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Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension: A Scientific Statement From the American Heart Association

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tion or active bleeding complications have resolved *(Class I; Level of Evidence B)*.

3. **Patients who receive retrievable IVC filters should be evaluated periodically for filter retrieval within the specific filter's retrieval window *(Class I; Level of Evidence C)*.**
4. **For patients with recurrent PE despite therapeutic anticoagulation, it is reasonable to place an IVC filter *(Class IIa; Level of Evidence C)*.**
5. **For IFDVT patients who are likely to require permanent IVC filtration (eg, long-term contraindication to anticoagulation), it is reasonable to select a permanent nonretrievable IVC filter device *(Class IIa; Level of Evidence C)*.**
6. **For IFDVT patients with a time-limited indication for an IVC filter (eg, a short-term contraindication to anticoagulant therapy), placement of a retrievable IVC filter is reasonable *(Class IIa; Level of Evidence C)*.**
7. **For patients with recurrent DVT (without PE) despite therapeutic anticoagulation, it is reasonable to place an IVC filter *(Class IIb; Level of Evidence C)*.**
8. **An IVC filter should not be used routinely in the treatment of IFDVT *(Class III; Level of Evidence B)*.**

Thromboreductive Strategies

Studies of DVT patients receiving anticoagulation suggest that rapid clot lysis may prevent valvular reflux, venous obstruction, recurrent VTE, and PTS.[261–276] In subgroup analyses from 2 prospective studies, the presence of residual thrombus on 6-month follow-up ultrasound doubled the risk of recurrent VTE and PTS.[263,264] A meta-analysis of 11 RCTs found that the amount of residual thrombus after anticoagulant therapy correlated strongly with the risk of recurrent VTE.[265] It is unknown whether this is a causal relationship, with residual thrombus creating a physical nidus for the development of new thrombus, or whether the presence of residual thrombus is simply a marker for a separate biological process that leads to recurrent VTE. The Acute venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis (ATTRACT) trial, a prospective, multicenter, randomized trial of patients with acute proximal DVT randomized to pharmacomechanical thrombectomy with alteplase and optimal anticoagulant therapy compared with optimal anticoagulant therapy alone is currently enrolling patients (ClinicalTrials.gov Identifier NCT00790335). The primary outcome is the cumulative incidence of PTS. Safety measures designated as secondary outcomes include major bleeding, symptomatic PE, all recurrent VTE, and death. The targeted enrollment is 692 patients. This trial will provide insight into the safety and efficacy of interventional therapy and will evaluate the role of intervention on quality of life and preservation of venous valves, potentially ameliorating the development of postthrombotic venous insufficiency.

Systemic Thrombolysis

In adult RCTs, >50% clot lysis was seen more frequently in proximal DVT patients treated with systemic intravenous administration of streptokinase than in patients treated with heparin (62% versus 17%, $P<0.0001$).[277] In limited long-term follow-up studies, the streptokinase-treated patients had significantly lower PTS rates (relative risk reduction 62% to 64%).[266,267] Turpie et al[268] found that systemic tissue plasminogen activator infusion achieved ≥50% clot lysis more often than heparin alone in proximal DVT patients (58% versus 0%, $P=0.002$), with a trend toward reduced PTS in successfully lysed patients (25% versus 56%, $P=0.07$). However, major bleeding was increased significantly with use of systemic thrombolysis (14% versus 4% for streptokinase infusions, $P<0.04$).[268,277,278] These studies did not focus solely on IFDVT, but such patients were included in the subject populations. Therefore, we recommend against the use of systemic thrombolysis for the treatment of IFDVT in adult patients. If thrombolysis is desired but endovascular expertise is not locally available, patient transfer to an institution that offers access to endovascular thrombolysis is recommended in preference to attempts at use of systemic thrombolysis.

Catheter-Directed Thrombolysis

Catheter-directed thrombolysis (CDT) refers to the infusion of a thrombolytic agent directly into the venous thrombus via a multiple–side-hole catheter with the use of imaging guidance.[182,273] In a 473-patient prospective multicenter registry, the use of urokinase CDT resulted in successful fibrinolysis in 88% of patients with acute IFDVT.[274] CDT was more often successful in patients with recent (≤10 to 14 days) onset of symptoms. In a follow-up study of 68 IFDVT patients from this registry who had initially successful CDT, Comerota et al[271] found these patients to have fewer PTS symptoms and improved quality of life at 16-month follow-up compared with a group of 30 retrospectively identified IFDVT patients who had received anticoagulation alone. AbuRahma et al[272] found more frequent 5-year symptom resolution (78% versus 30%, $P=0.0015$) in IFDVT patients receiving CDT plus anticoagulant than in those given anticoagulant alone in a small (n=51), prospective, nonrandomized study. In a small (n=35) RCT, Elsharawy et al[275] reported that streptokinase CDT plus anticoagulation yielded a higher rate of normal physiological venous function (72% versus 12%, $P<0.001$) and less valvular reflux (11% versus 41%, $P=0.04$) at 6 months than anticoagulation alone. In an open-label multicenter RCT of 118 IFDVT patients, Enden et al[276] found that rtPA CDT plus anticoagulation resulted in better 6-month venous patency (64% versus 36%, $P=0.004$), less functional venous obstruction (20% versus 49%, $P=0.004$), and no difference in femoropopliteal venous reflux (60% versus 66%, $P=0.53$) compared with anticoagulant alone.

In a 473-patient CDT registry[274] that evaluated patients treated in 62 US centers in the 1990s with a variety of urokinase dosing schemes, major bleeding occurred in 11.4%, which diminished initial enthusiasm for this treatment. In the recently published 118-patient Norwegian RCT noted above,[276] in which rtPA infusions of 0.01 $mg \cdot kg^{-1} \cdot h^{-1}$ were used, CDT plus anticoagulation was associated with major bleeding in 2.0% (major bleeding occurred in 1.7% of patients treated with anticoagulant alone; statistics not provided). In 4 retrospective studies that used similar rtPA infusion dosing, major bleeding rates were 2% to 4%.[278–281] The lower major bleeding rates in contemporary rtPA studies than in the urokinase registry may reflect the use of different

drug regimens, less access-site bleeding because of the incorporation of routine ultrasound-guided venipuncture into endovascular practice, the contemporary use of "subtherapeutic" heparin dosing while rtPA is being infused, different patient selection criteria, or a combination of these factors. In the 2 prospective studies noted above, the mean thrombolytic infusion time was approximately 54 hours. IVC filters were not routinely deployed, yet the rates of symptomatic PE were 1.3% (including 0.2% fatal PE) and 0%, respectively, with CDT.[274,276]

Reteplase and tenecteplase have also been used as fibrinolytic drugs for CDT of IFDVT,[282–284] and a new form of CDT that incorporates low-power ultrasound to enhance fibrinolysis has been introduced[285]; however, there are no rigorous prospective studies of these methods. The clinical spectrum of IFDVT treated successfully with CDT is broad and includes patients with phlegmasia cerulea dolens,[286,287] patients with thrombus progression or symptom worsening despite initial anticoagulation,[288] and patients receiving first-line CDT for PTS prevention.[275]

Percutaneous Mechanical, and Pharmacomechanical Thrombolysis

Percutaneous mechanical thrombectomy (PMT) refers to the use of a catheter-based device that contributes to thrombus removal via mechanical thrombus fragmentation, maceration, and/or aspiration.[182] There is no evidence that any particular device is sufficiently effective as a stand-alone therapy for DVT, and use of some devices without concomitant thrombolytic agent administration may be associated with symptomatic PE.[289–291] However, retrospective comparative studies suggest that pharmacomechanical CDT (PCDT, or thrombus dissolution via the combined use of CDT and PMT), provides comparable clot-removal efficacy as drug-only CDT but with major (40% to 50%) reductions in the needed thrombolytic drug dose, infusion time, and hospital resource use.[292–294] Several nonrandomized studies suggest that with the use of some devices, thrombus removal can be accomplished in a single procedure session, which obviates the need for overnight infusion.[295–300] However, there are no rigorously performed prospective studies to validate this finding, and there may be risks associated with greater mechanical manipulation of the thrombus and vein.[295,300] No PCDT studies have systematically evaluated recurrent DVT and PTS.

Thrombolysis in Pediatric Patients

Limited clinical studies have demonstrated that PTS affects both children and adults.[301,302] In very limited populations, systemic thrombolysis and endovascular thrombolysis have been used to treat children and adolescents deemed to be at particularly high risk for PTS.[303,304] In small numbers of older adolescents, adult CDT and PCDT regimens were used.[288,297,305]

Patient Selection for CDT or PCDT

Only operators experienced with these techniques should perform catheter-based intervention. The use of endovascular thrombolysis as an adjunct to anticoagulant therapy is reasonable for patients with acute IFDVT associated with limb-threatening circulatory compromise (ie, phlegmasia cerulea dolens), rapid thrombus extension despite anticoagulation, or symptomatic deterioration despite anticoagulation provided there is a low expected risk of bleeding complications. For first-line treatment of carefully selected patients with acute IFDVT, the use of CDT or PCDT (along with anticoagulation) to achieve more rapid relief of presenting DVT symptoms and to prevent PTS is reasonable. There are no published long-term outcome data from a multicenter RCT, so the potential benefits of therapy must be weighed carefully against the risk of bleeding. Patient selection should be based on a careful assessment of the severity of DVT symptoms, comorbidities, baseline capacity for ambulation, life expectancy, and patient preferences for an aggressive treatment approach. This approach should not be used for most IFDVT patients in whom the onset of DVT symptoms was >21 days before presentation or who are at higher expected risk for bleeding. In pediatric patients with occlusive IFDVT, the use of thrombolytic therapy to reduce the risk of PTS may be considered in carefully selected patients.

Choice of Endovascular Thrombolysis

No differences between the efficacy or safety of CDT, early-generation PCDT, or single-session PCDT have been established conclusively. Because PCDT reduces thrombolytic drug exposure and may therefore reduce bleeding, selection of PCDT instead of CDT may be reasonable in most patients undergoing endovascular thrombolysis. No differences between the efficacy or safety of different thrombolytic drugs used for CDT or PCDT have been established conclusively. When drug-only CDT is performed with rtPA, we suggest the use of 0.01 $mg \cdot kg^{-1} \cdot h^{-1}$ rather than higher doses. When drug-only CDT is performed using urokinase, we suggest the use of 120 000 to 180 000 U/h. We recommend against the use of PMT without a thrombolytic drug unless there are contraindications to use of a thrombolytic drug.

Use of Other Standard DVT Treatments in Patients Undergoing CDT or PCDT

Before and after CDT or PCDT, therapeutic-level anticoagulation with similar dosing, monitoring, and treatment duration as for IFDVT patients who are not undergoing thrombolysis should be used. During CDT infusions, reduced-dose UFH may be safer than therapeutic-level UFH. This is based on indirect evidence from arterial thrombolysis trials,[306] the finding that supertherapeutic heparin is associated with thrombolysis-related bleeding,[307] the low major bleeding rate observed in an RCT in which reduced-dose heparin was used along with CDT for the treatment of proximal DVT,[276] and expert consensus. However, during single-session PCDT or stand-alone PMT, both of which involve greater mechanical manipulation, it may be reasonable to use therapeutic-level UFH. LMWH has also been used along with PCDT, but there are no studies to support or refute this practice. No studies report on the concomitant use of fondaparinux or other parenteral anticoagulants, such as direct thrombin inhibitors, along with CDT or PCDT, or on the clinical outcomes associated with the use of antiplatelet therapies during or after thrombolysis. Like other patients

with proximal DVT, IFDVT patients who undergo CDT or PCDT should wear 30– to 40–mm Hg knee-high ECS for at least 2 years after the diagnosis of DVT. We recommend against periprocedural IVC filter placement for most IFDVT patients undergoing drug-only infusion CDT.[274,276] Preprocedure placement and postprocedure removal of retrievable IVC filters may be reasonable in carefully selected IFDVT patients undergoing PCDT or stand-alone PMT, depending on the thrombus extent, patient factors such as baseline cardiopulmonary status, and the specific clot-removal methods that will be used.[295,300]

Surgical Venous Thrombectomy

Contemporary surgical venous thrombectomy is an alternative method of removing thrombus in IFDVT. In 1 small RCT of 41 patients, the use of surgical thrombectomy as an adjunct to anticoagulation significantly reduced venous symptoms (58% versus 93%, $P<0.005$), venous obstruction (24% versus 65%, $P<0.025$), and valvular reflux (14% versus 59%, $P<0.05$) in acute IFDVT patients at 6-month follow-up.[269] After 5 years, many patients were lost to follow-up, but in those available, absence of symptoms was more common in the surgical patients (37% versus 18%), although this difference was not significant.[270] Operative intervention is invasive, requires general anesthesia, and may carry a small additional risk of PE. Nevertheless, given the potential to prevent PTS, in selected patients with acute IFDVT with contraindications to or failure of CDT or PCDT, surgical venous thrombectomy by experienced surgeons may be a reasonable strategy to decrease long-term morbidity due to PTS.

Recommendations for Endovascular Thrombolysis and Surgical Venous Thrombectomy

1. **CDT or PCDT should be given to patients with IFDVT associated with limb-threatening circulatory compromise (ie, phlegmasia cerulea dolens) *(Class I; Level of Evidence C)*.**
2. **Patients with IFDVT at centers that lack endovascular thrombolysis should be considered for transfer to a center with this expertise if indications for endovascular thrombolysis are present *(Class I; Level of Evidence C)*.**
3. **CDT or PCDT is reasonable for patients with IFDVT associated with rapid thrombus extension despite anticoagulation *(Class IIa; Level of Evidence C)* and/or symptomatic deterioration from the IFDVT despite anticoagulation *(Class IIa; Level of Evidence B)*.**
4. **CDT or PCDT is reasonable as first-line treatment of patients with acute IFDVT to prevent PTS in selected patients at low risk of bleeding complications *(Class IIa; Level of Evidence B)*.**
5. **Surgical venous thrombectomy by experienced surgeons may be considered in patients with IFDVT *(Class IIb; Level of Evidence B)*.**
6. **Systemic fibrinolysis should not be given routinely to patients with IFDVT *(Class III; Level of Evidence A)*.**
7. **CDT or PCDT should not be given to most patients with chronic DVT symptoms (>21 days) or patients who are at high risk for bleeding complications *(Class III; Level of Evidence B)*.**

Percutaneous Transluminal Venous Angioplasty and Stent Placement

Percutaneous transluminal venous angioplasty and stent placement have been used routinely concomitant with endovascular or surgical thrombus removal to treat obstructive lesions and prevent rethrombosis in patients with acute IFDVT. Specifically, the finding of a left common iliac vein stenosis in association with left-sided IFDVT, known as iliac vein compression syndrome (May-Thurner syndrome, Cockett syndrome), typically has been treated with stent placement in CDT studies.[273,274,288,308]

Acute DVT Setting

In a 473-patient CDT registry, patients who received iliac vein stents had greater venous patency at 1 year than those who did not, although these were not equivalent patient subsets.[274] A study that included 52 patients with acute IFDVT who underwent thrombus aspiration and PMT followed by stent placement observed primary stent patency in 83% at 6-month follow-up.[309] In 2 retrospective studies of 106 patients with acute IFDVT who had surgical venous thrombectomy, the intraoperative use of stents to treat iliac vein obstructive lesions was associated with 12% to 14% rates of early rethrombosis. In the larger study, a nonstented control group experienced postoperative early rethrombosis in 73% of cases ($P<0.01$).[310,311] In 1 of these studies, stent fracture with rethrombosis was observed in 1 pregnant woman.[311] However, in a study of 62 women who received left iliac vein stents, later became pregnant, and received LMWH prophylaxis during pregnancy, no patient had recurrent VTE during pregnancy or the postpartum period.[312] In that study, 4 patients had mechanical stent deformation shown by Duplex ultrasound late in pregnancy, but it resolved spontaneously postpartum without apparent clinical sequelae.

Treatment of PTS

The results of 2 large, nonrandomized, single-center experiences show that stent recanalization of chronically occluded iliac veins in patients with advanced PTS appears to offer significant potential to reduce PTS symptoms, improve quality of life, and enable healing of venous ulcers.[313–315] The anatomic success rate for stent-based recanalization of the occluded vein (without concomitant thrombolysis) was 83% to 98%.[314] Initial reduction in lower extremity pain and swelling occurred in >95% of patients and was maintained at 3 years in 79% and 66% of patients, respectively, in the larger study. Scores on the Chronic Venous Insufficiency Questionnaire, a validated venous disease–specific quality-of-life measure, were improved significantly, and ulcer healing occurred in 56% of affected patients. Another large study (n=493) found that in patients with PTS, self-expandable stent patency in those who required stent extension below the inguinal ligament to treat associated common femoral vein obstruction was reduced only slightly compared with patients in whom stents were limited to the iliac vein (90% versus 84%, $P=0.0378$).[313] Notably, stent fracture was rare (1 patient only), did not cause problems beyond thrombosis of that vessel, and was treated successfully with insertion of a second stent.

Use of Percutaneous Transluminal Venous Angioplasty and Stents

The use of stent placement is reasonable to treat venous lesions that obstruct flow in the iliac vein after preceding CDT, PCDT, or surgical venous thrombectomy for acute IFDVT in adults and older adolescents. For obstructive iliac vein lesions that extend into the common femoral vein, caudal extension of stents into the common femoral vein is reasonable if unavoidable. The use of percutaneous transluminal venous angioplasty (without stent placement) to treat lesions that obstruct flow in the femoral vein after initial CDT or PCDT in adults and older adolescents is reasonable. The use of percutaneous transluminal venous angioplasty in children may be reasonable, but this practice has not been well studied and may be associated with a greater risk of vasospasm. The placement of iliac vein stents to reduce PTS symptoms and heal venous ulcers in patients with advanced PTS and iliac vein obstruction is reasonable. After stent placement, the use of therapeutic-level anticoagulant therapy using similar dosing, monitoring, and duration as for IFDVT patients who do not have stents is reasonable for most patients. After stent placement, the use of concurrent antiplatelet therapy (ie, along with therapeutic anticoagulation) may be reasonable in selected patients believed to be at particularly high risk of rethrombosis (eg, because of poor inflow vein quality or an imperfect anatomic result after intervention) after an individualized assessment of the patient's bleeding risk.[310,314,316]

Recommendations for Percutaneous Transluminal Venous Angioplasty and Stenting

1. **Stent placement in the iliac vein to treat obstructive lesions after CDT, PCDT, or surgical venous thrombectomy is reasonable *(Class IIa; Level of Evidence C)*.**
2. **For isolated obstructive lesions in the common femoral vein, a trial of percutaneous transluminal angioplasty without stenting is reasonable *(Class IIa; Level of Evidence C)*.**
3. **The placement of iliac vein stents to reduce PTS symptoms and heal venous ulcers in patients with advanced PTS and iliac vein obstruction is reasonable *(Class IIa; Level of Evidence C)*.**
4. **After venous stent placement, the use of therapeutic anticoagulation with similar dosing, monitoring, and duration as for IFDVT patients without stents is reasonable *(Class IIa; Level of Evidence C)*.**
5. **After venous stent placement, the use of antiplatelet therapy with concomitant anticoagulation in patients perceived to be at high risk of rethrombosis may be considered *(Class IIb; Level of Evidence C)*.**

Chronic Thromboembolic Pulmonary Hypertension

CTEPH is a syndrome of dyspnea, fatigue, and exercise intolerance caused by proximal thromboembolic obstruction and distal remodeling of the pulmonary circulation that leads to elevated pulmonary artery pressure and progressive RV failure. Evidence suggests that CTEPH is triggered by failure to resorb at least 1 or multiple episodes of PE,[317,318] although up to 63% of patients with CTEPH were not previously aware of having had a PE,[319] and prior PE is not a criterion for diagnosis. Several mechanisms have been postulated to cause chronic pulmonary hypertension, including a recurrence of embolism after adequately treated pulmonary embolic events,[320] in situ thrombus propagation into branch pulmonary vessels,[321] and failure to dissolve the initial embolus, which leads to large- and small-vessel vasculopathy.[322]

Incidence of CTEPH

The true incidence of CTEPH is unknown. Ribeiro et al[323] prospectively assessed pulmonary hemodynamics using echocardiographic measures of pulmonary artery systolic pressure in a cohort of 78 patients with acute PE studied between 1988 and 1992 with up to 5 years of follow-up. In this cohort, 43.5% of patients had mild pulmonary hypertension, with a pulmonary artery systolic pressure >30 mm Hg or RV systolic dysfunction at 1 year, and 5.1% had a pulmonary artery systolic pressure >40 mm Hg at 1 year. Of those patients with pulmonary artery systolic pressure >40 mm Hg at 1 year, 75% underwent pulmonary endarterectomy surgery within 5 years, whereas no subjects with lower pulmonary artery systolic pressures required surgery. Pulmonary artery pressure declined to a plateau at approximately 38 days after the acute PE and then stabilized with no further resolution, with a similar plateau for RV function, which suggests that an echocardiogram 6 weeks after acute PE might predict subsequent CTEPH. Pengo et al[324] evaluated a cohort of 223 patients properly anticoagulated for 6 months after acute PE over a follow-up period of ≈94 months. The study used a CTEPH case definition of systolic and mean pulmonary artery pressures exceeding 40 and 25 mm Hg, respectively; normal pulmonary capillary wedge pressure; and angiographic evidence of thrombotic pulmonary artery obstruction.[324] Eighteen patients died within 2 days of the acute PE, for a case fatality rate of 8.1%. During follow-up, there were 23 additional deaths. Seven patients with a first-time PE developed CTEPH, for a cumulative 2-year incidence of CTEPH of 3.8%; no patients developed CTEPH later than 2 years after the index PE. These 2 studies suggest that as many as 1 in 25 patients with an initial episode of acute PE will subsequently develop CTEPH. Another estimate of CTEPH incidence, based on the 2003 US Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample Database, is 3.4%, which represents >5000 cases of CTEPH in the United States in 2003.[325] However, because ≈60% of individuals diagnosed with CTEPH have no antecedent history of acute VTE,[319] the true incidence of this disorder may be higher.

Pathophysiology of CTEPH

Treatment of acute PE usually results in improved pulmonary hemodynamic status,[323] but residual thrombus remains despite adequate anticoagulation at 1 year in as many as half of all patients.[326] If the acute PEs have not resolved in 1 to 4 weeks, the embolic material becomes incorporated into the pulmonary arterial wall at the main pulmonary artery, lobar, segmental, or subsegmental levels.[327] Over time, the initial embolic material is remodeled into connective and elastic