Outcome studies of pulmonary embolism versus accuracy: They do not equate

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Negative multidetector contrast enhanced computed tomographic (CT) angiograms of the chest failed to identify 11% of patients with pulmonary embolism (PE) among patients with an intermediate probability clinical assessment in the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) (1). Is this compatible with results of well performed outcome studies that showed recurrent PE in 1% or fewer untreated patients with a negative CT pulmonary angiogram? The Christopher Group, for example, showed PE on three-month follow-up of untreated patients with a negative CT angiogram in only 10 of 1,436 (0.7%) (2). An additional 8 of 1,436 (0.6%) had DVT on follow-up. Perrier et al. showed PE at three months in three of 294 (1.0%) of patients with low or intermediate probability clinical assessments, and an additional four of 294 (1.4%) had DVT, some of which was shown by compression ultrasound during initial testing (3). One possibility to consider is that the data from PIOPED II are inaccurate, perhaps due to an imperfect reference standard. Another possibility is that undiagnosed small PE would show a low incidence of symptomatic recurrent PE in outcome studies. The following data support the latter explanation.

It is reasonable to assume that the PE’s were small in the 11% of patients with an intermediate probability clinical assessment in PIOPED II in whom diagnostic quality CT angiograms were falsely negative. The positive predictive value of PE in main or lobar arteries was 97%, in segmental pulmonary arteries 68% and in subsegmental pulmonary artery branches 25% (4). It is unlikely, therefore, that large PE in main or lobar pulmonary arteries were not identified.

In the prior era of late diagnoses of PE based on clinical findings, Hermann et al. reported a 36% frequency of fatal recurrent PE (5). There was, in addition, a 21% frequency of non-fatal recurrent PE among untreated patients with clinically diagnosed PE (5). The PE was severe in these patients. Mortality from the initial PE was 37% (5).

With early diagnosis, the risk of recurrent PE is lower. In PIOPED I, 20 patients did not receive treatment because the diagnosis was not established until later when central readers identified the PE on pulmonary angiograms (6). Among these 20 untreated patients, fatal PE occurred in one (5%), and one patient had a non-fatal PE on follow-up (6). Therefore, 10% of patients with untreated mostly mild PE suffered a PE on follow-up.

The rate of recurrence of PE from data on the outcome of patients with suspected PE in whom treatment was withheld following non-diagnostic ventilation/perfusion lung scans and normal serial non-invasive leg tests can be calculated. For example, among 711 patients with suspected PE and nondiagnostic ventilation/perfusion lung scans evaluated by Hull et al., three-month outcome of untreated patients with negative serial impedance plethysmography showed PE in four of 627 (0.6%) (7). Among 711 patients with non-diagnostic V/Q scans, 22% (156 patients) would have had PE based on results of PIOPED I (8). Since 84 patients were identified with impedance plethysmography and treated, the group of 627 who were followed with no anticoagulant therapy would have included 74 patients with PE. On follow-up, four of 74 (5.4%) showed recurrent PE.

Similar calculations and similar results are shown in data of Wells et al. (9). Among 702 patients with suspected PE, non-
diagnostic ventilation/perfusion lung scans and a low or moderate pretest clinical probability of PE, outcome at three months in those with negative serial compression ultrasound showed PE in three of 665 (0.5%) (9). If, as in PIOPED I, 52% of patients with non-diagnostic ventilation/perfusion lung scans had pulmonary embolism, then 154 of 702 would have had PE. Among these, 37 patients were identified with venous compression ultrasound and treated. The group of 665 who were followed with no anticoagulant therapy, therefore, would have included 117 patients with PE. On follow-up, three of 117 (2.6%) showed recurrent PE.

Smith et al., during an average of 8.4-months follow-up, showed PE in one of 173 untreated patients (0.6%) with low-probability ventilation/perfusion lung scans (10). Assuming that 14% of patients with low probability lung scans would have had PE, as in PIOPED I, the rate of PE on follow-up would have been one of 24 (4.2%). Finally, Kahn et al. on one-year follow-up showed no PE in 90 patients with a low-probability interpretation of ventilation/perfusion lung scans (11). If 13 of these patients would have had PE, based on the rate shown in PIOPED I, the rate of recurrent PE would have been 0 of 13 (0%).

In these five investigations, therefore, recurrent PE is estimated to have occurred in 0%, 2.6%, 4.2%, 5.4% and 10% of untreated patients in whom the initial PE was mild, (6, 7, 9–11). In PIOPED II, among 31 patients in whom the CT angiogram did not show PE, the outcome committee did not identify any PE on three-month follow-up (95% CI = 0 to 12.2). Based on the above calculations, perhaps as many as three patients would have shown PE on follow-up, which is well within the 95% confidence interval of this observation.

If 5.4% of untreated patients develop symptomatic recurrent PE, then, in the outcome studies by Perrier et al. (3), and in the Christopher study (2), if a CTA failed to identify 18% of patients with PE, outcome would have shown symptomatic PE on follow-up in <1%. If 10% of untreated patients develop symptomatic recurrent PE, then if a CT angiogram failed to identify 10% of patients with PE, 1% would have shown PE on follow-up.

In conclusion, the percentage of patients with PE who were not identified by CT angiography in PIOPED II was within the range calculated to have been present in the outcome studies of Perrier et al. (3), and in the Christopher study (2). When assessing a diagnostic test such as CT angiography, results of outcome studies may be entirely different than results of accuracy studies. Differences need not imply a methodological error. Outcome studies provide guidance for clinical management in excluding disease, whereas accuracy studies are mandatory for a true understanding of test performance in both diagnosing and excluding disease. Accuracy studies lay down a foundation for outcome studies, and both complement each other in regard to clinical management.

References