Effectiveness and Cost-effectiveness of Thrombolysis in Submassive Pulmonary Embolism

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Background: Thrombolytic therapy is controversial in patients with submassive pulmonary embolism.

Methods: We performed a cost-effectiveness analysis to compare health effects and costs of treatment with alteplase plus heparin sodium vs heparin alone in hemodynamically stable patients with pulmonary embolism and right ventricular dysfunction by developing a Markov model and using data from clinical trials and administrative sources.

Results: Based on data from a recent randomized trial, we assumed that the risk of clinical deterioration requiring treatment escalation was almost 3 times higher in patients who received heparin alone (23.2% vs 7.6%) but that the risk of death was equal in the 2 cohorts (2.7%). Based on registry data, we assumed that the risk of intracranial hemorrhage was approximately 3 times higher in patients who received alteplase plus heparin (1.2% vs 0.4%). Under these and other assumptions, thrombolysis resulted in marginally higher total lifetime health care costs ($43 900 vs $43 300) and was slightly less effective (10.52 vs 10.57 quality-adjusted life-years) than treatment with heparin alone. Thrombolysis was more effective and cost less than $50 000 per quality-adjusted life-year gained when we assumed that the baseline risk of death in the heparin group was 3 times the base-case value (8.1%) and that alteplase reduced the relative risk of death by at least 10%.

Conclusions: Available data do not support the routine use of thrombolysis to treat patients with submassive pulmonary embolism. However, thrombolysis may prove to be cost-effective in selected subgroups of hemodynamically stable patients in whom the risk of death is higher.

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THE ROLE OF THROMBOLYTIC therapy in acute pulmonary embolism has long been debated.[1-3] Compared with heparin sodium alone, the addition of thrombolytic therapy improves hemodynamic and scintigraphic outcomes within 24 hours of administration, but these benefits diminish over time.[4-7] For patients with pulmonary embolism and arterial hypotension, thrombolysis is considered to be the standard of care because prognosis in this group is so poor without thrombolytic therapy that the potential benefits are thought to far outweigh the risks.[4,7-10] The controversy centers on treatment of hemodynamically stable patients with pulmonary embolism, especially those with right ventricular dysfunction. Right ventricular dysfunction is thought to be a sign of possible impending hemodynamic instability.[1] It is present in 40% to 50% of patients with pulmonary embolism who are hemodynamically stable at the time of presentation, and right heart failure is a common cause of death in these patients.[4,9,11,12] Patients with submassive pulmonary embolism and right ventricular dysfunction have mortality rates that are 2 times higher than those with normal right ventricular function.[9,11,13]

Proponents of thrombolytic therapy argue that its potential benefits justify the greater cost and the increased risk of intracerebral hemorrhage and other major bleeding complications in hemodynamically stable patients with right ventricular dysfunction. A recent randomized controlled trial[14] in this population demonstrated that primary thrombolysis with alteplase and heparin was more effective than treatment with heparin alone in preventing the combined end point of death or the requirement for treatment escalation, including the need for catecholamine infusion, mechanical ventilation, or secondary thrombolysis. However, mortality rates were lower than expected and similar in both treatment groups. The authors[14] concluded that their results supported the use of primary thrombolysis based on the less-frequent requirement for treatment escalation in the intervention group.

We performed a cost-effectiveness analysis to quantify the health effects and economic outcomes associated with the use of thrombolytic therapy. Specifically, we compared treatment with alteplase plus heparin vs heparin alone as primary therapy in

hemodynamically stable patients with acute pulmonary embolism and right ventricular dysfunction.

METHODS

We developed a Markov (state-transition) model to estimate the effectiveness and costs of treatment for acute pulmonary embolism.[15] We adopted the recommendations of the panel on Cost-effectiveness in Health and Medicine[16] for conducting and reporting a reference-case analysis from the societal perspective.

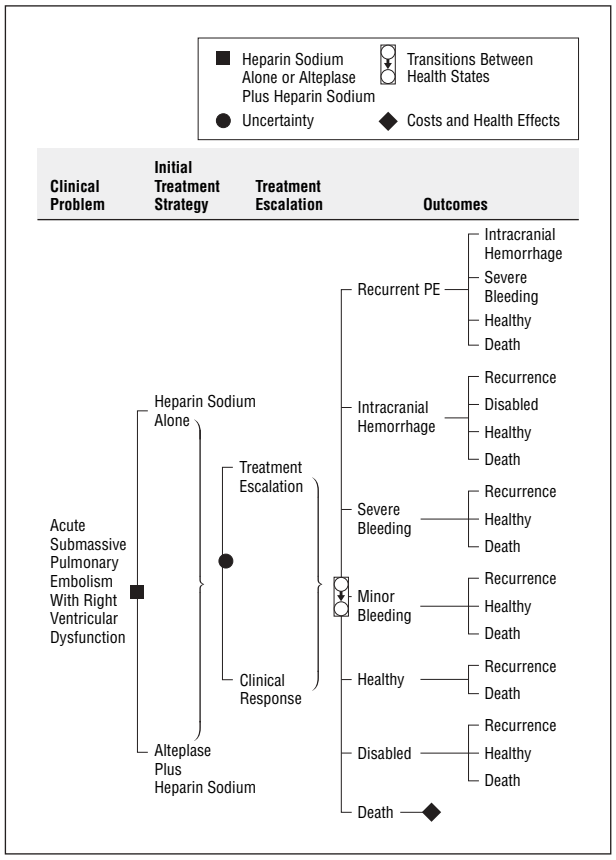

Figure 1. Schematic representation of the decision model. The model begins with the decision to treat acute submassive pulmonary embolism with heparin sodium alone or alteplase plus heparin (square node). Primary treatment determines the probability of clinical deterioration requiring treatment escalation (round uncertainty node). Primary treatment and clinical response determine monthly probabilities of transitions between health states (Markov node; 2 circles with arrow). Transitions continue until the last patient dies. The diamond signifies the costs and health effects associated with the full sequence of events within a particular path. PE indicates pulmonary embolism.

Figure 1 outlines the structure of the decision model; it illustrates the clinical problem, initial treatment strategy, possible requirement for treatment escalation, and patient outcomes. The target population included hemodynamically stable patients with submassive pulmonary embolism and right ventricular dysfunction. A hemodynamically stable patient was defined as one with a systolic blood pressure higher than 90 mm Hg.

We compared initial treatment with alteplase plus heparin vs treatment with heparin alone. Patients in either group who developed clinical deterioration based on worsening cardiopulmonary signs and symptoms required treatment escalation. Treatment escalation included the need for secondary or "rescue" thrombolysis, mechanical ventilation, catecholamine infusion, or embolectomy. Other outcomes included intracranial hemorrhage, severe and minor bleeding at other sites, recurrent pulmonary embolism, long-term disability from intracranial hemorrhage, time lost from work or leisure due to pulmonary embolism or treatment complications, and death from pulmonary embolism.

We gathered data about the effectiveness and safety of treatment strategies by reviewing clinical studies from the peer-reviewed literature, which we identified by searching MEDLINE and EMBASE from 1966 to December 2003. We updated the search in February 2006. We also scanned the reference lists of original research and review articles. We limited the search to English-language publications.

Base-case estimates for clinical probabilities, costs, and health state utilities (quality-of-life adjustments) are listed in **Table 1** and **Table 2**. We derived estimates of effectiveness from the largest randomized, controlled trial of thrombolysis in patients with submassive pulmonary embolism.[14] Estimates of the risk of bleeding complications were derived from other clinical data sources.[13,17-19] We estimated direct costs associated with pulmonary embolism treatment by adding costs for hospital care, physician services, and pharmaceuticals. We discounted all costs and health effects at an annual rate of 3%. We estimated resource utilization by using data from clinical trials and valued resources by using Medicare reimbursement rates and other administrative data sources. Details about additional assumptions and data sources are available at http://pulmonary.stanford.edu/documents/thrombolysis_appendixonly.pdf.

We expressed our results in terms of costs, life expectancy, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios. To perform the analysis, we used DecisionMaker software beta version 2003.3.3.2 (S. G. Pauker, F. A. Sonnenberg, J. B. Wong, C. G. Hagerty, New England Medical Center, Boston, Mass). We performed 1-way, 2-way, multiway, and probabilistic sensitivity analyses by varying values for model parameters within specified ranges.

Table 1. Estimates for Clinical Probabilities in the Decision Model

Variables: Clinical Effectiveness	Base-Case Estimate: Heparin Sodium Alone, %	Base-Case Estimate: Relative Risk for Alteplase Plus Heparin Sodium (Range)	Source
Mortality from PE	2.7	1.0 (0.36-6.80)	Konstantinides et al[14]
Patients requiring treatment escalation	23.0	0.4 (0.16-0.66)	Konstantinides et al[14]
ICH	0.4	3.0 (1.7-5.5)	Konstantinides et al[13]
Severe bleeding	1.3	4.2 (2.8-4.8)	GUSTO Investigators,[17] Simonneau et al[18]
Minor bleeding	4.1	2.3 (1.0-4.9)	Sors et al,[19] Simonneau et al[18]

Abbreviations: ICH, intracranial hemorrhage; PE, pulmonary embolism.
*Alteplase vs heparin sodium alone.

Table 2. Estimates for Clinical Probabilities, Costs, and Quality of Life Adjustments (Utilities) in the Decision Model

Variable	Both Heparin Sodium Alone and Alteplase Plus Heparin (Range)	Source
Patients who received specific interventions, %*		
Catecholamine infusion for persistent hypotension	24.0 (19.0-30.0)	Konstantinides et al[14]
Endotracheal intubation	13.0 (9.7-17.7)	Konstantinides et al[14]
Embolectomy	2.2 (0.1-4.8)	Konstantinides et al[14]
Rescue thrombolysis	100	Konstantinides et al[14]
Other clinical probabilities, %		
Early recurrent pulmonary embolism, first week	4.0 (2.5-6.4)	Carson et al[20]
Late recurrent pulmonary embolism, annual risk after first week	4.3 (2.7-6.8)	Carson et al,[20] Arcasoy and Kreit[21]
Death following recurrent PE	34 (30-44)	Goldhaber et al[9]
Death following ICH	45 (21-72)	Arcasoy and Kreit[21]
Death following severe bleeding	4.9 (2.7-8.9)	Goldhaber et al[9]
Neurological deficits in survivors of ICH	62 (53-71)	Gore et al[22]
Patients requiring long-term nursing care following ICH	12 (9-15)	Mark et al[23]
Cost variables, $		
Initial hospitalization including treatment with heparin alone	6781 (5086-8476)	American Medical Association,[24,25] Medical Economics,[26] *Length of Stay by Diagnosis, United States*,[27] Centers for Medicare and Medical Services[28]
Initial hospitalization including treatment with alteplase	9531 (7148-11 914)	American Medical Association,[24,25] Medical Economics,[26] *Length of Stay by Diagnosis, United States*,[27] Centers for Medicare and Medical Services[28]
Costs common to both treatment groups		
Recurrent late PE	8156 (6117-18 195)	American Medical Association,[24,25] Medical Economics,[26] *Length of Stay by Diagnosis, United States*,[27] Centers for Medicare and Medical Services[28]
Cost of treatment escalation	14 515 (10 886-18 144)	Konstantinides et al,[14] American Medical Association,[24,25] Medical Economics,[26] Solucient,[27] Centers for Medicare and Medical Services[28]
Minor bleeding	898 (673-1122)	Solucient,[27] American Medical Association[25]
Nursing home care for disability after ICH, annual	51 000 (38 250-63 750)	Mahaffey et al[29]
Cost of complications for patients responding to primary treatment		
ICH	6930 (5198-8663)	Gore et al,[22] American Medical Association,[24,25] Medical Economics,[26] Centers for Medicare and Medical Services[28]
Recurrent early PE	5601 (4201-7001)	American Medical Association,[24,25] Medical Economics,[26] *Length of Stay by Diagnosis, United States*,[27] Centers for Medicare and Medical Services[28]
Severe bleeding	2089 (1567-2611)	American Medical Association,[24,25] Medical Economics,[26] Solucient[27]
Cost of complications for patients requiring treatment escalation		
ICH	4890 (3667-6111)	Gore et al,[22] American Medical Association,[24,25] Solucient,[27] Mahaffey et al,[29] Centers for Medicare and Medical Services[28]
Recurrent early PE	4347 (3260-5433)	American Medical Association,[24,25] Solucient,[27] GUSTO III Investigators,[31] Centers for Medicare and Medical Services[28]
Severe bleeding	1370 (1027-1711)	American Medical Association,[24,25] Solucient[27]
Quality of life adjustments/utilities (duration of health state)†		
PE (7 d)	0.60 (0.20-0.80)	Bell et al,[30] Sarasin and Eckman[32]
ICH (9 d)	0.12 (0.00-0.91)	Gage et al[33]
Severe bleeding (2 d)	0.76 (0.50-0.99)	Gage et al,[33] Fryback et al[34]
Neurological disability following ICH (lifetime)	0.34 (0.00-1.00)	Gore et al,[22] Mark et al,[23] Fryback et al,[34] Lee et al[35]

Abbreviations: ICH, Intracranial hemorrhage; PE, pulmonary embolism.

*Among those requiring treatment escalation.

†To calculate the decrement in quality-adjusted life expectancy associated with temporary health states, multiply the utility value by the duration of the health state. For example, the decrement in quality-adjusted life expectancy associated with recurrent pulmonary embolism is 0.6×7 days, or 4.2 quality-adjusted days.

RESULTS

Based on data from the randomized, controlled trial performed by Konstantinides et al,[14] we assumed that patients who received heparin alone required treatment escalation (rescue thrombolysis, mechanical ventilation, catecholamine infusion, or embolectomy) approximately 3 times more often than patients who received heparin plus alteplase (23.2% vs 7.6%) but that there was no difference in the risk of death from pulmonary embolism between the

Table 3. Health and Economic Outcomes

Outcome	Heparin Sodium Alone	Alteplase Plus Heparin Sodium	Difference*
Present value of cost per patient, $†			
Initial treatment	6689	9402	2713
Treatment escalation	3322	1102	–2220
Complications	1133	1446	313
Future health care	32 137	31 986	–151
Total Health Care Cost	**43 281**	**43 936**	**655**
Life expectancy, y	10.57	10.52	–0.050
Quality-adjusted life expectancy, QALYs	8.04	7.99	–0.051
Incremental cost-effectiveness, life-year gained		Dominated	
Incremental cost-effectiveness, QALY gained		Dominated	
Results of probabilistic model, % of total			
Simulations with greater efficacy and lower cost	23	0	
Simulations with greater efficacy and cost <$50 000 per QALY gained	44	32	

Abbreviation: QALY, quality-adjusted life-year.
*Alteplase plus heparin minus heparin alone.
†Discounted at 3% annually.

2 groups (pooled risk, 2.7%). Based on data from a multicenter registry of 719 patients with acute pulmonary embolism, we estimated that the risk of intracranial hemorrhage (ICH) was 1.2% for patients treated with alteplase plus heparin and 0.4% for patients treated with heparin alone.[13] Based on data from other sources, we assumed that the risk of other major bleeding complications was 4.2 times higher in patients who received thrombolysis, and their risk of minor bleeding complications was more than twice as high.[17-19]

BASE-CASE RESULTS

Discounted life expectancy and QALYs were greater in patients treated with heparin alone (10.57 years and 8.04 QALYs, respectively) than they were in patients who received alteplase plus heparin (10.52 years and 7.99 QALYs, respectively). The incremental difference in life expectancy was approximately 19 days (0.05 life-years). Discounted total lifetime costs were approximately $43 300 for patients who received heparin alone and $43 900 for patients who were treated with alteplase plus heparin. The incremental difference in costs was approximately $650. Patients who received treatment with alteplase plus heparin had higher costs for initial treatment ($9400 vs $6700) and treatment complications ($1450 vs $1100), but these were partly offset by lower costs for treatment escalation ($1100 vs $3300). Thus, under base-case assumptions, treatment with heparin alone was less expensive and more effective than treatment with alteplase plus heparin (**Table 3**).

SENSITIVITY ANALYSIS

In 1-way sensitivity analysis, the cost-effectiveness of alteplase plus heparin depended critically on the relative risk of death from pulmonary embolism following thrombolytic therapy. Under other base-case assumptions, treatment with alteplase plus heparin became more effective than heparin alone when the relative risk of death was less than or equal to 0.74 (base-case value = 1.0). Thrombolysis was more effective and cost less than $50 000 per QALY gained when the relative risk of death was less than or equal to 0.68. Treatment with heparin alone remained more effective and less expensive when all other variables were tested across their specified ranges. Specifically, the cost-effectiveness of alteplase was not sensitive to the relative risk of treatment escalation or bleeding complications, the cost of alteplase, or the baseline risk of bleeding complications.

Figure 2 shows the results of a 2-way sensitivity analysis that examined the baseline risk of death from pulmonary embolism in patients treated with heparin alone and the relative risk of death from pulmonary embolism associated with thrombolytic treatment. In general, the effectiveness and cost-effectiveness of alteplase plus heparin became more favorable as the baseline risk of death from pulmonary embolism increased and the relative risk of death decreased. For example, when the risk of death in the heparin cohort was 3 times the base-case value (8.1%), as has been reported in several observational studies of patients with submassive pulmonary embolism,[9,13] thrombolytic therapy cost less than $50 000 per QALY gained, provided that the relative risk of death following treatment with alteplase was less than 0.90.

The results of a multiway sensitivity analysis that examined death from pulmonary embolism, intracranial hemorrhage, and treatment escalation showed that even when the relative risks of intracranial hemorrhage (1.7) and treatment escalation (0.16) were set at their lower limits, alteplase plus heparin cost less than $50 000 per QALY gained only when the relative risk of death was less than or equal to 0.86.

The results of a probabilistic sensitivity analysis favored heparin alone over alteplase plus heparin in more than 66% of 1000 simulations (Table 2). Heparin alone was more effective and less costly in 23% of all simulations, and it was more effective and cost less than $50 000 per QALY in another 44% of simulations. Alteplase plus

heparin was more effective and more costly in 34% of all simulations. Alteplase plus heparin was never more effective and less expensive than heparin alone; however, it was more effective and cost less than $50 000 per QALY gained in 32% of simulations. As shown in **Figure 3**, cost-effectiveness acceptability curves showed that at a societal willingness-to-pay threshold of $50 000 per QALY gained, there was a 66% probability that heparin alone was cost-effective but only a 33% probability that thrombolysis was cost-effective.[36]

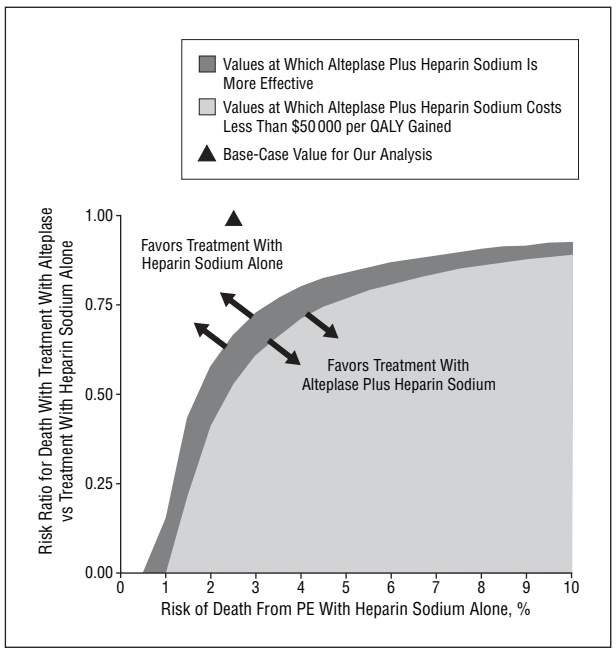

Figure 2. Two-way sensitivity analysis on risk of death from pulmonary embolism with heparin alone and relative risk of death for alteplase vs heparin alone. The striped area represents combinations of baseline risk and relative risk at which treatment with alteplase plus heparin costs less than $50 000 per quality-adjusted life-year (QALY) gained compared with heparin alone. The shaded area represents additional combinations of these variables at which treatment with alteplase plus heparin was more effective than treatment with heparin alone but cost more than $50 000 per QALY gained. The triangle indicates base-case values for these variables in our analysis. PE indicates pulmonary embolism.

COMMENT

Under the assumptions of this analysis, we found that treatment with heparin alone was more effective and less costly than thrombolytic treatment with alteplase plus heparin in patients with submassive pulmonary embolism and right ventricular dysfunction. We demonstrated that the major determinants of effectiveness and cost-effectiveness were the baseline risk of death from pulmonary embolism following heparin treatment and the potential reduction in the risk of death given treatment with alteplase plus heparin. In contrast, the probability of clinical deterioration requiring treatment escalation did not have an impact on cost-effectiveness across the ranges tested in sensitivity analysis. Likewise, varying the risk of intracranial hemorrhage alone did not change the results. Thus, we showed that alteplase plus heparin must reduce the risk of death from pulmonary embolism to be cost-effective, even under optimistic assumptions about the risks of intracranial hemorrhage and clinical deterioration requiring treatment escalation.

The largest and most recent randomized controlled trial of thrombolysis in hemodynamically stable patients with pulmonary embolism and right ventricular dysfunction showed that treatment with alteplase plus heparin reduced the frequency of clinical deterioration requiring treatment escalation but not mortality rates.[14] Although this study is the largest randomized trial performed to date (to our knowledge), it has several limitations that are relevant to this analysis. First, the patient population was defined as those with right ventricular dysfunction, yet only 30% of patients satisfied this definition based on echocardiographic criteria. Most met criteria for right ventricular dysfunction based on electrocardiographic findings alone. Second, the low combined mortality rate (2.7%) observed in this study suggests that the participants may have been less severely ill than patients with submassive pulmonary embolism and echocardiographic evidence of right ventricular dysfunction who were described in recent observational studies.[9,13] Third,

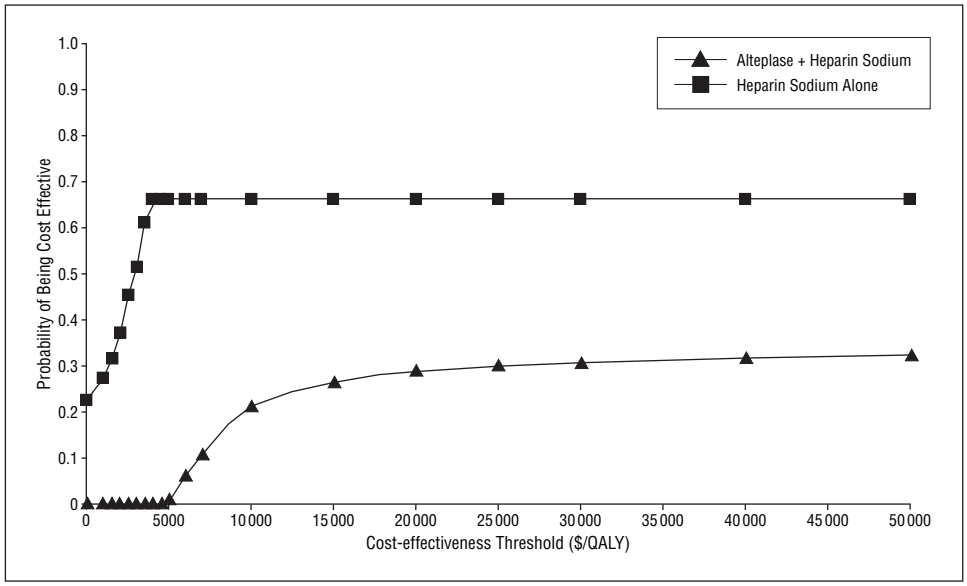

Figure 3. Cost-effectiveness acceptability curves. Each curve illustrates the probability that the intervention is cost-effective at varying thresholds of societal willingness to pay, based on the results of a probabilistic sensitivity analysis in which all key model parameters were assigned distributions and varied simultaneously in a 1000-iteration Monte Carlo simulation. QALY indicates quality-adjusted life-year.

the study protocol permitted investigators to break the treatment code for patients who were clinically deteriorating. Thus, in some cases, the decision to escalate treatment may have been influenced by knowledge of whether the patient was assigned to receive primary thrombolysis.[37,38] Although treatment with alteplase plus heparin was not associated with lower mortality rates in the randomized controlled trial, primary thrombolysis was associated with a reduced requirement for treatment escalation, prompting the study authors[14] to recommend primary therapy with alteplase. However, our results suggest that available data do not support the routine use of primary thrombolysis in this patient population.

Sensitivity analysis showed that the relative risk of death from pulmonary embolism had the greatest potential impact on the cost-effectiveness of thrombolytic therapy. Not surprisingly, a 2-way sensitivity analysis showed that treatment with alteplase plus heparin became a more attractive option as the baseline risk of death following treatment with heparin alone increased, provided that there was at least some reduction in the risk of death owing to treatment with alteplase plus heparin. This analysis underscores the potential importance of further risk stratification in hemodynamically stable patients with pulmonary embolism. Recent studies[39-41] of patients with elevated serum levels of B-type natriuretic peptide and cardiac troponins show promise in identifying a subgroup of hemodynamically stable patients for whom the risk of death is markedly elevated. More recently, Aujesky et al[42,43] developed and validated a clinical model that identified patients with an increased risk of death from acute pulmonary embolism. In future studies, use of this model and other prognostic biomarkers should help identify subgroups of patients who might benefit most from treatment with alteplase plus heparin.

Our analysis has several limitations. First, we did not consider several potential mechanisms by which alteplase may improve outcomes over heparin alone. These mechanisms include reducing the rate of recurrent pulmonary embolism and the potential reduction in long-term complications of venous thromboembolism such as pulmonary hypertension and the postthrombotic syndrome.[4,13,44] These potential benefits have not been conclusively demonstrated in clinical studies. If confirmed, primary thrombolysis would be a more attractive option. Second, we did not consider the use of vena cava filters in patients who developed severe bleeding. The need for vena cava filters would be higher in the group that received thrombolysis treatment, and not including this outcome would lead to bias in favor of thrombolysis. This does not threaten the validity of our conclusions because including vena caval filters would make the thrombolysis arm slightly less cost-effective than it already is in comparison with treatment with heparin alone. Last, although we assumed that alteplase plus heparin did not reduce the risk of death from pulmonary embolism (based on the best available data), observational studies suggest that primary thrombolysis may improve mortality rates in some populations of patients with submassive pulmonary embolism and right ventricular dysfunction. For example, in the Management Strategies and Determinants of Outcome in Acute Major Pulmonary Embolism registry, the population of patients with right ventricular dysfunction had a higher baseline mortality rate (8.1%) and satisfied a stricter definition of right ventricular dysfunction (echocardiographic or angiographic criteria rather than electrocardiographic criteria alone) compared with those patients included in the randomized controlled trial by Konstantinides et al.[13] In this registry, the unadjusted relative risk of death from PE following thrombolysis was 0.62.[13] In addition, smaller randomized trials have consistently shown that treatment with thrombolysis improves right ventricular dysfunction more than treatment with heparin alone.[2] However, it is not clear whether improvement in physiologic outcomes can be translated to improved survival.

It may be very difficult to perform a randomized, controlled trial that is adequately powered to demonstrate that alteplase plus heparin improves survival.[12] We estimate that such a trial would have to enroll at least 2800 participants in each arm to detect a 30% reduction in the risk of pulmonary embolism–related death with 80% power at an α level of .05, assuming that the baseline risk of death in the control group was 5%. The required sample size would need to be even larger to detect smaller reductions in risk. The promise of greater safety and efficacy with catheter-directed thrombolysis also requires confirmation in large clinical trials.

In summary, by synthesizing the best available evidence on effectiveness, complications, and costs, we found that treatment with alteplase plus heparin is less effective and more costly than treatment with heparin alone. Current evidence does not support the routine use of primary thrombolysis in hemodynamically stable patients with acute pulmonary embolism and right ventricular dysfunction, as defined by electrocardiographic criteria, echocardiographic criteria, or right heart catheterization. Future studies should explore whether thrombolytic therapy is more effective in other subgroups of hemodynamically stable patients who are at greater risk of death from acute pulmonary embolism.

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