Use of a Clinical Decision Rule in Combination With D-Dimer Concentration in Diagnostic Workup of Patients With Suspected Pulmonary Embolism

A Prospective Management Study

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Background: We designed a diagnostic strategy, based on clinical probability and D-dimer concentration, to select patients who were unlikely to have pulmonary embolism (PE), before further diagnostic workup was performed. The utility and safety of this strategy were evaluated in a prospective management study.

Methods: Consecutive patients with suspected PE had D-dimer testing and clinical probability assessment with a clinical decision rule. Patients with a low probability and a normal D-dimer concentration (<500 ng/mL) were considered not to have PE, and further diagnostic testing and anticoagulant therapy were withheld. In patients with a low probability and elevated D-dimer level or with a moderate or high probability, bilateral compression ultrasonography of the legs was performed. If deep venous thrombosis was detected, venous thromboembolism was diagnosed. If compression ultrasonography was normal, pulmonary angiography was performed. All patients were followed up for 3 months.

Results: Of the 234 consecutive patients, 26% had the combination of a low probability and normal D-dimer level. During the follow-up period, none of these patients died and 3 patients had recurrent complaints of PE. In these 3 patients, PE was excluded by objective testing. The 3-month thromboembolic risk was therefore 0% (95% confidence interval, 0%-6%). The prevalence of PE in the entire population was 22%.

Conclusions: The combination of a low clinical probability and a normal D-dimer concentration appears to be a safe method to exclude PE, with a high clinical utility, and is readily accepted by clinicians.

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PATIENTS AND METHODS

PATIENTS

Consecutive inpatients and outpatients older than 16 years, with clinically suspected acute PE seen at St Elisabeth Hospital, Tilburg, the Netherlands, were prospectively included in the study between January 1, 1998, and May 31, 2000. The protocol was approved by the local ethics committees, and written informed consent was obtained from all patients.

STUDY DESIGN AND DIAGNOSTIC STUDIES

The clinical decision rule (CDR) was completed and the patients were stratified into low, moderate, and high clinical probability categories of PE. The CDR consists, as described elsewhere, of risk factors for PE, signs and symptoms from history and physical examination, chest radiography, oxygen saturation tests, and electrocardiography, as well as the likelihood of an alternative diagnosis for the patient’s symptoms. The CDR was applied by a group of at least 10 attending physicians, who all received extensive instructions about how to use the rule before the start of the study. The plasma D-dimer concentration was then measured with a quantitative rapid enzyme-linked immunosorbent D-dimer assay (Vidas DD; bioMérieux, Inc, Paris, France). The concentration was expressed in nanograms per milliliter of fibrinogen equivalent units. The cutoff value, according to the manufacturer’s instructions, was 500 ng/mL. All measurements were carried out in duplicate by a technician who was unaware of the outcome of the CDR and the patient’s history.

Patients with a low probability of PE and a normal D-dimer test result (<500 ng/mL) did not undergo further diagnostic procedures and anticoagulant treatment was withheld. They were instructed to return to the thrombosis unit immediately when signs or symptoms of PE or deep venous thrombosis (DVT) recurred, and appropriate objective testing (CUS, lung scanning, or pulmonary angiography) was performed to confirm or refute the diagnosis.

RESULTS

During the investigation period, 251 consecutive patients with clinically suspected PE were studied. Seventeen patients (7%) were excluded because of refusal or inability to give consent (5 patients), contraindications to pulmonary angiography (2 patients), and absence of D-dimer measurement because of logistical problems (10 patients). Thus, the study population available for analysis consisted of 234 patients. The mean age of this cohort was 51 years (SD, 17 years) and the prevalence of VTE was 22%. Of the total population, 83% presented as outpatients and 11% had a history of previous VTE (Table). The 3-month follow-up period was completed in all patients.

LOW CLINICAL PROBABILITY AND NORMAL D-DIMER CONCENTRATION

The Figure summarizes the results of the evaluated diagnostic strategy. The clinical probability of PE, according to the CDR, was low in 120 patients (51%), moderate in 74 patients (32%), and high in 40 patients (17%). Of the patients with a low clinical probability, 60 had a normal D-dimer concentration, so no further diagnostic procedures were performed and the patients did not re-

who will not have this disease. Findings in recent studies in patients with suspected venous thromboembolism (VTE) support this assumption. The aim of the present study was to evaluate the utility and safety of a novel strategy in excluding PE in patients with a low clinical probability, according to a validated clinical decision rule, and a normal D-dimer concentration. In these patients, no further diagnostic investigations were performed and anticoagulant treatment was withheld. In the remaining patients we used compression ultrasonography (CUS), followed by pulmonary angiography if results were normal.
Results of the diagnostic strategy in 251 consecutive patients presenting with clinically suspected pulmonary embolism (PE). CUS indicates compression ultrasonography.

of the presenting cohort would have been spared further diagnostic procedures and anticoagulant therapy. One of these 85 patients had PE involving the segmental arteries, confirmed by pulmonary angiography (failure rate, 1.2%; 95% CI, 0.03%-6.40%). This patient was a 40-year-old woman who had recently had a neurosurgical operation (9 days before presentation) and who presented with a complaint of dyspnea of 3 days’ duration. The remaining 149 patients, ie, those with a low or moderate clinical probability and an elevated D-dimer concentration or with a high clinical probability, would have undergone further diagnostic procedures, which would have revealed PE in approximately one third (51 patients).

The D-dimer concentration was measured in all patients. The result was normal in 100 patients (43%) of the study population. One of these 100 patients actually had PE in segmental arteries on pulmonary angiography (same patient as described above). The D-dimer concentration of this patient was 480 ng/mL. The sensitivity of the D-dimer assay was 98% (95% CI, 90%-100%) and the negative predictive value, 99% (95% CI, 95%-100%).

**COMMENT**

The primary finding of this study is that the combination of a low clinical probability of PE and a normal D-dimer concentration is able to exclude the disease safely in a substantial proportion (26%) of patients presenting with suspected PE. This new strategy was introduced in a large teaching hospital that previously used lung scanning and pulmonary angiography and was well accepted by the clinicians (physicians, internists, pulmonologists, and surgeons) involved in the diagnostic workup of such patients.
Furthermore, the present study confirms that the combination of CUS and pulmonary angiography is a feasible, effective, and safe subsequent diagnostic strategy. Performing CUS of the deep leg veins in patients with a moderate or high clinical probability and elevated D-dimer levels (n = 174) was worthwhile: 16% had DVT detected by ultrasonography, and anticoagulant treatment was initiated. Taken together, the use of the clinical probability assessment, D-dimer assay, and CUS, all noninvasive methods, was able to confirm or refute the diagnosis in 37% of the patients of the original study cohort. Pulmonary angiography was performed without any complication, confirming earlier observations, although in 1 patient the initial PE was most likely missed. The outcome with respect to subsequent episodes of symptomatic VTE during the 3-month follow-up in patients with a low clinical probability and a normal D-dimer concentration (failure rate, 0%; 95% CI, 0%-6%) compared favorably with that of patients with normal pulmonary angiograms (failure rate, 0.8%; 95% CI, 0.02%-4.50%) and is in agreement with studies using normal perfusion scan results or serial ultrasound scan results to exclude VTE.

Only a limited number of prospective management studies with D-dimer, CDR, or a combination of both are available. Our observations of the combination of CDR and D-dimer are comparable with the findings of these studies. However, de Groot et al and Perrier et al used the combination only in patients with a nondiagnostic perfusion-ventilation lung scan result, whereas in the present study the combination was used as the first step in the diagnostic workup. Therefore, a larger proportion of our study cohort, approximately one quarter, was spared radiologic or nuclear investigations compared with these studies.

In a recent study by Perrier and colleagues, D-dimer measurements were used as the first test in the diagnostic workup of 444 outpatients with suspected PE. A total of 159 patients (36%) had normal D-dimer concentrations, and this method was used as the sole test to exclude VTE (subsequent failure rate was 0%; 95% CI, 0%-2.3%). If we had adopted a similar strategy, while we used exactly the same D-dimer assay, we would have missed 1 patient with significant PE, although our findings are still consistent with the CIs of that study. It should be noted that we studied both inpatients and outpatients and that combining clinical assessment and D-dimer testing was readily accepted by the specialists who see patients with suspected PE.

Several studies using CUS and pulmonary angiography in patients with suspected PE have been published. An abnormal venous ultrasonogram is found in 5% to 12% of patients with a nondiagnostic lung scan result. In a meta-analysis by van Rossum et al, the prevalence of DVT in patients with clinically suspected PE was approximately 18%, and in patients with proven PE, 36% to 45% (range, 10%-93%). Our observations with respect to the proportion of patients with abnormal CUS are comparable with the findings in patients with a high-probability lung scan result but are higher than the proportion of patients with a nondiagnostic lung scan result. Investigations that assessed the validity and safety of pulmo-

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