigh. She was re-admitted and a venous ultrasound showed the presence of an extensive deep vein thrombosis (DVT) with occlusions involving the lower IVC, right common iliac, internal iliac, external iliac, common femoral, superficial femoral, popliteal, and peroneal veins.



**Cite this article as:** Jonathan HS, Yen DC. Catheter-Directed Thrombolysis with Direct Intra-Catheter Administration of Argatroban and Alteplase for Extensive Deep Vein Thrombosis in a Patient with Heparin-Induced Thrombocytopenia. J Basic Clin Pharma. 2017;8:S036-S038.

Intravenous (IV) UFH was administered, with a bolus of 80 units/kg and an initial infusion rate of 18 units/kg/hr. Notable laboratory results upon admission included a platelet count of 64 x $10^3$/μL and a serum creatinine of 2.02 mg/dL. With a calculated 4 T's score of 6,[8] suggesting a high probability of HIT, the UFH infusion was discontinued and IV argatroban was initiated at 1 mcg/kg/min. The heparin anti-platelet factor 4 enzyme-linked immunosorbant assay returned positive, with an optical density elevated at 0.786 (reference range <0.400). The patient was diagnosed with HIT with thrombosis (HITT) and the argatroban infusion was continued to target an activated partial thromboplastin time (aPTT) of 50-70 seconds.

Given the widespread iliofemoral DVT with distal extension, the decision was made to implement CDT, with the goal of reducing acute symptoms and the chronic effects of PTS. This approach was chosen over suction thrombectomy due to the potential risk of mechanical wall trauma to the suture line from the patient's recent surgical procedure, especially with the extensive clot burden. Our institutional protocol for CDT calls for direct intra-catheter drug delivery of low-dose alteplase and low-dose UFH, with an aPTT that should not exceed 1.5 x baselines to minimize the risk of bleeding in the setting of concomitant alteplase administration. However, given the diagnosis of HITT, argatroban was to be substituted in place of UFH. After consulting with the vascular medicine interventionalists and clinical pharmacists, argatroban was to be infused via the venous sheath at a decreased rate to target a lower aPTT of 40-50 seconds. This approach would serve a three-fold purpose: maximize anticoagulant delivery to the target site, still maintain some degree of systemic anticoagulation in the setting of HITT, and minimize the risk of local and systemic bleeding by using a lower aPTT range.

During the procedure, access was obtained via the right popliteal vein and a 6 French sheath was placed. The EkoSonic® (EKOS®) Endovascular System (EKOS Corporation, BTG International Inc., Bothell, WA) was inserted (135 cm working length with 50 cm treatment zone), extending from the popliteal vein up to the infra-renal IVC. Prior to the start of the procedure, the patient's last known aPTT was 52.6 seconds on IV argatroban 1 mcg/kg/min. Once access via the popliteal vein was secured, the argatroban infusion was transferred over to be infused at 0.8 mcg/kg/min through the sidearm of the popliteal venous sheath with a goal aPTT of 40-50 seconds. Alteplase (50 mg in 500 mL 0.9% sodium chloride) was infused via the medication lumen of the EKOS® catheter at a rate of 1 mg/hr. The procedure was completed without any notable complications and the patient was transferred to the intensive care unit for post-operative monitoring. Two hours later, an aPTT was drawn and resulted at 48.2 seconds, which was within the target range.

Eight hours after the procedure, the patient's aPTT eventually became supratherapeutic on argatroban 0.8 mcg/kg/min via the venous sheath. Due to the bleeding concern, the decision was made to hold anticoagulant therapy until after the discontinuation of alteplase. The alteplase infusion ran continuously via the EKOS® catheter without interruptions for 18 hours, at which point the patient underwent a re-look venography. Patency was observed from the common femoral vein down to the peroneal vein. However, a high clot burden and stenosis were still seen in the lower IVC and common iliac vein. Thus, suction thrombectomy and balloon angioplasty were performed below the anastomotic site from the patient's recent surgical procedure, with post-intervention patency noted. The EKOS® catheter and venous sheath were ultimately removed. Argatroban was transitioned back over to be infused intravenously at 0.6 mcg/kg/min, with a reinstated aPTT goal of 50-70 seconds.

The platelet count began to recover on day 6 of hospitalization, after 5 days of argatroban therapy. An argatroban-to-warfarin bridge was successfully completed and no major bleeding events occurred during the post-operative course. Upon discharge, minor swelling was still noted in the right lower extremity, but the patient's pain had completely resolved.

## DISCUSSION

CDT has been associated with more rapid and complete thrombolysis and higher rates of venous patency in patients with iliofemoral DVT.[9,10] In addition, CDT can decrease the incidence of developing PTS in patients with iliofemoral DVT, as evidenced by a large randomized clinical trial and its subsequent 5-year follow-up.[11,12] The protocol utilized in this trial called for direct intra-thrombus infusion of alteplase 0.01 mg/kg/hr for up to 96 hours along with an IV infusion of UFH to target an aPTT 1.2-1.7x the upper limit of normal. In our case, the decision to implement CDT therapy for an extensive iliofemoral DVT in a patient with HITT posed a unique clinical challenge, since the use of an UFH infusion was contraindicated.

The DTI argatroban is an IV non-heparin anticoagulant with a labeled indication for the treatment of HIT.[13] Unfortunately, the current literature describing argatroban in patients with HIT undergoing CDT is relatively limited at this time. Several case reports and case series utilized argatroban, administered intravenously, during and/or after CDT in patients with confirmed or suspected HIT.[14-19] However, in our patient case, argatroban was to be administered via a direct intra-catheter infusion to maximize anticoagulant delivery to the target site given the extensive nature of the DVT. The available literature in this setting is even more limited. To our knowledge, there are only 3 publications describing this method of intra-catheter DTI administration during CDT.[20-22]

Sharifi *et al.* performed a retrospective analysis of 33 patients with massive iliac and femoropopliteal DVT who underwent CDT using the combined administration of argatroban and rtPA via the popliteal sheath(s).[20] Of note, none of the patients included in this study were diagnosed with HIT. For patients with unilateral DVT, intra-catheter rtPA was infused at 1 mg/hr and argatroban was infused at 0.5-1 mcg/kg/min through the sheath's side port for 20-24 hours. For patients with bilateral DVT, rtPA was infused at 0.75-1 mg/hr through each catheter and argatroban was infused at 0.3-0.75 mcg/kg/min through each side port. For all cases, the argatroban infusion rate was adjusted to target an aPTT of 50-90 seconds. Complete thrombus resolution, from the popliteal vein up to the IVC, was observed in 30 patients (91%) during the follow-up venography, which took place 20-30 hours after the intervention. No bleeding events or iatrogenic pulmonary embolism were reported.

Martinez *et al.* described a trauma patient who developed HITT after UFH and low-molecular-weight heparin exposure.[21] Extensive lower extremity thromboses were discovered, affecting the IVC and IVC filter, bilateral external iliac, common femoral, femoral, popliteal, posterior tibial, and peroneal veins. During the CDT procedure, 2 thrombolytic infusion catheters were placed via the bilateral iliac veins, which extended up to the IVC. Alteplase 0.5 mg/hr and bivalirudin 0.06 mg/kg/hr were initiated through each sheath, for a combined total dose of 1 mg/hr and 0.12 mg/kg/hr, respectively. The bivalirudin infusion was adjusted to maintain an aPTT of 45-75 seconds and the dose per sheath ranged from 0.06-0.072 mg/kg/hr (total dose: 0.12-0.144 mg/kg/hr). After 24 hours, a venography showed improvement in IVC and iliac venous flow, but residual clot remained in the IVC filter and narrowing was still observed in the left common iliac vein. Thus, the intra-catheter alteplase and bivalirudin infusions continued for an additional 12 hours, for a total of 36 hours. At that point, a repeat venography showed satisfactory resolution of all thromboses in the

IVC and iliac vein. A small residual thrombus was still noted in the IVC filter, but the filter was subsequently removed. The authors do not report on the status of distal vein occlusions.

Turba *et al.* reported the case of a patient diagnosed with HIT who underwent CDT for lower extremity arterial thromboses.[22] The patient had developed occlusions of the left distal superficial femoral, popliteal, posterior tibial, anterior tibial, and peroneal arteries. Intra-arterial rtPA was initiated at 1 mg/hr through the infusion catheter. Argatroban was concomitantly administered via the arterial sheath with an initial bolus of 350 mcg/kg followed by an infusion 25 mcg/kg/min, titrated to an aPTT 2-3x above baseline. The intra-arterial infusions continued for 14 hours, at which point a follow-up angiogram showed the previously occluded arterial segments were now patent. No intra-or post-operative complications were reported.

To our knowledge, this is the first case report to describe direct intra-catheter administration of both argatroban and alteplase during CDT for a patient with HIT who developed an extensive iliofemoral DVT with distal involvement. The patient was already receiving an IV argatroban infusion at 1 mcg/kg/min prior to the intervention, allowing us to derive a decreased intra-catheter dose of 0.8 mcg/kg/min during and after the procedure to target a slightly lower aPTT. Although continuing the IV argatroban during the procedure was discussed as an option, clinicians felt direct intra-catheter administration would have the advantage of achieving higher intra-thrombus concentrations of the anticoagulant. In addition, this method of direct administration theoretically avoids bypass of the drug around occluded veins via collateral circulation.[5]

There was concern for suboptimal results since the intra-catheter argatroban and alteplase infusions ran for only 8 and 18 hours, respectively, which is a shorter duration than what has been described in previous literature and protocols. However, the majority of vessels were patent on follow-up venography, from the common femoral down to the peroneal veins. A high clot burden was still observed in the common iliac vein. This was not surprising, given the extensive nature of the DVT, the shorter duration of CDT, and the fact that the common iliac is the furthest up from the popliteal access site where the intra-catheter infusions were delivered. The CDT therapy was able to dissolve enough of the clot burden so that suction thrombectomy could be safely performed to remove the remaining occlusion.

Although this case suggests CDT with direct intra-catheter administration of argatroban and alteplase was effective in significantly reducing the clot burden without any major complications, the available clinical evidence is not sufficient enough to devise a formal treatment or dosage recommendation. The chosen intra-catheter argatroban dose in our case was individualized and derived from previous patient-specific data. If clinicians are to opt for this direct route of administration, they should individualize pharmacotherapy and dosages with close monitoring of coagulation parameters and potential adverse reactions.

## CONCLUSION

A patient with HIT who developed an extensive iliofemoral DVT with distal involvement was treated with CDT using direct intra-catheter infusions of both argatroban and alteplase without any major complications.

## Conflicts of interest

The authors have no conflicts of interest to disclose.

## REFERENCES


1. Kearon C, Akl EA, Ornelas J. Antithrombotic therapy for VTE disease: CHEST guide line and expert panel report. Chest 2016;149:315-52.
2. Miessner MH, Gloviczki P, Comerota AJ. Early thrombus removal strategies for acute deep venous thrombosis: Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 2012;55:1449-62.
3. Jaff MR, McMurtry S, Archer SL. Management of massive and sub-massive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension. Circulation 2011;123:1788-1830.
4. Vedantham S, Sista AK, Klein SJ. Quality improvement guidelines for the treatment of lower-extremity deep vein thrombosis with use of endovascular thrombus removal. J Vasc Interv Radiol 2014;25:1317-25.
5. Vedantham S, Piazza G, Sista AK. Guidance for the use of thrombolytic therapy for the treatment of venous thromboembolism. J Thromb Thrombolysis 2016;41:68-80.
6. Kahn SR, Galanaud JP, Vedantham S. Guidance for the prevention and treatment of the post-thrombotic syndrome. J Thromb Thrombolysis 2016;41:144-53.
7. Patterson BO, Hinchliffe R, Loftus IM. Indications for catheter-directed thrombolysis in the management of acute proximal deep vein thrombosis. Arterioscler Thromb Vasc Biol 2010;30:669-74.
8. Lo GK, Juhl D, Warkentin TE. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost 2006;4:759-65.
9. Liew A, Douketis J. Catheter-directed thrombolysis for extensive iliofemoral deep vein thrombosis: review of literature and ongoing trials. Expert Rev Cardiovasc Ther 2016;14:189-200.
10. Du GC, Zhang MC, Zhao JC. Catheter-directed thrombolysis plus anticoagulation versus anticoagulation alone in the treatment of proximal deep vein thrombosis-a meta-analysis. Vasa 2015;44:195-202.
11. Enden T, Haig Y, Klow NE. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. Lancet 2012;379:31-8.
12. Haig Y, Enden T, Grotta O. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. Lancet Haematol 2016;3:e64-71.
13. Argatroban. Research Triangle Park (NC): GlaxoSmithKline; 2016.
14. Dee B, Lombardi Thomas L, Gulbis A. Use of argatroban and catheter-directed thrombolysis with alteplase in an oncology patient with heparin-induced thrombocytopenia with thrombosis. Am J Health Syst Pharm 2014;71:711-6.
15. Maldonado A. Argatroban and catheter-directed thrombolysis with alteplase for limb- and graft-threatening thromboses in a patient with a history of HIT. Am J Hematol 2009;84:251-3.
16. Lin SC, Mousa A, Bernheim J. Endoluminal recanalization in a patient with phlegmasia cerulea dolens using a multimodality approach-a case report. Vasc Endovascular Surg 2005;39:273-9.
17. LaMonte MP, Stallmeyer MJ. Acute ischemic stroke successfully treated using sequenced intravenous and intra-arterial thrombolysis and argatroban anticoagulation: a case study. J Thromb Thrombolysis 2004;17:151-6.
18. Shi W, Lou W, Hu X. The management of filter-related caval thrombosis complicated by heparin-induced thrombocytopenia and thrombosis. Int J Clin Exp Med 2015;8:13078-88.
19. Nitta N, Shitara S, Nozaki K. Heparin-induced thrombocytopenia in a glioblastoma multiforme patient with inferior vena cava filter placement for deep vein thrombosis. Neurol Med Chir 2011;51:445-8.
20. Sharifi M, Bay C, Nowroozi S. Catheter-directed thrombolysis with argatroban and tPA for massive iliac and femoropopliteal vein thrombosis. Cardiovasc Intervent Radiol 2013;36:1586-90.
21. Martinez LA, Burnett AE. Catheter-directed thrombolysis with alteplase and bivalirudin in a patient with heparin-induced thrombocytopenia. Am J Health Syst Pharm 2015;72:707-10.
22. Turba UC, Bozlar U, Simsek S. Catheter-directed thrombolysis of acute lower extremity arterial thrombosis in a patient with heparin-induced thrombocytopenia. Catheter Cardiovasc Interv 2007;70:1046-50.