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Indications for Catheter-Directed Thrombolysis in the Management of Acute Proximal Deep Venous Thrombosis

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***Abstract*—**Deep vein thromboses (DVTs) cause significant morbidity and mortality in the general population. Oral anticoagulation therapy may reduce thrombus propagation but does not cause clot lysis and therefore does not prevent postthrombotic syndrome (PTS). Catheter-directed thrombolysis (CDT) can be used to treat DVTs as an adjunct to medical therapy, but there is no consensus defining exact indications. Current evidence suggests that CDT can reduce clot burden and DVT recurrence and consequently prevents the formation of PTS compared with systemic anticoagulation. Appropriate indications include younger individuals with acute proximal thromboses, a long life expectancy, and relatively few comorbidities. Limb-threatening thromboses may also be treated with CDT, although the subsequent mortality remains high. A number of randomized controlled trials are currently under way comparing the longer-term outcomes of CDT compared with anticoagulation alone. Initial reports suggest that venous patency and valvular function are better maintained after CDT. The effectiveness of combined pharmacomechanical thrombectomy and the role of vena cava filters need to be investigated further before strong recommendations can be made. The reported short-term outcomes following catheter-based intervention for DVT are encouraging in selected patients. Further evidence is required to establish long-term benefits and cost-effectiveness. **(*Arterioscler Thromb Vasc Biol*. 2010;30:669-674.)**

Key Words: anticoagulants ■ thrombolysis ■ thrombosis ■ catheter directed thrombolysis

Deep vein thrombosis (DVT) is the third most common cardiovascular pathology, after coronary artery disease and stroke. In the United Kingdom, 1 in 1000 people develop DVT each year. It is likely that the incidence of DVT will increase in the future because of an aging population and increasing exposure to risk factors for DVT, such as hospital admissions, oral contraceptives, long-distance travel, and obesity. A European group estimated that there are almost half a million cases of DVT, 300 000 cases of pulmonary embolism, and 370 000 venous thromboembolism related deaths across 6 European Union countries per annum among inpatients. It must be presumed that many of these events could have been prevented.[1]

This article accompanies the DVT Series that was published in the March 2010 issue.

Postthrombotic syndrome (PTS) is a relatively common and highly significant sequel of DVT. Eighty percent of symptomatic DVTs are above the knee (proximal), with a cumulative incidence of PTS of 50% 2 years post-DVT.[2] Severe PTS is reported in 50% of cases, and leg ulceration is present in up to 10% of patients. These conditions lead to reduced quality of life and disability. The mean age of patients affected is 56, and more than 50% of patients are of working age, meaning that DVT is costly to society in general.[3] The cost of managing venous ulcers in the United Kingdom alone is £400 million per year.

PTS is caused by chronic venous hypertension secondary to venous reflux, venous obstruction, and valvular dysfunction. This manifests clinically as a painful, swollen, heavy leg and venous claudication. At the most severe end of the spectrum, PTS is associated with venous ulceration.[4]

PTS can be objectively defined using the Villalta score, which examines the severity of various clinical features.[4] Recent research has shown that quality of life among patients with PTS is poorer than that among patients of similar age with other chronic conditions, such as arthritis, chronic lung disease, or diabetes. Severe PTS leads to such a poor quality of life that it is comparable to experiencing angina, cancer, or congestive heart failure.[3]

In addition to PTS and ulceration, some patients with proximal DVTs will develop pulmonary embolism. Patients with 1 DVT are also at increased risk of recurrence. An uncommon but significant complication of DVT is phlegmasia caerulea dolens. This is caused by thrombosis at a capillary level as a consequence of venous stasis and appears as a swollen, cyanotic limb. Venous infarction and compartment syndrome and limb loss may follow, and the associated mortality is high.[5]

Treatment Modalities

It has been shown that anticoagulation for 3 to 6 months and the use of graduated compression stockings for 2 years significantly reduces the incidence of PTS.[2] Despite this, at 2

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Table 1. A Summary Previous Trials Investigating the Role of Catheter Delivered Therapy for DVT

Study (Year)	Design	Limbs Treated	Pathology	Arms	Agent	Short-Term Patency	Long-Term Patency
Bjarnason et al (1997)[25]	Institution series	87	Acute iliofemoral DVT	CDT (87)± angioplasty±stent±PMT	Urokinase	Immediate: 69 (79%), iliac, 86%; femoral, 63%	1 year: iliac, 63% primary, 78% secondary; femoral, 40% primary, 51% secondary
Mewissen et al (1999)[24]	National registry data	303	Acute and chronic suprapopliteal	CDT	Urokinase	Immediate: grade III in 96 (31%), II in 162 (52%), I in 54 (17%)	1 year: 181 (60%)
Gandini et al (1999)[33]	Institution series	8	Iliocaval thrombosis	PMT	None	Immediate: 6 (75%)	2 years: 6 (75%)
Elsharawy et al (2002)[34]	Single blind RCT	35	Iliofemoral DVT <10 days	CDT+ (18), Anticoagulation alone (17)	Streptokinase	1 week: CDT 11 (61%), control 0 (0%)	6 months: CDT, 2 (13%); control, 2 (12%)
Jackson et al (2005)[35]	Institution series	28	Acute supra popliteal DVT (4 had symptoms >14 days)	CDT±stenting±PMT		Immediate: 5 (18%) complete lysis, 20 (72%) partial	1 year: 22 (80%)
Lin et al (2006)[36]	Retrospective comparison of CDT and PMT	98	Acute symptomatic lower limb DVT	CDT (46), PMT (52)		CDT: 32 (75%) complete, 14 (25%) partial; PMT: 39 (75%) complete, 13 (25%) (Primary assisted)	1 year: CDT, 29 (64%); PMT, 35 (68%)
Protack et al (2007)[12]	Institution series	69	Lower extremity DVT	CDT (27), PMT (12), both (30)		Immediate: grade III in 46 (67%), II in 19 (26%), I in 4 (6%)	2 years: 57 (83%) freedom from rethrombosis
Rao et al (2009)[32]	Institution series	43	Symptomatic iliofemoral DVT (19, >14 days)	CDT+PMT	r-TPA	Immediate: grade III, III lysis in 41 (95%)	Not reported
Shi et al (2009)[37]	Institution series	16	Massive lower limb DVT	CDT+PMT+IVC filter	Urokinase	Immediate: grade III and III lysis in 14 (89%), I in 2 (11%)	Follow-up:* 12 (75%)
Baekgaard et al (2009)[14]	Institution series	103	DVT <14 days, open distal popliteal vein	CDT+stockings (103)+stent (57)	r-TPA	1 week: 95/103 (92%)	6 years: 84 (82%) mean follow-up 50 months
Enden et al (2009)[13]	Open multicenter RCT: short-term report	103	Iliofemoral DVT <21 days and symptoms	CDT+anticoagulation (50), anticoagulation alone (53)	r-TPA	Immediate: grade III in 24, II in 20 for CDT group	6 months: 32 (64%) of CDT group vs 19 (36%) of control

All patients were treated postprocedure with standard anticoagulation unless otherwise stated. Grade III lysis, complete; grade II lysis, 50% to 90%; grade I lysis, <50%.

*Timing not available.

years after proximal DVT, up to 50% of patients will have evidence of PTS.[6] A reason for this is that oral anticoagulation does not precipitate thrombolysis but stops thrombus propagation and protects against recurrence.[7] It is thought that chronic venous hypertension secondary to valvular destruction leads to PTS. Therefore, if valvular function can be effectively preserved through early clot lysis, there might be benefits in terms of a reduced incidence of PTS.

Systemic thrombolysis had been investigated in trials to achieve this early lysis, but it was associated with unacceptably high rates of serious bleeding complications, such as retroperitoneal hematoma and intracranial hemorrhage, with relatively modest rates of thrombus clearance.[8–10] Catheter-directed thrombolysis (CDT) involves a more localized delivery of thrombolytic agents directly into the thrombus. This may be more effective in achieving local resolution and restoring venous patency while significantly reducing the risks of bleeding complications.

A Cochrane review compared thrombolysis with standard anticoagulation across 12 randomized controlled trials (RCTs) comprising 700 patients. The majority of these studies included only patients treated with systemic thrombolysis. Clot lysis was seen more frequently in early (relative risk, 4.14; 95% CI, 1.22 to 14.01) and late (relative risk, 2.71; 95% CI, 1.84 to 3.99) follow-up. The incidence of PTS was reduced significantly (relative risk, 0.66; 95% CI, 0.47 to 0.94).[11] A 50% reduction of relative risk (although not statistically significant) in the formation of lower limb ulcers was demonstrated. Bleeding complications were significantly higher (relative risk, 1.73; 95% CI, 1.04 to 2.88). The suggestion was that thrombolysis offered potential advantages but that indications were not clearly defined. In addition to 2 RCTs, there are several institutional cases series reporting the use of CDT and mechanical thrombectomy (Table 1). They display considerable variation in design and the combination of therapies used, but all convey the message that venous patency can often be restored in the short and long terms with catheter-delivered therapy. In addition, significant improvements in quality of life have also been demonstrated.[6] Defining which groups of patients will benefit most from the use of this newer technology is one of the major challenges facing exponents of this technique.

Achieving Venous Patency

A 3-point scale has been proposed to define outcomes of therapy for DVT (Table 2),[12] with grades II and III signifying at least 50% luminal patency postlysis. This is classed as a satisfactory therapeutic outcome. A recent report describing

Table 2. Grade of Lysis Following Treatment of DVT (Adapted From Protack et al[12])

Grade of lysis	
Grade I	<50% lysis
Grade II	50–99% lysis
Grade III	Complete lysis

short-term follow-up results from the ongoing Norwegian CaVenT randomized control trial showed favorable patency rates when CDT was compared with anticoagulation and compression stockings.[13] Grade II–III lysis was achieved in 40% of patients immediately postprocedure. After 6-months, iliofemoral patency was found in 64% of the CDT group and compared with 35% of the control group, giving an absolute risk reduction of 28% (95% CI: 9.7% to 46.7%; $P=0.004$). Venous obstruction was present in 20% of the CDT group and 49% of controls, representing an absolute risk reduction of 29% (95% CI: 20.0% to 38.0%; $P=0004$). Recently, a Scandinavian group has reported 50-month follow-up data on of a series of 103 limbs treated by DCT in a group of 101 highly selected patients. More than 82% of patients had patent veins with competent valves and no skin symptoms.[14]

Timing of CDT

The success of venous recanalization, preservation of valve function, and symptom relief may depend on the timing of therapy postthrombosis. These factors influence effectiveness of intervention and the subsequent incidence of PTS. Freshly formed thromboses respond better to thrombolysis than established, organized thromboses. It has been suggested that 10 days may be the optimal interval from onset of symptoms during which to instigate treatment[15]; however, the ATTRACT trial in the United States has used 14 days and the CaVenT trial has used 21 days as the cut-off for recruitment.[16,17] This interval requires further definition through the results of these trials to determine the optimal time frame for intervention that will prevent valvular destruction and venous hypertension, which may result in an increase of the likelihood of longer-term sequalae.[18–20]

Percutaneous Mechanical Thrombectomy

Combining CDT and percutaneous mechanical thrombectomy (PMT) devices has been attempted to try to improve early mechanical thrombus removal and promote lysis of remaining clot. Several devices exist to perform PMT, but the optimum design and outcomes are not known, despite encouraging early reports and case series. Devices include rotating sinusoidal dispersion wires (Trellis-8, Bacchus Vascular Inc, Santa Clara, CA); pulsatile saline jets (Angiojet, Possis Medical Inc, Minneapolis, MN); and low-energy high-frequency ultrasound (Ekos, Bothell, WA).[21] A series of 43 patients with DVTs undergoing PMT within an average of 14 days of symptom onset recently reported short-term results with successful lysis 63% of clots after 1 session of PMT (greater than 50% clot lysis). One-third of patients had iliac stents deployed in conjunction with mechanical therapy. Freedom from DVT recurrence and reintervention was maintained in 95% of patients after 9 months. The ATTRACT trial will report on the merits of combined therapy in the future.[16]

Potential Complications

Many of the reported complications following CDT were related to hemorrhage, as may be expected. The US National Venous Registry reported infrequent but severe peri- and postprocedural complications that included intracranial hemorrhage (<1%); retroperitoneal hematoma (1%); and musculoskeletal, genitourinary, and gastrointestinal bleeds (3%).[22] Most incidents of bleeding were relatively minor, such as that associated with the access site. Catheterization of access veins under ultrasound guidance has been shown to reduce these complications by avoiding multiple vessel punctures.[23] In addition, aiming for the minimum infusion time to achieve the best results and minimizing the dose of thrombolytic agent reduces both local and systemic bleeding complications. The mechanical thrombectomy device might play a role in achieving this balance.

Some centers have reported an increased incidence of pulmonary embolism following percutaneous treatments, but this has not been supported by registry reports or trials data.[24,25] Finally, with regard to mortality, the reported rate of mortality for patients undergoing CDT is less than 1%. Currently, patients are highly selected for CDT, so the true postprocedural mortality is unknown. This said, it is likely to remain less than 1% in routine practice.

Table 3. A typical Protocol for Performing Thrombolysis in Cases of DVT

Patient is identified; if on LMWH,* this is stopped for 8 hours
Oral anticoagulants are stopped, ensuring international normalized ration (INR) <1.5
5000-U bolus of UFH administered
Infusion of UFH at 15 U/kg, keeping activated partial thromboplastin time (APTT) at 1.2–1.7 times normal
Appropriate venous access obtained under ultrasound guidance with local anesthetic
Wire/catheter is introduced above proximal thrombus, and venography is performed
20 mg of Alteplase administered in 500 mL of 0.9% NaCl at a rate of 0.01 mg/kg/hour to a maximum of 20 mg in 24 hours
During infusion, observation of hemodynamic stability and puncture site is performed
Clotting studies are performed daily with daily venography
Maximum time of therapy should be <96 hours
Balloon angioplasty/placement of venous stents may be performed if necessary
Catheters are removed, and manual pressure is used to control bleeding
Pressure dressing applied for a further 2 hours, with an additional dose of LMWH given 1 hour after catheters are removed
Anticoagulation is then established

Adapted from CaVent trial methodology.[17]
LMHW, low–molecular weight heparin, UFH, unfractionated heparin.

Controversies

The practice of CDT remains variable between centers. The choice of thrombolytic agent, the use of adjunctive venous stenting, and inferior vena cava (IVC) filters are areas in which this variability becomes most apparent.

Endogenous serine protease inhibitors such as urokinase and recombinant tissue plasminogen activator (r-TPA) have replaced streptokinase as the agent of choice in systemic thrombolysis. r-TPA is the most effective and is likely to be associated with fewer side effects. Consequently, the major RCTs under way are using Alteplase in their protocols (Table 3),

Table 4. A Summary of Series Reporting Use of CDT and Venous Stent Placement in Patients With May-Thurner Syndrome

Study (Year)	N	Pathology	Therapy	Initial Technical	Short-Term Patency	Long-Term Patency	Major Adverse Events
O'Sullivan et al (2000)[38]	39	M-T with DVT (19) and symptomatic (20)	Urokinase and stent (35 stented)	34/39 (87%)	>90% at 1 year of stented patients	Not reported	2
Patel et al (2000)[39]	10	M-T with acute iliofemoral DVT	Urokinase and stent	10/10 (100%)	10/10 (100%) at 1 year	Not reported	0
Heijmen et al (2001)[40]	6	M-T, symptomatic	Angioplasty and stent	6/6 (100%)	5/6 (83%) at 1 year	Not reported	0
Kwak et al (2005)[29]	22	M-T with DVT (+6 other causes of venous compression)	Urokinase and stent	26/27 (96%)	Primary 95% Secondary 100% At 1 year	Primary 95% Secondary 100% At 2 years	2
Kim et al (2006)[28]	21	M-T with DVT	18 urokinase and stent; 3 stent alone	20/21 (95%)	18/21 (85%) at 6 months	Not reported	1
Husmann et al (2007)[30]	11	M-T with DVT	Thrombectomy and stenting	11/11 (100%)		10/11 (91%)* up to 22 months	0

M-T, May-Thurner syndrome.
*Assisted primary patency rate.

and this is being used with increasing regularity in clinical practice.

The use of IVC filters as an adjunct to CDT remains controversial. Many series report their use in selected cases. Situations where they may prove useful include those in which standard indications would apply, such as a patient developing a thrombosis while on effective anticoagulation or the presence of a contraindication to anticoagulation. Filters should not be used routinely, as CDT has not been shown to increase the rate of pulmonary embolism (PE). There remains insufficient evidence to determine whether IVC filters should be used for free-floating thrombus or thrombus extending into the IVC. We recommend that use of filters be decided through multidisciplinary team discussion on an individual case-by-case basis, and where possible, temporary filters should preferentially be used. In practice, we rarely use them.

Endovascular venous stent placement in conjunction with thrombolysis may improve patency rates in selected cases, particularly if abnormal anatomy is the underlying cause of DVTs. May-Thurner syndrome is the most common of these conditions; in this syndrome, the left common iliac vein is compressed by the overlying right common iliac artery, leading to both extrinsic compression and vessel damage because of the repeated trauma of the arterial pulse. Other causes include pelvic tumors, osteophytes, chronic urinary retention, iliac artery aneurysms, endometriosis, pregnancy, and uterine masses.[26]

A review of case series with 5 or more patients revealed an initial technical success rate of 87% to 100% and 1 year patency of between 80% and 100% (Table 4). Patent venous outflow at 2 years has been reported after combined CDT and stenting in 1 study.[27–29] In 1 small series of May-Thurner patients, all those treated by CDT alone had evidence of rethrombosis on follow-up venogram, whereas only 11% of patients treated with CDT and stenting developed stent occlusion.[28,30] Further research has shown that the use of thrombolysis without stent placement, in cases of May-Thurner, can lead to restenosis in up to 75% of patients in the short term.[28,31] It should be noted that venous stents can induce long-term DVT recurrence because of low luminal flow rates. This may outweigh the apparent short-term benefits, but additional data are required. At present, not enough data exist to determine the exact indications for deployment of stents, but once again, the results of the randomized trials appear critical to provide clear answers.

Cost-Effectiveness and Quality of Life

Systemic anticoagulation with subcutaneous low–molecular weight heparin is easy to initiate, relatively convenient for patients, and inexpensive. As anticoagulation is still required after CDT, the procedural costs associated with CDT along with an inpatient admission will always be greater than for the outpatient management of oral anticoagulation alone.

This apparent drawback must be considered in the context of the economic burden of PTS and venous ulceration, not simply because of the utilization of hospital and community healthcare resources (which cost more than £400 million per year in the United Kingdom alone) but also in terms of lost opportunity costs. One study suggested that 81% of patients suffered loss of financial productivity post-DVT. This is of considerable interest in light of the fact that more than 50% of patients with proximal DVT are of working age.[15]

Health-related quality of life in patients receiving CDT has been shown to be improved in comparison with those treated with systemic anticoagulation alone at 16 and 22 months posttreatment.[32] In addition, patients with proximal DVTs treated by CDT reported better functional scores and fewer symptoms of PTS than those undergoing systemic anticoagulation.[12] These findings will be of importance in the cost-effectiveness analyses of the ongoing randomized trials.

Recommendations for Management

This review of the relevant literature suggests CDT can achieve superior clot lysis in the acute setting, with better long-term venous patency rates in comparison with anticoag-

Table 5. Possible Indications for DVT Thrombolysis

Extensive thrombosis with high risk of pulmonary embolism
Proximal DVT (iliofemoral or femoral vein)
Threatened limb viability
Underlying predisposing anatomic anomaly
Good physiological reserve (18–75 years old)
Life expectancy over 6 months
Recent onset of symptoms (<14 days)
Absence of contraindications to thrombolysis

Table 6. Contraindications for Thrombolysis

Bleeding diathesis/thrombocytopenia
Organ specific bleeding risk (eg recent myocardial infarction, cerebrovascular accident, gastrointestinal bleed, surgery, or trauma)
Renal or hepatic failure
Malignancy (ie brain metastases)
Pregnancy

ulation alone. This may avoid the clinical sequelae of PTS and venous ulceration. The indications for CDT are based on a number of small RCTs, registry data, and institutional series and a variety of expert opinions.

Current guidelines from the American College of Chest Physicians suggest that CDT should be used in those with life expectancy >1 year, good functional status, extensive iliofemoral thrombosis, and presenting soon after the onset of symptoms >14 days (level 2B evidence). The guidelines also advocate the use of venous angioplasty and stenting in the presence of reversible causes of thrombosis and discuss the efficacy of dual therapy with pharmacomechanical therapy.[12]

Those most likely to benefit from CDT (Table 5) are individuals with a long life expectancy, as the reductions in PTS and ulceration are likely to be the most important benefits. These outcomes have a measurable incidence at 2 years postthrombosis, and so the differences in outcomes between medically treated patients and those with CDT might be most easily interpreted at this stage. Those patients of working age are likely to derive the most benefits at the lowest risk of intervention.

Higher rates of PTS are seen with more proximal thrombi and in the absence of contraindications, CDT should be considered in these cases. This would include both iliofemoral and femoral vein thromboses. Adjunctive venous stenting is appropriate in cases in which there is an underlying anatomic abnormality.

Unfortunately, some groups of patients with proximal thrombosis would currently be excluded from management by CDT using currently published criteria (Table 6). This may include trauma victims or patients who have undergone recent surgery, although these patients may stand to gain most significantly from effective treatment of extensive thrombosis. The role for mechanical thrombectomy devices might lie in these patient subgroups. In individual cases, a combination of the focused delivery of thrombolytic agent with or without the addition of mechanical therapy may be not only safe but also highly effective.

Oncology patients are at high risk of thromboembolism, and the mortality in this group is significantly higher than that of the general population following DVT. Life expectancy and the risk of hemorrhage (ie, likelihood of brain or liver metastases) must be considered and assessed before CDT. A full assessment would realistically include a current head and chest-abdomen-pelvis computed tomography scan to identify metastases. The current inclusion criteria for CDT may need to be broadened if more patient groups such as this are to benefit, but this is not likely to occur until the full benefit of CDT has been quantified in more selected subgroups of patients.

Given the high associated mortality of phlegmasia caerulea dolens and the lack of an effective alternative, CDT is probably justified in this patient group, despite a high mortality due to the underlying disease, and may lead to effective limb salvage in up to 100% of cases.[12]

Extensive, free-floating or IVC thromboses may be at high risk of causing pulmonary embolism. Timely reduction of clot burden using CDT would seem to offer a better chance of avoiding such events than simply relying on systemic anticoagulation to prevent their propagation. Whether IVC filters should be used remains an area of considerable debate.

The outcome of the CaVenT, ATTRACT, and the proposed United Kingdom–based RCTs should provide further guidance regarding exclusion and inclusion criteria for CDT (Table 7). Detailed health-economic analyses of the use of CDT and thrombectomy devices are required to establish the cost-effectiveness of this treatment. Finally, encouraging results regarding CDT in the management of DVTs should not detract from meticulous DVT prophylaxis in all at-risk patients.

Conclusions

Venous thromboembolism is common and has a significant socioeconomic impact. The present therapeutic strategy in the form of oral anticoagulation does not prevent the PTS and venous ulceration, even when combined with elastic compression stockings.

CDT is effective in achieving clot lysis in acute thrombosis, and this may help to prevent PTS and subsequent ulceration. The incidence of serious complications is acceptable following these procedures. Patient selection is of importance to achieve maximum benefit at the lowest risk,

Table 7. A Summary of Major Ongoing Trials Investigating the Role of Catheter Delivered Therapy for DVT

Study	Design	N	Pathology	Arms	Therapy	Primary End	Secondary End	Reporting
CaVenT[17]	Open RCT	200	Iliofemoral DVT present for <21 days	CDT/conventional anticoagulation	r-TPA	6 month patency/ incidence of PTS at 24 months	Doppler patency/ QOL*/cost effectiveness	Short-term patency reported Dec 2009; complete 2017
ATTRACT[16]	Open multicenter RCT	692	Iliac, common femoral and femoral vein; DVT <14 days	PMT+CDT/ conventional anticoagulation	r-TPA	Incidence of PTS at 24 months	Symptom resolution/adverse events/QOL	4.5 years after commencing
UK RCT (proposed)	Assesor-blinded multicenter RCT	400	Proximal DVT <14 days	CDT/conventional anticoagulation+ compression stockings	r-TPA	Incidence of PTS at 24 months	Leg ulceration/ QOL/cost-effectiveness	Awaiting funding decision

QOL, quality of life.

and the reports of several ongoing RCTs are awaited to help define who will benefit most. Based on these trial results, the cost-effectiveness of CDT will be effectively determined. This is needed before the routine use of CDT can be advocated.

Disclosures

None.

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