The Impact of the Introduction of a Rapid D-Dimer Assay on the Diagnostic Evaluation of Suspected Pulmonary Embolism

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Background: Rapid D-dimer assays are being used in the diagnostic evaluation of suspected pulmonary embolism (PE). Although this hypothesis is anticipated to decrease the use of ventilation-perfusion (VQ) scans and other diagnostic tests for PE, it has not been tested in a “real-world” environment.

Subjects and Methods: A randomized prospective trial was conducted on 470 of the 5390 enrolled patients aged 60 years and older who had previously undergone any diagnostic tests for PE at an urban teaching hospital. The use of D-dimer as part of the diagnostic evaluation for PE was promulgated in the 2 randomly chosen intervention firms. The remaining 2 firms served as controls.

Main Outcome Measures: The number of VQ scans, spiral computed tomographic scans, and pulmonary angiograms performed. Secondary outcomes included mortality and thromboembolic or bleeding events during 3 months of follow-up.

Results: Of the 470 inpatients who underwent evaluation for PE on a per PE workup basis, fewer VQ scans were performed in the intervention firms (63.8% vs 81.3%; \( P < .01 \)). However, the number of patients evaluated for PE nearly doubled in the intervention firms (304 vs 166; \( P < .01 \)), so that more VQ scans were performed in the intervention than in the control firms (194 vs 135; \( P < .01 \)). Ninety-four patients from the control firms and 160 patients from the intervention firms were diagnosed and treated for venous thromboembolic disease (PE and/or deep vein thrombosis). There were no perceived changes in secondary outcomes during the 3-month follow-up.

Conclusions: The introduction of a rapid D-dimer assay increased the number of VQ scans performed because the number of patients screened for PE increased. A larger number of patients in the intervention firms were diagnosed as having venous thromboembolic disease (PE and/or deep vein thrombosis). There were no perceived changes in mortality or venous thromboembolic events during the 3-month follow-up.

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PULMONARY embolism (PE) is a serious and life-threatening disease that has an incidence of 23 per 100000 patient-years and causes 200000 deaths annually in the United States, with untreated mortality rates as high as 30%. Among treated patients, fatal PE is a rare event, with clinical recurrence occurring in 8% to 26%. Thus, the goal of treatment is to prevent death from the initial and recurrent PE and generally consists of the administration of intravenous heparin followed by at least 6 months of oral anticoagulation. Because anticoagulant use can cause serious complications, including fatal hemorrhage, accurate diagnosis of PE is crucial.

With no pathognomonic clinical features, the diagnosis of PE requires objective testing. Pulmonary angiography is the gold standard technique for diagnosis of PE, however, it is costly, invasive, and not uniformly available. Noninvasive procedures, such as the radioisotope ventilation-perfusion (VQ) scan and lower extremity duplex ultrasonography, have simplified the diagnostic approach to venous thromboembolic (VTE) disease. However lung scans are costly and are diagnostic in only 30% to 50% of patients with suspected PE, while duplex ultrasonography reveals a deep vein thrombosis (DVT) in only 8% to 19% of patients who have a nondiagnostic lung scan.

Plasma D-dimer (DD) is a cross-linked fibrin degradation product, resulting from activation of the coagulation and fibrinolysis processes. Plasma DD has been extensively studied in the setting of suspected PE and DVT. Using enzyme-linked immunosorbent assays (ELISAs) at the clinically validated cutoff value of 500 µg/L, the specificity of DD is low (20%-
SUBJECTS AND METHODS

STUDY LOCATION AND POPULATION

The study was conducted within the inpatient medical wards of Barnes-Jewish Hospital, St Louis, Mo, a 1200-bed, urban teaching hospital. The inpatient teaching medical service at Barnes-Jewish Hospital is divided into 4 similar firms (A, B, C, and D). Patients hospitalized in the medical wards of firms A, B, C, or D between September 1999 and February 2000 were included in the study if they underwent any diagnostic testing for clinically suspected PE, including a VQ scan, pulmonary angiogram, DD test, or spiral computed tomography. Group randomization was achieved by making the DD test readily available to patients admitted to firms B and D (intervention firms) and discouraging its use in firms A and C (control firms). To enlist house staff cooperation with our study, we undertook several formal educational talks with the house staff of all 4 firms, as well as providing house staff and attending physicians with information on the purpose of this investigation. For the intervention firms, we presented current literature regarding the applicability of the SimpliRED assay, including its test characteristics and its utility as a screening tool in non–high-risk patients. To the control firms, we explained the study protocol and requested that suspected PE be investigated in the traditional manner, without using the SimpliRED assay. Using this approach, we planned to study the impact that the introduction of the DD assay would have on test ordering and clinical outcomes. Control and intervention firms were randomly assigned. The Human Studies Committee of Washington University School of Medicine, St Louis, approved the study protocol and waived the need for patient written informed consent.

DATA COLLECTION

A dedicated clinical research nurse (S.W.) prospectively recorded data from the patients’ medical records, bedside computerized nursing station (EMTEK Health Care Systems, Tempe, Ariz), and the hospital’s mainframe computer. She recorded the following admission variables: age, sex, admission diagnosis, and preadmission diagnoses of comorbid conditions (malignancy, congestive heart failure, chronic obstructive pulmonary disease, and the presence of infection). During the patient’s hospitalization, she recorded the ordering and results of diagnostic tests performed for the evaluation of suspected PE including: DD assay, VQ scan, spiral computed tomography, and pulmonary angiography. At 3 months after hospital discharge, the research nurse telephoned participants to assess for the following outcomes: death, recurrent VTE events, and bleeding complications.

D-DIMER DETERMINATION

We used a recently developed assay for the rapid detection of plasma DD (SimpliRED). The test reagent contains a composite antibody formed by the conjugation of a monclonal antibody that reacts with high affinity to a site on the γ-chain of DD (3B6/22), with a red cell–binding antibody (RAT-1C3/86). In the presence of elevated levels of DD, the antibody induces agglutination of the patient’s red blood cells.

Trained laboratory personnel, who were blinded to the clinical data, performed all tests. Blood samples for DD determination were requested to be drawn within 24 hours of the clinical suspicion for PE. For each test sample, a 10-µL drop of whole blood was instilled by pipette into a reaction well on an agglutination tray. One drop of test reagent was added to the blood sample and mixed using gentle rocking of the agglutination tray for 2 minutes. Although it is possible to grade the degree of red cell agglutination with the SimpliRED DD test, for the purposes of this study a DD test was defined as positive if any agglutination was observed and negative if no agglutination was observed.

DIAGNOSIS OF VTE

For the purpose of this study, the diagnosis of VTE (PE and/or DVT) was considered established if the firm physician team instituted a therapeutic intervention (anticoagulation, thrombolysis, or inferior vena cava filter placement) following performance and interpretation of appropriate diagnostic tests (VQ scan, spiral computed tomography, pulmonary angiography, duplex ultrasonography).

STATISTICAL ANALYSIS

The primary outcome measure was the number of VQ scans, pulmonary angiograms, and spiral computed tomographic scans ordered in each group for the evaluation of suspected PE. Secondary outcomes included mortality, duration of hospitalization, and 3-month incidence of recurrent VTE events or bleeding complications. All comparisons were unpaired and tests of significance were 2-tailed. Continuous variables were compared using the t-test for normally distributed variables and the Wilcoxon rank sum test for nonnormally distributed variables. The χ² or Fisher exact tests were used to compare categorical variables. The primary data analysis compared patients in control firms (A and C) with patients in intervention firms (B and D). Logistic regression analysis was used to test the relationship between DD result and patient age and comorbidities. The proportion of patients undergoing VQ scanning was compared using standard methods (Snedecor and Cochran).
Table 1. Characteristics of Patients With Clinically Suspected Pulmonary Embolism*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group (n = 166)</th>
<th>Intervention Group (n = 304)</th>
<th>P (Univariate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>61.9 (16.1)</td>
<td>65.4 (17.4)</td>
<td>.02</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>71 (42.8)</td>
<td>113 (37.2)</td>
<td>.24</td>
</tr>
<tr>
<td>Women</td>
<td>95 (57.2)</td>
<td>191 (62.8)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>87 (52.4)</td>
<td>157 (51.6)</td>
<td>.70</td>
</tr>
<tr>
<td>Black</td>
<td>79 (47.6)</td>
<td>147 (48.4)</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>42 (25.3)</td>
<td>89 (29.3)</td>
<td>.36</td>
</tr>
<tr>
<td>COPD</td>
<td>28 (16.9)</td>
<td>43 (14.1)</td>
<td>.43</td>
</tr>
<tr>
<td>Malignancy</td>
<td>30 (18.1)</td>
<td>45 (14.8)</td>
<td>.36</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>22 (13.3)</td>
<td>38 (12.5)</td>
<td>.82</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>30 (18.1)</td>
<td>43 (14.1)</td>
<td>.26</td>
</tr>
<tr>
<td>Active infection</td>
<td>46 (27.7)</td>
<td>88 (28.9)</td>
<td>.78</td>
</tr>
<tr>
<td>DVT prophylaxis</td>
<td>57 (34.3)</td>
<td>117 (38.5)</td>
<td>.37</td>
</tr>
</tbody>
</table>

*All values are given as number (percentage), except for age. CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease; and DVT, deep vein thrombosis.

RESULTS

A total of 470 consecutive patients being evaluated for clinically suspected PE from firms A, B, C, and D were enrolled in the study. During enrollment, the total number of inpatient admissions were similar among the 2 groups (2700 in the control firms vs 2690 in the intervention firms). At the time of enrollment, no significant differences were found among the intervention and control firms regarding sex, ethnicity, presence of chronic obstructive pulmonary disease, congestive heart failure, malignancy, clinical infection, recent surgery, immunocompromised state, or receipt of DVT prophylaxis, but patients in the intervention group were older (Table 1).

DIAGNOSTIC TESTS FOR PE

In the intervention firms, significantly more patients were investigated for possible PE (of the 2690 enrollees: 304 [11.3%] vs 166 [6.2%]; P < .01). Among the patients investigated for PE (Figure 1), the intervention group had significantly more DD assays performed (191 [62.8%] vs 53 [31.9%]; P < .01) and a lower rate of VQ scans (194 [63.8%] vs 135 [81.3%]; P < .01) performed.

From the total inpatient firm pool, the diagnostic test group underwent significantly more DD assays (191 [7.1%] vs 53 [2.0%]; P < .01) and a greater rate of VQ scans (194 [7.2%] vs 135 [5.0%]; P < .01). There was no difference between the 2 groups in the use of spiral computed tomography or pulmonary angiography (Figure 2).

Among patients having a DD assay (n = 244), those in the intervention group demonstrated a trend toward a lower likelihood of having a positive DD assay compared with patients in the control group (89 [46.6%] vs 32 [60.4%]; P = .08). Logistic regression analysis showed that the presence of chronic obstructive pulmonary disease (adjusted odds ratio [AOR], 3.3; 95% confidence interval [CI], 2.1-5.2; P = .007), clinical infection (AOR, 2.0; 95% CI, 1.5-2.7; P = .02), and increasing patient age (1-year increments) (AOR, 1.04; 95% CI, 1.03-1.05; P < .001) were independently associated with a positive DD assay result. Patients with a positive DD assay were more likely to undergo a VQ scan than patients with a negative assay (58.7% vs 30.1%; P < .01).

Overall more VTE episodes were diagnosed in the intervention group (160 of 2690 admissions) than in the control group (94 of 2700 admissions) (P < .01). Patients in the intervention group were also more likely to undergo a VQ scan in the case of a positive DD assay (64.0% vs 43.8%; P = .046).

The sensitivity, specificity, negative predictive value, and positive predictive value of the SimpliRED assay, with the 95% CIs, were as follows: 60.0% (51.5%-68.5%), 53.0% (44.0%-62.0%), 50.4% (41.6%-59.2%), and 54.5% (45.7%-63.3%).

SECONDARY OUTCOMES

No statistically significant differences were detected in hospital mortality or length of stay between the 2 groups. Of the patients in the control and intervention firms, 45%
and 48%, respectively, were successfully reached for the 3-month follow-up. No differences were detected in total mortality, recurrent VTE events, or bleeding complications (Table 2).

### Table 2. Outcomes of Patients With Clinically Suspected Pulmonary Embolism*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control Group (n = 166)</th>
<th>Intervention Group (n = 304)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS, mean (SD), d</td>
<td>7.1 (8.6)</td>
<td>7.1 (9.5)</td>
<td>.94</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>5 (3.7)</td>
<td>11 (3.8)</td>
<td>.80</td>
</tr>
<tr>
<td>Mortality at 3-mo</td>
<td>6 (7.9)</td>
<td>11 (7.4)</td>
<td>.90</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>2 (2.6)</td>
<td>9 (6.1)</td>
<td>.34</td>
</tr>
<tr>
<td>Readmission</td>
<td>19 (25.0)</td>
<td>41 (27.7)</td>
<td>.66</td>
</tr>
<tr>
<td>Bleeding complications</td>
<td>3 (3.9)</td>
<td>8 (5.4)</td>
<td>.75</td>
</tr>
</tbody>
</table>

*All values are given as number (percentage) unless otherwise indicated. LOS indicates length of stay; VTE, venous thromboembolism. Three-month follow-up based on available data (45% and 48% of control and intervention groups, respectively, were reached for 3-month follow-up).

Our study demonstrated that the introduction of the SimpliRED DD assay resulted in an increase in the number of VQ scans performed. The availability of this rapid, inexpensive, and sensitive test also resulted in an increase in the number of patients screened for PE, as well as increasing the numbers of patients diagnosed as having VTE. The prevalence of a negative assay (49.6%) was fairly high even in a medical inpatient population with multiple comorbidities.

Our study was unique in that it was based in a “real-world” environment where the ultimate decisions regarding the diagnostic and therapeutic approaches were determined by individual physicians. Contrary to predictions,23–28 that the introduction of a DD assay would reduce more costly and invasive tests for PE, the widespread adoption of a DD assay increased resource utilization by increasing the number of patients screened for PE. The increased screening resulted in a significant increase in the number of VTE events diagnosed. We were unable to show a difference in mortality or in the occurrence of recurrent VTE events at 3-month follow-up. However, follow-up was incomplete and the study was not designed or powered to detect such potential differences.

Given the excellent reported negative predictive value of DD assays in non–high-risk patients, several investigators have predicted that the use of DD would decrease the number of VQ scans performed in patients with suspected PE.23–29 Ginsberg and colleagues24 showed that a normal DD result by SimpliRED was useful in excluding PE in patients who had a low clinical suspicion for PE, with a negative predictive value of 99%. Because 44% of the participants had a low pretest probability, they hypothesized that introduction of a DD assay would reduce the number of VQ scans significantly. De Moerloose and colleagues25 evaluated a rapid ELISA method in 195 emergency department patients with suspected PE; 29% of these patients had a negative DD result and none of them experienced thromboembolic events during 6 months of follow-up. The authors thus speculated that 29% of the emergency department patients could have avoided further testing. Oger and coworkers26 studied 386 patients in the emergency department with suspected PE using a rapid ELISA (Liatest). They demonstrated a sensitivity of 100% for PE, with 21% of their patients having a negative test result. This study also speculated that DD would reduce further investigations and shorten hospital stay. However, the impact of introducing a DD assay on physicians’ ordering patterns had never been tested previously. We found that the introduction of SimpliRED had the effect of increasing use of VQ scans due to the increase in the number of patients screened for VTE.

This increased utilization of a DD assay is preceded by other situations in which the introduction of safer, quicker, inexpensive, or more sensitive tests have increased the number of patients screened for disease. Examples include the impact of prostate-specific antigen determinations on the frequency of prostate biopsies,30 as well as diagnostic tests for colorectal cancer following the introduction of stool occult blood testing.31 Similarly, a readily available assay for DD such as SimpliRED, which is inexpensive and noninvasive, may allow greater numbers of patients to be screened for VTE, resulting in more diagnoses of VTE as well as greater overall diagnostic test utilization.

Our study has several limitations. First, it was performed within a single institution using patients cared for by house staff who had been educated about the usefulness and limitation of DD testing, and as such may not be generalizable to some settings. Second, the study was limited to medical inpatients and is not applicable to nonmedical specialties (eg, surgical or obstetrical patients) or to outpatients. Third, despite discouraging its use, 32% of patients in the control group had DD tests performed. Fourth, 3-month follow-up was incomplete with approximately 50% of patients being available for follow-up. Finally, we did not dictate the utilization of diagnostic tests or treatment for VTE. Therefore, comparisons with other institutions using different diagnostic and therapeutic approaches is problematic.

The introduction of the SimpliRED DD assay in medical inpatients with clinically suspected PE resulted in a significant increase in the number of patients diagnosed as having VTE, at the expense of a significant increase in VQ scans ordered. Despite the overall increase in the screening for PE, the utilization of VQ scans per individual workup was reduced. The introduction of the SimpliRED assay did not result in any changes in mortality or recurrent VTE at 3 months’ follow-up. Despite advanced age and multiple comorbidities, half of the medical inpatients in this study had a negative DD assay. We conclude that the unrestricted use of the SimpliRED DD assay in medical inpatients resulted in an increase in the number of VTE events diagnosed at the cost of increased VQ scanning with no significant change in mortality or recurrent VTE events at 3 months. Larger mortality and cost-effectiveness studies are needed to evaluate whether the increase in VTE events diagnosed with the
availability of DD assays justifies the increased utilization of VQ scanning.

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