

## 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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Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on  
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Venous thromboembolism (VTE) is responsible for the hospitalization of >250 000 Americans annually and represents a significant risk for morbidity and mortality.<sup>1</sup> Despite the publication of evidence-based clinical practice guidelines to aid in the management of VTE in its acute and chronic forms,<sup>2,3</sup> the clinician is frequently confronted with manifestations of VTE for which data are sparse and optimal management is unclear. In particular, the optimal use of advanced therapies for acute VTE, including thrombolysis and catheter-based therapies, remains uncertain. This report addresses the management of massive and submassive pulmonary embolism (PE), iliofemoral deep vein thrombosis (IF-DVT), and chronic thromboembolic pulmonary hypertension (CTEPH). The goal is to provide practical advice to enable the busy clinician to optimize the management of patients with these severe manifestations of VTE. Although this document makes recommendations for management, optimal medical decisions must incorporate other factors, including patient wishes, quality of life, and life expectancy based on age and comorbidities. The appropriateness of these recommendations for a specific patient may vary depending on these factors and will be best judged by the bedside clinician.

### Methods

A writing group was established with representation from the Council on Peripheral Vascular Disease and Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation of the American Heart Association and vetted by American Heart Association leadership. All writing group members were required to disclose all relationships with industry and other entities relevant to the subject. The writing group was subdivided into the 3 areas of statement focus, and each subgroup was led by a member with content expertise (deep venous thrombosis [S.V.], pulmonary embolism [S.Z.G.], and chronic thromboembolic pulmonary hypertension [P.A.T.]). The writing groups systematically reviewed and summarized the relevant published literature and incorporated this information into a manuscript with draft recommendations. Differences in opinion were dealt with through a face-to-face meeting and subsequently through electronic and telephone communications. The final document reflects the consensus opinion of the entire committee. Areas of uncertainty are also noted in hopes that both basic and clinical research will advance knowledge in this area. The American Heart Association Levels of Evidence were adopted (Table

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on January 5, 2011. A copy of the statement is available at <http://www.americanheart.org/presenter.jhtml?identifier=3003999> by selecting either the "topic list" link or the "chronological list" link. To purchase additional reprints, call 843-216-2533 or e-mail [kelle.ramsay@wolterskluwer.com](mailto:kelle.ramsay@wolterskluwer.com).

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Table 1. Applying Classification of Recommendations and Level of Evidence

		SIZE OF TREATMENT EFFECT →			
		CLASS I <i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment <b>SHOULD</b> be performed/administered	CLASS IIa <i>Benefit &gt;&gt; Risk</i> Additional studies with <i>focused objectives</i> needed <b>IT IS REASONABLE</b> to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives</i> needed; additional registry data would be helpful Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III <i>Risk ≥ Benefit</i> Procedure/Treatment should <b>NOT</b> be performed/administered <b>SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL</b>
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> <li>■ Recommendation that procedure or treatment is useful/effective</li> <li>■ Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation in favor of treatment or procedure being useful/effective</li> <li>■ Some conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation's usefulness/efficacy less well established</li> <li>■ Greater conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>■ Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> <li>■ Recommendation that procedure or treatment is useful/effective</li> <li>■ Evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation in favor of treatment or procedure being useful/effective</li> <li>■ Some conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation's usefulness/efficacy less well established</li> <li>■ Greater conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>■ Evidence from single randomized trial or nonrandomized studies</li> </ul>
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> <li>■ Recommendation that procedure or treatment is useful/effective</li> <li>■ Only expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation in favor of treatment or procedure being useful/effective</li> <li>■ Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation's usefulness/efficacy less well established</li> <li>■ Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>■ Only expert opinion, case studies, or standard of care</li> </ul>
Suggested phrases for writing recommendations†		should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

\* Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

† For recommendations (Class I and IIa; Level of Evidence A and B only) regarding the comparative effectiveness of one treatment with respect to another, these words or phrases may be accompanied by the additional terms "in preference to" or "to choose" to indicate the favored intervention. For example, "Treatment A is recommended in preference to Treatment B for ..." or "It is reasonable to choose Treatment A over Treatment B for ...." Studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

1). External reviewers appointed by the American Heart Association independently reviewed the document. Each recommendation required a confidential vote by the writing group members after external review of the document. Any writing group member with a relationship with industry relevant to the recommendation was recused from the voting on that recommendation. Disclosure of relationships is included in this document (Writing Group Disclosure Table).

## Massive, Submassive, and Low-Risk PE

### Massive PE

Outcomes in acute PE vary substantially depending on patient characteristics.<sup>4,5</sup> To tailor medical and interventional therapies for PE to the appropriate patients, definitions for subgroups of PE are required. The qualifiers "massive," "submassive," and "nonmassive" are often encountered in the

literature, although their definitions are vague, vary, and lead to ambiguity.<sup>6</sup> Although it is attractive to stratify types of acute PE on the basis of the absolute incidence of complications such as mortality, this approach is complicated by comorbidities; for example, a nonmassive acute PE might be associated with a high risk for complications in a patient with many comorbidities,<sup>7</sup> such as obstructive airway disease or congestive heart failure. Massive PE traditionally has been defined on the basis of angiographic burden of emboli by use of the Miller Index,<sup>8</sup> but this definition is of limited use. Registry data support the assertion that hypotension and circulatory arrest are associated with increased short-term mortality in acute PE. In the International Cooperative Pulmonary Embolism Registry (ICOPER), the 90-day mortality rate for patients with acute PE and systolic blood pressure <90 mm Hg at presentation (108 patients) was

52.4% (95% confidence interval [CI] 43.3% to 62.1%) versus 14.7% (95% CI 13.3% to 16.2%) in the remainder of the cohort.<sup>9</sup> Similarly, in the Germany-based Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET) of 1001 patients with acute PE, in-hospital mortality was 8.1% for hemodynamically stable patients versus 25% for those presenting with cardiogenic shock and 65% for those requiring cardiopulmonary resuscitation.<sup>10</sup> Both the Geneva and Pulmonary Embolism Severity Index (PESI) clinical scores identify hypotension (blood pressure <100 mm Hg) as a significant predictor of adverse prognosis.<sup>7,11</sup>

We propose the following definition for *massive PE*: Acute PE with sustained hypotension (systolic blood pressure <90 mm Hg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular [LV] dysfunction), pulselessness, or persistent profound bradycardia (heart rate <40 bpm with signs or symptoms of shock).

### Submassive PE

Several techniques have been used to identify subjects at increased risk for adverse short-term outcomes in acute PE (Table 2). These data are based on series of adult patients; there are limited data for prognosis of PE for pediatric patients.

### Clinical Scores

Registry data support the idea that clinical features, including age and comorbidities, influence prognosis in acute PE.<sup>4,5,71</sup> These features have been incorporated into clinical scores to estimate prognosis,<sup>7,11–17,72,73</sup> including the Geneva and PESI scores.<sup>7,11</sup> Clinical scores do predict adverse outcomes in acute PE independent of imaging or biomarkers.<sup>69</sup>

### Echocardiography

Echocardiography identifies patients at increased risk of adverse outcomes from acute PE in many studies,<sup>4,5,18–23,74–81</sup> although there is diversity in criteria for right ventricular (RV) dysfunction on echocardiography. Sanchez et al<sup>82</sup> performed a (selective) meta-analysis and calculated an odds ratio for short-term mortality for RV dysfunction on echocardiography (defined variably; Table 2) of 2.53 (95% CI 1.17 to 5.50).

### Computed Tomographic (CT) Scan

CT scan measurements of RV dilation predict adverse short-term events,<sup>25,33</sup> including in-hospital death,<sup>27</sup> 30-day mortality,<sup>26</sup> and mortality at 3 months.<sup>28</sup> The criterion for RV dilation has varied among studies; an RV diameter divided by LV diameter >0.9 in a 4-chamber view was used by Quiroz et al<sup>25</sup> and Schoepf et al.<sup>26</sup> Results from 1 large cohort of 1193 patients suggested that ventricular septal bowing was predictive of short-term mortality but that the ratio of RV diameter to LV diameter was not.<sup>29</sup> This same group found that RV diameter divided by LV diameter was predictive of other adverse outcomes, including admission to an intensive care unit.<sup>24</sup> An additional study did not support RV dilation as being predictive of adverse prognosis, although a 4-chamber view was not used.<sup>32</sup> Clot burden measured by CT angiography does not predict adverse prognosis.<sup>30</sup>

### Elevated Troponins

Elevated troponins, including troponin I and troponin T, are associated with adverse prognosis in acute PE.<sup>43–55,83,84</sup> Becattini et al<sup>85</sup> summarized the literature in a meta-analysis and demonstrated that in submassive PE, troponin elevations had an odds ratio for mortality of 5.90 (95% CI 2.68 to 12.95).

### Elevated Natriuretic Peptides

Elevated natriuretic peptides, including brain natriuretic peptide (BNP)<sup>34–38,86</sup> and N-terminal pro-BNP,<sup>39–42</sup> have been shown to be predictive of adverse short-term outcomes in acute PE. In the meta-analysis by Sanchez et al,<sup>82</sup> the odds ratios for short-term mortality for BNP or N-terminal pro-BNP elevations in patients with submassive PE were 9.51 (95% CI 3.16 to 28.64) and 5.74 (95% CI 2.18 to 15.13), respectively. Cavallazzi et al<sup>87</sup> and Klok et al<sup>88</sup> also showed that BNP and N-terminal pro-BNP elevations were predictive of mortality. Other novel biomarkers, including D-dimer and heart-type fatty acid-binding protein, also have prognostic value.<sup>89–92</sup>

### Electrocardiography

Electrocardiography helps identify patients at risk of adverse outcomes in acute PE. Abnormalities reported with acute PE include sinus tachycardia, atrial arrhythmias, low voltage, Q waves in leads III and aVF (pseudoinfarction), S1Q3T3 pattern, Qr pattern in V<sub>1</sub>, P pulmonale, right-axis deviation, ST-segment elevation, ST-segment depression, QT prolongation, and incomplete or complete right bundle-branch block.<sup>30,93–110</sup> Of these, sinus tachycardia, new-onset atrial arrhythmias, new right bundle-branch block (complete or incomplete), Qr pattern in V<sub>1</sub>, S1Q3T3, negative T waves in V<sub>1</sub> through V<sub>4</sub>, and ST-segment shift over V<sub>1</sub> through V<sub>4</sub> have been shown to correlate with worse short-term prognosis in acute PE.<sup>101–104,106–110</sup>

### Hybrid Studies

Hybrid studies, which involve multiple prognostic variables,<sup>14,30,37,54,56–70,111–113</sup> demonstrate that combinations of RV dysfunction, elevated natriuretic peptides, or elevated troponin are markers of adverse prognosis. Although the techniques described above have utility for predicting prognosis in acute PE, clinical judgment is required to determine which of these is appropriate for an individual patient.

We propose the following definition for *submassive PE*: Acute PE without systemic hypotension (systolic blood pressure ≥90 mm Hg) but with either RV dysfunction or myocardial necrosis.

- RV dysfunction means the presence of at least 1 of the following:
  - RV dilation (apical 4-chamber RV diameter divided by LV diameter >0.9) or RV systolic dysfunction on echocardiography
  - RV dilation (4-chamber RV diameter divided by LV diameter >0.9) on CT
  - Elevation of BNP (>90 pg/mL)
  - Elevation of N-terminal pro-BNP (>500 pg/mL); or

**Table 2. Studies of Prognosis in Acute PE**

Studies by Type of Variable Tested and First Author	Year Published	No. of Subjects	Included Subjects	Variable(s) Tested	Outcome	Effect
<b>Clinical scores</b>						
Wicki <sup>11</sup>	2000	296	Acute PE	Geneva score	Death, recurrent VTE, or major bleeding at 3 mo	OR 15.7 for high risk vs low risk (95% CI not reported)
Nendaz <sup>12</sup>	2004	199	Acute PE	Geneva score	Death, recurrent VTE, or major bleeding at 3 mo	OR 7.2 for high risk vs low risk (95% CI not reported)
Aujesky <sup>7</sup>	2005	15 531	Acute PE	PESI clinical score	30-d mortality	OR 29.2 for class V vs I (95% CI not reported)
Uresandi <sup>13</sup>	2007	681	Outpatients with acute PE	Spanish clinical score	Death, recurrent VTE, or major/minor bleeding at 10 d	OR 4.7 for high risk vs low risk (95% CI not reported)
Jiménez <sup>14</sup>	2007	599	Acute PE	PESI and Geneva scores	30-d mortality	OR 4.5 for PESI class V, OR 3.1 for Geneva high risk (95% CI not reported)
Donzé <sup>15</sup>	2008	357	Acute PE	PESI clinical score	90-d mortality	OR 12.4 for PESI class III–V vs I–II (95% CI not reported)
Choi <sup>16</sup>	2009	90	Acute PE	PESI clinical score	30-d mortality	OR 19.8 for PESI class V vs PESI I
Ruiz-Giménez <sup>17</sup>	2008	13 057	Acute PE	Bleeding risk score	Major bleeding at 3 mo	LR 2.96 (95% CI 2.18–4.02) for high risk
<b>Echocardiography</b>						
Ribeiro <sup>18</sup>	1997	126	Acute PE	Moderate-severe RV systolic dysfunction on echo	In-hospital mortality	OR ∞ (no deaths observed with normal RV function)
Goldhaber <sup>4</sup>	1999	2454	Acute PE	RV hypokinesis on echo (in addition to age >70 y, cancer, CHF, COPD, hypotension, and tachypnea)	All-cause mortality at 3 mo	HR 2.0 (95% CI 1.2–3.2) for RV hypokinesis
Grifoni <sup>5</sup>	2000	209	Acute PE	≥1 of RV dilation (EDD >30 mm or RVEDD/LVEDD ratio >1 in apical 4-chamber view), paradoxical septal motion, or RVSP >30 mm Hg	In-hospital all-cause mortality	OR 4.7 (95% CI not reported)
Vieillard-Baron <sup>19</sup>	2001	161	“Massive” PE defined as at least 2 lobar PAs occluded	RVEDA/LVEDA >0.6 on echo	In-hospital all-cause mortality	NS in multivariate model
Kucher <sup>20</sup>	2005	1035	Acute PE with systolic BP >90 mm Hg	RV hypokinesis on echo	30-d mortality	HR 1.94 (95% CI 1.23–3.06)
Jiang <sup>21</sup>	2007	57	“Normotensive” acute PE	RV dilation, PASP >30 mm Hg, TR jet velocity >2.8 m/s	In-hospital mortality	OR 5.6 (95% CI not reported)
Frémont <sup>22</sup>	2008	950	Acute PE	RVEDD/LVEDD ≥0.9	In-hospital mortality	OR 2.66, <i>P</i> =0.01 (95% CI not reported)
Kjaergaard <sup>23</sup>	2009	283	“Nonmassive” acute PE	PA acceleration time	All-cause mortality at 1 y	HR 0.89 (95% CI 0.83–0.97)
<b>CT scan</b>						
Araoz <sup>24</sup>	2003	173	Acute PE	RV/LV diameter ratio, ventricular septal bowing, clot burden	In-hospital mortality	All variables NS
Quiroz <sup>25</sup>	2004	63	Acute PE	RVD/LVD >0.9 (reconstructed 2- and 4-chamber views studied)	Adverse events (30-d mortality, CPR, ventilation, pressors, thrombolysis, or embolectomy)	OR 4.02 (95% CI 1.06 to 15.19) for RVD/LVD >0.9 in 4-chamber view
Schoepf <sup>26</sup>	2004	431	Acute PE	RVD/LVD >0.9 in reconstructed 4-chamber view	30-d mortality	HR 5.17 (95% CI 1.63–16.35)
Ghuysen <sup>27</sup>	2005	82	Acute PE	RVD/LVD >1.46	In-hospital mortality	OR 5.0 (95% CI not reported)
van der Meer <sup>28</sup>	2005	120	Acute PE	RVD/LVD >1.0 in short-axis view	Mortality at 3 mo	Hazard not reported, but negative predictive value was 100% (95% CI 93.4–100)
Araoz <sup>29</sup>	2007	1193	Acute PE	Ventricular septal bowing, RVD/LVD, clot burden	30-d mortality	No consistent predictor variable
Subramaniam <sup>30</sup>	2008	523	Acute PE	Clot burden and electrocardiography score	All-cause mortality at 1 y	NS for both
Findik <sup>31</sup>	2008	33	Massive acute PE (systolic BP <90 mm Hg)	RV dysfunction, main PA diameter, ventricular septal shape, clot burden	In-hospital mortality	NS for all variables
Stein <sup>32</sup>	2008	76	Acute PE	RVD/LVD >1 (in transverse images)	In-hospital mortality	No in-hospital mortality observed
Nural <sup>33</sup>	2009	85	Acute PE	RVD/LVD in short axis, RVD (short axis), ventricular septal shape, SVC diameter	In-hospital mortality	RVD OR 1.24 (95% CI 1.04–1.48); Note: threshold not specified
<b>Natriuretic peptides</b>						
Kucher <sup>34</sup>	2003	73	Acute PE	BNP >90 pg/mL	Adverse events (death or CPR, ventilation, pressors, thrombolysis, or embolectomy)	OR 8.0 (95% CI 1.3–50.1)
ten Wolde <sup>35</sup>	2003	110	Acute PE	BNP >21.7 pg/mL	All-cause mortality at 3 mo	OR 9.4 (95% CI 1.8–49.2)
Krüger <sup>36</sup>	2004	50	Acute PE	BNP >90 pg/mL	RV dysfunction, in-hospital mortality	OR 28.4 (95% CI 3.22–251.12) for RV dysfunction, but NS for in-hospital mortality
Pieralli <sup>37</sup>	2006	61	Normotensive acute PE	BNP >487 pg/mL	PE-related deterioration or death	OR ∞, no events were observed for BNP <487 pg/mL
Ray <sup>38</sup>	2006	51	Acute PE	BNP >200 pg/mL	ICU admission or death	OR 3.8 (95% CI not reported)

(Continued)

Table 2. Continued

Studies by Type of Variable Tested and First Author	Year Published	No. of Subjects	Included Subjects	Variable(s) Tested	Outcome	Effect
Kucher <sup>39</sup>	2003	73	Acute PE	proBNP >500 pg/mL	Adverse events (death or CPR, ventilation, pressors, thrombolysis, or embolectomy)	OR 14.6 (95% CI 1.5–139.0)
Pruszycki <sup>40</sup>	2003	79	Acute PE	NT-proBNP >600 pg/mL	In-hospital death or serious adverse events	OR 1.89 (95% CI 1.12–3.20)
Kostrubiec <sup>41</sup>	2007	113	Acute PE	NT-proBNP >7500 ng/L on admission	30-d mortality	OR 13.9 (95% CI not reported)
Alonso-Martinez <sup>42</sup>	2009	93	Acute PE	pro-BNP >500 ng/L	30-d mortality	OR 1.03 (95% CI 1.01–1.05)
Troponin						
Giannitsis <sup>43</sup>	2000	56	Acute PE	Troponin T $\geq 0.1$ $\mu$ g/L	In-hospital mortality	OR 29.6 (95% CI 3.3–265.3)
Janata <sup>44</sup>	2003	136	Acute PE	Troponin T $\geq 0.09$ ng/mL	In-hospital mortality	OR 46.0 (95% CI not reported)
Bova <sup>45</sup>	2005	60	Normotensive acute PE	Troponin T $\geq 0.01$ ng/mL	In-hospital mortality	OR 9 (95% CI not reported)
Post <sup>46</sup>	2009	192	Acute PE	Troponin T $\geq 0.1$ ng/mL	30-d mortality	OR 11.6 (95% CI not reported)
Konstantinides <sup>47</sup>	2002	106	Acute PE	Troponin T $\geq 0.1$ ng/mL, troponin I $\geq 1.5$ ng/mL	In-hospital mortality	OR 6.50 (95% CI 1.11–38.15; troponin T), OR 16.91 (95% CI 1.61–177.69; troponin I)
Douketis <sup>48</sup>	2002	24	“Submassive” acute PE, defined as acute PE with systolic BP >90 mm Hg	Troponin I >0.4 $\mu$ g/L	Hypotension, clinical RV failure	OR not reported, but 1/5 with troponin I >0.4 $\mu$ g/L had hypotension
Mehta <sup>49</sup>	2003	38	Acute PE	Troponin I >0.4 ng/mL	Subsequent cardiogenic shock	OR 8.8 (95% CI 2.5–21.0)
La Vecchia <sup>50</sup>	2004	48	Acute PE	Troponin I >0.6 ng/mL	In-hospital mortality	OR 12 (95% CI not reported)
Douketis <sup>51</sup>	2005	458	“Submassive” acute PE, defined as acute PE with systolic BP >90 mm Hg	Troponin I >0.5 $\mu$ g/L	All-cause death (time point not specified)	OR 3.5 (95% CI 1.0–11.9)
Amorim <sup>52</sup>	2006	77	Acute PE	Troponin I >0.10 ng/mL	Proximal PA emboli	OR 12.0 (95% CI 1.6–88.7)
Aksay <sup>53</sup>	2007	77	Acute PE	Troponin I >0.5 ng/mL	In-hospital mortality	OR 3.31 (95% CI 1.82–9.29)
Gallotta <sup>54</sup>	2008	90	Normotensive acute PE	Troponin I >0.03 $\mu$ g/L	Hemodynamic instability, in-hospital mortality	HR 9.8 (95% CI 1.2–79.2; for hemodynamic instability), NS for in-hospital mortality
Alonso-Martinez <sup>55</sup>	2009	164	Acute PE	Troponin I >0.5 $\mu$ g/L	In-hospital mortality	NS
Hybrid studies						
Kucher <sup>34</sup>	2003	73	Acute PE	BNP >90 pg/mL, troponin T >0.01 ng/mL	Adverse events (death or CPR, ventilation, pressors, thrombolysis, or embolectomy)	OR 8.0 (95% CI 1.3–50.1; for BNP), OR 4.3 (95% CI 0.8–24.1; for troponin T, that is, NS)
Kostrubiec <sup>56</sup>	2005	100	Normotensive acute PE	NT-proBNP >600 ng/mL, troponin T >0.07 $\mu$ g/L	All-cause mortality within 40 d	HR 6.5 (95% CI 2.2–18.9; for troponin T) NS for NT-proBNP in multivariate model
Scridon <sup>57</sup>	2005	141	Acute PE	Troponin I >0.10 $\mu$ g/L, echo RVD/LVD >0.9 on apical 4-chamber view	30-d mortality	HR 7.17 (95% CI 1.6–31.9) for both tests positive
Binder <sup>58</sup>	2005	124	Acute PE	NT-proBNP >1000 pg/mL, RV dysfunction on echo, troponin T >0.04 ng/mL	In-hospital death or complications	HR 12.16 (95% CI 2.45–60.29) for both NT-proBNP and echo positive, HR 10.00 (95% CI 2.14–46.80) for both troponin T and echo positive
Pieralli <sup>37</sup>	2006	61	Normotensive acute PE	BNP >487 pg/mL, RV dysfunction on echo	In-hospital death or clinical deterioration	OR $\infty$ for BNP (no events seen for BNP <487 pg/mL), OR $\infty$ for RV dysfunction on echo (no events seen with no RV dysfunction)
Kline <sup>59</sup>	2006	181	Acute PE with systolic BP >100 mm Hg	Panel of pulse oximetry, 12-lead ECG, and troponin T, as well as RV dysfunction on echo	In-hospital circulatory shock or intubation, or death, recurrent PE, or severe cardiopulmonary disability	OR 4.0 for panel (95% CI not reported), OR 2.1 for RV dysfunction on echo (95% CI not reported)
Hsu <sup>60</sup>	2006	110	Acute PE	Troponin I 0.4 ng/mL, RVD/LVD >1 on echo	Mortality at 1 y	HR 2.584 (95% CI 1.451–4.602)
Logeart <sup>61</sup>	2007	67	Normotensive acute PE	Troponin I >0.10 $\mu$ g/mL, BNP >200 pg/mL	RV dysfunction on echo	OR 9.3 for troponin I, OR 32.7 for BNP (95% CIs not reported)
Maziere <sup>62</sup>	2007	60	Acute PE	Troponin I >0.20 $\mu$ g/mL, BNP >1000 pg/mL	In-hospital death, CPR, ventilation, pressors, thrombolytic, embolectomy, or ICU admission	OR 10.8 for troponin I, OR 3.4 for BNP (95% CIs not reported)
Zhu <sup>63</sup>	2007	90	Acute PE	Troponin I >0.11 ng/mL, RV dysfunction on echo (RVD/LVD >0.65 in parasternal long-axis view)	14-d death, pressors, intubation, or CPR	OR 11.4 for troponin I, OR 10.5 for RVD/LVD >0.65 (95% CIs not reported)
Tulevski <sup>64</sup>	2007	28	Normotensive acute PE	BNP >10 pmol/L, troponin T >0.010 ng/mL	In-hospital death	OR $\infty$ for BNP and troponin T positive (no events observed with negative BNP or troponin T)
Kline <sup>65</sup>	2008	152	Acute PE, systolic BP >100 mm Hg	BNP >100 pg/mL, troponin I >0.1 ng/mL	Mortality at 6 mo	HR 2.74 (95% CI 1.07–6.96; for BNP) HR 1.41 (95% CI 0.54–3.61; for troponin I, ie, NS)

(Continued)

Table 2. Continued

Studies by Type of Variable Tested and First Author	Year Published	No. of Subjects	Included Subjects	Variable(s) Tested	Outcome	Effect
Palmieri <sup>66</sup>	2008	89	Normotensive acute PE	PESI clinical score IV–V, troponin T >0.10 $\mu\text{g/L}$ , RV dysfunction on echo (RV area/LV area >0.9 in apical 4-chamber view)	In-hospital death	OR 2.6 (95% CI 1.2–5.9; for PESI IV–V); NS for both troponin T and RV dysfunction on echo in multivariate model
Gallotta <sup>64</sup>	2008	90	Normotensive acute PE	Troponin I >0.03 $\mu\text{g/L}$ , RV dysfunction on echo	In-hospital death	Troponin I as continuous variable: Adjusted LR 2.2/ $\mu\text{g/L}$ (95% CI 1.1–4.3)
Toosi <sup>67</sup>	2008	159	Acute PE	Shock Index >1, multiple echo parameters	In-hospital death	Shock Index >1 independently predictive, but OR not reported
Jiménez <sup>68</sup>	2008	318	Normotensive acute PE	Troponin I >0.1 ng/mL, PESI clinical score V	30-d mortality	OR 1.4 (95% CI 0.6–3.3; for Troponin I, ie NS) OR 11.1 (95% CI 1.5–83.6; for PESI score of V)
Subramaniam <sup>30</sup>	2008	523	Acute PE	Electrocardiography score, clot burden on CT	Mortality at 1 y	NS for both variables
Bova <sup>69</sup>	2009	201	Normotensive acute PE	RV dysfunction on echo (RVD/LVD on apical view >1), troponin I >0.07 ng/mL, BNP >100 pg/mL, Geneva score $\geq 3$ , $\text{PaO}_2$ <60 mm Hg on room air, D-dimer >3 ng/mL	In-hospital death or clinical deterioration	HR 7.4 (95% CI 1.2–46.0; Geneva score $\geq 3$ ) HR 12.1 (95% CI 1.3–112.0; troponin I) All other variables NS on multivariable analysis
Vuilleumier <sup>70</sup>	2009	146	Normotensive acute PE	Troponin I >0.09 ng/mL, NT-proBNP >300 pg/mL, myoglobin >70 ng/mL, H-FABP >6 ng/mL, D-dimer >2000 ng/mL	Death or recurrent VTE or bleeding at 3 mo	Univariate: OR 15.8 (95% CI 21.1–122; NT-proBNP); OR 4.7 (95% CI 1.5–14.8; H-FABP); OR 3.5 (95% CI 1.2–9.7; troponin I); OR 8.0 (95% CI 1.1–64.5; D-dimer); OR 3.4 (95% CI 0.9–12.2; myoglobin); Multivariate: Only NT-proBNP significant, but OR not reported

PE indicates pulmonary embolism; VTE, venous thromboembolism; mo, month(s); OR, odds ratio; CI, confidence interval; PESI, pulmonary embolism severity index; LR, likelihood ratio; RV, right ventricular; echo, echocardiography; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; EDD, end-diastolic diameter; RVEDD, right ventricular end-diastolic diameter; LVEDD, left ventricular end-diastolic diameter; RVSP, right ventricular systolic pressure; RVEDA, right ventricular end-diastolic area; LVEDA, left ventricular end-diastolic area; NS, not significant; PA, pulmonary artery; BP, blood pressure; PASP, pulmonary artery systolic pressure; TR, tricuspid regurgitant; CT, computed tomography; LV, left ventricular; RVD, right ventricular diameter; LVD, left ventricular diameter; CPR, cardiopulmonary resuscitation; ECG, electrocardiogram; BNP, brain natriuretic peptide; SVC, superior vena cava; ICU, intensive care unit; proBNP, pro-brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; and H-FABP, heart-type fatty acid-binding protein.

- Electrocardiographic changes (new complete or incomplete right bundle-branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion)
- Myocardial necrosis is defined as either of the following:
  - Elevation of troponin I (>0.4 ng/mL) or
  - Elevation of troponin T (>0.1 ng/mL)

### Low-Risk PE

The literature summarized in Table 2 demonstrates that patients with the lowest short-term mortality in acute PE are those who are normotensive with normal biomarker levels and no RV dysfunction on imaging. Recent cohorts in which these parameters have been evaluated together suggest that prognosis is best in those with normal RV function and no elevations in biomarkers,<sup>46,66,69</sup> with short-term mortality rates approaching  $\approx 1\%$ . We suggest the qualifier “low risk” to describe this group, because absence of RV dysfunction and normal biomarkers identifies a set of patients with excellent prognosis. We recognize that some patients with low-risk PE, as we have defined it here, may still have significant rates of morbidity and mortality that are functions of older age and comorbidities.<sup>7,11</sup> It is therefore important to incorporate risk stratification into the clinical decisions for each individual patient.

We propose the following definition for *low-risk PE*: Acute PE and the absence of the clinical markers of adverse prognosis that define massive or submassive PE.

### Therapy for Acute Massive, Submassive, and Low-Risk PE

Resuscitation and medical therapy for acute PE have been reviewed elsewhere.<sup>2,3</sup> Patients with objectively confirmed PE and no contraindications should receive prompt and appropriate anticoagulant therapy with subcutaneous low-molecular-weight heparin (LMWH), intravenous or subcutaneous unfractionated heparin (UFH) with monitoring, unmonitored weight-based subcutaneous UFH, or subcutaneous fondaparinux. For patients with suspected or confirmed heparin-induced thrombocytopenia, a non-heparin-based anticoagulant, such as danaparoid (not available in the United States), lepirudin, argatroban, or bivalirudin, should be used.<sup>114</sup> Patients with intermediate or high clinical probability of PE should be given anticoagulant therapy during the diagnostic workup.<sup>2,3</sup> Considerations about choice of chronic anticoagulant and duration of therapy are reviewed elsewhere.<sup>2,3</sup>

#### Recommendations for Initial Anticoagulation for Acute PE

1. Therapeutic anticoagulation with subcutaneous LMWH, intravenous or subcutaneous UFH with monitoring, unmonitored weight-based subcutaneous UFH, or subcutaneous fondaparinux should be given to patients with objectively confirmed PE and no contraindications to anticoagulation (*Class I; Level of Evidence A*).
2. Therapeutic anticoagulation during the diagnostic workup should be given to patients with intermediate or

**Table 3. Pharmacological Profile of Plasminogen-Activating Fibrinolytic Agents**

Fibrinolytic	FDA Indication for PE?	Direct Plasminogen Activator?	Fibrinolytic Dose	Fibrin Specificity (Relative to Fibrinogen)	PAI Resistance*
Streptokinase	Yes	No	250 000-IU IV bolus followed by 100 000-IU/h infusion for 12–24 h <sup>116</sup>	—	—
Urokinase	Yes	No	4400-IU/kg bolus, followed by 4400 IU · kg <sup>-1</sup> · h <sup>-1</sup> for 12–24 h <sup>117</sup>	—	—
Alteplase	Yes	Yes	100-mg IV infusion over 2 h <sup>118</sup>	++	++
Reteplase	No	Yes	Double 10-U IV bolus† 30 min apart <sup>119</sup>	+	+
Tenecteplase	No	Yes	Weight-adjusted IV bolus over 5 s (30–50 mg with a 5-mg step every 10 kg from <60 to >90 kg) <sup>120</sup>	+++	+++

FDA indicates US Food and Drug Administration; PE, pulmonary embolism; PAI, plasminogen activator inhibitor; IV, intravenous; +, relative strength (+ < ++ < +++).

\*PAI is a 52-kDa circulating glycoprotein that is the primary native of plasminogen-activating enzymes, and greater PAI resistance confers a longer duration of fibrinolysis.

†Ten units includes approximately 18 mg of reteplase and 8 mg of tranexamic acid per dose.

**high clinical probability of PE and no contraindications to anticoagulation (Class I; Level of Evidence C).**

### Thrombolysis

#### Pharmacology of Thrombolytic Agents

In contrast to the passive reduction of thrombus size allowed by heparin, thrombolytic agents actively promote the hydrolysis of fibrin molecules.<sup>115</sup> All fibrinolytic drugs approved by the US Food and Drug Administration (FDA) are enzymes that convert the patient's native circulating plasminogen into plasmin. Plasmin is a serine protease that cleaves fibrin at several sites, liberating fibrin-split products, including the D-dimer fragment. Table 3 qualitatively compares several clinically relevant features of fibrinolytic agents that have received approval for use by the FDA. In 2010, the FDA label for alteplase (Activase, Genentech, San Francisco, CA) explicitly stated that the agent is indicated for "... massive pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lung, or for unstable hemodynamics, ie, failure to maintain blood pressure without supportive measures."<sup>121</sup>

#### Potential Benefits and Harm

The decision to administer a fibrinolytic agent in addition to heparin anticoagulation requires individualized assess-

ment of the balance of benefits versus risks. Potential benefits include more rapid resolution of symptoms (eg, dyspnea, chest pain, and psychological distress), stabilization of respiratory and cardiovascular function without need for mechanical ventilation or vasopressor support, reduction of RV damage, improved exercise tolerance, prevention of PE recurrence, and increased probability of survival. Potential harm includes disabling or fatal hemorrhage, including intracerebral hemorrhage, and increased risk of minor hemorrhage, resulting in prolongation of hospitalization and need for blood product replacement.

#### Quantitative Assessment of Outcomes

Patients treated with a fibrinolytic agent have faster restoration of lung perfusion.<sup>79,122–125</sup> At 24 hours, patients treated with heparin have no substantial improvement in pulmonary blood flow, whereas patients treated with adjunctive fibrinolysis manifest a 30% to 35% reduction in total perfusion defect. However, by 7 days, blood flow improves similarly ( $\approx 65\%$  to  $70\%$  reduction in total defect). Table 4 summarizes the results of various fibrinolytic agents compared with placebo in the evaluation of the impact of therapy on mean pulmonary arterial pressure.

Thirteen placebo-controlled randomized trials of fibrinolysis for acute PE have been published,<sup>79,118,120,124,126–134</sup> but

**Table 4. Summary of PAP Measurements Made in the First Hours After Treatment in Placebo-Controlled Randomized Trials of Fibrinolysis for Acute PE**

First Author/ Study	Year	Lytic Agent	No. Given Lytic	No. Given Placebo	Timing of Second Measurement, h	Fibrinolytic Treatment, mm Hg		Placebo, mm Hg	
						Mean PAP (Pre)	Mean PAP (Post)	Mean PAP (Pre)	Mean PAP (Post)
Tibbut <sup>126</sup>	1974	SK	11	12	72	30.8	18.5	34.3	29.6
PIOPED <sup>127</sup>	1990	tPA	9	4	1.5	28	25	33	33
Konstantinides <sup>128</sup>	1998	tPA	27	13	12	34	22	29	27
NHLBI <sup>129</sup>	1973	UK	82	78	24	26.2	20	26.1	25
Dalla-Volta <sup>124</sup>	1992	tPA	20	16	2	30.2	21.4	22.3	24.8
Mean (SD)						29.8 (3.0)	21.4 (2.4)	28.9 (4.9)	27.9 (3.5)

PAP indicates pulmonary artery pressure; PE, pulmonary embolism; Pre, before treatment; Post, after treatment; SK, streptokinase; PIOPED, Prospective Investigation Of Pulmonary Embolism Diagnosis; tPA, tissue-type plasminogen activator; NHLBI, National Heart, Lung, and Blood Institute; UK, urokinase; and SD, standard deviation.

only a subset evaluated massive PE specifically. These trials included 480 patients randomized to fibrinolysis and 464 randomized to placebo; 6 of the 13 trials studied alteplase, representing 56% of all patients ( $n=504$ ). These 6 studies used variable infusion regimens. Two studies administered alteplase by bolus intravenous injection (100 mg or 0.6 mg/kg), and 4 infused 90 to 100 mg of alteplase intravenously over a 2-hour period. Three of the 4 used concomitant infusion of intravenous unfractionated heparin (1000 to 1500 U/h). Four studies used intravenous streptokinase, together enrolling 94 patients. All 4 studies of streptokinase used a bolus dose (250 000 to 600 000 U) followed by a 100 000 U/h infusion for 12 to 72 hours. Two studies that examined urokinase, published in 1973 and 1988, together enrolled 190 patients (Table 5). One study randomized 58 patients to receive weight-adjusted single-bolus intravenous tenecteplase (30 to 50 mg, with a 5-mg increase in dose for every 10 kg of weight from  $<60$  kg to  $>90$  kg) or placebo.

The odds ratios were calculated by use of fixed effects and random effects models.<sup>135</sup> Table 5 suggests that alteplase treatment was associated with a significantly higher rate of hemorrhage than anticoagulation alone, although these events included skin bruising and oozing from puncture sites. Neither recurrent PE nor death was significantly different in the alteplase versus placebo groups. Alteplase was associated with a trend toward decreased recurrent PE. Similar findings have been reported by Wan et al<sup>136</sup> and Thabut et al.<sup>137</sup> When Wan et al<sup>136</sup> restricted their analysis to those trials with massive PE, they identified a significant reduction in recurrent PE or death from 19.0% with heparin alone to 9.4% with fibrinolysis (odds ratio 0.45, 95% CI 0.22 to 0.90).<sup>136</sup>

### Number Needed to Treat

Wan et al,<sup>136</sup> in their analysis restricted to trials that included fibrinolysis for massive PE, found the number needed to treat to prevent the composite end point of recurrent PE or death was 10. This end point was not statistically significant when all trials, including those that studied less severe forms of PE, were included.<sup>136</sup> In this analysis, there was no significant increase in major bleeding, but there was a significant increase in nonmajor bleeding; the number needed to harm was 8.<sup>136</sup> On the other hand, Thabut et al,<sup>137</sup> using data from all trials regardless of PE severity but before the publication of the largest randomized trial to date, estimated the number needed to harm at 17.

### Impact of Fibrinolysis on Submassive PE

At least 4 registries have documented the outcomes of patients with PE (MAPPET,<sup>10</sup> ICOPER,<sup>4,9</sup> RIETE [Registro Informatizado de la Enfermedad TromboEmbólica],<sup>71,139</sup> and EMPEROR [Emergency Medicine Pulmonary Embolism in the Real-World Registry]<sup>140</sup>), and the data from these are summarized in Table 6. The data suggest a trend toward a decrease in all-cause mortality from PE, especially massive PE in those patients treated with fibrinolysis. The 30-day mortality rate directly attributed to PE in normotensive patients in the recently completed EMPEROR registry was 0.9% (95% CI 0 to 1.6). Data from these registries indicate that the short-term mortality rate directly attributable to

submassive PE treated with heparin anticoagulation is probably  $<3.0\%$ . The implication is that even if adjunctive fibrinolytic therapy has extremely high efficacy, for example, a 30% relative reduction in mortality, the effect size on mortality due to submassive PE is probably  $<1\%$ . Thus, secondary adverse outcomes such as persistent RV dysfunction, CTEPH, and impaired quality of life represent appropriate surrogate goals of treatment.

### Impact of Fibrinolysis on Intermediate Outcomes

Among PE patients, to determine whether adjunctive fibrinolytic therapy can effectively reduce the outcome of dyspnea and exercise intolerance from PE caused by persistent pulmonary hypertension (World Health Organization [WHO] Group 4 pulmonary hypertension), it is first necessary to examine the incidence of persistently elevated RV systolic pressure (RVSP) or pulmonary arterial pressure, measured 6 or more months after acute PE. The current literature includes only 4 studies that report baseline and follow-up RVSP or pulmonary arterial pressures by use of pulmonary arterial catheter or Doppler echocardiography.<sup>142–145</sup> Table 7 summarizes these findings. These data suggest that compared with heparin alone, heparin plus fibrinolysis yields a significant favorable change in RVSP and pulmonary arterial pressure incident between the time of diagnosis and follow-up.

The largest study, accounting for 162 of the 205 patients, was the only one that was prospectively designed to assess outcomes for all survivors at 6 months.<sup>145</sup> All patients were normotensive at the time of enrollment. Follow-up included Doppler echocardiographic estimation of the RVSP, a 6-minute walk test, and New York Heart Association (NYHA) classification. The study protocol in that report recommended addition of alteplase (0.6 mg/kg infused over 2 hours) for patients who experienced hemodynamic deterioration, defined as hypotension, cardiac arrest, or respiratory failure requiring mechanical ventilation. Figure 1 shows the change in individual RVSP values for each patient in the study. Among the 144 patients who received heparin only, 39 (27%) demonstrated an increase in RVSP at 6-month follow-up, and 18 (46%) of these 39 patients had either dyspnea at rest (NYHA classification more than II) or exercise intolerance (6-minute walk distance  $<330$  m). The mean 6-minute walk distance was 364 m for the alteplase group versus 334 m for the heparin-only patients. No patient treated with adjunctive alteplase demonstrated an increase in RVSP at 6-month follow-up, which suggests that thrombolytic therapy may have the benefit of decreasing the incidence of CTEPH.

### Contraindications to Fibrinolysis

Because of small sample sizes and heterogeneity, the clinical trials presented in Table 5 provide limited guidance in establishing contraindications to the use of fibrinolytic agents in PE. Contraindications must therefore be extrapolated from author experience and from guidelines for ST-segment elevation myocardial infarction.<sup>146</sup> Absolute contraindications include any prior intracranial hemorrhage, known structural intracranial cerebrovascular disease (eg, arteriovenous malformation), known malignant intracranial neoplasm, ischemic stroke within 3 months, suspected aortic dissection, active

**Table 5. Pooled Results of Published Outcomes From 13 Placebo-Controlled, Randomized Trials of Fibrinolytics to Treat Acute PE**

First Author/Study	Agent	No. of Patients		Any Bleed, n		Major Bleed, n		ICH, n		Recurrent PE, n		Death, n	
		Lytic	Placebo	Lytic	Placebo	Lytic	Placebo	Lytic	Placebo	Lytic	Placebo	Lytic	Placebo
Konstantinides <sup>128</sup>	Alteplase	27	13	0	0	0	0	0	0	0	0	1	1
Konstantinides <sup>118</sup>	Alteplase	118	138	1	5	1	5	0	0	4	4	4	3
Levine <sup>130</sup>	Alteplase	33	25	15	1	0	0	0	0	0	0	1	0
PIOPED <sup>127</sup>	Alteplase	9	4	1	0	1	0	0	0	0	0	1	0
Dalla-Volta <sup>124</sup>	Alteplase	20	16	14	6	3	2	1	0	1	3	2	1
Goldhaber <sup>79</sup>	Alteplase	46	55	3	3	3	2	0	1	0	5	0	2
Subtotal		253	251	34	15	8	9	1	1	5	12	9	7
Alteplase vs placebo													
OR (fixed effects)				2.446 (95% CI 1.222–4.894)		0.85 (95% CI 0.319–2.264)		0.981 (95% CI 0.128–7.53)		0.462 (95% CI 0.167–1.279)		1.101 (95% CI 0.431–2.814)	
OR (random effects)				2.129 (95% CI 0.533–8.508)		0.958 (95% CI 0.328–2.802)		0.984 (95% CI 0.099–9.762)		0.44 (95% CI 0.096–2.024)		1.161 (95% CI 0.428–3.147)	
Becattini <sup>120</sup>	TNK	23	28	13	1	2	1	1	0	1	1	0	1
Tibutti <sup>126</sup>	SK	11	12	4	4	1	1	0	0	0	0	0	0
Jerjes-Sanchez <sup>131</sup>	SK	4	4	0	0	0	0	0	0	0	0	0	4
Dotter <sup>132</sup>	SK	15	16	9	5	1	2	0	0	1	3	1	2
Ly <sup>133</sup>	SK	14	11	4	2	4	2	0	0	0	2	1	2
Subtotal		44	43	17	11	6	5	0	0	1	5	2	8
SK vs placebo													
OR (fixed effects)				2.018 (95% CI 0.776–5.251)		1.108 (95% CI 0.3–4.094)		NA		0.221 (95% CI 0.034–1.446)		0.211 (95% CI 0.047–0.942)	
OR (random effects)				2.021 (95% CI 0.768–5.319)		1.117 (95% CI 0.289–4.312)		NA		0.226 (95% CI 0.034–1.513)		0.223 (95% CI 0.036–1.393)	
NHLBI <sup>129</sup>	UK	82	78	37	21	22	11	2	0	5	5	6	7
Marini <sup>134</sup>	UK	20	10	1	0	0	0	0	0	0	0	0	0
Subtotal		160	142	59	34	32	18	2	0	6	12	9	17
Grand total		457	436	110	60	46	32	3	1	12	29	20	32
All lytics vs placebo													
OR (fixed effects)				2.251 (95% CI 1.472–3.443)		1.439 (95% CI 0.83–2.495)		1.799 (95% CI 0.368–8.803)		0.509 (95% CI 0.249–1.042)		0.706 (95% CI 0.376–1.325)	
OR (random effects)				2.155 (95% CI 1.251–3.713)		1.534 (95% CI 0.858–2.741)		1.754 (95% CI 0.28–10.979)		0.588 (95% CI 0.272–1.269)		0.773 (95% CI 0.391–1.53)	

PE indicates pulmonary embolism; ICH, intracranial hemorrhage; PIOPED, Prospective Investigation Of Pulmonary Embolism Diagnosis; OR, odds ratio; CI, confidence interval; TNK, tenecteplase; SK, streptokinase; NA, not available; NHLBI, National Heart, Lung, and Blood Institute; and UK, urokinase.

**Table 6. Mortality Rates for Acute PE From Published Results of Registries and a Publicly Available Database (HCUP-NIS)**

Source	Year	N	Follow-Up	Mortality Rate, %			
				Massive PE	Submassive PE	Massive PE Given Lytic	Submassive PE Given Lytic
MAPPET <sup>138</sup>	1997	719	30	NA	9.6	NA	4.7
ICOPER <sup>9</sup>	1999	2284	90	52.4	14.7	46.3	21
RIETE <sup>71,139</sup>	2007	6264	90	9.3	3.0	1.3	7.7
EMPEROR <sup>140</sup>	2008	1840	In-hospital	14.6	3.0	0	9.5
HCUP-2007 NIS <sup>141</sup>	2007	32 263	In-hospital		3.6		NA

PE indicates pulmonary embolism; HCUP-NIS, Healthcare Cost and Utilization Program Nationwide Inpatient Sample; MAPPET, Management strategy And Prognosis of Pulmonary Embolism regisTry; NA, not available; ICOPER, International COoperative Pulmonary Embolism Registry; RIETE, Registro Informatizado de la Enfermedad TromboEmbólica; and EMPEROR, Emergency Medicine Pulmonary Embolism in the Real-world Registry.

bleeding or bleeding diathesis, recent surgery encroaching on the spinal canal or brain, and recent significant closed-head or facial trauma with radiographic evidence of bony fracture or brain injury. Relative contraindications to fibrinolysis include age >75 years; current use of anticoagulation; pregnancy; noncompressible vascular punctures; traumatic or prolonged cardiopulmonary resuscitation (>10 minutes); recent internal bleeding (within 2 to 4 weeks); history of chronic, severe, and poorly controlled hypertension; severe uncontrolled hypertension on presentation (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg); dementia; remote (>3 months) ischemic stroke; and major surgery within 3 weeks. Recent surgery, depending on the territory involved, and minor injuries, including minor head trauma due to syncope, are not necessarily barriers to fibrinolysis. *The clinician is in the best position to judge the relative merits of fibrinolysis on a case-by-case basis.*

### Synthesis of Data Into a Treatment Algorithm

Figure 2 summarizes the treatment options for acute PE. Patients with low-risk PE have an unfavorable risk-benefit ratio with fibrinolysis. Patients with PE that causes hypotension probably do benefit from fibrinolysis. Management of submassive PE crosses the zone of equipoise, requiring the clinician to use clinical judgment.

Two criteria can be used to assist in determining whether a patient is more likely to benefit from fibrinolysis: (1) Evidence of present or developing circulatory or respiratory insufficiency; or (2) evidence of moderate to severe RV injury. Evidence of circulatory failure includes any episode of hypotension or a persistent shock index (heart rate in beats per minute divided by

systolic blood pressure in millimeters of mercury) >1.<sup>147</sup> The definition of respiratory insufficiency may include hypoxemia, defined as a pulse oximetry reading <95% when the patient is breathing room air and clinical judgment that the patient appears to be in respiratory distress.<sup>147,148</sup> Alternatively, respiratory distress can be quantified by the numeric Borg score, which assesses the severity of dyspnea from 0 to 10 (0=no dyspnea and 10=sensation of choking to death); fewer than 10% of patients with acute PE report a Borg score >8 at the time of diagnosis.<sup>149</sup> Evidence of moderate to severe RV injury may be derived from Doppler echocardiography that demonstrates any degree of RV hypokinesis, McConnell's sign (a distinct regional pattern of RV dysfunction with akinesis of the mid free wall but normal motion at the apex), interventricular septal shift or bowing, or an estimated RVSP >40 mm Hg. Biomarker evidence of moderate to severe RV injury includes major elevation of troponin measurement or brain natriuretic peptides. A limitation of this approach is that these variables are generally presented as dichotomous, and there are no universally agreed on thresholds for minor or major abnormalities. Practical judgment of the bedside physician is required.

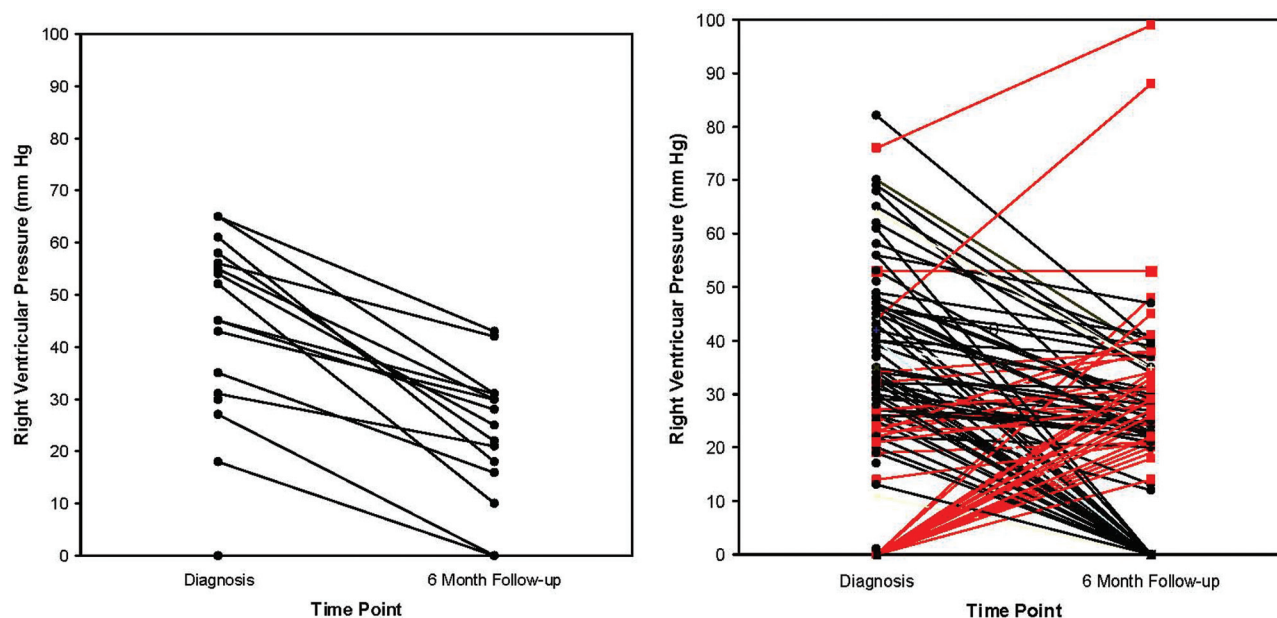
We recommend administration of a fibrinolytic via a peripheral intravenous catheter.<sup>150</sup> Figure 2 incorporates the FDA-recommended infusion dose of alteplase at 100 mg as a continuous infusion over 2 hours.<sup>121</sup> The FDA recommends withholding anticoagulation during the 2-hour infusion period.

Two ongoing randomized controlled trials (RCTs) will help address the controversial question about which patients with submassive PE will benefit from fibrinolysis. Both trials use tenecteplase as the fibrinolytic, an agent that is not

**Table 7. Pooled Data From Studies That Reported Right Ventricular Systolic Pressure Measurements Made Several Months or More After Acute PE**

Author	Heparin				Fibrinolytic			
	Baseline PASP, mm Hg	Follow-Up PASP, mm Hg	% Change	N	Baseline PASP, mm Hg	Follow-Up PASP, mm Hg	% Change	N
De Souza <sup>142</sup> and Schwarz <sup>143</sup>	47±13	33±7	30±24	13	61±14	24±5	61±22	7
Sharma <sup>144</sup>	27±2	22±1.4	17±7	11	28±1.9	17±1.3	39±7	12
Kline <sup>145</sup>	23±21	17±18	26±99	144	40±21	20±14	50±61	18
Mean/total	32±12	24±9	25±43	168	43±12	20±7	50±30	37

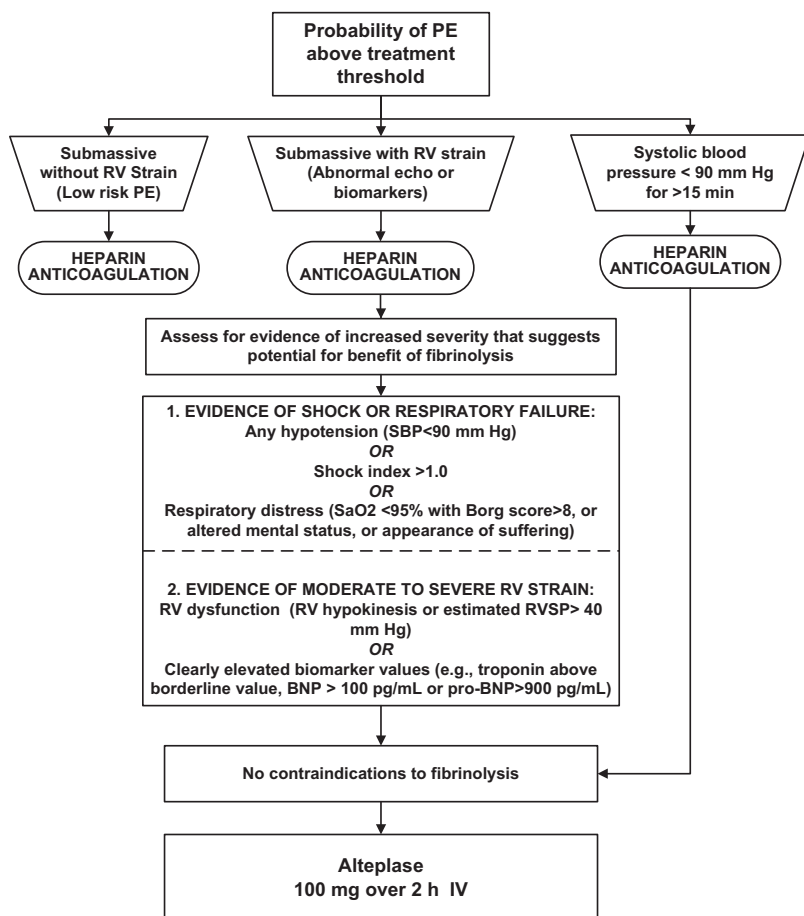
PE indicates pulmonary embolism; PASP, pulmonary artery systolic pressure.



**Figure 1.** Right ventricular systolic pressures at diagnosis and 6 months after acute submassive pulmonary embolism. **Left Panel,** Patients initially treated with heparin and alteplase. **Right Panel,** Patients who received heparin alone. Plots for patients with a net increase in systolic pressure are highlighted in red. Reprinted from Kline et al<sup>145</sup> with permission of the publisher. Copyright © 2009, American College of Chest Physicians.

approved by the FDA for treatment of PE. The larger trial (the Pulmonary Embolism Thrombolysis Study [PEITHO]; ClinicalTrials.gov Identifier NCT00639743) is being conducted in Europe and has enrolled 500 of the planned

enrollment of 1000 patients. Its inclusion criteria are RV dysfunction on echocardiography plus a positive troponin I or T measurement. The primary outcomes are development of circulatory shock or respiratory failure as an inpatient. The



**Figure 2.** Suggested treatment algorithm for use of fibrinolytics to treat acute pulmonary embolism. PE indicates pulmonary embolism; RV, right ventricular; SBP, systolic blood pressure; RVSP, right ventricular systolic pressure; BNP, brain natriuretic peptide; and IV, intravenously.

US trial (Tenecteplase Or Placebo: Cardiopulmonary Outcomes At Three Months [TOPCOAT]; ClinicalTrials.gov Identifier NCT00680628) will enroll 200 normotensive PE patients with either RV hypokinesis on echocardiography, an abnormal troponin measurement, a BNP >90 pg/mL or pro-BNP >900 pg/mL, or a pulse oximetry reading <95% when breathing room air (at altitudes <100 feet above sea level). The main outcome in TOPCOAT is evidence of RV dysfunction associated with an NYHA classification worse than II and a 6-minute walk distance <330 m at 3-month follow-up.

It is preferable to confirm the diagnosis of PE with imaging before fibrinolysis is initiated. When direct imaging is unavailable or unsafe because of the patient's unstable condition, an alternative approach favors aggressive early management, including fibrinolysis, of the patient with sustained hypotension (systolic blood pressure <90 mm Hg for at least 15 minutes or requiring inotropic support, not clearly due to a cause other than PE) when there is a high clinical pretest probability of PE and RV dysfunction on bedside transthoracic echocardiography.<sup>2,151</sup> We do not endorse the strategy of treating subjects with undifferentiated cardiac arrest with fibrinolysis, because this approach lacks clinical benefit.<sup>152</sup>

#### **Recommendations for Fibrinolysis for Acute PE**

1. Fibrinolysis is reasonable for patients with massive acute PE and acceptable risk of bleeding complications (*Class IIa; Level of Evidence B*).
2. Fibrinolysis may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis) and low risk of bleeding complications (*Class IIb; Level of Evidence C*).
3. Fibrinolysis is not recommended for patients with low-risk PE (*Class III; Level of Evidence B*) or submassive acute PE with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening (*Class III; Level of Evidence B*).
4. Fibrinolysis is not recommended for undifferentiated cardiac arrest (*Class III; Level of Evidence B*).

#### **Catheter-Based Interventions**

Percutaneous techniques to recanalize complete and partial occlusions in the pulmonary trunk or major pulmonary arteries are potentially life-saving in selected patients with massive or submassive PE.<sup>153</sup> Transcatheter procedures can be performed as an alternative to thrombolysis when there are contraindications or when emergency surgical thrombectomy is unavailable or contraindicated. Catheter interventions can also be performed when thrombolysis has failed to improve hemodynamics in the acute setting. Hybrid therapy that includes both catheter-based clot fragmentation and local thrombolysis is an emerging strategy. The goals of catheter-based therapy include (1) rapidly reducing pulmonary artery pressure, RV strain, and pulmonary vascular resistance (PVR); (2) increasing systemic perfusion; and (3) facilitating RV recovery.

There are 3 general categories of percutaneous intervention for removing pulmonary emboli and decreasing thrombus

burden: (1) Aspiration thrombectomy, (2) thrombus fragmentation, and (3) rheolytic thrombectomy. Aspiration thrombectomy uses sustained suction applied to the catheter tip to secure and remove the thrombus. The Greenfield suction embolectomy catheter (Medi-tech/Boston Scientific, Natick, MA) was introduced in 1969 and remains the only FDA-approved device.<sup>154</sup> Thrombus fragmentation has been performed with balloon angioplasty,<sup>155</sup> a pigtail rotational catheter,<sup>156</sup> or a more advanced fragmentation device, the Amplatze catheter (ev3 Endovascular, Plymouth, MN), which uses an impeller to homogenize the thrombus.<sup>157</sup> Rheolytic thrombectomy catheters include the AngioJet (MEDRAD, Warrendale, PA), Hydrolyser (Cordis, Miami, FL), and Oasis (Medi-tech/Boston Scientific, Natick, MA) catheters, which use a high-velocity saline jet to fragment adjacent thrombus by creating a Venturi effect and removing the debris into an evacuation lumen.<sup>158</sup>

Other interventional catheters designed to aspirate, macerate, and remove pulmonary artery thrombus include the Rotarex and Aspirex rotational thrombectomy devices (Straub Medical, Wangs, Switzerland).<sup>159</sup> Ideal thrombectomy catheters for use in the pulmonary circulation must be readily maneuverable, effective in removal of thromboemboli, and safe by virtue of minimizing distal embolization, mechanical hemolysis, or damage to cardiac structures and pulmonary arteries.

In a systematic review of available cohort data comprising a total of 348 patients, clinical success with percutaneous therapy alone for patients with acute massive PE was 81% (aspiration thrombectomy 81%; fragmentation 82%; rheolytic thrombectomy 75%) and 95% when combined with local infusion of thrombolytic agents (aspiration thrombectomy 100%; fragmentation 90%; rheolytic thrombectomy 91%).<sup>160</sup> In a retrospective report of 51 patients with massive or submassive PE (28% with shock, 16% with hypotension, and 57% with echocardiographic evidence of RV dysfunction) treated with AngioJet rheolytic thrombectomy, technical success was achieved in 92%, 8% experienced major bleeding, and in-hospital mortality was 16%.<sup>161</sup> Patients with submassive PE treated with rheolytic thrombectomy had similar improvement, with decreased obstruction, improved perfusion, and improved Miller indices.

Only operators experienced with these techniques should perform catheter-based intervention. Interventionalists must be comfortable managing cardiogenic shock, bradyarrhythmias, anticoagulation, and cardiac tamponade. Invasive arterial access is recommended for patients with shock or hypotension to help guide vasopressor management. Patients with massive PE who have contraindications to fibrinolytic therapy who present to centers unable to offer catheter or surgical embolectomy should be considered for urgent transfer to a center with these services available so that they can be evaluated for this therapy. There should be a plan in place for expedition of such transfers. Institutions with expertise in advanced intervention for PE should be identified in advance so that criteria and procedures for transfer can be agreed on explicitly. To ensure transfer is safe, only appropriately trained and equipped ambulance crews should be used to transfer these critically ill unstable patients.

Although there are many individual approaches to catheter-based pulmonary thrombectomy, the following is a suggested approach. Through a 6F femoral venous sheath, a 6F angled pigtail catheter is advanced into each main pulmonary artery, followed by injection of low-osmolar or isosmolar contrast (30 mL over 2 seconds). Either UFH 70 IU/kg intravenous bolus, with additional heparin as needed to maintain an activated clotting time >250 seconds, or the direct thrombin inhibitor bivalirudin (0.75 mg/kg intravenous bolus, then 1.75 mg · kg<sup>-1</sup> · h<sup>-1</sup>) should be used for anticoagulation. For rheolytic thrombectomy, a 6F multipurpose guiding catheter may be used to reach the thrombus, which is crossed with a 0.014-inch hydrophilic guidewire (Choice PT Extra-Support, Boston Scientific, Natick, MA). Temporary transvenous pacemaker insertion may be required during rheolytic thrombectomy.

In general, mechanical thrombectomy should be limited to the main and lobar pulmonary arterial branches. For patients with massive PE, the procedure should continue until systemic hemodynamics stabilize, regardless of the angiographic result. Substantial improvement in pulmonary blood flow may result from what appears to be only modest angiographic improvement. Direct intra-arterial delivery of thrombolytics, such as recombinant tissue-type plasminogen activator (rtPA; 0.6 mg/kg, up to 50 mg) over 15 minutes, may be helpful when mechanical thrombectomy strategies are ineffective.

Pulmonary hemorrhage and right atrial or ventricular perforation leading to cardiac tamponade represent rare but serious complications. Perforation or dissection of a major pulmonary artery branch may cause acute massive pulmonary hemorrhage and death. The risk of perforation increases when vessels smaller than 6 mm in diameter are treated.<sup>162</sup>

### Surgical Embolectomy

Emergency surgical embolectomy with cardiopulmonary bypass has reemerged as an effective strategy for managing patients with massive PE or submassive PE with RV dysfunction when contraindications preclude thrombolysis.<sup>163</sup> This operation is also suited for acute PE patients who require surgical excision of a right atrial thrombus or paradoxical embolism. Surgical embolectomy can also rescue patients whose condition is refractory to thrombolysis.<sup>164</sup> The results of embolectomy will be optimized if patients are referred before the onset of cardiogenic shock. Older case series suggest a mortality rate between 20% and 30% despite surgical embolectomy, although this is likely lower than the mortality rate of untreated patients.<sup>165</sup> In a more recent study, 47 patients underwent surgical embolectomy in a 4-year period, with a 96% survival rate.<sup>166</sup> The procedure can be performed off bypass, with normothermia, and without aortic cross-clamping or cardioplegic or fibrillatory arrest. It is imperative to avoid blind instrumentation of the fragile pulmonary arteries. Extraction is limited to directly visible thromboembolus, which can be accomplished through the level of the segmental pulmonary arteries. The decision to proceed with catheter-based versus surgical embolectomy requires interdisciplinary teamwork, discussion that involves

the surgeon and interventionalist, and an assessment of the local expertise.

### Recommendations for Catheter Embolectomy and Fragmentation

1. Depending on local expertise, either catheter embolectomy and fragmentation or surgical embolectomy is reasonable for patients with massive PE and contraindications to fibrinolysis (*Class IIa; Level of Evidence C*).
2. Catheter embolectomy and fragmentation or surgical embolectomy is reasonable for patients with massive PE who remain unstable after receiving fibrinolysis (*Class IIa; Level of Evidence C*).
3. For patients with massive PE who cannot receive fibrinolysis or who remain unstable after fibrinolysis, it is reasonable to consider transfer to an institution experienced in either catheter embolectomy or surgical embolectomy if these procedures are not available locally and safe transfer can be achieved (*Class IIa; Level of Evidence C*).
4. Either catheter embolectomy or surgical embolectomy may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory failure, severe RV dysfunction, or major myocardial necrosis) (*Class IIb; Level of Evidence C*).
5. Catheter embolectomy and surgical thrombectomy are not recommended for patients with low-risk PE or submassive acute PE with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening (*Class III; Level of Evidence C*).

### Inferior Vena Cava Filters

The use of both permanent and retrievable inferior vena cava (IVC) filters has increased markedly in the United States over the past 20 years.<sup>167,168</sup> A single prospective randomized study of IVC filter placement for the prevention of PE<sup>169</sup> and a large population-based retrospective analysis examining recurrent VTE in patients with IVC filters<sup>170</sup> are the only 2 methodologically rigorous data sets from which sound conclusions can be drawn. In addition, the ICOPER registry examined clinical outcomes in patients treated with IVC filters for PE.<sup>9</sup> There are no trials of IVC filters in the pediatric population.

The PREPIC Trial (Prévention du Risque d'Embolie Pulmonaire par Interruption Cave)<sup>169</sup> randomized 400 patients with proximal deep venous thrombosis (DVT) at high risk for PE in a 2-by-2 factorial design to receive UFH versus LMWH, with or without an IVC filter. The primary efficacy outcome was objectively documented PE at 8 years. Recurrent DVT, death, and major bleeding were also analyzed at 12 days, 2 years, and 8 years. All patients received parenteral anticoagulation for 8 to 12 days and vitamin K antagonists for at least 3 months, with 35% of patients in both groups receiving long-term oral anticoagulation. IVC filters significantly reduced the incidence of recurrent PE at 12 days (1.1% versus 4.8%, *P*=0.03) and at 8 years (6.2% versus 15.1%, *P*=0.008); however, IVC filters were associated with an increased incidence of recurrent DVT at 2 years (20.8%

versus 11.6%,  $P=0.02$ ). There were no differences in major bleeding, postthrombotic chronic venous insufficiency, or death during the study period. In summary, the beneficial effects of IVC filters to prevent recurrent PE in patients with DVT at high risk for PE were offset by an increased incidence of recurrent DVT with no effect on overall mortality.

The population-based observational study performed by White et al<sup>170</sup> provides useful data about the efficacy of IVC filters. Using the linked hospital discharge abstracts in California from 1991 to 1995, the investigators identified 3632 patients treated with IVC filters and 64 333 control subjects admitted with a principal diagnosis of VTE. Patients treated with IVC filters had significantly greater incidence of prior PE, recent major hemorrhage, malignant neoplasm, and stroke. As in the PREPIC trial, IVC filter placement significantly reduced the 1-year incidence of rehospitalization for PE but was associated with a higher incidence of rehospitalization for DVT in patients who initially presented with PE.

The ICOPER registry<sup>9</sup> explored the frequency of fibrinolysis and IVC filter placement in patients with massive PE, assessing how these therapies affected clinical outcome. One hundred eight patients with massive PE and 2284 patients with nonmassive PE, defined by systolic arterial pressure <90 mm Hg and ≥90 mm Hg, respectively, were studied. Only 11 of the 108 patients with massive PE received an IVC filter in this registry. None of the patients with IVC filters developed recurrent PE, and 10 of 11 survived at least 90 days. Although it is difficult to draw conclusions with such small numbers, IVC filters reduced 90-day mortality in this registry (hazard ratio 0.12, 95% CI 0.02 to 0.85), which suggests that placement of IVC filters in patients with poor cardiopulmonary reserve might be reasonable.

Complications associated with IVC filter placement can occur early or late and can result in death in ≈0.1% of patients.<sup>171</sup> Early complications are procedurally related and include device malposition (1.3%), pneumothorax (0.02%), hematoma (0.6%), air embolism (0.2%), inadvertent carotid artery puncture (0.04%), and arteriovenous fistula (0.02%). Most are due to vascular access issues and can be minimized by careful venipuncture with ultrasound-based or fluoroscopic guidance.<sup>172–174</sup> The most frequent early complication occurs after sheath removal and manifests as access-site thrombosis (8.5%) of the common femoral vein. Careful application of manual pressure without pressure bandages should be used in attempts to avoid this complication.<sup>175</sup> Late complications of IVC filter placement include recurrent DVT (21%), IVC thrombosis (2% to 10%), IVC penetration (0.3%), and filter migration (0.3%).<sup>172</sup> IVC filter fractures have also been reported.<sup>176</sup>

For review of the issues about permanent or retrievable IVC filter types, please see the relevant section on IVC filters for IFDVT. IVC filter placement, whether with permanent or retrievable filters, should be accompanied by subsequent anticoagulation once the patient can safely be given anticoagulant drugs. Retrievable filters should be removed when initial indications no longer exist or contraindications to anticoagulation have resolved.

### *Recommendations on IVC Filters in the Setting of Acute PE*

1. Adult patients with any confirmed acute PE (or proximal DVT) with contraindications to anticoagulation or with active bleeding complication should receive an IVC filter (*Class I; Level of Evidence B*).
2. Anticoagulation should be resumed in patients with an IVC filter once contraindications to anticoagulation 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 acute PE despite therapeutic anticoagulation, it is reasonable to place an IVC filter (*Class IIa; Level of Evidence C*).
5. For DVT or PE patients who will require permanent IVC filtration (eg, those with a long-term contraindication to anticoagulation), it is reasonable to select a permanent IVC filter device (*Class IIa; Level of Evidence C*).
6. For DVT or PE patients with a time-limited indication for an IVC filter (eg, those with a short-term contraindication to anticoagulation therapy), it is reasonable to select a retrievable IVC filter device (*Class IIa; Level of Evidence C*).
7. Placement of an IVC filter may be considered for patients with acute PE and very poor cardiopulmonary reserve, including those with massive PE (*Class IIb; Level of Evidence C*).
8. An IVC filter should not be used routinely as an adjuvant to anticoagulation and systemic fibrinolysis in the treatment of acute PE (*Class III; Level of Evidence C*).

### **Paradoxical Embolization**

Paradoxical embolization can occur in patients with massive PE and is a devastating disorder that increases morbidity and mortality related to PE.<sup>177,178</sup> The presence of a patent foramen ovale (PFO) in patients with a massive PE increases the risk of death (relative risk 2.4), ischemic stroke (relative risk 5.9), peripheral arterial embolism (relative risk >15), and a complicated hospital course (relative risk 5.2).<sup>177</sup> Other studies have shown that patients with a PFO are more likely to have a paradoxical embolism and hypoxemia in the setting of PE.<sup>178</sup> In patients with PE, the presence of a PFO was associated with an increased risk of silent brain infarct (33%) compared with those without a PFO (2%).<sup>179</sup>

Screening PE patients for PFO by adding a bubble study to routine transthoracic echocardiography increases the detection of impending paradoxical embolism (ie, biatrial thromboembolus entrapped within a PFO). The presence of a PFO in patients with PE is an independent predictor of adverse events. Therefore, patients with an intracardiac shunt should be considered for aggressive therapeutic options, including catheter-based techniques, surgical embolectomy (particularly if intracardiac thrombus is identified), and appropriate antithrombotic therapy. Although the optimal treatment for patients with impending paradoxical embolism remains unclear, surgical thrombectomy may result in the lowest rate of stroke, whereas thrombolysis may be associated with the

highest mortality compared with surgery or medical treatment with heparin.<sup>180</sup>

Important contemporary questions, which are currently unanswered, include (1) how to screen for PFO or pulmonary arteriovenous fistula in patients with massive or submassive PE, (2) how PFO presence should change management of PE, (3) when to consider PFO closure in patients with concomitant paradoxical embolism and PE, (4) how PFO shunt size and morphology influence the risk of adverse events, and (5) how to stage the timing of IVC filter placement and PFO closure in patients with paradoxical embolism and PE. The currently enrolling cryptogenic stroke trials randomizing patients to medical therapy versus PFO closure will not address these issues related to patients with acute PE. Until future studies address these issues, we have provided guidance to clinicians based on the best available data.

### **Recommendations on PFO in the Face of a PE**

1. For patients with massive or submassive PE, screening for PFO with an echocardiogram with agitated saline bubble study or transcranial Doppler study for risk stratification may be considered (*Class IIb; Level of Evidence C*).
2. For patients with any type of PE found to have impending paradoxical embolism (thrombus entrapped within a PFO), surgical embolectomy may be considered (*Class IIb; Level of Evidence C*).

### **Iliofemoral Deep Vein Thrombosis**

The anatomic categorization of lower extremity DVT typically has been limited to distinguishing proximal DVT (highest thrombus extent in the popliteal vein or proximally), which carries an increased risk of symptomatic PE, from distal DVT (isolated calf vein thrombosis). However, physicians have long suspected that proximal DVT patients with the most extensive thrombus burden may be at higher risk for poor clinical outcomes than those with less extensive, but still proximal, DVT.

IFDVT refers to complete or partial thrombosis of any part of the iliac vein or the common femoral vein, with or without involvement of other lower extremity veins or the IVC. In a recently published prospective multicenter cohort study of patients diagnosed with acute symptomatic lower extremity DVT, 39% of cases of proximal DVT (or 24% of all lower extremity DVT cases) involved the common femoral vein or iliac vein.<sup>181</sup> The inclusion of the common femoral vein within the “iliofemoral” designation is based on clinical studies, concordant clinical observations of expert physicians, and knowledge of venous physiology.<sup>182</sup> When the femoral vein is thrombosed, the primary collateral route by which blood leaves the extremity is by drainage into the deep (profunda) femoral vein (which empties into the common femoral vein).<sup>183</sup> As a result, venous thrombosis above the entry point of the deep femoral vein (ie, thrombosis in or above the common femoral vein) causes more severe outflow obstruction, which often results in more dramatic initial DVT symptoms and late clinical sequelae.<sup>184</sup>

Compelling evidence supporting the importance of distinguishing IFDVT from less extensive proximal DVT is pro-

vided by several prospective contemporary studies that evaluated clinically important patient outcomes. In a prospective study of 1149 patients with symptomatic DVT, patients with IFDVT had a 2.4-fold increased risk of recurrent VTE over 3 months of follow-up compared with patients with less extensive DVT.<sup>185</sup> In a prospective, multicenter, 387-patient cohort study of patients diagnosed with acute symptomatic DVT, patients with DVT involving the common femoral vein or iliac vein had significantly increased severity of the post-thrombotic syndrome (PTS) over 2 years of follow-up ( $P<0.001$ ).<sup>181</sup> These findings corroborate previous studies in which venous claudication, physiological abnormalities, venous ulcers, and impaired quality of life were commonly observed in IFDVT patients.<sup>186–189</sup>

Because the presence of IFDVT predicts a higher risk of a poor clinical outcome, the risk-benefit analyses that determine appropriate treatment for proximal DVT may be altered. In this section, we evaluate the published literature in this respect. We note that these recommendations refer specifically to patients with IFDVT as opposed to patients with less extensive proximal DVT. We also note that the lack of subgroup analyses focused on IFDVT in published trials limits the scope and certainty of our recommendations, and we strongly encourage separate reporting of IFDVT subgroup outcomes in future VTE trials.

### **Initial Anticoagulant Therapy**

IFDVT patients should receive initial anticoagulant therapy for the prevention of PE and recurrent DVT.<sup>190</sup> Because there is no published evidence to support the use of different anticoagulant dosing schemes for IFDVT patients as opposed to other patients with proximal DVT, we recommend the initial use of 1 of the following regimens in adults: (1) Intravenous UFH at an initial bolus of 80 U/kg followed by a continuous intravenous infusion, initially dosed at  $18 \text{ U} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ , with dose adjustment to target a partial thromboplastin time prolongation that corresponds to plasma heparin levels of 0.3 to 0.7 IU/mL anti-factor Xa activity, for 5 to 7 days<sup>191–194</sup>; (2) LMWH by subcutaneous injection, without routine anti-factor Xa monitoring (regimens such as enoxaparin twice daily at 1 mg/kg or once daily at 1.5 mg/kg, dalteparin once daily at 200 IU/kg or twice daily at 100 IU/kg, or tinzaparin once daily at 175 anti-Xa IU/kg)<sup>195–202</sup>; or (3) fondaparinux by subcutaneous injection once daily at 5 mg for patients weighing  $<50 \text{ kg}$ , 7.5 mg for patients weighing 50 to 100 kg, or 10 mg for patients weighing  $>100 \text{ kg}$ .<sup>203,204</sup> Fixed-dose weight-adjusted subcutaneous UFH could also be considered, although data are more limited for this regimen.<sup>205</sup> In children, the weight-based dosing of agents will vary with patient age.<sup>206–209</sup> No published studies directly address the appropriateness of outpatient therapy with UFH, LMWH, or fondaparinux for the IFDVT subgroup specifically. After consideration of the patient's overall medical condition, the presence of symptomatic PE, and the need for home support services, it is reasonable to administer LMWH or fondaparinux to selected IFDVT patients in the outpatient setting.<sup>208–213</sup> In IFDVT patients with suspected or proven heparin-induced thrombocytopenia, we recommend initial anticoagulation

with intravenous direct thrombin inhibitors (eg, argatroban, lepirudin), as for other proximal DVT patients with heparin-induced thrombocytopenia.<sup>214–217</sup>

#### **Recommendations for Initial Anticoagulation for Patients With IFDVT**

1. In the absence of suspected or proven heparin-induced thrombocytopenia, patients with IFDVT should receive therapeutic anticoagulation with either intravenous UFH (*Class I; Level of Evidence A*), UFH by subcutaneous injection (*Class I; Level of Evidence B*), an LMWH (*Class I; Level of Evidence A*), or fondaparinux (*Class I; Level of Evidence A*).
2. Patients with IFDVT who have suspected or proven heparin-induced thrombocytopenia should receive a direct thrombin inhibitor (*Class I; Level of Evidence B*).

#### **Long-Term Anticoagulant Therapy for Patients With IFDVT**

Most adult patients with IFDVT receive oral warfarin as first-line long-term anticoagulant therapy, overlapped with initial anticoagulant therapy for a minimum of 5 days and until the international normalized ratio (INR) is  $\geq 2.0$  for at least 24 hours, and then targeted to an INR of 2.0 to 3.0.<sup>218–227</sup> Recently published RCT data suggest that the oral direct thrombin inhibitor dabigatran is as safe and effective as warfarin for acute VTE and does not require laboratory monitoring,<sup>228</sup> although data about dabigatran for IFDVT specifically are unavailable. Although it is possible that the higher risk of recurrent DVT and PTS in IFDVT patients<sup>181,185</sup> merits more rigorous therapy than for proximal non-IFDVT, there is no current evidence to support the use of a higher intensity or longer duration of warfarin, or longer-term use of parenteral anticoagulants, in this subgroup. Treatment duration decisions should be based on VTE risk factors, presence of recurrent VTE episodes, tolerance of anticoagulation, bleeding risk factors, and patient preferences.<sup>229,230</sup>

Three major patient groups can be defined: (1) In general, anticoagulation may be safely stopped after 3 months in most patients with a *first-episode of DVT related to a major reversible risk factor* (ie, recent surgery or trauma).<sup>219,220,231–234</sup> (2) Patients with *recurrent DVT* or *unprovoked DVT* should be considered for treatment of indefinite duration, with periodic reassessment of risk and benefit.<sup>221,224,235–237</sup> (3) For most *cancer patients with DVT*, first-line therapy should be weight-based LMWH monotherapy for at least 3 to 6 months, or as long as the cancer or its treatment (eg, chemotherapy) is ongoing.<sup>238–240</sup> LMWH monotherapy regimens (without oral anticoagulation) studied in RCTs of adult cancer patients with normal renal function have included the following: (1) Dalteparin administered by once-daily subcutaneous injection at 200 IU/kg (maximum 18 000 IU) for the first 4 weeks, followed by  $\approx 150$  IU/kg thereafter; (2) tinzaparin administered by once-daily subcutaneous injection at 175 anti-Xa IU/kg; and (3) enoxaparin given by once-daily subcutaneous injection at 1.5 mg/kg. If there are barriers to long-term use of LMWH, the use of warfarin with a target INR of 2.0 to 3.0 is a reasonable alternative. The use of direct thrombin inhibitors

for the initial and long-term treatment of DVT has also shown significant promise.<sup>228</sup> If shown to be effective after further study, the use of these or other new agents may alter optimal medical therapy for IFDVT.

In children, the use of LMWH monotherapy as either the first-line or a second-line method for long-term DVT treatment may be reasonable.<sup>241–243</sup>

#### **Recommendations for Long-Term Anticoagulation Therapy for Patients With IFDVT**

1. Adult patients with IFDVT who receive oral warfarin as first-line long-term anticoagulation therapy should have warfarin overlapped with initial anticoagulation therapy for a minimum of 5 days and until the INR is  $\geq 2.0$  for at least 24 hours, and then targeted to an INR of 2.0 to 3.0 (*Class I; Level of Evidence A*).
2. Patients with first-episode IFDVT related to a major reversible risk factor should have anticoagulation stopped after 3 months (*Class I; Level of Evidence A*).
3. Patients with recurrent or unprovoked IFDVT should have at least 6 months of anticoagulation and be considered for indefinite anticoagulation with periodic reassessment of the risks and benefits of continued anticoagulation (*Class I; Level of Evidence A*).
4. Cancer patients with IFDVT should receive LMWH monotherapy for at least 3 to 6 months, or as long as the cancer or its treatment (eg, chemotherapy) is ongoing (*Class I; Level of Evidence A*).
5. In children with DVT, the use of LMWH monotherapy may be reasonable (*Class IIb; Level of Evidence C*).

#### **Compression Therapy**

##### **Use for Prevention of PTS**

The daily use of sized-to-fit, 30- to 40-mm Hg knee-high graduated elastic compression stockings (ECS) for 2 years after the diagnosis of first-episode proximal DVT was found in 3 European single-center RCTs to be associated with marked reductions in the frequency of PTS.<sup>244–246</sup> Limitations of these studies included lack of placebo control, blinding, and separate delineation of outcomes in IFDVT patients. An RCT that assessed the use of ECS starting 1 year after diagnosis in DVT patients without signs of PTS did not find evidence of benefit in preventing the subsequent development of PTS.<sup>247</sup> No studies directly address the comparative efficacy of thigh-high versus knee-high ECS in IFDVT patients. Limitations of ECS therapy include patient noncompliance due to difficulty in applying the garments, discomfort while wearing them daily, and their cost. Also, no RCT has specifically addressed the use of thigh-high ECS in IFDVT patients. Nevertheless, given the concordance of the results of the RCTs evaluating early use of ECS and the very low likelihood of causing harm with this intervention, we recommend daily use of 30- to 40-mm Hg knee-high ECS for patients with IFDVT for at least 2 years after the diagnosis of proximal DVT.

##### **Use of ECS Treatment of Established PTS**

No studies directly address the efficacy of ECS for treating established PTS in IFDVT. Given the frequent presence of

irreversible abnormalities of venous structure and function in IFDVT patients, it is possible that there are differences in ECS efficacy between patients with IFDVT versus less extensive proximal DVT. Despite the lack of direct supportive evidence, given its safety and potential for benefit, use of ECS to reduce symptoms in patients with established PTS is reasonable. In patients with severe edema, an initial trial of intermittent sequential pneumatic compression followed by ECS may be reasonable.<sup>248</sup>

### **Recommendations for Use of Compression Therapy**

1. **Patients with IFDVT should wear 30- to 40-mm Hg knee-high graduated ECS on a daily basis for at least 2 years (Class I; Level of Evidence B).**
2. **In patients with prior IFDVT and symptomatic PTS, daily use of 30- to 40-mm Hg knee-high graduated ECS is reasonable (Class IIa; Level of Evidence C).**
3. **In patients with prior IFDVT and severe edema, intermittent sequential pneumatic compression followed by daily use of 30- to 40-mm Hg knee-high graduated ECS may be considered (Class IIb; Level of Evidence B).**

### **IVC Filters in Patients With IFDVT**

#### **Permanent, Nonretrievable Filters**

IVC filters are indicated for IFDVT patients who have contraindications to or complications of anticoagulation, symptomatic PE despite therapeutic-level anticoagulation, or severe cardiorespiratory compromise.<sup>3,9</sup> In other circumstances, caution is urged in the use of IVC filters in anticoagulation candidates because of ongoing uncertainty about their long-term risk-benefit ratio.<sup>170</sup> In the only available RCT, which was underpowered to detect an effect on fatal PE, filters prevented symptomatic PE (6.2% versus 15.1% at 8 years,  $P=0.008$ ) but did not alter mortality.<sup>169,249</sup> Symptomatic recurrent DVT was increased in the filter group, but the overall rates of symptomatic recurrent VTE (PE plus DVT) and PTS did not differ significantly between the 2 groups. For these reasons, in most noncompromised patients with IFDVT who are candidates for anticoagulation, we recommend against the routine use of filters.

There is no direct evidence to guide therapy in patients who experience warfarin failure, manifested by recurrent DVT (without PE). However, given the efficacy and safety of LMWH monotherapy<sup>250,251</sup> and the uncertain long-term risk-benefit ratio of the use of filters, the use of a second-line anticoagulation regimen instead of IVC filter placement in most IFDVT patients who develop recurrent DVT despite therapeutic anticoagulation may be reasonable. Because of the lack of direct evidence on this point, it is reasonable to consider the patient's life expectancy and comorbidities in making this decision.

There are no well-designed studies that directly compare different permanent, nonretrievable IVC filter devices, and we have no recommendation about the choice of specific device. When permanent, nonretrievable IVC filters are placed, it is reasonable to continue or resume anticoagulation in patients who do not have contraindications.<sup>169,170,249</sup>

The use of IVC filters to prevent PE in children with long-term contraindications to anticoagulation may be reasonable. Whether anticoagulation is required to maintain filter patency (when contraindications to anticoagulation no longer exist) is not clear.

#### **Retrievable Filters**

The advent of retrievable IVC filter designs appears to have lowered thresholds for IVC filter placement. Unfortunately, there are few data to support or refute this practice evolution.<sup>252</sup> The following issues should be considered in clinical decisions to use these devices:

1. It is not yet clear whether the long-term stability and mechanical integrity of retrievable IVC filters are comparable to those of older permanent devices. These properties are likely to be specific to the individual manufacturer, but in the relatively short time since retrievable filters were introduced, the published literature has identified many cases of device migration.<sup>253–257</sup> Therefore, once a decision has been made that an IVC filter is needed, in 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 rather than a retrievable IVC filter device.<sup>257</sup>
2. Once a decision has been made that an IVC filter is needed, in IFDVT patients with a time-limited indication for an IVC filter (eg, a short-term contraindication to anticoagulant therapy or poor cardiopulmonary status), placement of a retrievable IVC filter is reasonable (based on expert consensus, limited data on the feasibility of filter placement and retrieval, and limited data on the associated short-term clinical outcomes).<sup>252,253,256,258,259</sup>
3. To prevent long-term adverse events from unneeded filters, patients should be reassessed periodically for possible filter retrieval for 3 to 12 months after placement, depending on the specific filter's retrieval window (see product instructions for use).
4. Venography should be performed immediately before filter removal. If there is significant thrombus in the IVC filter or within the IVC below the filter, it is reasonable to leave the filter in place, continue anticoagulation, and reassess the patient for filter retrieval at a later date. It is unclear whether the presence of residual iliofemoral thrombus should affect the timing of filter retrieval. Consideration of the patient's life expectancy, cardiopulmonary status, and comorbidities can be useful in making this decision.
5. In children, lack of filter retrievability due to thrombosis has been reported.<sup>260</sup> To avoid late sequelae, a high threshold for use in children, with prompt removal as soon as possible, is reasonable.

### **Recommendations for Use of IVC Filters in Patients With IFDVT**

1. **Adult patients with any acute proximal DVT (or acute PE) with contraindications to anticoagulation or active bleeding complication should receive an IVC filter (Class I; Level of Evidence B).**
2. **Anticoagulation should be resumed in patients with an IVC filter once contraindications to anticoagulation are resolved.**

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.<sup>261–276</sup> 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.<sup>263,264</sup> A meta-analysis of 11 RCTs found that the amount of residual thrombus after anticoagulant therapy correlated strongly with the risk of recurrent VTE.<sup>265</sup> 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%,  $P<0.0001$ ).<sup>277</sup> In limited long-term follow-up studies, the streptokinase-treated patients had significantly lower PTS rates (relative risk reduction 62% to

64%).<sup>266,267</sup> Turpie et al<sup>268</sup> found that systemic tissue plasminogen activator infusion achieved  $\geq 50\%$  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,  $P<0.04$ ).<sup>268,277,278</sup> 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.<sup>182,273</sup> In a 473-patient prospective multicenter registry, the use of urokinase CDT resulted in successful fibrinolysis in 88% of patients with acute IFDVT.<sup>274</sup> CDT was more often successful in patients with recent ( $\leq 10$  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<sup>271</sup> 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<sup>272</sup> 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<sup>275</sup> 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, Ender et al<sup>276</sup> 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<sup>274</sup> 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,<sup>276</sup> in which rtPA infusions of  $0.01 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  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%.<sup>278–281</sup> 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.<sup>274,276</sup>

Reteplase and tenecteplase have also been used as fibrinolytic drugs for CDT of IFDVT,<sup>282–284</sup> and a new form of CDT that incorporates low-power ultrasound to enhance fibrinolysis has been introduced<sup>285</sup>; 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,<sup>286,287</sup> patients with thrombus progression or symptom worsening despite initial anticoagulation,<sup>288</sup> and patients receiving first-line CDT for PTS prevention.<sup>275</sup>

### **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.<sup>182</sup> 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.<sup>289–291</sup> 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.<sup>292–294</sup> 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.<sup>295–300</sup> 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.<sup>295,300</sup> 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.<sup>301,302</sup> 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.<sup>303,304</sup> In small numbers of older adolescents, adult CDT and PCDT regimens were used.<sup>288,297,305</sup>

### **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 ce-

rulea 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  $0.01 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  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,<sup>306</sup> the finding that supertherapeutic heparin is associated with thrombolysis-related bleeding,<sup>307</sup> 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,<sup>276</sup> 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.<sup>274,276</sup> 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.<sup>295,300</sup>

### 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.<sup>269</sup> 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.<sup>270</sup> 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.<sup>273,274,288,308</sup>

### 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.<sup>274</sup> 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.<sup>309</sup> 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 ( $P<0.01$ ).<sup>310,311</sup> In 1 of these studies, stent fracture with rethrombosis was observed in 1 pregnant woman.<sup>311</sup> 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.<sup>312</sup> 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.<sup>313–315</sup> The anatomic success rate for stent-based recanalization of the occluded vein (without concomitant thrombolysis) was 83% to 98%.<sup>314</sup> 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%,  $P=0.0378$ ).<sup>313</sup> 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.<sup>310,314,316</sup>

### 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,<sup>317,318</sup> although

up to 63% of patients with CTEPH were not previously aware of having had a PE,<sup>319</sup> 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,<sup>320</sup> in situ thrombus propagation into branch pulmonary vessels,<sup>321</sup> and failure to dissolve the initial embolus, which leads to large- and small-vessel vasculopathy.<sup>322</sup>

### Incidence of CTEPH

The true incidence of CTEPH is unknown. Ribeiro et al<sup>323</sup> 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<sup>324</sup> 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.<sup>324</sup> 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.<sup>325</sup> However, because ≈60% of individuals diagnosed with CTEPH have no antecedent history of acute VTE,<sup>319</sup> the true incidence of this disorder may be higher.

### Pathophysiology of CTEPH

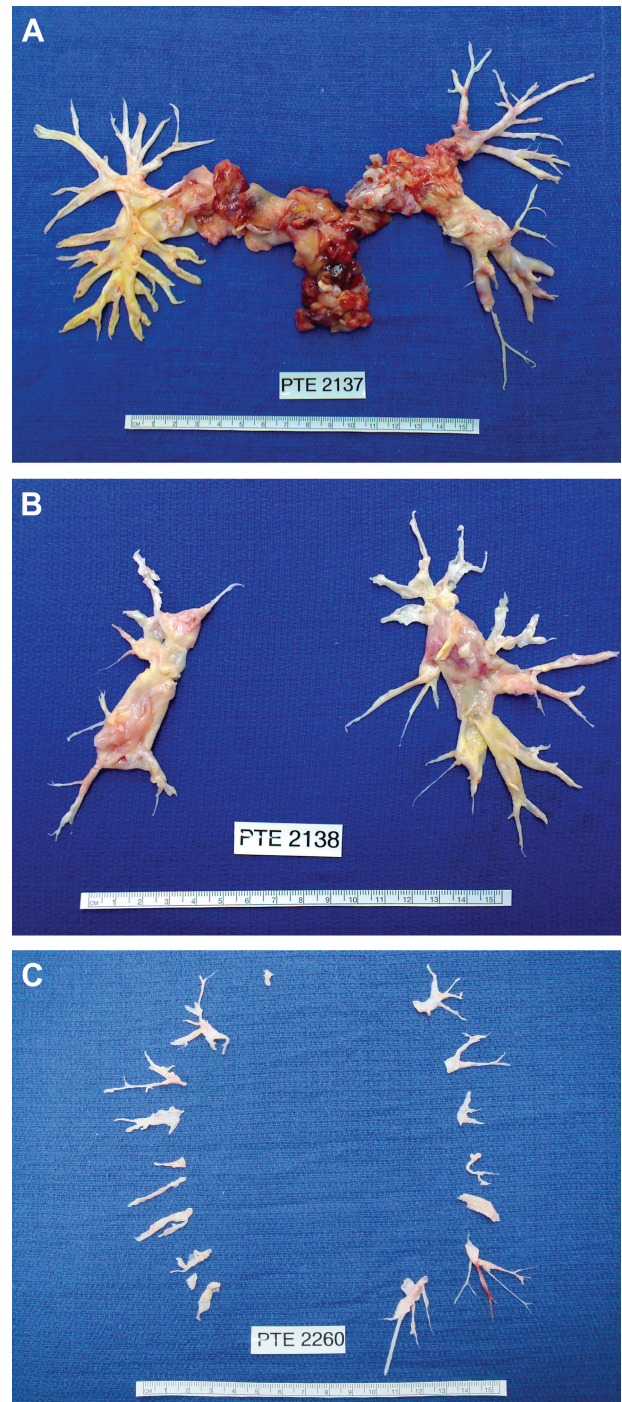
Treatment of acute PE usually results in improved pulmonary hemodynamic status,<sup>323</sup> but residual thrombus remains despite adequate anticoagulation at 1 year in as many as half of all patients.<sup>326</sup> If the acute PEs have not resolved in 1 to 4 weeks, the embolic material becomes incorporated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

tissue, which contains endothelial and smooth muscle precursor cells.<sup>328</sup> Visualization of the pulmonary arteries by angiography a few weeks after unresolved PE reveals vessel narrowing at the site of embolic incorporation and vessel wall remodeling.<sup>329</sup> In some patients, recanalization of some of the pulmonary arterial branches occurs, with the formation of fibrous tissue called bands and webs.<sup>330</sup> In most cases, these changes do not result in CTEPH. However, by a mechanism that is poorly understood, chronic thromboembolic obstruction may also lead to a small-vessel arteriolar vasculopathy characterized by excessive vascular and inflammatory cell proliferation around small precapillary arterioles in the pulmonary circulation.<sup>331</sup> These pulmonary microvascular changes resemble the arteriopathy observed in WHO Group I or idiopathic pulmonary hypertension and are gaining increased recognition as contributors to disease progression in CTEPH.<sup>332</sup> Pulmonary hypertension results when the capacitance of the remaining healthy vascular beds cannot absorb the cardiac output, either because of the degree of primary obstruction by thromboembolic material and adjacent remodeling or because of the combination of a proximal obstruction and secondary small-vessel vasculopathy. The importance of pulmonary arteriolar remodeling in the development of CTEPH is supported by the following observations: (1) There is often a lack of correlation between elevated pulmonary arterial pressure and the degree of angiographic pulmonary vascular bed obstruction; (2) pulmonary hypertension can progress in the absence of recurrent thromboembolism; and (3) total PVR is still significantly higher in CTEPH patients than in acute PE patients with a similar degree of proximal vascular bed obstruction.<sup>333,334</sup>

### Thromboembolic Disease Classification

Four major types of pulmonary occlusive disease, which are based on anatomic location of thrombus and vessel wall pathology, have been described.<sup>335</sup> This classification of disease may be useful in predicting outcomes after pulmonary endarterectomy<sup>335,336</sup>:

1. *Type 1 disease* ( $\approx 25\%$  of cases of thromboembolic pulmonary hypertension; Figure 3A): Fresh thrombus in the main or lobar pulmonary arteries.
2. *Type 2 disease* ( $\approx 40\%$  of cases; Figure 3B): Intimal thickening and fibrosis with or without organized thrombus proximal to segmental arteries. In these cases, only thickened intima can be seen on initial dissection into the pulmonary arteries, occasionally with webs in the main or lobar arteries.
3. *Type 3 disease* ( $\approx 30\%$  of cases; Figure 3C): Fibrosis, intimal webbing, and thickening with or without organized thrombus within distal segmental and subsegmental arteries only. This type of disease presents the most challenging surgical situation. No occlusion of vessels can be seen initially. The endarterectomy plane must be raised individually in each segmental and subsegmental branch. Type 3 disease may represent “burned out” disease, in which most of the proximal embolic material has been reabsorbed.
4. *Type 4 disease* (fewer than 5% of cases): Microscopic distal arteriolar vasculopathy without visible thromboembolic disease. Type 4 disease does not represent



**Figure 3.** Representative pulmonary endarterectomy specimens.

**A**, Type 1 disease ( $\approx 25\%$  of cases of thromboembolic pulmonary hypertension): Fresh thrombus in the main or lobar pulmonary arteries. **B**, Type 2 disease ( $\approx 40\%$  of cases): Intimal thickening and fibrosis with or without organized thrombus proximal to segmental arteries. In these cases, only thickened intima can be seen on initial dissection into the pulmonary arteries, occasionally with webs in the main or lobar arteries. **C**, Type 3 disease ( $\approx 30\%$  of cases): Fibrosis, intimal webbing, and thickening with or without organized thrombus within distal segmental and subsegmental arteries only. No occlusion of vessels can be seen initially.

classic CTEPH and is inoperable. In this entity, there is intrinsic small-vessel disease, although secondary thrombus may occur as a result of stasis.<sup>332</sup> Small-vessel disease may be unrelated to thromboembolic events (misdiagnosed WHO Group I pulmonary arterial hypertension [PAH]) or occur in relation to previous (now resolved) thromboembolic vascular occlusion as a result of a high-flow or high-pressure state in previously unaffected vessels.

### Predisposing Factors for CTEPH

The cohort of symptomatic post-PE patients studied by Pengo and colleagues<sup>324</sup> suggested that predictors of CTEPH include multiple episodes of PE, larger perfusion defect, and younger age. Case series have suggested an increased risk of CTEPH in patients with prior splenectomy, permanent intravenous catheters, ventriculoatrial shunts, and chronic inflammatory conditions, including inflammatory bowel disease and osteomyelitis.<sup>337–339</sup> In addition to these observations, associations with sickle cell disease, hereditary stomatocytosis, Klippel-Trenaunay syndrome, thyroid hormone-replacement therapy, and history of malignancy have been described.<sup>319</sup> The approximate 2:1 predominance of CTEPH among women and the higher overall incidence of chronic thromboembolic disease in Japanese patients compared with cohorts in the United States<sup>340</sup> suggest possible differences due to race, sex, or environmental exposure. Laboratory abnormalities that may predispose patients to CTEPH after prior PE include the lupus anticoagulant (10% of CTEPH patients),<sup>341</sup> antiphospholipid antibodies in general (20% of CTEPH patients),<sup>342</sup> elevated plasma levels of factor VIII (39% of patients),<sup>343</sup> and inherited deficiencies of antithrombin III, protein C, and protein S.<sup>344–346</sup> Other hematologic abnormalities observed in CTEPH include heparin-induced platelet antibodies,<sup>347</sup> increased resistance to fibrinolysis,<sup>348</sup> and decreased thrombomodulin levels.<sup>349</sup> However, the majority of cases of CTEPH are not linked to a specific coagulation defect or underlying medical condition.

### Natural History of CTEPH

Traditionally, the prognosis of CTEPH has been presumed to be very poor, although the asymptomatic or less severe cases of CTEPH may have been unrecognized previously,<sup>145</sup> which would bias estimates of prognosis. The risk of death due to right-sided heart failure in patients with undiagnosed or untreated CTEPH is correlated with pulmonary artery pressure at diagnosis. In 1 series, the mortality rate was  $\approx 70\%$  among patients with a mean pulmonary artery pressure  $>40$  mm Hg, increasing to  $90\%$  at  $>50$  mm Hg.<sup>350</sup> Despite improved understanding of pathogenesis, diagnosis, and management, untreated CTEPH is usually a fatal disease.

### Clinical Presentation of CTEPH

Patients with CTEPH usually present with subtle or nonspecific symptoms. The most common symptom is progressive exertional dyspnea with exercise intolerance.<sup>351</sup> Because of the large area of the pulmonary vascular bed, 60% to 70% of the vasculature must be occluded before pulmonary hypertension is observed in a patient at rest.<sup>352</sup> Dyspnea experi-

enced by patients with CTEPH is usually out of proportion to any abnormalities found on clinical examination. As the disease progresses, additional symptoms such as chest pain, light-headedness, and syncope may develop. Nonspecific chest pain occurs in  $\approx 50\%$  of patients with more severe CTEPH.<sup>353</sup> Hemoptysis may result from abnormally dilated vessels distended by intravascular pressures. Peripheral edema, early satiety, and epigastric fullness or pain may develop as the right side of the heart fails. There are no consistent physical signs in patients with CTEPH, and the physical examination may be unrevealing if right-sided heart failure has not occurred. With advancing right-sided heart disease, typical signs of pulmonary hypertension are found, including large V waveforms in the jugular venous pulse, an RV heave palpable at the left lower sternal border, a loud P<sub>2</sub> sound of pulmonary valve closure, and an S<sub>3</sub> or S<sub>4</sub> gallop auscultated over the RV. Patients with advanced disease may be hypoxic and cyanotic.

### Diagnostic Evaluation of CTEPH

Patients with a history of DVT, PE, or both who present with dyspnea, exercise intolerance, or clinical evidence of right-sided heart failure should undergo diagnostic evaluation for CTEPH. Pulmonary vascular disease should be considered in the differential diagnosis of unexplained dyspnea. The diagnostic evaluation for CTEPH has 3 aims: (1) To establish the presence and severity of pulmonary hypertension and resultant cardiac dysfunction, (2) to determine its cause, and (3) if thromboembolic disease is present, to determine to what degree it will be correctable surgically. The differential diagnosis of patients with possible CTEPH mandates a battery of tests to establish 3 criteria:

1. *There is pulmonary hypertension.* This requires measurement by right-sided heart catheterization of PVR  $>3$  Wood units at rest and resting systolic and mean pulmonary artery pressures exceeding 40 and 25 mm Hg, respectively.<sup>355</sup> An echocardiogram is useful for screening but insufficient for diagnosis.
2. *Angiography or ventilation-perfusion scintigraphy shows evidence of obstruction in the main, lobar, segmental, or subsegmental arteries within the pulmonary arterial tree despite 3 months of therapeutic anticoagulation.* A normal pulmonary angiogram or ventilation-perfusion ( $\dot{V}/\dot{Q}$ ) scan excludes the diagnosis.<sup>356</sup> Importantly, a relatively normal CT angiogram can be observed in CTEPH despite substantial  $\dot{V}/\dot{Q}$  scan abnormalities; thus, a  $\dot{V}/\dot{Q}$  scan is important in the evaluation of CTEPH.<sup>357</sup>
3. *Other causes of pulmonary hypertension, such as WHO Group II (pulmonary hypertension associated with left-sided heart disease) and WHO Group III (pulmonary hypertension associated with a parenchymal lung disease), have been excluded.* To exclude left-sided heart disease as a cause of pulmonary hypertension, a pulmonary capillary wedge pressure  $<15$  mm Hg is generally required.<sup>358</sup> In some patients, the wedge pressure may be higher because of severe RV dilation, interventricular dependence, and resultant LV diastolic dysfunction; in these cases, the PVR is usually high ( $>600$  dyne  $\cdot$  s  $\cdot$  cm<sup>-5</sup>).

The workup for a patient with CTEPH should include a history, physical examination, posteroanterior and lateral chest roentgenogram, electrocardiogram, pulmonary function testing, arterial blood gases,  $\dot{V}/\dot{Q}$  lung scanning, right-sided heart catheterization, and conventional invasive pulmonary angiography. Pulmonary angiography may be deferred to the expert surgical center.

Chest radiography is often unrevealing in the early stages of CTEPH. As CTEPH progresses, several radiographic abnormalities may be found. These include hilar fullness caused by enlarged central pulmonary arteries, clear or oligemic lung fields, and RV enlargement. Peripheral lung opacities suggestive of scarring from previous infarction may also be seen.

Pulmonary function tests are necessary to evaluate dyspnea and are used to exclude the presence of obstructive airway or fibrotic lung disease. Single-breath diffusion capacity for carbon monoxide (DLCO) may be moderately reduced, and it has been reported that 20% of patients will have a mild to moderate restrictive defect that is caused by parenchymal scarring.<sup>359</sup> Arterial blood oxygen levels may be normal even in the setting of significant pulmonary hypertension; hypercapnia is rare and generally indicates WHO Group III pulmonary hypertension related to severe chronic obstructive pulmonary disease, interstitial lung disease, or obesity-hypoventilation syndrome. Most patients, however, will experience a decline in  $\text{Po}_2$  with exertion.<sup>360</sup>

Transthoracic echocardiography is used to provide objective evidence of pulmonary hypertension. An estimate of pulmonary artery pressure can be made by Doppler evaluation of the tricuspid regurgitant envelope.<sup>361</sup> Additional echocardiographic findings vary depending on the stage of the disease and include enlargement of the right side of the heart, leftward displacement of the interventricular septum, and encroachment of the enlarged RV on the LV cavity, with abnormal systolic and diastolic function of the LV.<sup>362</sup> Contrast echocardiography may demonstrate a PFO, the result of high right atrial pressures opening the previously closed intra-atrial communication.<sup>363</sup>

Radioisotope  $\dot{V}/\dot{Q}$  lung scanning is critical to establish the diagnosis of CTEPH.<sup>357</sup>  $\dot{V}/\dot{Q}$  scanning typically demonstrates 1 or more mismatched segmental defects caused by obstructive thromboembolism.<sup>364</sup> This is in contrast to the normal or "mottled" perfusion scan seen in patients with WHO Group I PAH.<sup>357</sup> Any lobar, segmental, or subsegmental defect should lead to further evaluation.  $\dot{V}/\dot{Q}$  scanning may underestimate the magnitude of perfusion defects in CTEPH because partial recanalization of the vessel lumen can occur while still leaving significant obstruction to flow.<sup>365</sup>

Invasive cardiac evaluation and coronary arteriography are required in the evaluation of patients with CTEPH. RV catheterization quantifies the severity of pulmonary hypertension and assesses right- and left-sided heart filling pressures. Measurement of oxygen saturations in the superior and inferior vena cava, right-sided chambers, and pulmonary artery may document previously undetected left-to-right shunting.<sup>366</sup> Response to vasodilator challenge, such as administration of inhaled nitric oxide, may be tested.<sup>367</sup> For patients >50 years of age, coronary angiography and left-

sided heart catheterization provide additional evidence about those at risk for coronary artery or valvular disease.<sup>368</sup> This information is necessary for the preoperative risk assessment of patients deemed candidates for pulmonary endarterectomy and to determine whether concomitant coronary artery bypass grafting or valve repair/replacement needs to be undertaken at the time of pulmonary endarterectomy.

Pulmonary angiography is the "gold standard" test for definition of pulmonary vascular anatomy and is performed to identify whether chronic thromboembolic obstruction is present, to determine its location and surgical accessibility (operative planning), and to rule out other diagnostic possibilities.<sup>369</sup> In angiographic imaging, thrombi appear as unusual filling defects, pouches, webs, or bands or as completely thrombosed vessels that may resemble congenital absence of a vessel. Organized material along a vascular wall produces a scalloped or serrated luminal edge.<sup>370</sup> Because of both vessel wall thickening and dilatation of proximal vessels, the contrast-filled lumen may appear normal in diameter. Despite concerns about the safety of performing pulmonary angiography in patients with pulmonary hypertension, pulmonary angiography can be performed safely at specialized centers, even in patients with severe pulmonary hypertension.<sup>371</sup> Biplane imaging is preferred, which offers the advantage of lateral views that provide greater anatomic detail than the overlapped and obscured vessel images often seen with the anterior-posterior view.<sup>372</sup> Pulmonary angiography to assess operability should be performed at the center where surgery would be performed or at centers with an established cooperation with the surgical team.

Pulmonary angioscopy may be performed in conjunction with pulmonary angiography to confirm the diagnosis in cases in which the diagnosis of CTEPH is equivocal. The pulmonary angioscope is a diagnostic fiber optic device that was developed to visualize the intima of central pulmonary arteries. It is placed into the pulmonary arteries under fluoroscopic guidance.<sup>329</sup> Inflation of a latex balloon affixed to the tip of the angioscope results in obstruction of blood flow in the artery and permits visualization of the arterial intima.<sup>373</sup> The presence of embolic disease, occlusion of vessels, or gross thrombotic material is also diagnostic. Despite the potential benefits of angioscopy, this test is uncommonly performed in the evaluation of CTEPH.

Other studies that may be performed to distinguish CTEPH from other lung diseases include multidetector CT angiography with 3-dimensional reconstruction,<sup>374–376</sup> single-photon emission CT fusion imaging,<sup>377</sup> and magnetic resonance imaging scanning.<sup>355,378–380</sup> Although magnetic resonance and CT imaging are frequently used as primary imaging techniques in selected patients before pulmonary endarterectomy, few comparative studies between diagnostic modalities have been published, and conventional angiography remains the "gold standard" for diagnostic and preoperative evaluation. Importantly, a relatively normal CT angiogram can be observed in CTEPH despite significant abnormalities on ventilation-perfusion scintigraphy.<sup>357</sup> Features of chronic thromboembolic disease seen by these modalities include evidence of

**Table 8. Pulmonary Endarterectomy Hemodynamic Results From a Single-Center Cohort of 1100 Patients<sup>384</sup>**

Variable	All Patients (n=1100)	PTE Patients (n=988)	PTE-CABG Patients (n=94)	PTE-Valve Patients (n=18)
Mean decrease in PAS, mm Hg	29±20	29±20	29±18	25±20
Mean decrease in PAD, mm Hg	10±10	10±10	8±10	8±7
Mean decrease in PVR, $\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5}$	563±394	567±392	539±412	488±382
Mean increase in CO, L/min	1.5±1.6	1.5±1.6	1.6±1.6	1.2±1.3
Mean decrease in tricuspid regurgitant velocity, m/s	1.1±0.8	1.1±0.8	1.1±0.7	0.3±0.9

PTE indicates pulmonary endarterectomy; PTE-CABG, pulmonary endarterectomy plus coronary artery bypass graft; PTE-Valve, pulmonary endarterectomy plus valve repair; PAS, pulmonary artery systolic pressure; PAD, pulmonary artery diastolic pressure; PVR, pulmonary vascular resistance; and CO, cardiac output.

Data are shown as mean±standard deviation.

organized thrombus lining the pulmonary vessels in an eccentric fashion, enlargement of the RV and central pulmonary arteries, variation in size of segmental arteries (relatively smaller in the affected segments than in uninvolved areas), and parenchymal changes compatible with pulmonary infarction. The CT scan in CTEPH typically shows inhomogeneous perfusion with a mosaic that reflects areas of the lung that are hyperperfused (high attenuation) and others that are hypoperfused (low attenuation).<sup>381</sup> This “ground glass” or mosaic pattern can also be observed in pulmonary venoocclusive disease; however, in that disease, the ground glass appearance is coupled by thickening of the interlobular septa not usually seen in CTEPH.

#### **Recommendations for Diagnostic Evaluation of CTEPH**

1. Patients presenting with unexplained dyspnea, exercise intolerance, or clinical evidence of right-sided heart failure, with or without prior history of symptomatic VTE, should be evaluated for CTEPH (*Class I; Level of Evidence C*).
2. It is reasonable to evaluate patients with an echocardiogram 6 weeks after an acute PE to screen for persistent pulmonary hypertension that may predict

the development of CTEPH (*Class IIa; Level of Evidence C*).

#### **Pulmonary Endarterectomy**

Pulmonary endarterectomy was pioneered at the University of California, San Diego, and is now performed at major cardiovascular centers throughout the world.<sup>382,383</sup> More than 2500 pulmonary endarterectomy operations have been performed at the University of California, San Diego, since 1970, and the volume of reported cases performed elsewhere has grown to ≈1200 cases. After this operation, pulmonary pressures and resistance often normalize and are accompanied by improvements in pulmonary blood flow and cardiac output; typically, such results are both immediate and sustained. Perioperative mortality in smaller series ranges from 0% to 24% and is 4.7% in the largest recently reported series.<sup>384</sup>

#### **Short-Term Outcomes**

Table 8 lists the hemodynamic outcomes for a recent series of 1100 patients who underwent pulmonary endarterectomy with respect to hemodynamic improvement,<sup>384</sup> whereas Table 9 presents results for the same patient group stratified for thromboembolic disease classification. Before the operation, >91.3% of the patients were in NYHA Functional class III or

**Table 9. Pulmonary Endarterectomy Hemodynamic Results by Classification From a Single-Center Cohort<sup>384</sup>**

Variable	All Patients (n=1100, 100%)	Type 1 (n=430, 39.1%)	Type 2 (n=424, 38.5%)	Type 3 (n=223, 20.3%)	Type 4 (n=23, 2.1%)
PVR, $\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5}$	859±440	924±450	800±417	863±454	885±412
	290±196	270±177	270±191	351±183	595±360
CO, L/min	3.9±1.3	3.7±1.4	4.1±1.3	4.0±1.5	3.8±1.2
	5.4±1.5	5.5±1.5	5.5±1.5	5.2±1.4	4.5±1.1
Systolic PA pressure, mm Hg	76±19	77±19	75±20	76±16	78±16
	46±17	44±15	44±15	53±17	74±32
Mean PA pressure, mm Hg	46±11	47±11	45±12	46±10	50±10
	28±10	27±9	28±9	32±10	42±16
Mortality, %	52 (4.7)	16 (3.9)	22 (4.7)	12 (6.3)	4 (16.7)

PVR indicates pulmonary vascular resistance; CO, cardiac output; and PA, pulmonary artery.

Data are shown as mean±standard deviation or number (percentage). Top numbers are preoperative values and bottom numbers are postoperative values obtained immediately before removal of the Swan-Ganz catheter.

**Table 10. Pulmonary Endarterectomy Hemodynamic Results From Published Cohorts of More Than 20 Patients**

First Author	Year	N	Perioperative Deaths	Mean PAP, mm Hg		Mean PVR, dyne · s · cm <sup>-5</sup>	
				Preoperative	Postoperative	Preoperative	Postoperative
Puis <sup>385</sup>	2005	40	NR	50	38	1246	515
Kramm <sup>386</sup>	2005	22	1	45	36	768	503
Heinrich <sup>374</sup>	2005	60	NR	47	NR	906	290
D'Armini <sup>387</sup>	2005	134	13	47	25	1149	322
Tanabe <sup>388</sup>	2006	95	3	42.8	NR	876	NR
Reesink <sup>389</sup>	2006	27	3	44	24	837	415
Piovella <sup>390</sup>	2006	134	13	47	25	1149	322
Ogino <sup>391</sup>	2006	88	7	45.2	18.6	1028	320
Mellemkjaer <sup>392</sup>	2006	50	12	50	37	819	373
Matsuda <sup>393</sup>	2006	102	8	46	21	1072	386
Macchiarini <sup>394</sup>	2006	30	1	57	25	1110	279
Lindner <sup>395</sup>	2006	21	1	54.8	NR	NR	NR
Ji <sup>396</sup>	2006	30	1	91.4	48.3	NR	NR
Suntharalingam <sup>397</sup>	2007	111	15	47.6	28.6	12.7 Wood units	6.2 Wood units
Rubens <sup>398</sup>	2007	116	10	47	28	810	215
Reesink <sup>399</sup>	2007	42	0	48	NR	976	NR
Maeba <sup>400</sup>	2007	51	0	NR	NR	NR	NR
Hardziyenka <sup>401</sup>	2007	58	6	44.9	NR	847	NR
D'Armini <sup>402</sup>	2007	45	1	48	22	1143	296
Borderman <sup>403</sup>	2007	181	12	45.8	25.4	586	269
Yoshimi <sup>404</sup>	2008	40	3	NR	NR	NR	NR
Thomson <sup>405</sup>	2008	150	22	52	29	740	336
Mikus <sup>406</sup>	2008	40	2	48	25.9	791	280
Freed <sup>407</sup>	2008	229	0	47	25	800	244
Corsico <sup>408</sup>	2008	157	18	47.6	23.9	1140	327
Condliffe <sup>409</sup>	2008	236	37	48.3	26.8	1091	464
Von Haehling <sup>410</sup>	2009	32	NR	73	NR	810	NR
Skoro-Sajer <sup>367</sup>	2009	62	NR	48.2	NR	747	383
Shigeta <sup>411</sup>	2009	78	12	44.2	NR	827	NR
Saouti <sup>412</sup>	2009	72	7	43	22	572	NO
Lindner <sup>413</sup>	2009	36	NR	58	25.7	1162	202
Ishida <sup>414</sup>	2009	23	1	47	25	925	337
Condliffe <sup>415</sup>	2009	236	NR	NR	NR	NR	NR
Bonderman <sup>416</sup>	2009	248	NR	50	NR	830	NR
Van der Plas <sup>417</sup>	2010	47	4	42.8	NR	769	NR
Narayana lyengar <sup>418</sup>	2010	41	5	41	24.1	418	142

PAP indicates pulmonary artery pressure; PVR, pulmonary vascular resistance; NR, not reported.

IV in this cohort; at 1 year after operation, 91.4% of patients were reclassified as NYHA Functional class I or II. In addition, other echocardiographic studies have demonstrated that with elimination of sustained pressure overload, RV geometry rapidly reverts toward normal.<sup>361</sup> In successful cases, right atrial and RV hypertrophy and dilatation regress. Tricuspid valve function returns to normal within a few days as a result of restoration of tricuspid annular geometry after the remodeling of the RV, and therefore, tricuspid valve repair is not performed with this operation.<sup>369</sup> In the entire University of California, San Diego, cohort, overall perioperative mortality was 6.4%

over a time span of >30 years (unpublished data). In the past 3 years, surgical mortality for pulmonary endarterectomy was 2.5%, which reflects the learning curve for safe performance of this operation and the refinements in surgical technique that have enhanced patient outcome (unpublished data). For the majority of patients undergoing pulmonary endarterectomy, the restoration of blood flow to previously occluded lung regions results in an immediate reduction in PVR, with a consequent increase in cardiac output. Table 10 summarizes survival and hemodynamic outcome after pulmonary endarterectomy from a growing body of surgical experience at centers worldwide.

### Pulmonary Vascular Resistance

The most important prognostic factor in endarterectomy cases is the severity of elevation in PVR and the ability to lower it to a normal range at operation. Those patients with high PVR and minimal vascular obstruction on angiogram (type 4 small-vessel vasculopathy indistinguishable from WHO Group I PAH) have the worst prognosis, and surgery does not correct pulmonary hypertension in this population.<sup>335,369</sup> Arteriolar precapillary vasculopathy without larger-vessel thromboembolic diseases is not influenced by blind endarterectomy of the proximal pulmonary arterial tree. The majority of early deaths after this operation are in this subgroup, and efforts are being directed at better identifying these patients in the preoperative setting to avoid unnecessary operation.<sup>419</sup>

### RV Function

In the setting of severe CTEPH, the RV is almost uniformly enlarged, hypertrophied, and hypokinetic. Early studies found a rapid decrease in RV and right atrial dimension after successful pulmonary endarterectomy.<sup>420</sup> More recent reports demonstrated a significant improvement in tricuspid regurgitation severity after pulmonary endarterectomy, particularly in patients with a favorable intraoperative classification of CTEPH and a significant postoperative drop in pulmonary artery pressure.<sup>419,421</sup> More novel Doppler echocardiographic parameters of RV function, including systolic velocity of the tricuspid annulus<sup>422</sup> and the RV myocardial performance index,<sup>361</sup> have been shown to correlate with PVR in CTEPH and can help predict postoperative improvement in PVR. There is no apparent "point of no return" in terms of RV enlargement or dysfunction that would disqualify a CTEPH patient for endarterectomy.<sup>423</sup> Patients with massive RV enlargement and severe RV dysfunction show marked improvement in both parameters after successful pulmonary endarterectomy.<sup>424</sup> Preoperative pulmonary angiography and intraoperative findings are better indicators of postoperative RV performance than preoperative RV size or function.<sup>425</sup> Similar to the improvements seen in LV size and function after relief of severely elevated afterload (eg, aortic stenosis), the RV has the ability to remodel favorably and regain systolic function after pulmonary endarterectomy. Thus, patients with severe RV failure should not be excluded from referral to a center with experience in pulmonary endarterectomy.

### CTEPH Classification

A large retrospective study has shown that patients with type 3 and 4 disease have more residual postoperative tricuspid regurgitation, higher postoperative pulmonary artery systolic pressures, and a higher postoperative PVR than those with type 1 or 2 disease.<sup>335</sup> Patients with distal thromboembolic disease (types 3 to 4) also have a higher perioperative mortality, require longer inotropic support, and have longer hospital stays than patients with type 1 or 2 thromboembolic disease. The degree of improvement in pulmonary hypertension and tricuspid regurgitation after pulmonary endarterectomy is determined by the type and location of pulmonary thromboembolic disease.<sup>426</sup>

### Emerging Biomarkers

Several small studies have been performed to examine the utility of serum cardiac markers, serum inflammatory markers, and endothelial surface markers as an adjunct to predicting mortality after pulmonary endarterectomy. BNP,<sup>427,428</sup> N-terminal pro-BNP,<sup>397,410,412,429,430</sup> heart-type fatty acid-binding protein,<sup>431</sup> C-reactive protein,<sup>432</sup> and thrombomodulin<sup>349</sup> all have been shown to correlate with other surrogate markers of disease severity in CTEPH patients undergoing pulmonary endarterectomy, such as PVR or RV function. Widespread use of these tests for risk stratification after pulmonary endarterectomy has not yet occurred. Preoperative risk stratification with these markers requires further development and testing in large cohorts of patients.

### Postoperative Morbidity

Severe reperfusion injury manifesting as pulmonary edema is the most frequent complication after pulmonary endarterectomy, occurring in  $\approx 5\%$  to  $15\%$  of patients.<sup>433</sup> Of patients with reperfusion injury, the majority recover after a short period of ventilatory support and aggressive diuresis. A minority of patients with severe lung reperfusion injury require prolonged periods of ventilatory support, whereas extreme cases require veno-venous extracorporeal support for oxygenation and blood carbon dioxide removal.<sup>434</sup> Neurological complications from circulatory arrest have mostly been eliminated by shorter circulatory arrest periods and the use of a direct cooling jacket placed around the head, which provides even cooling to the surface of the cranium.<sup>435</sup> Pulmonary hemorrhage after pulmonary endarterectomy is rare.<sup>436</sup> In a cohort of 1100 patients undergoing pulmonary endarterectomy,<sup>384</sup> reexploration for bleeding was only required in  $3.8\%$ . Average duration of surgery was 6.7 hours (range 3.5 to 13.1 hours), with a perioperative wound infection rate of only  $2.4\%$ .

### Long-Term Outcome After Pulmonary Endarterectomy

A survey of surviving patients who underwent pulmonary endarterectomy between 1970 and 1995 at the University of California, San Diego, formally evaluated long-term outcome from this operation.<sup>437</sup> Questionnaires were mailed to 420 patients, and responses were obtained from 308 patients. Survival, functional status, quality of life, and the subsequent use of medical assistance were assessed. Survival after pulmonary endarterectomy was found to be  $75\%$  at 6 years or more. Patients reported that their symptoms were permanently, markedly reduced after operation. Ninety-three percent of the patients were found to be in NYHA class I or II, compared with  $\approx 95\%$  in NYHA class III or IV before surgery. Of the population desiring employment,  $62\%$  of patients who were unemployed before the operation returned to work. Patients who had undergone pulmonary endarterectomy scored several quality-of-life components slightly lower than healthy individuals but significantly higher than the patients before their operations. Only  $10\%$  of patients used oxygen after the surgery. Although the response rate of this survey was low, and the fate of the nonresponders is unknown, these data suggest that pulmonary endarterectomy can offer substantial improvement in survival, function, and

quality of life. Hemodynamic benefit after pulmonary endarterectomy has been reported by many groups in follow-up periods as long as 5 years. This is accompanied by improvements in gas exchange, functional status, quality of life, and survival.<sup>369,404,408,412,437–440</sup> For comparison, the Scientific Registry of Transplant Recipients reports that the mean 1- and 5-year survival rates for lung and heart-lung transplantation for all isolated pulmonary hypertension are 75.1% and 51.9%, respectively.<sup>441</sup> Corresponding survival rates for pulmonary endarterectomy are 97.7% in the perioperative period and 75% to 92.3% after 6 years.<sup>404,408,437</sup>

## Therapy for CTEPH

### Pulmonary Endarterectomy

The treatment of choice for CTEPH is pulmonary endarterectomy. This recommendation echoes that of other recently published consensus documents<sup>355,442</sup> and is based on the fact that pulmonary endarterectomy is potentially curative, with nearly normalized pulmonary hemodynamics and substantial clinical improvement seen in many patients.<sup>443</sup> Pulmonary endarterectomy should be considered in patients who have evidence of hemodynamic or ventilatory impairment at rest or with exercise. Patients with CTEPH should be referred for surgical evaluation at an experienced center as soon as possible, even if symptoms are mild. Patients undergoing surgery typically exhibit a preoperative PVR  $>300 \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}$ , often in the range of 800 to 1400  $\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5}$ .<sup>435</sup> There is no upper limit of PVR or degree of RV dysfunction or tricuspid regurgitation that excludes a patient from surgery at a center experienced with this operation, and patients with suprasystemic pulmonary artery pressures can safely undergo pulmonary endarterectomy.<sup>444</sup> Severe hemodynamic or echocardiographic abnormalities should not be used by physicians to deem a patient “inoperable.”<sup>384,423</sup>

The preoperative differentiation of operable from inoperable CTEPH remains one of the most problematic issues of CTEPH management. The success of pulmonary endarterectomy is dependent on surgical expertise and the degree of microvascular disease present and its contribution to overall PVR. Surgical expertise is required to ensure that obstruction in the segmental and subsegmental vessels can be removed with this operation.<sup>369,435</sup> Beyond surgical expertise, a critical element in the preoperative assessment of CTEPH is the determination of the relative contributions from microvascular disease (inoperable, small-vessel, precapillary arteriopathy) compared with macroscopic disease in surgically accessible vessels. Patients with significant pulmonary hypertension but with little or no visible evidence of thromboembolic pathology are considered poor candidates for surgery.<sup>445</sup> This latter group generally displays a significant mismatch between the degree of proximal obstruction and magnitude of hemodynamic impairment in terms of PVR. The presence of comorbid conditions that may affect early and long-term survival must be considered in the evaluation of patients with CTEPH for surgery. Currently, advanced age (ie,  $>80$  years of age), renal insufficiency, and hepatic dysfunction are not considered absolute contraindications to pulmonary endarterectomy, although they do affect risk

assessment.<sup>446</sup> Severe underlying parenchymal lung disease is considered a contraindication for operation, because pulmonary endarterectomy may result in hemodynamic improvement but will not reverse the symptoms and progression of the underlying lung disease.<sup>369</sup>

### Medical Therapy for CTEPH: Anticoagulation

Before evaluation for pulmonary endarterectomy, standard medical therapy includes warfarin targeted to an INR of 2 to 3. Supportive treatment with warfarin anticoagulation reduces the likelihood of recurrent PE, and lifelong anticoagulation after surgery is recommended.<sup>369</sup> There are no data for novel anticoagulants in CTEPH, such as the oral direct thrombin inhibitor dabigatran.

### Other Medical Therapy

Although PAH (WHO Group I)-specific medical therapy in patients with CTEPH has been tried as a bridge to pulmonary endarterectomy surgery,<sup>447,448</sup> this therapy should not delay referral for surgical intervention for this disease. A strategy of using these PAH-specific medical therapies to reduce perioperative risk by improving perioperative hemodynamics has not been tested in clinical trials. In a retrospective study, preoperative treatment of CTEPH with PAH-specific therapy did not result in improved outcomes after pulmonary endarterectomy and was associated with significant delay in surgical intervention.<sup>449</sup> In addition, it has been reported that some degree of tissue alteration may occur with prolonged medical therapy, and this may affect operability. Increased fragility of thromboemboli has been noted after as little as 2 weeks of treatment with prostacyclins.<sup>443</sup>

The only multicenter, randomized, placebo-controlled trial for a PAH-specific therapy in CTEPH is the BENEFiT (Bosentan Effects in Inoperable Forms of Chronic Thromboembolic Pulmonary Hypertension) trial, which evaluated bosentan. This study enrolled 157 patients with inoperable CTEPH or residual disease after surgery. After 16 weeks of therapy, a modest reduction in PVR was observed,<sup>450</sup> although the effect was less than reductions in PVR observed with pulmonary endarterectomy.<sup>384</sup> There was no improvement in either exercise capacity or 6-minute walk distance. Thus, there are no data from RCTs of any medical therapy for CTEPH that clearly demonstrate a benefit in terms of symptoms, exercise capacity, or survival. Other data with PAH-specific medical therapy come from small, uncontrolled series and retrospective evaluations, including open-label trials assessing endothelin receptor antagonists, prostanoids, and phosphodiesterase-5 inhibitors in patients deemed inoperable and in patients who have residual pulmonary hypertension after pulmonary endarterectomy (Table 11). These data do not define whether one class of drugs might be superior to another or whether combination therapy is a rational approach. Survival benefit for the use of PAH-specific drugs in CTEPH has not been proven, either as sole therapy or in conjunction with pulmonary endarterectomy.<sup>353,462</sup> More clinical trials are needed to guide care in this field; specifically, trials are needed to demonstrate whether medical therapy is beneficial, in terms of quality of life, exercise capacity, and survival, for those unable to

**Table 11. Studies of Medical Therapy in CTEPH**

Study Drug and First Author of Study	Date of Study	Type of Study	Patients, n	Indication for Therapy	Mean Treatment Time, mo	PVR, dyne · s · cm <sup>-5</sup>		6-min Walk Distance, m	
						Pretreatment	Posttreatment	Pretreatment	Posttreatment
Bosentan									
Jais <sup>450</sup>	2008	Double-blind, placebo controlled	157	Inoperable CTEPH	3.8	795	668	322	325
				Post-PEA PH		735	542	383	384
Seyfarth <sup>451</sup>	2007	Open label	12	Inoperable CTEPH;	24	1008±428	NR	319±85	391±77
			2	Post-PEA PH					
Ulrich <sup>452</sup>	2007	Open label	15	Inoperable CTEPH	6	852±319	657±249	389±78	443±79
Hughes <sup>453</sup>	2006	Open label	47	All CTEPH	12	916±77	841±81	312±17	364±18
Bonderman <sup>454</sup>	2005	Open label	16	Inoperable CTEPH	6	712±213	NR	299±131	391±110
Hoeper <sup>455</sup>	2005	Open label	15	Inoperable CTEPH	3	914±329	611±220	340±102	413±130
			4	Post-PEA CTEPH					
Hughes <sup>456</sup>	2005	Open label	15	Inoperable CTEPH	3	964±406	918±275	NR	NR
			5	Post-PEA PH					
Sildenafil									
Suntharalingam <sup>457</sup>	2008	Double-blind, placebo-controlled	17	Inoperable CTEPH	12	722±383	573±330	NR	NR
Reichenberger <sup>458</sup>	2007	Open label	104	Inoperable CTEPH	3	863±38	759±62	310±11	366±18
Sheth <sup>459</sup>	2004	Open label	6	Inoperable CTEPH	1.5	809	725	NR	NR
Ghofrani <sup>460</sup>	2003	Open label	12	Inoperable CTEPH	6.5	1935±228	1489	312±30	366±28
Epoprostenol									
Cabrol <sup>461</sup>	2007	Open label	23	Inoperable CTEPH	20	2400/m2*	1760/m2*	299	357
			4	Post-PEA PH					
Bresser <sup>462</sup>	2004	Open label	9	Bridging therapy to PEA surgery	10.9	10.9	1007	907	NR
Scelsi <sup>463</sup>	2004	Open label	11	Inoperable CTEPH	12.4	960±480	NR	253±51	352±119
Nagaya <sup>448</sup>	2003	Open label	12	Bridging therapy to PEA surgery	1.5	1510±53	1088±58	NR	NR
Treprostinil									
Skoro-Sajer <sup>464</sup>	2007	Open label	17	Inoperable CTEPH	12	924±347	808±372	271±107	376±89
			8	Post-PEA PH					

CTEPH indicates chronic thromboembolic pulmonary hypertension; PVR, pulmonary vascular resistance; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; and NR, not reported.

\*Reported as indexed PVR in  $\text{U}/\text{m}^2$ .

undergo pulmonary endarterectomy or who have residual PAH after surgery that is not amenable to endarterectomy at an experienced center.

In general, medical therapy should be considered only in carefully selected patients who (1) are deemed to be inoperable by a multidisciplinary team with extensive surgical experience or (2) have residual functional impairment or hemodynamic abnormalities after pulmonary endarterectomy. In these latter patients, consideration should be given to a repeat pulmonary endarterectomy at a more experienced center.<sup>320,465</sup> Under no circumstances should a trial of medical therapy delay prompt evaluation for surgery.

#### **Recommendations for Medical Therapy and Pulmonary Endarterectomy in Patients With CTEPH**

1. Patients with objectively proven CTEPH should be promptly evaluated for pulmonary endarterectomy, even if symptoms are mild (*Class I; Level of Evidence B*).
2. Patients with objectively proven CTEPH should receive indefinite therapeutic anticoagulation in the absence of contraindications (*Class I; Level of Evidence C*).
3. PAH (WHO Group I)-specific medical therapy may be considered for patients with CTEPH who are not surgical candidates (because of comorbidities or patient choice) or who have residual pulmonary hypertension after operation not amenable to repeat

**pulmonary endarterectomy at an experienced center (*Class IIb; Level of Evidence B*).**

4. PAH (WHO Group I)-specific medical therapy should not be used in lieu of pulmonary endarterectomy or delay evaluation for pulmonary endarterectomy for patients with objectively proven CTEPH who are or may be surgical candidates at an experienced center (*Class III; Level of Evidence B*).

#### **Conclusions**

Standard management of uncomplicated PE and DVT has been well described in multiple publications. This scientific statement has evaluated the body of literature for management of massive and submassive acute PE, IFDVT, and CTEPH to make recommendations to guide the busy clinician. It shares a significant limitation with other guideline documents in that the body of evidence to guide management for these forms of VTE is incomplete, and therefore, some recommendations must rely on lower levels of evidence or expert opinion.<sup>466</sup> There are several important clinical questions in the management of acute VTE that could be tested in RCTs. In addition to guiding practice, the authors humbly anticipate that this document will help highlight these gaps and support the case for future clinical trials for these serious forms of VTE and their novel therapies. We strongly advise further clinical trials of the advanced therapies for VTE reviewed here.

## Disclosures

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\*Modest.

†Significant.

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\*Modest.

†Significant.

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KEY WORDS: AHA Scientific Statements ■ venous thrombosis ■ anticoagulants ■ diagnosis ■ thrombolysis ■ disease management ■ fibrinolysis

# Correction

In the article by Jaff et al, “Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension,” which published ahead of print on March 21, 2011, and appeared in the April 26, 2011, issue of the journal (*Circulation*. 2011;123:1788–1830), several corrections were needed:

1. On page 1801, in the second column, the first recommendation under “Recommendations on IVC Filters in the Setting of Acute PE,” the Level of Evidence has been changed to “B.” The recommendation read,

**1. Adult patients with any confirmed acute PE (or proximal DVT) with contraindications to anticoagulation or with active bleeding complication should receive an IVC filter (Class I; Level of Evidence C).**

It has been changed to read,

**1. Adult patients with any confirmed acute PE (or proximal DVT) with contraindications to anticoagulation or with active bleeding complication should receive an IVC filter (Class I; Level of Evidence B).**

2. On page 1811, in the first column, first paragraph, the first sentence read, “The workup . . . physical examination, and pulmonary artery and lateral . . .” It has been changed to read, “The workup . . . physical examination, posteroanterior and lateral . . .”

These corrections have been made to the current online version of the article, which is available at <http://circ.ahajournals.org/content/123/16/1788>.