# APPLYING EVIDENCE TO CLINICAL DECISIONS: CASE STUDY OF A PATIENT WITH POSSIBLE PULMONARY EMBOLUS

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The application of evidence-based medicine (EBM) to practice requires many skills, including the ability to define a focused clinical question, to competently and efficiently search the medical literature, and to critically appraise relevant articles. In addition, the evidence obtained must be carefully evaluated in the context of the individual patient, with consideration for the patient's values and preferences. This article uses a common clinical scenario—a patient who presents with a possible pulmonary embolus (PE)—to demonstrate the fundamental skills required to integrate EBM into clinical practice. In the following scenario, imagine that you are a clinical faculty member supervising a general medicine service at a teaching hospital. An intern has just evaluated this patient upon her admission to the hospital.

## Case Presentation

A 61-year-old woman is admitted for cellulitis at the site of a recent left mastectomy incision. In addition, she reports a 4-day history of nonproductive cough, shortness of breath, pleuritic chest pain, and transient left calf pain. She denies lower extremity redness, warmth, and edema. She has no known cardiac or pulmonary disease. Her past medical history is significant for bilateral breast cancer and remote upper extremity venous thrombosis following a crush injury to her right arm.

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Abnormal physical examination findings include a localized area of erythema, warmth, and tenderness overlying the left mastectomy scar. Results of cardiopulmonary and extremity examinations are normal. Laboratory evaluations performed in the emergency department reveal a hemoglobin level of 10.8 g / dL. Electrolytes, chest radiograph, and electrocardiogram are normal. Bilateral lower extremity duplex compression ultrasonography reveals no evidence of deep venous thrombosis (DVT).

## Clinical Decision #1: Making the Diagnosis

You are concerned about the possibility of a PE and wonder whether a negative lower extremity ultrasound is sufficient to exclude the diagnosis of PE. You decide to perform a literature search to answer your question.

### Framing the Clinical Question

Before beginning a search, a well-built clinical question should be formulated [1]. The first component of a clinical question defines the patient or problem of interest (patient with suspected PE). The second component defines the intervention (duplex compression ultrasonography). The third component, if applicable, defines the comparison intervention (a "gold standard" such as pulmonary angiography). The final component defines the outcome measure (diagnosis of PE).

You phrase your well-built clinical question as follows: "In a patient with suspected PE, how useful is lower extremity compression ultrasonography, compared with pulmonary angiography, for the diagnosis of PE?"

### Searching the Literature

The search engine available to you is PubMed (*see Appendix on page 28 for additional resources*). PubMed contains predefined filters that can be accessed through the "Clinical Queries" link on the main menu [2]. You select the "diagnosis" and "specificity" buttons to find studies that assess predictive value (Figure 1). (Detailed

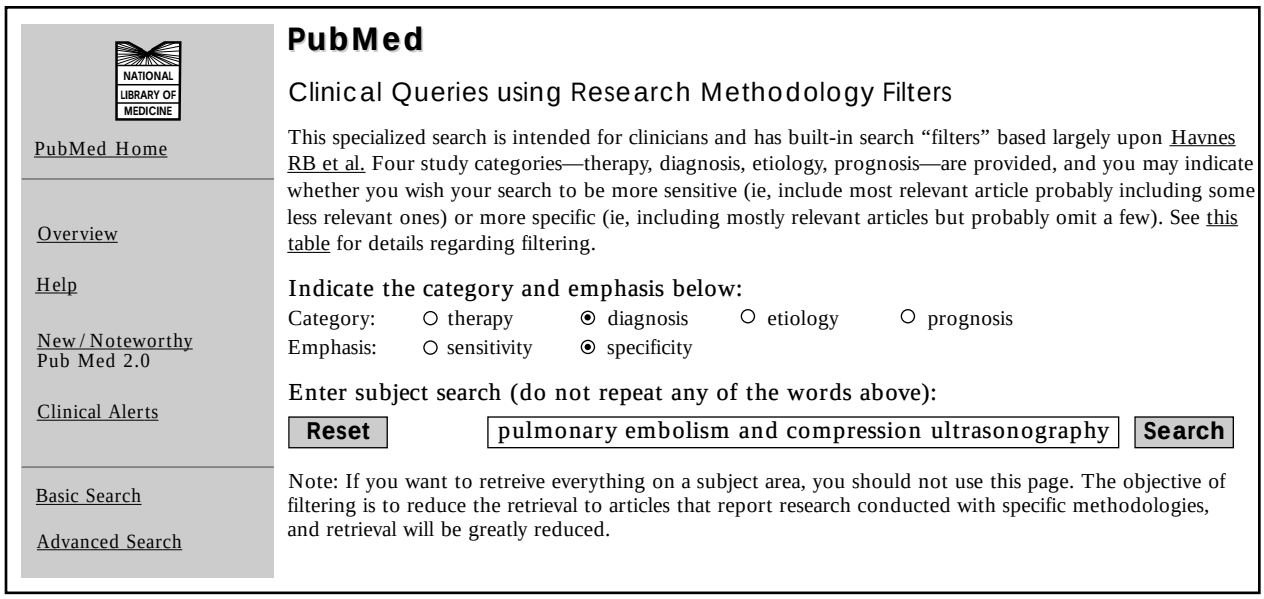


Figure 1. Example of a diagnostic search using PubMed, showing choice of search filters.

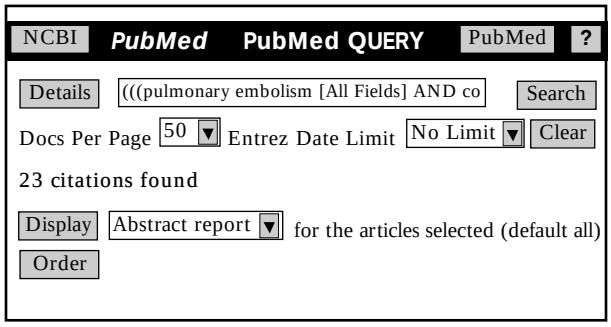


Figure 2. Results of sample diagnostic search using PubMed.

information regarding the search filters can be seen by clicking the "this table" link in the explanatory paragraph above the filter buttons.) You enter "pulmonary embolism and compression ultrasonography" as your subject search terms and click on the "Search" button. To view the abstracts of the 23 articles that are retrieved, you choose "abstract report" from the "Display" menu (Figure 2). You find 2 original research articles that may be of interest [3,4], but a review of these abstracts reveals that 1 study [3] assessed only 30 subjects. You choose to review the larger study by Turkstra et al [4].

### Appraising the Quality of the Evidence

To decide whether the information in the articles retrieved can be used in clinical decisions, the next step is to assess the validity of the research (ie, was it methodologically performed to be representative of the truth?). Table 1 lists the criteria of a valid diagnostic study.

The Turkstra et al study [4] was a blinded comparison measuring the diagnostic accuracy of compression ultrasonography, compared with the gold standards of ventilation-perfusion lung scanning and pulmonary angiography, in the diagnosis of PE. It included 397 patients over age 18 years who were recruited from inpatient and outpatient settings and who were suspected of having a PE. Perfusion lung scanning was performed in all patients, and selective angiography was attempted in patients who had a nondiagnostic lung scan. Compression ultrasonography, the methods of which were described in detail, was performed by an investigator blinded to previous test results. Results obtained on compression ultrasonography did not influence the decision to perform ventilation-perfusion lung scanning or pulmonary angiography.

After reviewing of the article, you are satisfied that it was well designed and should provide valid information regarding the utility of compression ultrasonography in the diagnosis of PE.

### Interpreting the Results

The next step involves interpreting the results. Data from Table 2 can be converted into a $2 \times 2$ table used to determine the test's characteristics (Figure 3). These include sensitivity (test positivity in the presence of disease), specificity (test negativity in the absence of disease), and likelihood ratios (LRs). LRs represent the

odds that a given diagnostic test result would occur in a patient with a disease versus a patient without a disease.

Of these parameters, LRs provide the most clinically meaningful information because they enable the clinician to interpret the results of a given diagnostic test in the context of a clinical scenario [5,6]. LRs indicate how much a given diagnostic test result will raise or lower a clinician's clinical suspicion (pretest probability) of disease. An LR of 1 indicates that the posttest probability (suspicion of disease after a diagnostic test) is the same as the pretest probability. An LR greater than 1 increases the probability that a disease is present, whereas an LR less than 1 decreases the probability of disease. The further away from 1 the LR is, the more impact the test result has on a patient's pretest probability.

Given the classic symptoms of PE in the setting of multiple risk factors, you conclude that your patient's pretest probability of PE approaches 80%. Using the data in Figure 3, you determine that the positive likelihood ratio ($LR^+$) for compression ultrasonography in the diagnosis of PE is 9.67; the negative likelihood ratio (LR–) is 0.7.

Because the results of your patient's compression ultrasound were negative, the LR– will be used to convert the pretest probability into the posttest probability. Although a mathematical calculation can be used for this conversion [7], a more practical method uses a nomogram [8]. Using the nomogram in Figure 4, affix a ruler to your pretest probability (80%) on the first column and rotate it to line up with the LR– on the second column (0.7). The intercept of the ruler on the third column is the posttest probability. In this example, your patient's posttest probability falls only to 75%, verifying the minimal effect of this negative test result (with an LR– near 1) on your clinical suspicion of disease.

### Applying the Evidence

Because the posttest probability is 75%, your suspicion for undiagnosed PE is too high to rule out the diagnosis. You decide to order further diagnostic studies, which eventually demonstrate multiple bilateral pulmonary emboli.

## Clinical Decision #2: Choosing Therapy

After reviewing the diagnosis of PE with your residents, one asks you whether low-molecular-weight heparin (LMWH) might be used in place of unfractionated heparin (UH) while awaiting therapeutic oral anticoagulation. You are aware that multiple randomized controlled trials documenting the efficacy of LMWH in the treatment of DVT were recently reviewed in a meta-analysis [9], but you are uncertain about its use in a patient with PE.

Table 1. Criteria for Evaluating and Applying the Results of Studies of Diagnostic Tests

| |
|---|
| **Validity** |
| Primary guides |
| Did the study include an independent, blinded comparison with a reference standard? |
| Did the study population include an appropriate spectrum of patients to whom the diagnostic test will be applied in clinical practice? |
| Secondary guides |
| Did the results of the test being evaluated influence the decision to perform the reference standard? |
| Are the methods for performing the test described in sufficient detail to permit replication? |
| **Results** |
| Are likelihood ratios or the data necessary for their calculation provided? |
| **Utility** |
| Will the reproducibility of the test result and its interpretation be satisfactory in my setting? |
| Are the results applicable to my patient? |
| Will the results change my patient management practices? |
| Will patients be better off as a result of the test? |

Adapted with permission from Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 1994;271:389–91.

### Framing the Clinical Question

You construct your well-built clinical question as follows: "In a patient with PE, how effective is LMWH, compared with UH, in preventing recurrent thromboembolic events or death?"

### Searching the Literature

You choose the "therapy" and "specificity" filters from the Clinical Queries page on PubMed. You search for "pulmonary embolism and low molecular weight heparin and unfractionated heparin" and retrieve the titles of 32 articles, none of which appears to directly address your question. The problem here is that, although search filters are extremely useful for limiting searches, they also can be too restrictive, especially if the searcher is unfamiliar with the underlying assumptions of the filters. You return to the Clinical Queries page and click

Table 2. Results of Compression Ultrasonography for Detection of Venous Thrombosis of the Leg in 397 Consecutive Patients Clinically Suspected of Having PE

| Variable | Study Patients (*n*) | Patients with Abnormal Results on Ultrasonography | |
|---|---|---|---|
| | | *n* | % (95% CI) |
| PE proven | | | |
| All patients | 149 | 43 | 29 (22–37) |
| High-probability lung scan | 116 | 35 | 30 (21–38) |
| Nondiagnostic lung scan and abnormal angiogram | 33 | 8 | 24 (11–42) |
| PE excluded* | 178 | 5 | 3 (0.9–6.4) |
| PE uncertain† | 30 | 4 | 13 (4–33) |

CI = confidence interval; PE = pulmonary embolism. (Adapted with permission from Turkstra F, Kuijer PM, van Beek EJ, Brandjes DP, ten Cate JW, Buller HR. Diagnostic utility of ultrasonography of leg veins in patients suspected of having pulmonary embolism. Ann Intern Med 1997;126:775–81.)

*Patients with normal lung scan or angiogram.

†Patients with nondiagnostic lung scan and either no angiography performed or angiogram not interpretable.

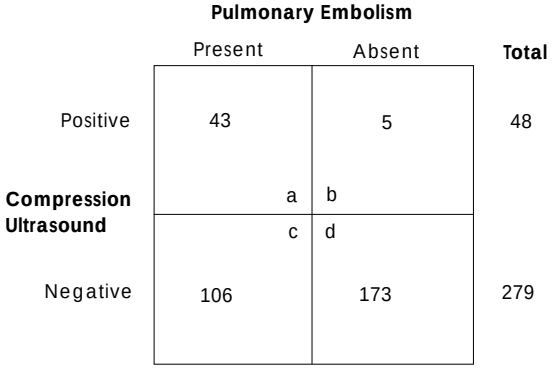


Figure 3. Example of a 2 × 2 table. LR+ = positive likelihood ratio; LR– = negative likelihood ratio. (Data from Turkstra F, Kuijer PM, van Beek EJ, Brandjes DP, ten Cate JW, Buller HR. Diagnostic utility of ultrasonography of leg veins in patients suspected of having pulmonary embolism. Ann Intern Med 1997;126:775–81.)

the "this table" link to review the filters in detail. After reviewing the descriptions, you realize that the "therapy" and "specificity" filters exclude all studies that are not either double blind or placebo controlled. Studies assessing LMWH versus UH, because of logistical reasons, are often not conducted in a double-blind fashion, and treating someone who has a known PE with a placebo is dangerous and unethical. By using the specificity filter in this case, you have unwittingly excluded most studies of interest.

You realize your mistake and retrieve 113 titles using the "therapy" and "sensitivity" filters. Most of the studies retrieved assess prophylactic use of LMWH or use of LMWH in DVT or they are reviews. However, 4 articles appear to be of interest [10–13]. After you review the abstracts, you exclude 3 studies [10,12,13] because they do not directly address your clinical question. You select the study by Simonneau et al [11] for closer appraisal.

## Appraising the Quality of the Evidence

As with diagnostic studies, studies that evaluate therapy must be assessed for validity to ensure that the results accurately demonstrate the effect of a therapeutic intervention. Established criteria (Table 3) guide the reader in evaluating the validity and applicability of therapeutic studies [14].

The Simonneau et al study [11], which evaluated the effect of LMWH versus UH in the treatment of acute PE, is a multicenter, randomized, controlled, unblinded trial comparing continuous, adjusted-dose UH with once-daily subcutaneous injection of LMWH (tinzaparin) in patients with acute symptomatic PE. At the start of the trial, patients were similar with respect to age, gender, thromboembolic risk factors, heart disease, and the presence and location of DVT. Results were calculated using an intention-to-treat analysis. Outcomes including death, symptomatic recurrent thromboembolism, and major bleeding were determined within the first 8 days and at 90 days postintervention.

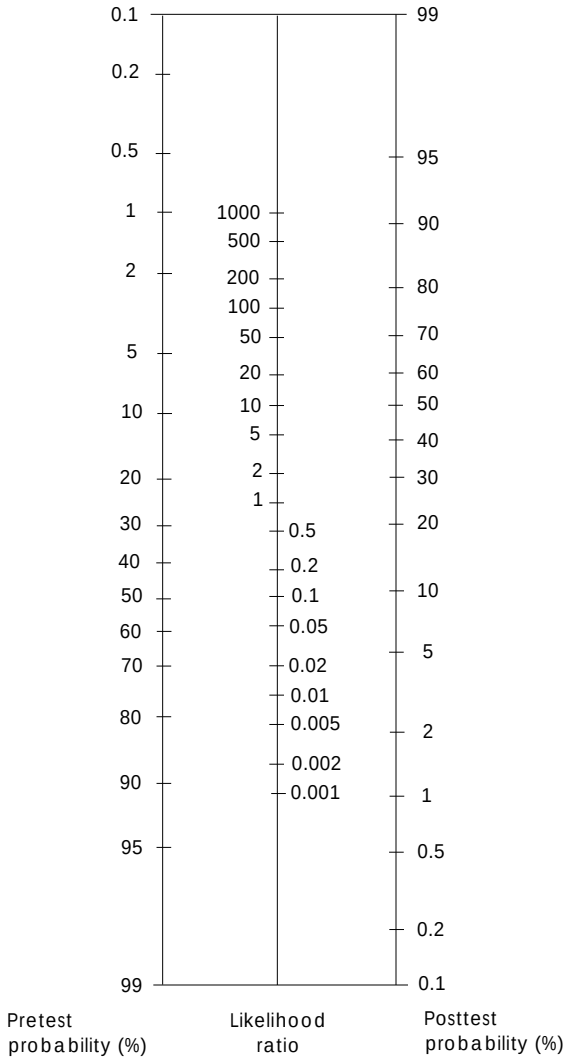


Figure 4. Likelihood ratio nomogram. (Adapted with permission from Fagan TJ. Nomogram for Bayes Theorem [letter]. N Engl J Med 1975;293:257.)

Table 3. Criteria for Evaluating and Applying the Results of Studies of Therapy

| |
|---|
| **Validity** |
| Primary guides |
| Was the assignment of patients to treatments randomized? |
| Were all patients who entered the trial properly accounted for at its conclusion? |
| Was follow-up complete? |
| Were patients analyzed in the groups to which they were randomized? |
| Secondary guides |
| Were patients, health workers, and study personnel blind to treatment? |
| Were the groups similar at the start of the trial? |
| Aside from the experimental intervention, were the groups treated equally? |
| **Results** |
| How large was the treatment effect? |
| How precise was the estimate of the treatment effect? |
| **Utility** |
| Can the results be applied to my patient? |
| Were all clinically important outcomes considered? |
| Are potential harms and costs balanced by likely treatment benefits? |

Adapted with permission from Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 1993;270:2598–601.

Although this appears to be a well-conducted study, you have concerns. First, the study was relatively small and included only 615 patients in randomization. You question whether the sample size was large enough to detect a difference in the 2 therapies (referred to as *statistical power*). Second, the study excluded patients with massive embolism, and you are uncertain whether your patient would have met the inclusion criteria for this study, given her multiple bilateral emboli. Third, although patients in each group were generally treated equally after randomization, a greater number of patients randomized to LMWH received therapeutic doses of UH prior to the study's initiation. Because 73% of patients randomized to receive LMWH also received therapeutic doses of UH prior to entering the study, you wonder whether this may have affected the results and inflated the effect of LMWH.

### Interpreting the Results

The results of the study demonstrated no significant differences between LMWH and UH with respect to the combined outcomes of mortality, recurrent thromboembolism, and major bleeding ($P = 0.55$), suggesting equivalence between LMWH and UH in the treatment of acute, hemodynamically stable PE [11]. Based on these results, either treatment could be appropriate depending on clinical circumstances, patient preferences, local experience, and your assessment of the study's limitations as they impact the strength of the evidence.

### Applying the Evidence

After reconsidering the case of your high-risk patient with bilateral PE, you advise continued therapy with

UH while awaiting therapeutic oral anticoagulation. You remain concerned that your patient may not have been a candidate for LMWH in the study by Simonneau et al [11] and that the study may not have had sufficient statistical power to detect a difference.

When you discuss this case again with your residents, you reinforce the importance of not basing clinical decisions on evidence alone. You remind them that even the best evidence must be critically appraised for validity and that the strength of the evidence must be assessed for applicability to each individual patient's circumstances (ie, the patient's social condition, needs, preferences, and values). Making decisions based on these combined factors will lead to the best patient care.

## Conclusion

This case study illustrates a simplified approach to evidence-based decision making and demonstrates the skills necessary for incorporating EBM into clinical practice. As the "conscientious, explicit, and judicious use of current best evidence in clinical decision making" [15], EBM is a learned skill that requires practice. Daily application of EBM to clinical decisions allows the clinician to refine critical appraisal skills and enhance patient care. This type of critical appraisal exercise can be successfully utilized as a method of teaching EBM, as demonstrated in the internal medicine residency program at the Mayo Graduate School of Medicine [16,17] and in other training programs.

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