Society of Interventional Radiology Position Statement: Treatment of Acute Iliofemoral Deep Vein Thrombosis with Use of Adjunctive Catheter-directed Intrathrombus Thrombolysis

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J Vasc Interv Radiol 2006; 17:613–616

Abbreviations: CDT = catheter-directed intrathrombus thrombolysis, DVT = deep vein thrombosis, PE = pulmonary embolism, PTS = postthrombotic syndrome, QOL = quality of life

STATEMENT

THE Society of Interventional Radiology (SIR) considers the use of catheter-directed intrathrombus thrombolysis (CDT) as an adjunct to anticoagulant therapy to represent an acceptable initial treatment strategy for carefully selected patients with acute iliofemoral deep vein thrombosis (DVT). The SIR defines acute iliofemoral DVT as complete or partial thrombosis of any part of the iliac vein and/or the common femoral vein with or without associated femoropopliteal DVT, in which symptoms have been present for 14 days or less or for which imaging studies indicate that venous thrombosis has occurred within the past 14 days (1).

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None of the authors have identified a conflict of interest.

DOI: 10.1097/01.RVI.0000203802.35689.66

Rationale

Any treatment for acute proximal DVT must be evaluated on its ability to achieve the following major goals: (*a*) prevention of pulmonary embolism (PE) and DVT propagation, (*b*) provision of early symptom relief, and (*c*) prevention of postthrombotic syndrome (PTS). CDT is a targeted image-guided therapy in which a pharmacologic thrombolytic agent is delivered directly into the venous thrombus through an infusion catheter and/or wire embedded within the thrombosed vein (1,2). The published literature suggests that adjunctive CDT plus anticoagulant therapy is an acceptable initial treatment strategy for many patients with acute iliofemoral DVT for the following reasons:

1. Stand-alone anticoagulant therapy fails to prevent PTS in a significant proportion of patients with acute proximal DVT, leading to significant disability, quality of life (QOL) impairment, and socioeconomic costs.

PTS is a symptom complex that commonly includes chronic limb edema, heaviness, pain, lifestyle-limiting venous claudication, stasis dermatitis, and, in advanced cases, venous ulcerations (3). Anticoagulant therapy prevents recurrent ipsilateral DVT, a major risk factor for PTS, and may thereby confer some protection against PTS but only to a limited degree (4). Recent prospective studies have found a PTS prevalence of 49%–60% within 2 years after a first episode of symptomatic proximal DVT in patients who do not wear compression stockings (5,6). Two single-center randomized trials and one large registry suggest that daily use of individually fitted knee-high 30- to 40-mm Hg graduated compression stockings for 2 years after an initial DVT episode can decrease the rate of PTS to approximately 25% (4–6). However, in actual clinical practice, many patients are not consistently compliant with compression therapy, and some experience difficulty in maintaining therapeutic vitamin K antagonist levels. Hence, the rate of PTS probably exceeds 25% in many populations. Even compliant patients often find long-term compression therapy to be highly inconvenient. In any case, even a 25% incidence of PTS should be of major concern, given the incidence of DVT.

PTS often leads to QOL impairment, and the severity of PTS and chronic venous disease have been shown to correlate with the degree of QOL impairment (3,7–9). In addition, PTS has profound socioeconomic impact via increased medical costs and

the indirect costs of work disability. In a Swedish study (10), the average overall direct medical cost of treatment of late complications of DVT was US $4,659, or approximately 75% of the cost of treatment of the primary DVT; venous ulcer development was the most costly complication. The direct cost of treatment of chronic venous disease is thought to exceed $300 million yearly in the United States, and it is estimated that 2 million workdays are lost annually as a result of leg ulcers (11,12). These and other studies confirm the severe clinical disability and high socioeconomic costs associated with PTS, and they highlight its profound impact as a major health care problem for which a better preventive strategy is needed.

2. Patients with iliofemoral DVT are at particularly high risk for PTS and late disability.

The natural history of iliofemoral DVT is different from that of isolated femoropopliteal DVT. In the latter group, endogenous recanalization of the femoropopliteal venous segment and development of collateral vessels often enhance venous outflow and limit the severity of PTS. By contrast, a thrombosed iliac vein rarely recanalizes via endogenous processes, and persistent venous outflow obstruction often leads to major increases in ambulatory venous pressures (13). In one study (14), recurrent DVT was observed to occur twice as frequently in patients with iliofemoral DVT than in those with infrainguinal DVT. It is therefore not surprising that high rates of PTS-related disability have been observed in cohorts with iliofemoral DVT (8,15,16). In a recent long-term study of patients with iliofemoral DVT (8), 44% experienced significant venous claudication during a median follow-up of 5 years. The affected limbs performed poorly on plethysmographic physiologic venous testing, and these patients experienced significant clinical impairment as assessed by validated measures of venous disease severity and QOL (8). Specifically, patients with iliofemoral DVT showed poorer physical functioning, physical role, general health, social functioning, and mental functioning than did healthy individuals after adjustment for age and sex.

3. Treatment strategies that feature early thrombus removal may prevent PTS.

Early removal of venous thrombus has shown strong potential to eliminate venous obstruction, preserve valvular function, maintain late venous patency, and prevent PTS. Small randomized trials (17–19) evaluating contemporary surgical thrombectomy and systemic thrombolysis (in which a thrombolytic drug was administered through an intravenous catheter distant from the affected limb) have observed lower rates of PTS and limb ulceration in cases of acute DVT treated with early thrombus removal. A recent metaanalysis of randomized trials evaluating any thrombolytic method for acute DVT (20) found a significantly reduced risk of PTS in patients who were treated with thrombolysis. The modest sample sizes and the fact that a validated method of measurement of PTS was not used are major limitations of these studies. The invasiveness of surgical thrombectomy and the frequent bleeding complications associated with systemic thrombolysis have precluded their widespread use for acute DVT (21,22).

4. CDT has significant potential to prevent PTS and offers distinct advantages compared with surgical venous thrombectomy, systemic thrombolysis, and anticoagulation alone.

Adjunctive CDT has been consistently successful in the removal of thrombus in acute iliofemoral DVT, with approximately 90% of patients experiencing significant thrombolysis (23,24). Unlike surgical thrombectomy, which is also effective in removing thrombus, CDT does not require general anesthesia, a surgical incision, or a prolonged recovery period (19,22).

The enhanced effectiveness of CDT compared with systemic thrombolysis in reestablishing iliofemoral venous patency is thought to be a result of two main factors: (*a*) catheter-directed delivery enables a higher intrathrombus drug concentration to be achieved, enhancing thrombus removal and reducing the needed dose; and (*b*) catheter access into the venous system enables the use of balloon angioplasty and stents to treat underlying venous obstruction that might otherwise predispose to recurrent DVT.

Three recent comparative studies (25–27) provide support for the potential of adjunctive CDT to prevent PTS. First, in a case–control study of data from a prospective multicenter registry (25), patients with acute iliofemoral DVT treated with successful CDT and anticoagulation experienced a significantly decreased incidence of PTS and improved health-related QOL at a mean of 20 months of follow-up compared with control individuals who had received anticoagulation alone. Second, a single-center randomized trial (26) found a significantly higher rate of normal venous function (by Duplex ultrasonography and plethysmography) in patients with acute DVT treated with CDT and anticoagulation than in patients treated with anticoagulation alone (72% vs 12%) at 6 months. Third, a prospective nonrandomized study (27) found significantly more frequent symptom resolution (defined according to the Clinical, Etiology, Anatomic, Pathophysiology classification system) in patients treated with adjunctive CDT than in those treated with anticoagulation alone (78% vs 30%) at 5-year follow-up.

The main disadvantage of adjunctive CDT is thought to be an increased risk of bleeding. A pooled analysis of 19 published studies in which CDT was used for acute DVT was recently performed to estimate the rate of CDT-related major bleeding, defined according to SIR reporting standards as intracranial bleeding or any bleeding severe enough to result in death, surgery, cessation of therapy, or blood transfusion (23,28). In the studies evaluated, the cumulative major bleeding rate for CDT was 8%, and most bleeding events were confined to the vascular access site. Intracranial bleeding was rare (0.2%).

5. Adjunctive CDT is likely to provide faster symptom relief than anticoagulation alone and does not increase the risk of symptomatic PE.

No large randomized trials have directly compared the rates of early symptom relief and PE in patients with acute DVT treated with adjunctive CDT versus those treated with anticoagulation alone. However, the proportion of patients with acute iliofemoral DVT who experience significant thrombus regression, reestablishment of venous patency, and early symptom relief with CDT is reported to be approximately 90% (23,24). Pro-

ponents of CDT have observed that symptom relief tends to be faster and more complete with adjunctive CDT than with anticoagulant therapy alone.

In a pooled analysis of 19 published studies involving 1,046 patients with acute DVT treated with adjunctive CDT, the cumulative incidences of symptomatic PE and PE-related death were 0.9% and 0.1%, respectively (23). These frequencies do not appear to exceed those in DVT cohorts treated with anticoagulation alone. Hence, there is no evidence to support a contention that PE prevention would be adversely affected by the use of adjunctive CDT.

DISCUSSION

SIR supports the use of anticoagulant therapy for DVT and the use of adjunctive CDT or surgical thrombectomy for patients with limb-threatening phlegmasia (29). SIR is aware of the controversy within the medical community regarding the use of adjunctive CDT for patients with acute DVT who do not exhibit signs of impending circulatory compromise. SIR recognizes the methodologic limitations of the studies supporting CDT and strongly believes that the execution of a multicenter randomized trial to conclusively quantify the risk–benefit ratio of CDT in patients with acute proximal DVT should be considered an important national health care priority. In the meantime, physicians are still obligated to carefully consider the short-term and long-term consequences of DVT and to recommend the best possible overall treatment strategy to patients based on the currently available, albeit imperfect, evidence. Although there are no large randomized trials to mitigate for or against CDT, the preponderance of the available evidence favors the existence of a clinical benefit to adjunctive CDT for the subset of patients with acute iliofemoral DVT, as described earlier.

Given the unanswered questions concerning the risk–benefit ratio of CDT, SIR recommends that physicians use an individualized approach to determine which patients should receive adjunctive CDT as initial therapy for acute iliofemoral DVT. Most importantly, a careful assessment should be performed first to detect clinical factors that might increase the risk of bleeding or diminish the importance of any clinical benefit achieved. After this assessment, ambulatory patients with acute iliofemoral DVT with reasonable life expectancy and a low expected bleeding risk should be presented with a balanced discussion of the long-term risks of PTS and the possible benefits of adjunctive CDT. The risks of CDT, the possible lack of long-term benefits, and the absence of conclusive supportive data should be presented as well. SIR believes that these practices will promote proper use of adjunctive CDT in patients who are most likely to attain clinically meaningful benefits and who are least likely to be harmed by the intervention.

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