
Value of Quantitative D-dimer Assays in Identifying Pulmonary Embolism: Implications from a Sequential Decision Model

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Abstract

Objectives: To examine the cost-effectiveness of a quantitative D-dimer assay for the evaluation of patients with suspected pulmonary embolism (PE) in an urban emergency department (ED).

Methods: The authors analyzed different diagnostic strategies over pretest risk categories on the basis of Wells criteria by using the performance profile of the ELISA D-dimer assay (over five cutoff values) and imaging strategies used in the ED for PE: compression ultrasound (CUS), ventilation-perfusion (VQ) scan (over three cutoff values), CUS with VQ (over three cutoff values), computed tomography (CT) angiogram (CTA) with pulmonary portion (CTP) and lower-extremity venous portion, and CUS with CTP. Data used in the analysis were based on literature review. Incremental costs and quality-adjusted-life-years were the outcomes measured.

Results: Computed tomography angiogram with pulmonary portion and lower-extremity venous portion without D-dimer was the preferred strategy. CUS-VQ scanning always was dominated by CT-based strategies. When CTA was infeasible, the dominant strategy was D-dimer with CUS-VQ in moderate- and high-Wells patients and was D-dimer with CUS for low-Wells patients. When CTP specificity falls below 80%, or if its overall performance is markedly degraded, preferred strategies include D-dimer testing. Sensitivity analyses suggest that pessimistic assessments of CTP accuracy alter the results only at extremes of parameter settings.

Conclusions: In patients in whom PE is suspected, when CTA is available, even the most sensitive quantitative D-dimer assay is not likely to be cost-effective. When CTA is not available or if its performance is markedly degraded, use of the D-dimer assay has value in combination with CUS and a pulmonary imaging study. These conclusions may not hold for the larger domain of patients presenting to the ED with chest pain or shortness of breath in whom PE is one of many competing diagnoses.

ACADEMIC EMERGENCY MEDICINE 2006; 13:755-766 © 2006 by the Society for Academic Emergency Medicine

Keywords: cost-effectiveness, pulmonary embolism, D-dimer decision

Pulmonary embolisms (PEs) often have a variable presentation and require resource-intensive diagnostic modalities. The mortality rate of 22%–35%

in known untreated cases^{1,2} drops to roughly 10% with anticoagulation.¹ Although the vast majority of PEs arise from deep venous thromboses (DVTs), these DVTs are not detected uniformly in patients with PE.³ Consequently, simple compression ultrasound (CUS) testing of the lower extremities is not considered a reliable stand-alone test for the diagnosis of PE.

Direct imaging studies for PE readily available in most urban emergency departments (EDs) are computed tomography angiogram (CTA) and the ventilation perfusion scan (VQ). VQ scan results are categorized under the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) classification system as very low (near normal), low, intermediate, and high. Choosing the VQ result that triggers therapy is an active clinical decision.⁴⁻⁶

Several highly sensitive serum markers for the breakdown products of blood clots exist to aid in the evaluation of patients with suspected venous thromboembolism (VTE). One of the most widely used quantitative assays is

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Received September 19, 2005; revision received February 20, 2006; accepted February 20, 2006.

The views expressed here are those of the authors and do not necessarily reflect those of the Department of Veterans Affairs. Dr. Duriseti was supported by a Postdoctoral Fellowship from the Department of Veterans Affairs, Palo Alto, CA.

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the VIDAS enzyme-linked immunosorbent assay (ELISA) D-dimer test (bioMérieux SA, Marcy l'Etoile, France).⁷

Consensus panels have provided recommendations as to which clinical scenarios are appropriate for the use of such a test. Such recommendations are predicated on opinions of an acceptable posterior probability of disease, rather than health outcome value measures.⁸ From a clinical standpoint, a probability helps establish a measure of certainty but does not explicitly identify the decision with the most value: such a consideration must include a notion of resource allocation in combination with health outcomes.

Some investigators have analyzed the cost-effectiveness of CTA for the diagnosis of PE without considering the use of D-dimer.^{9,10} One study analyzed the cost-effectiveness of PE diagnostic strategies including D-dimer but did not consider the impact of different cutoffs for either the VQ scan or the D-dimer result, nor the use of a CTA with pulmonary portion (CTP) and lower-extremity venous portion (CTV) alone with D-dimer.

We applied a sequential decision model to evaluate the cost-effectiveness of different imaging strategies for patients in different risk categories. Clinical prediction rules, such as that developed by Wells and colleagues,¹¹ help clinicians stratify patients into risk categories on the basis of a scoring rule. Wells' scoring rule has been validated prospectively by several investigators and has been found to be at least as effective as other available clinical prediction rules.¹¹⁻¹⁵ By allowing for different cutoff values for the ELISA D-dimer assay and VQ scans, actively framing clinical assessment into the model, and explicitly representing the causal relationship between DVT and PE, we extend previous work to more accurately reflect the clinical decision and associated outcome measures in a cost-effectiveness framework.

METHODS

Study Design

This was a retrospective analysis of published data to assess the cost-effectiveness of various strategies for the evaluation of patients with suspected PE.

Model Development

Sequential Decision Model. We assumed the following sequence of events: 1) a patient with a suspected PE is

given an initial clinical evaluation (history, exam, vital signs, 12-lead electrocardiogram, and chest radiograph) and a Wells score, 2) the decision to order a test is made, 3) if a D-dimer is ordered, the clinician decides on the cutoff value to trigger an imaging test (if any), 4) if a VQ scan is involved, the cutoff value of the VQ scan is chosen for when anticoagulation and hospitalization for PE is initiated, and 5) treatment is delivered on the basis of the results of the imaging test. We assessed the cost-effectiveness of ten testing strategies with either no D-dimer or with any of five different cutoff values for the D-dimer, creating a total of 60 different policies that were examined for each Wells pretest category (Table 1). As with many tests, neither the D-dimer nor the VQ scan delivers a binary indication (normal or abnormal); our sequential model incorporates that notion.

We modeled the sequential decision process on the basis of the influence diagram (ID) that is depicted in Figure 1. The ID implies an assessment order on the relevant probabilities and explicit conditional independence assumptions. The ID includes the relevant observations, decisions, and the associated value of a diagnostic policy. The ID is constructed in the causal direction for intuitive reasons and to simplify assessment.¹⁶ For example, the conditional probability $P\{\text{PE present} \mid \text{Wells Score, DVT present}\}$ was drawn from the literature, but the conditional probability $P\{\text{Wells} \mid \text{PE present, DVT present}\}$ must be inferred from the other distributions. We assigned conditional probabilities on the basis of data available in the published literature. The probability of PE is conditioned on the Wells pretest risk category (low, moderate, or high). The test indication is rendered conditionally independent of the specific population under consideration once the probabilities of PE and DVT are established.¹⁷ In this way, differences in the prevalence of PE in the Wells study population and data from various studies on the accuracy of a particular imaging test can be used together in the same probabilistic network.^{11,18,19} We assumed that a CTA may include a pulmonary portion and a deep venous portion. The decisions concerning which cutoffs to choose for a D-dimer and for a VQ scan are subsumed in the decision to order the test. Uncertainty nodes that send arrows to decision nodes are observed

Table 1

The Sixty Evaluation Strategies Considered for Each of the Five Pre-test Categories Identified in the Model

Imaging Strategy	D-dimer Usage Strategy					
	No D-dimer	Cutoff I	Cutoff II	Cutoff III	Cutoff IV	Cutoff V
No imaging	X	X	X	X	X	X
CUS alone and treat if positive	X	X	X	X	X	X
CUS first; if CUS is negative, then treat if V/Q > normal	X	X	X	X	X	X
CUS first; if CUS is negative, then treat if V/Q > low	X	X	X	X	X	X
CUS first; if CUS is negative, then treat if V/Q > intermediate	X	X	X	X	X	X
Treat if V/Q > normal	X	X	X	X	X	X
Treat if V/Q > low	X	X	X	X	X	X
Treat if V/Q > intermediate	X	X	X	X	X	X
CTA (CTP and CTV)	X	X	X	X	X	X
CUS first; if CUS is negative, then treat if CTP positive	X	X	X	X	X	X

CUS = compression ultrasound; VQ = ventilation-perfusion scan; CTA = computed tomographic angiogram; CTP = CTA with pulmonary portion; CTV = CTA with lower extremity venous portion.

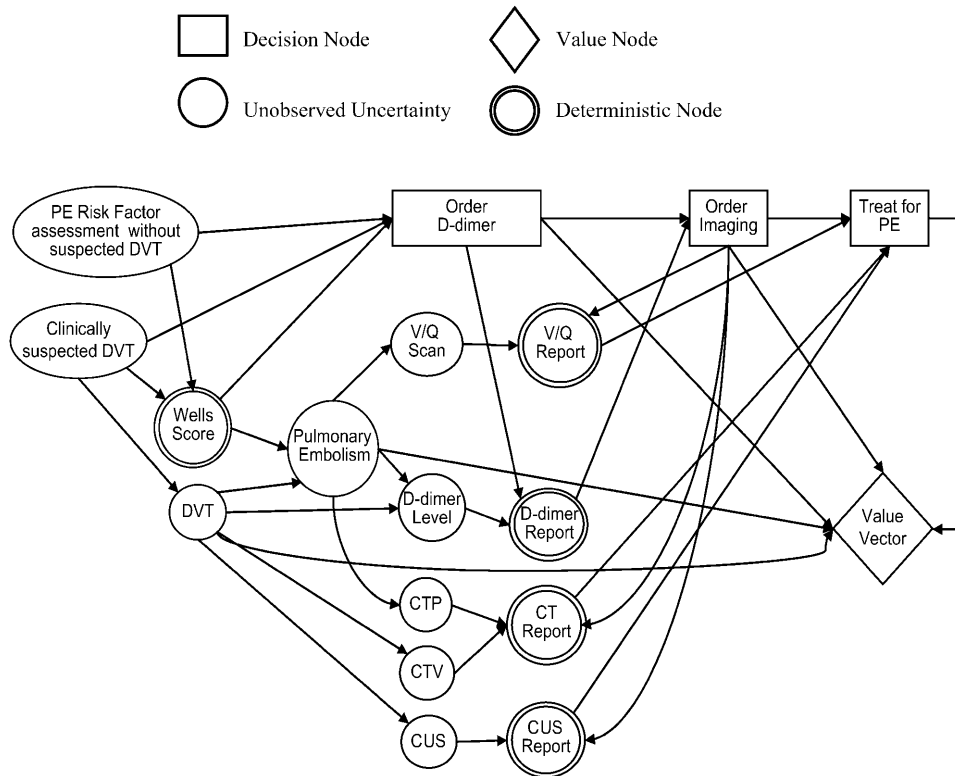


Figure 1. Directed acyclic graph of the decision network. The diagram depicts the complexity of this decision-making problem. The structure and the implied order of probability assessment partially are dictated by the conditional probabilities that are available in the literature. PE = pulmonary embolism; V/Q = ventilation-perfusion; DVT = deep venous thromboembolism; CTP = CT angiogram with pulmonary portion; CTV = CT angiogram with lower-extremity venous portion; CUS = compression ultrasound.

before these decisions are made. The node labeled “Value Vector” includes an incremental cost component and a quality-adjusted life-year (QALY) component.

Tests were assumed to be conditionally independent. Whenever a D-dimer is used with an imaging strategy, the imaging strategy is executed only if the D-dimer test is positive. Within a “compound imaging strategy,”

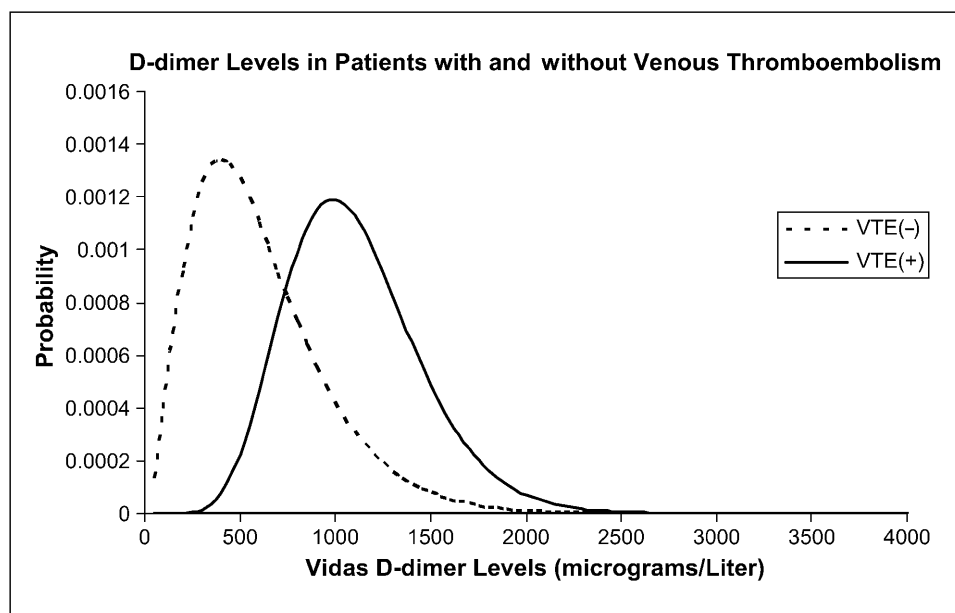


Figure 2. Model input: gamma distributions for D-dimer levels in patients with and without venous thromboembolism. The curves each have two degrees of freedom, which can be fully specified by knowing the sensitivity and specificity of two cutoff values.

Table 2
Conditional Probabilities for VIDAS ELISA D-dimer Assay

D-dimer Level (μL)	Pr{VTE ⁺ D-dimer Level}	Pr{VTE ⁻ D-dimer Level}	D-dimer Sensitivity for PE	D-dimer Specificity for PE
Cutoff I (200)	0.00005	0.99995	0.99998	0.08312
Cutoff II (350)	0.00689	0.99311	0.99820	0.25954
Cutoff III (500)	0.03944	0.96056	0.98119	0.45825
Cutoff IV (650)	0.11168	0.88832	0.92071	0.63065
Cutoff V (800)	0.20817	0.79183	0.79997	0.76085

These probabilities represent the percentage of patients with or without VTE who will have a D-dimer value less than or equal to the listed value. More formally, they are the cumulative distribution of the conditional probability. The published sensitivity for cutoff II is 99.5%, with a specificity of 27%. The published sensitivity for cutoff III is 98%, with a specificity of 47%.
ELISA = enzyme-linked immunosorbent assay; VTE = venous thromboembolism; PE = pulmonary embolism.

where CUS is considered along with a VQ scan or a CTP, we assumed that the VQ scan or the CTP is performed only if the CUS is negative.

The model was coded using Visual Basic in Excel (Microsoft Corp., Redmond, WA) and is available as an online Data Supplement (available at <http://www.aemj.org/cgi/content/full/j.aem.2006.02.011/DC1>).

Input Data. Conditional distributions on the incidence of DVT for patients with known and suspected PE were drawn from the literature^{3,20–24} and varied in sensitivity analyses. Mortality rates for patients with treated and untreated PE (10% and 22%–35%, respectively) were drawn from the literature and varied in sensitivity analysis.^{1,25,26}

Three Wells pretest categories were considered: high, moderate, and low. On the basis of several prospective studies of the Wells prediction rule, we assumed that 7% of patients would be in the high Wells category; 36%, in the moderate Wells category; and 57%, in the low Wells category.^{11–13,18} We initially assumed PE incidence in each category to be 40.6%, 16.2%, and 1.3%, respectively.^{11–13,18} Within the high and moderate Wells categories, patients for whom DVT was suspected were considered separately from those for whom DVT was not suspected, because the conditional distributions on the presence of DVT likely differ in these two populations.^{3,21} Because of limitations in the published data, we initially assumed that the pretest probability of PE for high- and moderate-Wells patients does not vary with suspicion of a DVT. By varying the conditional probability of PE in moderate- and high-Wells category patients from 0.013 to 0.95, we tested how clinical suspi-

cion of DVT, either its presence or absence, might alter the conditional probability of PE in moderate and high Wells patients. This tested the strong assumption that within a given Wells category, suspected DVT does not alter the pretest probability of PE when compared with patients without suspected DVT. By definition, patients in the low Wells category cannot have a clinically suspected DVT.

On the basis of the performance of two cutoff values (350 ng/mL and 500 ng/mL) for the VIDAS D-dimer assay,^{7,27–29} we fitted the assay's behavior to a gamma distribution over populations with and without VTE (Figure 2). This allowed us to estimate the sensitivity and specificity of three other cutoff values for the VIDAS D-dimer assay (Table 2). The gamma distribution is a probability distribution for nonnegative values. It has two critical parameters whose degrees of freedom can be specified fully with the associated sensitivity and specificity of two cutoff values.

Table 3 displays the number of patients in each VQ scan category and PE state (presence or absence as determined by pulmonary angiogram) noted in the original PIOPED study, and the associated conditional probabilities used in our analysis.^{4–6}

Initial CTV sensitivity for DVT was set at 0.8, with specificity of 0.98.^{23,30,31} Initial CUS sensitivity for DVT was set at 0.93, with specificity of 0.98.^{14,32–35} Initial CTP sensitivity was 0.9, with specificity of 0.8.^{9,10,23,36–40} We performed extensive univariate and multivariate sensitivity analysis on CTP and CTV sensitivity and specificity.

We used an average age of presentation of 55 years (the average age of subjects in the PIOPED study was 56.3 yr)⁵ and an average remaining lifetime of 25 years.⁴¹

Table 3
Original PIOPED Study Data and Computed Conditional Probabilities

VQ Scan Result	PIOPED Study Data ⁵			Computed Conditional Probabilities		
	With PE	No PE	Total	Result Frequency	Pr{Result PE ⁺ }	Pr{Result PE ⁻ }
High	103	15	118	0.133	0.408	0.024
Intermediate	104	241	345	0.389	0.413	0.380
Low	40	256	296	0.334	0.159	0.402
Near normal	5	123	128	0.144	0.020	0.194
Total	252	635	887	1.000	1.000	1.000

PIOPED = Prospective Investigation of Pulmonary Embolism (PE) Diagnosis; VQ = ventilation-perfusion.

Table 4
Quality Adjustments for Health States

Clinical Scenario	Initial QALY Value*	Sensitivity Range†
Untreated DVT and live	0.98	Not ranged
No PE and treated‡	0.95	0.92–0.98
No DVT and treated‡	0.95	Not ranged
Has DVT and treated‡	0.931	0.92–0.94
Has DVT and not treated	0.914	0.903–0.933
Has PE and treated‡	0.855	0.828–0.882
Has PE and not treated§	0.651	0.651–0.744

Because many of these values represent computations over conditional probabilities in the model such as the mortality rate of pulmonary embolism (PE) with and without treatment, the probability of PE in the presence of deep venous thromboembolism (DVT), and the probability of major complications on anticoagulation, ranging these values is often, but not always, derived by ranging those conditional probabilities.

* Among the tests considered, CT angiogram (CTA) is the only one that carries measurable risk (because of the use of injected contrast dye). On the basis of the expected incidence (0.0008 under initial assumptions) of adverse effects from the contrast injection,⁹ we incorporated a quality adjustment for patients who undergo a CTA. This quality adjustment involves a simple expected value computation involving the incidence of a serious contrast reaction (allergic or renal) and the quality-of-life multiplier that is associated with these outcomes.

† The range shown represents the value over which the parameter was ranged in one-way, two-way, and (in some cases) three-way sensitivity analyses.

‡ The quality adjustment for anticoagulation alone was taken as 0.98. This was extrapolated from patients who were on anticoagulation for a stroke without any residual neurological deficits, in whom anticoagulation usually involves agents and doses of like agents with a lower incidence of bleeding complications.⁴³

§ We assumed that the quality-adjusted life-year (QALY) value for a patient with an untreated PE who lives is 0.93, that the QALY value for an untreated patient with PE who dies is 0, and that the chance of death from an untreated PE is 0.70. Thus, under initial assumptions, we calculated $(0.93 \times 0.70) + (0 \times 0.30) = 0.651$. This value was ranged up to 0.744 by including intermediate states in which some patients with an untreated PE suffer long-term cardiopulmonary consequences (e.g., pulmonary hypertension or chronic dyspnea), whereas others do not.

establish an appropriate duration of treatment for a PE. However, treatment durations beyond six months for DVT have a declining cost-to-benefit ratio.⁸ We considered both lifetime and six-month treatment.

Outcome Measures and Data Analysis

For each strategy, we calculated net present incremental costs and QALYs by using a 3% discount rate.⁴² Dominant strategies minimized incremental cost and maximized QALYs simultaneously. Preferred strategies either maximized QALYs at a low incremental cost when compared with the lowest cost strategy or provided high but nonmaximal QALY outcomes with an incremental cost per QALY that was well in excess of \$50,000 in moving to the QALY-maximizing outcome.

Quality adjustments for some clinical states were obtained in some cases from the published literature on patient assessments of various clinical states.⁴³ When published estimates were not available for a given clinical state, we used quality adjustments for an approximately equivalent state: for example, we used the state of *anticoagulation with history of stroke and no residual neurological deficits* as a benchmark for the state of *anticoagulation without PE* (Table 4). We ordered the outcomes by preference to confirm that the quality assessments from these heterogeneous sources were consistent with a reasonable preference ordering over the prospects: for example, we verified that the state of *no DVT and under treatment* was preferred to the state of *has DVT and under treatment*. We performed extensive sensitivity analyses on the quality adjustments (Table 4).

Incremental costs (Table 5) include those monetary costs incurred beyond the initial clinical evaluation. Costs of anticoagulation were assessed from the literature.⁴⁴ Costs of the D-dimer and imaging tests were estimated on the basis of Medicare data.^{45–47} In sensitivity analysis, we analyzed the impact of high-range cost estimates (Tables 5 and 6).

In addition to incremental testing and treatment costs, we included liability payments for missed cases and for unnecessary treatment. We searched national malpractice databases to establish the average payout for missed

We performed sensitivity analysis on expected remaining lifetime to model the impact of different ages of presentation.

Treatment durations for PE and DVT were assumed to be the same. Insufficient published evidence exists to

Table 5
Incremental Costs of Testing and Treatment

Test or Clinical Scenario	Initial Assumed Value		Extreme Values Considered in Sensitivity Analysis	
	Direct Cost (\$)	Indirect Cost (\$)*	Direct Cost (\$)	Indirect Cost (\$)
CTA†	400	400	2000	0
VQ scan	700	800	2000	0
CUS	100	200	500	0
D-dimer	20	200	150	0
Treatment for PE	1250‡	NA	5000	NA
No treatment and PE (liability)	250,000	NA	1,000,000	NA
Treatment and no VTE (liability)	25,000	NA	100,000	NA

CTA = CT angiogram; VQ = ventilation–perfusion; CUS = compression ultrasound; PE = pulmonary embolism; VTE = venous thromboembolism; CTP = CTA with pulmonary portion; CTV = CTA with lower extremity venous portion; ED = emergency department.

* Indirect cost is intended to capture the incremental costs incurred as a result of increased nursing and physician care associated with different workups. On the basis of an average Medicare payment of roughly \$400 per ED visit with average length of stay per visit of 2.0 hours in a busy urban ED, we estimated the indirect cost of each test to be \$200 multiplied by the average time to obtain a result from the test (in hours).^{49,50}

† We assumed that CTA including both CTP and CTV cost \$400, whereas CTP alone cost \$200 on the basis of Medicare data.^{45,46}

‡ This is the cost of treatment discounted over the duration of therapy. For a lifetime of therapy with an estimated remaining life of 25 years, the net present value at this cost with a 3% discount rate is \$22,419.

Table 6
Summary Description of Sensitivity Analyses Performed

Parameter	Initial Value Assumed	Sensitivity Analysis Range	Two-way Sensitivity Analysis	Three- and Four-way Sensitivity Analysis
CTA costs	\$800	\$400–\$2400	i) CTA accuracy ii) prior probabilities	i) prior probabilities, CTA accuracy, treatment costs
VQ costs	\$1500	\$700–\$2000	i) prior probabilities	i) prior probabilities, CTA accuracy, treatment costs
CUS costs	\$300	\$100–\$500	i) CTA accuracy ii) prior probabilities	i) prior probabilities, CTA accuracy
D-dimer costs	\$20	\$20–\$200	i) prior probabilities	None
Treatment costs per yr	\$1250	\$1250–\$5000	i) prior probabilities ii) imaging test accuracy	i) prior probabilities, imaging test accuracy
Liability costs	\$250,000	\$0–\$1,000,000	i) prior probabilities ii) imaging test accuracy	i) prior probabilities, imaging test accuracy ii) imaging test costs, prior probabilities, CTA accuracy
QALY values	Table 4	Table 4	i) prior probabilities ii) imaging test accuracy iii) cost assessments	i) prior probabilities, cost assessments, imaging test accuracy
P{DVT ⁺ PE ⁻ ; suspect DVT ⁺ }	0.3	0.2–0.6	i) prior probabilities ii) CTA and CUS accuracy iii) cost assessments	i) prior probabilities, CTA and CUS accuracy
P{DVT ⁺ PE ⁻ ; suspect DVT ⁻ }	0.01	0.01–0.1	i) prior probabilities ii) CTA and CUS accuracy iii) cost assessments	i) prior probabilities, CTA and CUS accuracy
P{DVT ⁺ PE ⁺ ; suspect DVT ⁺ }	0.8	0.8–0.99	i) prior probabilities ii) CTA and CUS accuracy iii) cost assessments	i) prior probabilities, CTA and CUS accuracy
P{DVT ⁺ PE ⁺ ; suspect DVT ⁻ }	0.52	0.3–0.6	i) prior probabilities ii) CTA and CUS accuracy iii) cost assessments	i) prior probabilities, CTA and CUS accuracy
P{Death PE ⁺ ; no treatment}	0.3	0.2–0.35	i) prior probabilities ii) CTA and CUS accuracy iii) cost assessments	i) prior probabilities, CTA and CUS accuracy
P{Death PE ⁺ ; treatment}	0.1	0.05–0.2	i) prior probabilities ii) CTA and CUS accuracy iii) cost assessments	i) prior probabilities, CTA and CUS accuracy
CTP sensitivity, specificity	0.9, 0.98	0.7–0.95, 0.8–0.98	i) prior probabilities ii) CTV accuracy iii) CTP costs	i) prior probabilities, CTV accuracy, treatment costs
CTV sensitivity, specificity	0.8, 0.98	0.7–0.95, 0.8–0.98	i) prior probabilities ii) CTP accuracy iii) CTV costs	i) prior probabilities, CTV accuracy, treatment costs

The columns describe the sensitivity over which values were ranged and the other parameters with which they were varied in two-way and in three- and four-way sensitivity analyses.
CUS = compression ultrasound; VQ = ventilation–perfusion scan; CTA = CT angiogram; CTP = CTA with pulmonary portion; CTV = CTA with lower extremity venous portion; QALY = quality-adjusted life-year; DVT = deep venous thromboembolism; PE = pulmonary embolism.

cases of PE (average because every missed case does not necessarily result in a payout). Because such numbers are highly variable, we performed sensitivity on this cost, ranging it from \$0 to \$1 million.

We included indirect costs that were associated with the time of workup. Each test ordered engenders a cost to the ED in terms of bed occupation and additional caregiver time that is devoted to the patient. We set indirect costs (Table 5) to be proportional to the time that it takes

to complete the study and obtain the results based on data from Medicare reimbursements for ED visits.^{47–49} In the sensitivity analysis, we excluded indirect costs.

RESULTS

Results from the model under the initial assumptions are summarized in Table 7. In Figures 3–5, strategies are distinguished according to categories of D-dimer usage:

Table 7
Summary of Model Results under the Initial Assumptions

Wells Pretest Category	Testing Strategy When CTA Is an Option		Cost per QALY Gained by Moving from Cost Minimizer to QALY Maximizer (\$)	Preferred Testing Strategy When CTA Is Not an Option*		Value Measure Change When CTA Is Not an Option†	
	Cost Minimizing	QALY Maximizing		Imaging	D-dimer Use	QALY Decrease	Cost Increase
High; DVT suspected	CUS-CTP, D-dimer with Cutoff II	CTA, no D-dimer	11,937	CUS and VQ > low	Cutoff III	0.293	\$9,631
High; no DVT suspected	CUS-CTP, D-dimer with Cutoff II	CTA, no D-dimer	6,334	CUS, and VQ > low	Cutoff III	0.545	\$22,480
Moderate; DVT suspected	CUS-CTP, D-dimer with Cutoff II	CTA, no D-dimer	53,250	CUS, and VQ > intermediate	Cutoff II	0.242	\$2,954
Moderate; no DVT suspected	CUS-CTP, D-dimer with cutoff II	CTA, no D-dimer	6,232	CUS, and VQ > Intermediate	Cutoff II	0.405	\$8,772
Low	CUS-CTP, D-dimer with cutoff IV	CTA, no D-dimer	9,088	CUS	Cutoff IV	0.310	−\$2,071

CUS = compression ultrasound; VQ = ventilation-perfusion scan; CTA = CT angiogram; CTP = CTA with pulmonary portion; CTV = CTA with lower extremity venous portion; QALY = quality-adjusted life-year; DVT = deep venous thromboembolism.
 * Preferred strategies either maximize QALYs at a low incremental cost or provide high but nonmaximal QALY outcomes with an incremental cost per QALY that is well in excess of \$50,000 in moving to the QALY-maximizing outcome.
 † Value measure change shown is the change in the preferred strategy's value measure, starting with the case in which CTA is an option and then moving to the preferred strategy in which CTA is not an option.

1) no D-dimer, 2) D-dimer cutoff II, 3) D-dimer cutoff III, and 4) D-dimer cutoff IV. Each category of D-dimer usage has ten data labels for the ten different testing strategies. Cutoffs I and V were discarded because they were strictly dominated by the other cutoffs: strategies that used the other cutoffs generated more QALYs at lower cost.

Under the initial assumptions, strategies using a CTA were dominant for high–Wells category patients (Figures 3 and 4). CTP-CTV without D-dimer maximized QALYs, whereas CUS-CTP with D-dimer use minimized cost (Figures 3 and 4). Moving to the QALY-maximizing strategy of CTP-CTV with no D-dimer from the cost-minimizing strategy of CUS-CTP with D-dimer generally was preferred, with an incremental cost of less than \$12,000 per QALY gained (Table 7).

For patients in the moderate- and low–Wells pretest categories, under initial assumptions, use of CTA was also dominant. For moderate Wells patients when DVT is suspected, the incremental cost per QALY that was gained in moving to the QALY-maximizing strategy of CTP-CTV without D-dimer, from the cost-minimizing strategy of CUS-CTP with D-dimer, was higher than that in any other pretest category but still was less than \$55,000. This particular behavior of the moderate–Wells–with–DVT–suspected category was magnified in several of the sensitivity analyses but only exceeded \$50,000 per QALY gained when extremes of parameter ranges were analyzed. In all such cases, CUS-CTP with D-dimer (cutoff II or cutoff III) was the preferred strategy.

When CTA was not available or was not feasible for the patient in question, the preferred strategy for patients in high and moderate Wells categories was CUS-VQ with D-dimer (cutoff II or III), and CUS with D-dimer (cutoff IV) in low–Wells category patients (Table 7).

For moderate and high Wells categories, the dominance of CTA persisted over a broad range of reasonable values for QALY valuations, mortality rates, and different age of presentation with PE and over increased complication rates with older age of presentation, over stronger

correlation between the presence of PE and detectable DVT, over different accuracies for the clinical detection of DVT, over higher costs for anticoagulation and testing, over removal of indirect costs, and over a range of liability costs (including no liability costs).

A common criticism of prior analyses examining different diagnostic strategies for PE is that they used optimistic assessments of CTA performance.^{2,10} When we reduced the specificity of CTP to 80%, CTP-CTV with D-dimer became the dominant strategy for both high Wells patients (cutoff II is dominant) and moderate Wells patients (cutoff III is preferred). For low Wells patients, when CTP specificity was set to 0.8, moving from the cost-minimizing policy of CUS with D-dimer cutoff IV to a QALY-maximizing CTA-based strategy cost more than \$200,000 per QALY gained.

We jointly reduced CTP sensitivity to 74.1% and CTP specificity to 89.5%, as found in a recent meta-analysis.⁴⁰ In this case, CTP-CTV without D-dimer was preferred to the low-cost strategies for high Wells patients, for moderate Wells patients when DVT is not suspected, and for low Wells patients. In all cases, the incremental cost per QALY gained was less than \$34,000. For moderate Wells patients when DVT is suspected, CUS-CTA with D-dimer cutoff III was the dominant strategy. By using the lower values for CTP accuracy, we performed various two-way and three-way sensitivity analyses on other parameters (liability costs, testing and treatment costs, age of presentation, presence of DVT when DVT is suspected, association between PE and detectable DVT, and QALY adjustments). The preferred strategies were unchanged.

Perrier et al. used CTP sensitivity of 70% and specificity of 91%.² When we used these values for CTP performance, movement from the cost-minimizing strategy of CUS-CTP with D-dimer to the QALY-maximizing strategy of CTP-CTV incurred incremental costs of less than \$27,000 per QALY gained, except for in the case of moderate Wells patients for whom DVT was suspected, in whom CUS-CTP with D-dimer cutoff II was the dominant strategy.

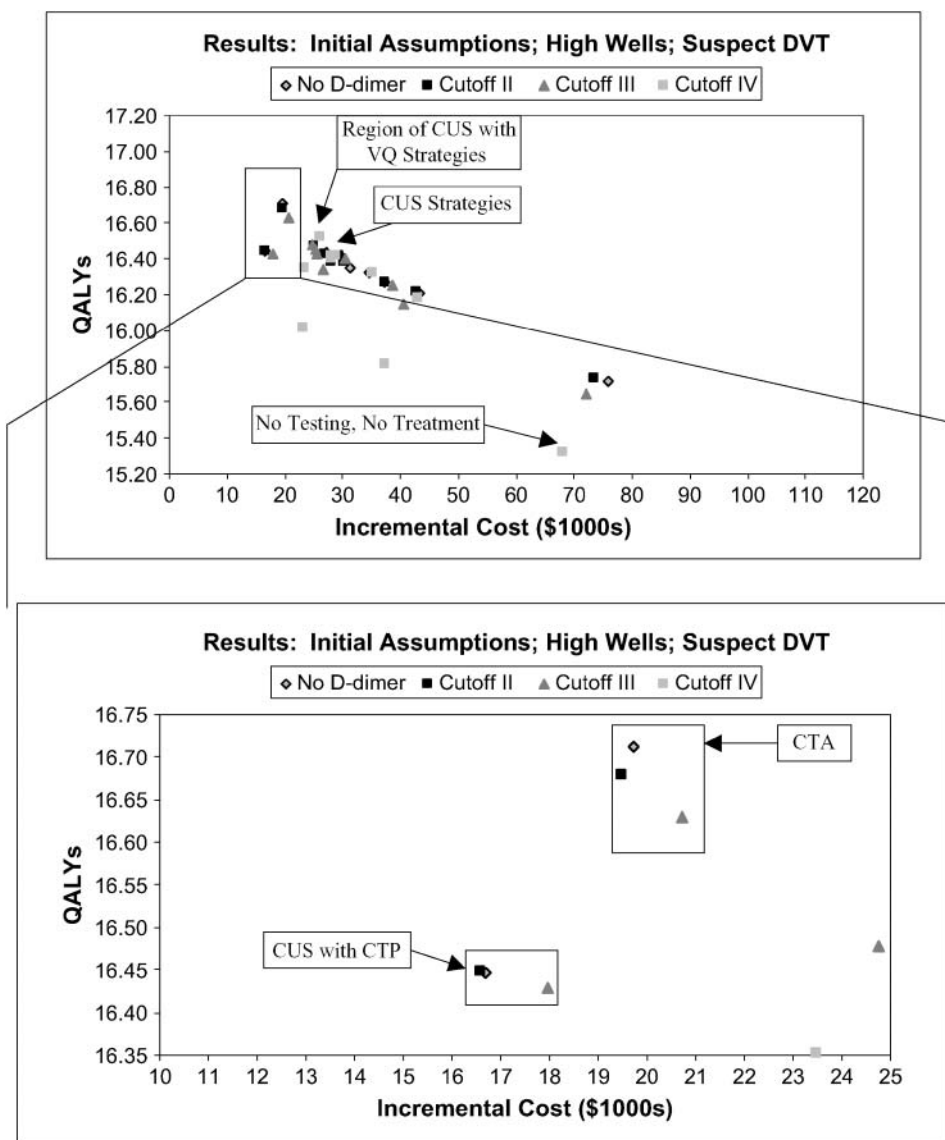


Figure 3. Results under initial assumptions for high-Wells category patients who were suspected to have deep venous thromboembolism. CUS = compression ultrasound; VQ = ventilation-perfusion scan; CTA = CT angiogram; CTP = CT angiogram with pulmonary portion; CTV = CT angiogram with lower-extremity venous portion; QALY = quality-adjusted life-year.

When we eliminated liability costs for missed VTE, moving from the cost-minimizing strategy to the QALY-maximizing strategy of CTP-CTV without D-dimer always was preferred, with incremental cost of less than \$12,500 per QALY gained. Similarly, for liability payments of up to \$1 million per missed case, movement to the QALY-maximizing strategy of CTA with no D-dimer from the cost-minimizing strategy of CUS-CTA with D-dimer (cutoff II for high and moderate Wells and cutoff IV for low Wells) incurred an incremental cost of less than \$21,000 per QALY gained. When CTA is infeasible and liability costs are high, CUS-VQ with D-dimer in moderate and high Wells patients and CUS with D-dimer in low Wells patients still were preferred, but with lower D-dimer and VQ scan cutoffs (i.e., a lower threshold for treatment).

DISCUSSION

For patients with suspected PE, the use of CTP-CTV without D-dimer is a robust strategy for diagnosis of PE under a wide range of assumptions. Although it almost never is a dominant strategy, it frequently is preferred over a wide range of assumptions, and when it is not, CTA remains part of a dominant mixed strategy with CUS and D-dimer use. When CTA is not available, D-dimer (cutoff II or III) with CUS-VQ is the dominant strategy for high- and moderate-Wells category patients, whereas D-dimer cutoff IV with CUS is the dominant strategy for low-Wells category patients.

Pessimistic assessments of CTP accuracy alter the results only at extremes and even then, they do so primarily in moderate Wells patients for whom DVT is suspected.

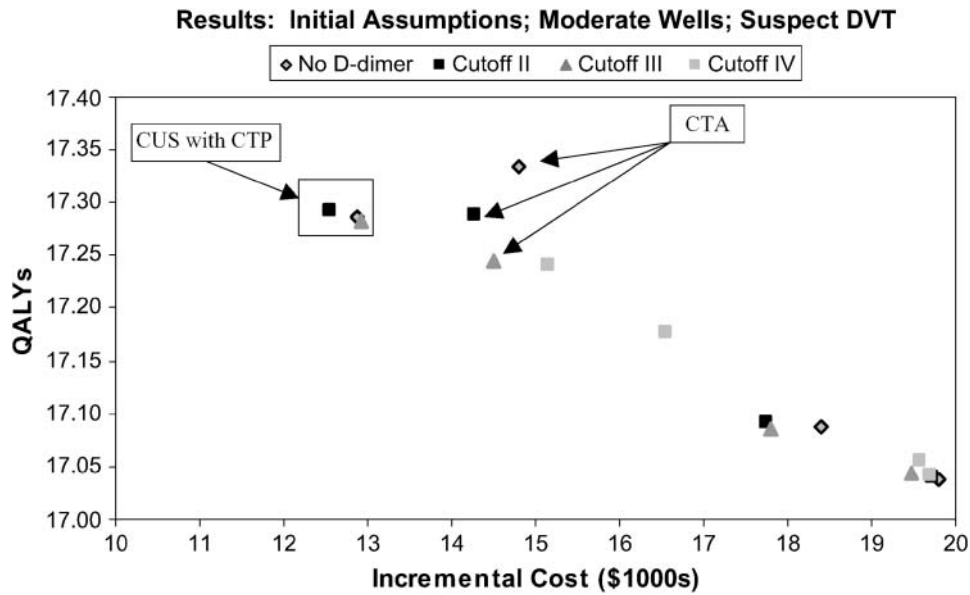


Figure 4. Results under initial assumptions for moderate-Wells category patients who were suspected to have deep venous thromboembolism (DVT). Only the preferred-strategy view appears. CUS = compression ultrasound; CTA = CT angiogram; CTP = CT angiogram with pulmonary portion; CTV = CT angiogram with lower-extremity venous portion; QALY = quality-adjusted life-year.

This is an important realization given the often-cited criticism that optimistic assessments of CTP performance bias the cost-effectiveness estimates of helical-CT-based diagnostic strategies for PE.^{2,10}

When CTA is not available, the difference in QALYs that is gained between preferred imaging strategies incorporating D-dimer cutoffs II and III was negligible in almost all cases (differences on the order of hundredths of QALYs). However, cutoff II was preferred in all but a few circumstances.

Our results agree in some respects with those obtained by Perrier et al.² Perrier et al. did not consider D-dimer with CTP-CTV but did note that CTP alone was “marginally cost-effective” in low-probability patients.² In moderate- and high-probability patients, when considering multidetector CTP use alone, they concluded that “multidetector CT-based strategies were clearly the most cost-effective,” but those strategies consisted of CTP alone or of CTP with a combination of D-dimer and CUS.² Van Erkel et al. did not consider D-dimer use but also found

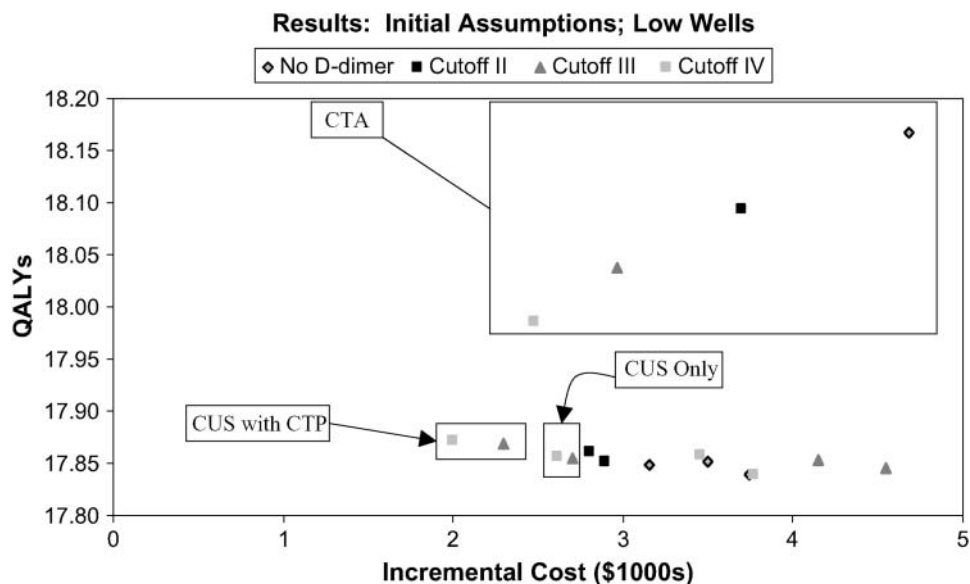


Figure 5. Results under initial assumptions for low-Wells category patients. Only the preferred-strategy view appears. CUS = compression ultrasound; CTA = CT angiogram; CTP = CT angiogram with pulmonary portion; CTV = CT angiogram with lower-extremity venous portion; QALY = quality-adjusted life-year.

that CUS followed by CTP was the most cost-effective strategy.^{9,46}

We found that in all cases studied, including multiple sensitivity analyses, CTA without D-dimer is cost-effective except in cases of extreme parameter adjustments in moderate Wells patients for whom DVT is suspected. Our model explicitly accounts for DVTs as separate but causal and related detectable entities when compared with PEs. By specifically accounting for the causal relationship between DVT and PE, we were able to consider the following mutually exclusive and collectively exhaustive states: no DVT and no PE, DVT but no PE, DVT and PE, and no DVT but PE. This allows us to more accurately measure health outcomes. For example, if a testing sequence misses a DVT in the DVT-but-no-PE state, the QALYs lost are those lost from an untreated DVT, not from an untreated PE. This is a subtle point that is captured best with a causal model. Because the relationship between symptom complexes and disease can be so highly variable, even though the population under consideration is one where PE is suspected, missing a VTE is not necessarily commensurate with missing a PE.

Some policy analysts believe that inclusion of liability costs in a cost-effectiveness analysis is detrimental to the interests of the patient. We believe that an analysis that does not incorporate the liability concerns of physicians does not acknowledge the reality for the average clinician in the United States. In a 2002 Harris Poll of American physicians, 79% of respondents indicated that they order more tests than they otherwise would, "based only on professional judgment of what is medically needed."⁵⁰ In our analysis, all dominant or preferred strategies with liability cost inclusion remained preferred when liability costs were excluded even in extensive sensitivity analyses. Inclusion of liability costs, therefore, did not alter our qualitative findings.

LIMITATIONS

Our analysis is based on the best available data. When the data from PIOPED II become available, the analysis can be refined further. A sequential decision network such as ours is an efficient and computationally tractable means by which to model the process and facilitate careful analysis.

In the absence of full data from the assay's manufacturer, the sensitivity and specificity of various D-dimer cutoff values had to be estimated with gamma distributions. Although the distributions could be fully specified with the two published cutoffs, it is possible that the shapes of the assay's "true" distributions, and therefore the sensitivity and specificity of the other cutoffs generated, are not reflected accurately by a gamma distribution.

It is too early on the basis of the above results to completely discount the importance of a quantitative D-dimer assay in the evaluation of the more general patient who presents for evaluation of chest pain or shortness of breath. Our results are robust to sensitivity analysis on a wide range of parameters but may depend critically on the breadth of the clinical situation that we assumed: diagnosis of PE in a patient who is suspected of having PE. In the common acute-care setting, PE is usually one

of several competing diagnoses. A model that is explicitly designed to consider the possibility of PE alone may not account for alterations in conditional probabilities that are generated by the diagnoses competing with PE in the standard patient who presents with symptoms that might lead clinicians to suspect the presence of a PE. Many diseases, some quite disparate in severity and organ system involvement, can cause similar symptoms. In the larger domain of patients with chest pain and shortness of breath, the ease and relatively low cost of the D-dimer assay might well make it cost-effective.

Furthermore, although many three-way sensitivity analyses and even four-way sensitivity analyses over parameter values were performed, one cannot definitively rule out the possibility of certain joint conditions not considered that might alter the conclusions. We tried to minimize this possibility with the breadth and depth of the sensitivity analyses performed.

CONCLUSIONS

Intuition alone often is unreliable for evaluating the utility of policies in complex diagnostic scenarios. Intuition might suggest that use of the relatively low-cost D-dimer assay will improve detection of PEs, thereby improving health outcomes and rendering the test unequivocally cost-effective. This is not the case. Our analysis shows that use of the D-dimer in patients suspected of having a PE and who are under evaluation for a PE generally does not appear to maximize QALYs or to reduce costs enough to be part of a cost-effective strategy for diagnosing PE in patients with suspected PE. Extending this conclusion to the more general category of patients presenting with shortness of breath or chest pain is not yet justified.

The authors thank John Cavallaro, doctoral candidate in Decision and Risk Analysis at the Stanford University School of Engineering, for his helpful advice and donation of both time and references and thank Dr. Doug Owen for advice and donation of time.

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