Rethinking Testing for Pulmonary Embolism: Less Is More

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SEE RELATED ARTICLE, P. 613.

Since Virchow’s first description of pulmonary embolism, experts and clinicians have struggled with the diagnosis and treatment of this common condition. In Virchow’s time, the absence of diagnostic tests made pulmonary embolism a late diagnosis, one suspected just before death and often confirmed on autopsy. Today, pulmonary angiography, ventilation: perfusion nucleotide scanning, and most recently, computed tomographic (CT) pulmonary angiography have dramatically changed this. We now regularly diagnose pulmonary embolisms so different, both clinically and anatomically, from those described by Virchow that we must ask ourselves whether the 2 conditions are clinically distinct. In the modern era, pulmonary embolisms that were routinely missed are now the predominant type diagnosed, and overtesting to detect these events is rampant. Numerous contemporary studies have attempted to reduce testing for pulmonary embolism; however, the medical effect and root causes of this problem have not been widely examined.

THE MODERN SHIFT

Two studies are apt bookends for the modern era, illustrating a stark shift in the approach to pulmonary embolism. In 1959, Barritt and Jordan published the first and only trial testing the efficacy of heparin for clinical pulmonary embolism. Heparin was seen as risky, and with no confirmatory imaging available the diagnosis and treatment of pulmonary embolism was considered late and infrequently. Subjects were typically hypotensive, with acute right-sided heart failure or hemoptysis by the time of study enrollment, and nearly 20% died (6/35). Fifty years later, Kline et al performed an observational study of emergency department (ED) testing for pulmonary embolism. In this contemporary investigation, the diagnosis was considered early and often. However, despite more than 8,000 patients considered and tested for pulmonary embolism and nearly 500 pulmonary embolisms reported, just 0.2% of this modern cohort (13/8,138) died because of pulmonary embolism (JA Kline, written communication, 2011).

This roughly 100-fold difference in mortality between studies is not likely due to treatment. Although the study by Barritt and Jordan is often cited as evidence that anticoagulation decreases mortality from pulmonary embolism, the trial involved no placebos and no blinding, enrolled just 35 subjects, and relied on unconfirmed clinical diagnoses. In addition, a Cochrane review discovered only 1 controlled trial testing anticoagulation for known venous thromboembolism. The trial was performed on 90 ambulatory patients with deep venous thrombosis and compared heparin and warfarin with an oral nonsteroidal anti-inflammatory drug. There was no benefit in clot resolution, prevention of pulmonary embolism, or mortality. Thus, the efficacy of anticoagulation remains questionable, and the marked disparity between the 1960 results obtained by Barritt and Jordan and the 2008 results obtained by Kline et al is unlikely to be due to treatment. The difference is better explained by a more conspicuous disparity: the patients.

In the current issue of Annals, the thorny issue of patient selection for pulmonary embolism is the object of yet another study, this one using a computer algorithm to reduce testing. The algorithm was moderately successful in reducing testing but led to considerable physician dissatisfaction, results that have interesting implications for clinical practice and informatics. But these findings point to a broader and more bracing reality: it will take more than a computer algorithm to reimagine testing for pulmonary embolism.

MEDICAL HARMS AND BENEFITS OF TESTING

To chart the future of pulmonary embolism testing, we must first gauge the current arithmetic. Harms and benefits in medical testing often coexist in a fragile balance, and pulmonary embolism is no exception. Measurable medical harms of testing are fairly concrete and include cancer caused by imaging, renal damage from contrast, and iatrogenic complications of treating patients with positive results. The benefits, however, are more ticklish. When patients with possible pulmonary embolism present to an outpatient environment with physiologic compromise (hypotension, hypoxia, etc), the importance of establishing a diagnosis seems clear. But the bulk of pulmonary embolism testing in outpatient settings is conducted in physiologically normal patients, for whom the current pulmonary embolism poses no threat. Rather, what chills the marrow of clinicians in such patients is “the next one,” a fatal or severe second pulmonary embolism. With this conception of
benefit in mind, it is possible to estimate how often just such an event will occur and thus to compare benefits with harms in pulmonary embolism testing.

Calculating Harms and Benefits

For calculating an estimated aggregate effect of testing for pulmonary embolism, we use a “balance sheet” approach that calculates and juxtaposes patient-oriented benefits and harms (see Appendix E1 for rationale and calculations; available online at http://www.annemergmed.com). As a primary data source to represent current testing practices for pulmonary embolism, we use the 2008 prospective validation study of the Pulmonary Embolism Rule-out Criteria decision aid by Kline et al, the largest and most rigorous contemporary investigation of pulmonary embolism testing in the ED. The study involved 13 EDs in 2 countries (United States and New Zealand) and was structured to identify and follow all patients tested for pulmonary embolism, most commonly using D-dimer (74% of subjects) and CT pulmonary angiography (51%). Follow-up was excellent and enrollment of tested patients typically exceeded 85%. These data appear to be the most valid representation of contemporary pulmonary embolism testing in the ED.

Benefits. The first step in outlining the benefits of testing is to determine the number of tested persons with detectable pulmonary embolism. In the pulmonary embolism rule-out criteria validation study, 7% of all patients were found to have imaging results positive for pulmonary embolism. This number, however, includes false positives and omits false negatives. To find true prevalence, we estimated value sets with 2×2 tables, using known sensitivity and specificity ranges for CT, the most common imaging test, and applying these to the pulmonary embolism rule-out criteria data set. The true prevalence of pulmonary embolism will be notably lower than the reported number of positive test results because the majority of tested patients are disease negative. Therefore, unless specificity reaches greater than 99%, false positives will outnumber false negatives, ultimately decreasing a true prevalence estimate. Results of meta-analyses suggest that CT pulmonary angiography sensitivity ranges from 74% to 88% and specificity from 90% to 94%.

The point of these estimations is 2-fold. First, by determining the number of true pulmonary embolisms we determine the number of persons who could be helped by a strategy that vigorously seeks to identify and treat all pulmonary embolisms. Second, by determining the number of pulmonary embolisms missed by such a strategy (false negatives) and observing that one person in the pulmonary embolism rule-out criteria validation study died of a pulmonary embolism during follow-up after a negative test result, we can derive a rough estimate of the consequences of missed pulmonary embolisms. For all calculations, we use the most optimistic projections of anticoagulant efficacy, assuming that 80% of fatalities can be averted with treatment. According to our 2×2 table showing the highest rate of potential fatalities, we estimate that 6 deaths would have occurred in the overall cohort had there been no testing, 5 of which were prevented. We then use credible intervals to express a margin of error based on the highest and lowest outcome rates observed in our calculations. In the case of deaths prevented by testing, we further extend the upper boundary of the credible interval to presume that we could be underestimating benefits of anticoagulation by a factor of 100%.

In estimating the number of nonfatal pulmonary embolism events prevented, we do not include persons who return with an uncomplicated pulmonary embolism requiring only standard treatment. In such a case, there is no medical harm, only a temporal displacement of treatment. We consider there to be harm because of a missed diagnosis when a complicated pulmonary embolism with abnormal vital signs requiring ICU care occurs. Prospective prognostic data suggest that approximately 20% of complicated pulmonary embolism patients die. Using our estimate of fatal events, we therefore calculate that 24 complicated pulmonary embolism patients survive for every 6 fatal pulmonary embolisms. For the Table, we again adjust the denominator to a value of 10,000 for simplicity, and for the credible interval we incorporate alternate values from the lowest estimates in our 2×2 tables. The upper limit of the credible interval is based on the assumption that we could be underestimating benefits by a factor of 100% overall.

Harms: contrast-induced nephropathy. Most existing data on the topic of contrast-induced nephropathy are from coronary catheterization data sets. We are aware of 3 prospective data sets of moderate to high quality examining this question in the ED, all from 1 author group (JA Kline, written communication, 2011). Estimates of acute renal failure ranged from 0% to 2% and death from 0% to 1.2%. Our point estimate represents the value from the highest-quality data set and is consistent with earlier findings from coronary catheterization settings. The credible interval represents the lower and upper boundaries of the lowest and highest estimates from these studies.

Harms: cancers caused by CT pulmonary angiography. We used a 51% rate of CT pulmonary angiography imaging, a 2:1 female to male ratio, and a mean age of 49 years, as observed in the pulmonary embolism rule-out criteria data set. Radiation doses are from published estimates of exposure when CT pulmonary angiography is performed to detect pulmonary embolism. Within these parameters the attributable increase in cancer due to CT pulmonary angiography amounts to 1 case per 2000 persons tested for pulmonary embolism or 5 cases per 100,000, half of which are projected to be fatal. Credible intervals are based on interquartile ranges for radiation exposure per CT pulmonary angiography.

Major hemorrhages caused by anticoagulation. After a diagnosis of pulmonary embolism, patients are typically administered anticoagulation for 6 months or more. Published 6-month bleeding risk is 2.8%, according to a meta-analysis examining major hemorrhage during oral anticoagulant therapy. In the pulmonary embolism rule-out criteria data set,
using our middle estimate of true pulmonary embolism prevalence and adjusting to a denominator of 10,000, we expect positive test results leading to treatment in 590 patients, 2.8% of whom will experience a major hemorrhage. This results in 14 nonfatal hemorrhages and 3 fatal hemorrhages. Credible intervals are based on the highest and lowest hemorrhage rates from existing data sets.

AGGREGATE HARM-BENEFIT INFLUENCE

The results of these calculations suggest that testing for pulmonary embolism in the pulmonary embolism rule-out criteria study prevented 6 deaths because of pulmonary embolism and 24 major, nonfatal pulmonary embolism events. In comparison, testing also caused 36 deaths and 37 nonfatal major medical harms (Table). Although the exact value of each input may be debatable and will vary with patient characteristics, it is clear that testing is unlikely to produce a net benefit. Our estimates of harm are conservative and our estimates of benefit are quite optimistic. We did not account for cumulative effects of radiation among patients exposed to more than 1 CT pulmonary angiography, and we halted all hemorrhage risk calculations at 6 months of anticoagulant exposure. We also presumed an optimistic 80% efficacy of anticoagulation in reducing mortality, and we accepted a fatality rate of 3.8% for pulmonary embolisms missed by testing, a number considerably higher than previous reviews have found.27,28 Despite these exuberant presumptions, we conclude that the current model of testing causes roughly 6 times as many deaths as lives saved.

CAUSES FOR A PREPONDERANCE OF HARM

From Virchow’s earliest reports, physicians have been taught that pulmonary clot is invariably perilous and pathologic, and the current model of disease presumes this to be true. This is a problematic extrapolation because Virchow had no control group. He could not compare the lungs of healthy individuals

Table. Benefits and harms of testing for pulmonary embolism in the PERC study.

<table>
<thead>
<tr>
<th>Benefits per 10,000 (Credible Interval)</th>
<th>Harms per 10,000 (Credible Interval)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preventable PE complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>24 (5–48)</td>
<td>Fatal events extrapolated from expected CTA miss rate and the finding that 1 patient with a negative test result died because of PE during follow-up11; treatment of PEs is estimated to have prevented 80% of deaths,10 so 6 deaths were prevented in total; nonfatal estimates derived from a large prognostic database of PEs, suggesting that there are approximately 4 nonfatal serious PEs for every fatal PE.</td>
</tr>
<tr>
<td>Fatal</td>
<td>6 (1–12)</td>
<td></td>
</tr>
<tr>
<td><strong>Renal failure (contrast dye)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>20 (0–40)</td>
<td>Mitchell et al23 reported the most rigorous and largest examination of contrast dye effects associated with CT examinations in the ED for 633 subjects. Contrast-induced nephropathy (&gt;25% increase in creatinine level) occurred in 11%, renal failure in 1%, and death associated with renal failure in 0.7%.</td>
</tr>
<tr>
<td>Fatal</td>
<td>30 (0–60)</td>
<td></td>
</tr>
<tr>
<td><strong>Cancers induced (radiation)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>2.5 (1.5–3.5)</td>
<td>Smith-Bindman et al24 projected cancer rates based on BEIR VII phase 2 projections, using age- and anatomic CT–specific estimates. Projections extracted here presume the PERC validation cohort11 demographics of mean age 49 y, two thirds women; all estimates presume CT chest with contrast maximized to detect pulmonary embolism. Credible intervals are interquartile ranges based on published radiation dose variations.</td>
</tr>
<tr>
<td>Fatal</td>
<td>2.5 (1.5–3.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Major hemorrhage (anticoagulation)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>14 (9–27)</td>
<td>Calculations examine effects of 6 mo of anticoagulation; hemorrhage rates based on study by Dahir and Loewen,26 with 7 included studies (&gt;10,000 subjects, 4 prospective); overall data quality poor, range of rates 1.6%–5.8%; restricting to 3 highest-quality data sets, estimate is 11 nonfatal and 2 fatal.</td>
</tr>
<tr>
<td>Fatal</td>
<td>3 (2–7)</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>24 (5–48)</td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>6 (1–12)</td>
<td></td>
</tr>
</tbody>
</table>

PE, Pulmonary embolism; CTA, CT pulmonary angiography; BEIR, Biological Effects of Ionizing Radiation; PERC, pulmonary embolism rule-out criteria.

*Presumes 51% CT scan rate based on PERC11; 12 inhospital PE deaths (all treated) were excluded from harm-benefit analyses because of obvious physiologic compromise at presentation (JA Kline, written communication, 2011). Details of all calculations are provided in Appendix E1, available online at http://www.annemergmed.com.
with those examined in his morgue, and he could not survey the behavior of pulmonary clot in the living state. With hindsight, and with the advantage of nearly 2 centuries of research, it has become evident that Virchow’s view was doubtful.

Autopsy studies,29-31 data reviews,32-36 and editorials37,38 not only conclude that pulmonary embolism is overwhelmingly nonfatal but also suggest that small clot is both transient and normal. Although patients with physiologic derangements are at increased risk of adverse outcomes,19,39-41 in the physiologically normal individual the benefit of diagnosing pulmonary embolism is highly questionable because the spectrum of pulmonary embolisms we diagnose with modern technology includes a preponderance of benign, physiologically harmless clots. There are numerous examples of data that support this postulate. One autopsy study reported a 20% prevalence of pulmonary embolism among individuals who died instantly because of accidental trauma29; 2 others suggest that, despite a 5% or lower rate of clinical pulmonary embolism, routine autopsy revealed pulmonary embolism in 64% and 90% of cases.30,31 Among patients in the only modern controlled trial of anticoagulation to our knowledge, half of patients with deep venous thrombosis had asymptomatic pulmonary embolism on routine imaging studies13; the validation results of a prognostic risk score for pulmonary embolism found that patients without physiologic compromise had a mortality rate of zero,19 and in a recent registry of more than 2,000 pulmonary embolisms from the outpatient and ED environments, just 1% were fatal overall.40 These findings do not change the fact that pulmonary embolism can be deadly. But they clarify an emerging reality: when the goal is to detect all clots, the harms of testing outpace the threat of disease.

CONSTRUCTING A SOLUTION

To improve our future, we must confront our past. A stirring narrative (“pulmonary embolism is deadly”) and an unsubstantiated faith in therapy have led to aggressive testing, despite an evidence base that does not support this approach. Thus, we could begin by confronting the knowledge gap: We have not yet defined which patients with pulmonary embolism are at risk for a “next one” event, nor have we established whether anticoagulation is effective therapy for pulmonary embolism. The investigation by Barritt and Jordan10 would not be considered important or publishable today, and the study by Nielsen et al.,13 the only well-controlled trial of anticoagulation of which we are aware, suggests no benefit to anticoagulation. In addition to being unproven, this modality is risky and complicated and consumes substantial resources, making placebo-controlled efficacy trials both essential and ethical. Research to improve characterization of clot burden in healthy controls and high-quality studies of prognosis will also help us learn to identify those pulmonary embolisms that may benefit from diagnosis and treatment.

Risk to the patient is not the only risk that has driven testing for pulmonary embolism. The clinician’s instinct to forgo testing has often been trumped by a stronger instinct, self-protection. Particularly in the United States, legal jeopardy, an ever-present threat, has forced us to codify poor practice, creating a false “standard of care” that few believe in and that the evidence does not support. To correct this, clinicians and researchers can, by spoken and written word, testify against this false standard. A powerful first step would be to broadly acknowledge that testing under the current paradigm is a dubious, largely harmful endeavor and that there is, and must be, an acceptable “miss” rate. In the meantime, we can support medical liability reform that will allow physicians to comfortably bypass testing in situations in which it is likely to produce more harm than benefit.

In the outpatient setting, patients without physiologic compromise (no vital sign derangements and no clinically apparent physiologic compromise) are a decidedly low-risk subgroup. Evidence suggests that risk among patients tested in the ED is currently low enough that harm trumps benefit in testing. Thus, for any group with a risk profile lower than that of the overall group, such as individuals without physiologic compromise, it is sensible to forgo laboratory testing (ie, D-dimer) or imaging of any kind. When pulmonary embolism is present in this group, data indicate that patients have a mortality approaching zero,19 and harm-benefit analysis strongly suggests that testing such patients will result in more fatal events than not testing. Furthermore, studies have validated the safety of applying D-dimer testing in patients with moderate risk levels (up to a Wells score of 4).14,41 With the omission of testing for patients with no physiologic compromise and D-dimer to potentially avoid CT pulmonary angiography in individuals at moderate risk, safe reductions in testing can be achieved.

Despite the aggregate reduction in morbidity and mortality that will accompany reduced testing, there will also be rare individuals with this approach who die suddenly of an undiagnosed or missed pulmonary embolism. Such an event must be judged in the context of the aggregate effects of testing in a population of similar patients, rather than with the inevitable bias of case-based hindsight.42,43

CONCLUSION

The diagnostic approach to pulmonary embolism and our view of the condition are at a crossroads. We are testing too much and at risk of compromising our oath. The emphasis on pursuing and treating this diagnosis should shift to a group at higher risk of clinically important outcomes, patients with physiologic compromise. With a new emphasis on research for both therapy and diagnosis, and vigilant monitoring of outcomes, we can reduce testing while increasing benefit. Less will be more.

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REFERENCES


APPENDIX E1.

Explanation of calculations used to create the evidence table.

Benefits of Identification and Treatment (Deaths Prevented)

It is not a trivial exercise to determine the number of persons in a population who have pulmonary embolism. The fundamental problem is the lack of an operational definition of pulmonary embolism. Everyone would agree that a saddle embolus causing right-sided heart failure and easily detected by multiple diagnostic modalities is indeed a pulmonary embolism. But what about a subsegmental pulmonary embolism observed on computed tomography (CT) only that is producing no detectable cardiopulmonary abnormality and is too small to be reliably detected? Without a clearly outlined operational definition of pulmonary embolism, the determination of sensitivity and specificity is problematic: sensitivity and specificity for detecting what? For our operational definition, we calculated the number of detectable pulmonary embolisms. We began with the data set from the pulmonary embolism rule-out criteria validation study for reasons outlined in our article. However, we assumed that the performance characteristics of the diagnostic imaging used in that study were not perfect (accepting the reported pulmonary embolism prevalence from pulmonary embolism rule-out criteria, which was largely based on CT imaging results, would presume that the results of CT imaging were 100% accurate). Rather, we presumed that the performance of CT in the pulmonary embolism rule-out criteria was consistent with performance in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED)-II study, the most recent highly rigorous evaluation of CT for the diagnosis of pulmonary embolism. Thus, we started with the number of positive CT results (the true positives + false positives) in the pulmonary embolism rule-out criteria and then estimated the number of these that were true positives by applying the reported test characteristics from PIOPED-II.1 In the pulmonary embolism rule-out criteria validation study, there were 480 positive test results for pulmonary embolism, yielding a 7% prevalence of positive test results in the sample.2 The 7% figure represents the sum of true-positive and false-positive results and does not include false-negative results (pulmonary embolisms missed by the test).

Using the test characteristics reported in the PIOPED-II study, we then adjusted the observed values to derive an estimate of true values. We did this by creating a 2×2 table containing 480 positive test results (as reported in pulmonary embolism rule-out criteria) and assumed that CT actually performed with the sensitivity and specificity reported in PIOPED-II (83% and 96%, respectively) (Table E1).

Table E1. 

<table>
<thead>
<tr>
<th></th>
<th>Pulmonary Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Positive</td>
<td>162</td>
</tr>
<tr>
<td>Negative</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>188</td>
</tr>
<tr>
<td>Test performance</td>
<td>0.83</td>
</tr>
<tr>
<td>Pulmonary embolism prevalence</td>
<td>0.023</td>
</tr>
</tbody>
</table>

According to these data, we conclude that 2.3% of all subjects had a pulmonary embolism and that the positive predictive value of a positive test result was 34% (162/480). Using these estimates, we can then calculate the aggregate benefits of testing for pulmonary embolism.

To generate a credible range of values, we also adjusted our prevalence estimate upward to be between the 7% positive value in the pulmonary embolism rule-out criteria and the 2.3% prevalence value found above. We did this because we believed that it may be intuitively difficult to believe that the true prevalence is this low. Therefore, we roughly double the lower estimate to 4.5% and set the specificity of CT to 98%. We cannot fully achieve the value set with a lower specificity because of the increased number of false-negative results, which results in a decreased number of false-positive results (because the total number of positive results is fixed at 480). At the same time, there are greater numbers of false-negative results because of the increased true-positive results, which decreases the number of true-negative results (because the total number of negative test results is fixed at 7,658). Thus, 2 numbers used to calculate sensitivity (true-positive and false-negative results) both decrease, but the numerator decreases proportionally more than the denominator (because the denominator is considerably larger), and consequently the specificity must increase if sensitivity is to be maintained.

Table E2 shows the value set generated from this second estimate of prevalence (4.5%). This table produces a positive predictive value of 64% (305/480).

Table E2.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Positive</td>
<td>305</td>
</tr>
<tr>
<td>Negative</td>
<td>61</td>
</tr>
<tr>
<td>Total</td>
<td>366</td>
</tr>
<tr>
<td>Test performance</td>
<td>0.83</td>
</tr>
<tr>
<td>Pulmonary embolism prevalence</td>
<td>0.045</td>
</tr>
</tbody>
</table>

We generated a final table by maintaining the prevalence of 4.5% and specificity of 96% but allowing the sensitivity to float. The resulting Table E3 has a sensitivity of 49%. This table has a positive predictive value of 38% (180/480).
The point of the exercise is 2-fold. First, by determining the number of true-positive results, we determine the number of persons who could be detected and thus helped by a strategy that vigorously seeks to identify and treat all pulmonary embolisms. Second, by determining the number of pulmonary embolisms missed by such a strategy (false-negative results) and observing that one test-negative person in the pulmonary embolism rule-out criteria validation study died of a pulmonary embolism during the follow-up period, we can estimate the consequences of a missed pulmonary embolism.

Using Table E1, we have 162 detected pulmonary embolisms and 26 missed pulmonary embolisms. In the pulmonary embolism rule-out criteria validation study, 1 person died of a pulmonary embolism after a negative test result. Because this person presumably came from the 26 persons who were missed, then 3.8% of missed pulmonary embolism patients died in this calculation. If we apply this same percentage to the 162 persons with a pulmonary embolism that was successfully detected, we would expect that 6 deaths would have occurred had no testing been performed (in other words, had all of the pulmonary embolisms been missed). Among these 6 deaths, 80%, or 5, could presumably have been averted with treatment.

Using identical algebra on the numbers in the Tables E2 and E3, we calculate 4 additional deaths with the Table E2 and 1 additional death with Table E3. To be conservative, we use the largest number in our balance sheet (adjusting all numbers to a population of 10,000 rather than 8,138) but incorporate the other results into the lower limit of the credible interval. The upper limit of our interval is based on an empiric assumption that we may be underestimating by as much 100%.

Finally, we determine the number of nonfatal important complications prevented. We do not include persons who return with an uncomplicated pulmonary embolism that requires standard treatment because they are receiving exactly what they would have received had their disease been detected initially, only with a delay. We therefore base these calculations on patients who return with a complicated pulmonary embolism and with abnormal vital signs, requiring ICU care. If 6 persons had fatal pulmonary embolism and 20% of persons with serious pulmonary embolisms died, then there are 30 persons who had a serious pulmonary embolism, 24 of whom survived. Again we adjust this value to a denominator of 10,000 and incorporate alternate values into the lower limit of the credible interval. The upper limit of the credible interval is based on the assumption that we could be off by a factor of 100% overall.

Contrast-Induced Nephropathy, Renal Failure, and Death Associated With Contrast-Induced Nephropathy

Most existing data on the topic of contrast-induced nephropathy are from coronary catheterization data sets or randomized trials of agents designed to reduce nephropathy. The former data sets reflect renal failure rates that may be higher than values expected in an outpatient pulmonary embolism testing environment. The latter tend to include patients at very low risk of serious outcomes and therefore renal failure rates (typically zero) that are likely lower than might be expected in the ED environment. We therefore sought original data from ED environments and found 3 prospective data sets examining this question, all from 1 author group.

The first of these studies is an observational examination of patients undergoing contrast-enhanced CT in the ED. As a secondary analysis of a post hoc question, the sample was analyzed for existing pre- and postcontrast renal function assessments, and these were found to have been performed in 354 (29%) of 1,224 subjects. Renal failure was not operationally or rigidly defined and follow-up was moderate. The second study was powered, designed, and performed specifically to identify “severe renal failure,” defined as new dialysis or creatinine level increase greater than 3.0 mg/dL because of contrast among ED-ordered contrast-enhanced CT examinations. The data set includes improved follow-up and a substantially greater proportion of before/after assessments of renal function (70%) among the study sample. A third, unpublished subgroup analysis from the second data set focuses entirely on CT examinations for pulmonary embolism in the ED (JA Kline, written communication, 2011).

In the first of these data sets, contrast-induced nephropathy (>25% increase in creatinine level because of contrast) occurred in 4% of patients and renal failure was not identified in any subject. In the second study, contrast-induced nephropathy occurred in 11% of patients, whereas severe renal failure occurred in 1%, or 6/633 subjects. Five of 6 subjects with renal failure died, and 4 of these were independently adjudicated to have died at least in part because of renal failure. Thus, 0.7% (4/633) of the total sample died in association with the administration of contrast dye.

The third (unpublished) subgroup analysis examined 174 subjects who underwent contrast-enhanced studies exclusively for the detection of pulmonary embolism. In this analysis, 3 of 174 subjects (2%) experienced severe renal failure or death believed to be due to renal failure, including 1 renal failure without death and 2 renal failures with death. Mortality associated with contrast-induced nephropathy in this sample was 1.2% (JA Kline, written communication, 2011).

In summary, we find that the values observed in the highest-quality prospective data for this question suggest 1% for severe renal failure and 0.7% for death caused in part or entirely by renal failure. Our point estimate represents the middle value from these 3 investigations, and this study is also the highest-quality data set

<table>
<thead>
<tr>
<th>Test result</th>
<th>Present</th>
<th>Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>180</td>
<td>300</td>
<td>480</td>
</tr>
<tr>
<td>Negative</td>
<td>187</td>
<td>7,471</td>
<td>7,658</td>
</tr>
<tr>
<td>Total</td>
<td>367</td>
<td>7,771</td>
<td>8,138</td>
</tr>
</tbody>
</table>

**Table E3.**

Pulmonary Embolism

<table>
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<th>Test result</th>
<th>Present</th>
<th>Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>180</td>
<td>300</td>
<td>480</td>
</tr>
<tr>
<td>Negative</td>
<td>187</td>
<td>7,471</td>
<td>7,658</td>
</tr>
<tr>
<td>Total</td>
<td>367</td>
<td>7,771</td>
<td>8,138</td>
</tr>
</tbody>
</table>

**Test performance**

<table>
<thead>
<tr>
<th>Test result</th>
<th>Present</th>
<th>Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>0.49</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0.045</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pulmonary embolism prevalence**

**Table E3.**
of the 3. The credible interval covers the lower bound of the study with the lowest incidence and the upper bound from the study with the highest estimate. These point estimates are consistent with angiographic data examining the incidence of contrast-induced acute renal failure rates (defined as new dialysis) that exhibit a range of 0.5% to 1.1%. 7

Cancers Caused by CT Radiation Exposure in the Pulmonary Embolism Rule-Out Criteria Validation Cohort

49 y mean age, 8,138 subjects
2/3 female = 5,453 female, 2,685 male
51% of cohort exposed to CT angiography = 4,127
CTs = 2,765 female, 1,362 male
CT-induced cancer rate11 = 1/775 female patients (interquartile range [IQR] 1/520, 1/1,025), 1/1,552 male patients (1/1,020, 1/2,000)

From pulmonary embolism rule-out criteria derivation
= 3.6 (IQR 2.7 to 5.3) female cancers, 1 (IQR 0.7 to 1.3) male cancer
Cancers induced in 10,000 persons tested
= 5 total, 4 female patients, 1 male patient
Per BEIR-VII, we can expect that half of these cancers will be fatal.12
Thus, 2.5 nonfatal and 2.5 fatal cancers per 10,000.
Credible intervals are interquartile ranges based on radiation dose variations.

Bleeding From Anticoagulation—Dahri, 2006 Meta-analysis

Data in meta-analysis:
Landefeld = 32/184×18 months, or 5.8%/6m (wt = 1.7%) = weighted (5.8×0.017) = 0.099
Beyth, Wells, Aspinall = 82/1755×18m, or 1.6%/6m (16.3%) = (1.6×0.163) = 0.26
Kuijer = 19/780×3 months, or 4.9%/6m (7.2%) = (4.9×0.072) = 0.35
Gage = 67/1535×10 months, or 2.6%/6m (14.2%) = (2.6×0.142) = 0.37
Shireman = 95/6533×3 months, or 2.9%/6m (60.1%) = (2.9×0.601) = 1.74

Aggregate weighted mean hemorrhage rate for 6 months anticoagulation = 2.819 = 2.8%
Approximately 20% of hemorrhages result in death; thus, 0.6% total fatality rate.13,14
5.8% of 590 = 34 events, 7 fatal (highest observed rate)
2.8% of 590 = 17 events, 3 fatal (pooled data overall)
1.8% of 590 = 11 events, 2 fatal (highest-quality data only, homogeneous enough to pool)

1.6% of 590 = 9 events, 2 fatal (lowest observed rate)

According to the Kline data, we anticipate that testing 10,000 persons will produce 590 positive scan results; hence, 590 persons receiving anticoagulant therapy. We anticipate 17 events, 4 fatal, with the pooled estimate, with a credible interval using the highest and lowest observed values from all data sets.

REFERENCES