Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies: a systematic review

Kruip M J, Leclercq M G, van der Heul C, Prins M H, Buller H R

CRD summary
This review evaluated diagnostic strategies designed to exclude pulmonary embolism. The authors concluded that there was evidence to support strategies starting with a normal perfusion lung scan or a combination of normal D-dimer levels and low clinical probability, and after initial testing the use of angiography or lung scintigraphy was warranted. The conclusions of the review were balanced and appeared to be robust.

Authors' objectives
To evaluate diagnostic strategies designed to exclude pulmonary embolism (PE).

Searching
MEDLINE (from 1966 to February 2003), EMBASE, and DARE were searched for English language studies; the MeSH terms were reported. In addition, the references of identified studies and review articles were checked, and investigators in the field were contacted. Studies published in abstract form only were included if they provided sufficient data for analysis.

Study selection
Study designs of evaluations included in the review
Prospective studies that enrolled consecutive patients, which provided a detailed description of the method of follow-up and had a minimum follow-up of 3 months, and in which less than 10% of the patients were lost were eligible for inclusion.

Specific interventions included in the review
Studies that reported a priori the diagnostic strategy used to exclude or confirm the diagnosis of PE were eligible for inclusion. The specific tests evaluated were: pulmonary angiography, venography, lung scans, serial impedance plethysmography, clinical probability testing, D-dimer concentrations, compression ultrasonography, helical computed tomography (CT) and spiral CT. These were used alone or in combination to provide the diagnostic work-up strategies. The studies also had to withhold anticoagulant treatment when PE was excluded.

Reference standard test against which the new test was compared
The reference standard was clinical outcome during 3 months' follow-up.

Participants included in the review
Studies that assessed patients with recurrent symptoms of venous thromboembolism were eligible for inclusion. The patients included in the review were assessed in both in- and out-patient departments.

Outcomes assessed in the review
No inclusion criteria were specified in relation to the outcomes. The outcome assessed was the failure rate. This was defined as the frequency with which symptomatic venous thromboembolic events were confirmed by objective testing during a 3-month follow-up period in patients who had negative results on diagnostic tests for PE at baseline.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.
**Data extraction**

Three reviewers independently extracted the data, with any disagreements being resolved by discussion. Data were extracted on: the study size and setting; patient sampling and characteristics; prevalence of PE; diagnostic strategy and tests; the number of patients with a negative test result; the number of symptomatic thromboembolic events confirmed by objective testing in patients without PE and without anticoagulant treatment; and the duration and method of follow-up.

The failure rate and the upper 95% confidence interval (CI) were estimated for each study. Diagnostic strategies were considered safe if the upper 95% CI of the observed rate of confirmed episodes did not exceed 3% during the 3-month follow-up.

**Methods of synthesis**

**How were the studies combined?**

The studies were grouped according to the diagnostic strategies used: tests done in all referred patients, tests performed after a first diagnostic round, and tests performed in patients with non-diagnostic results after two diagnostic rounds. Studies with similar diagnostic strategies were combined in a meta-analysis. Pooled and weighted estimates of the failure rate were calculated, along with the associated 95% CIs. Publication bias was not assessed.

**How were differences between studies investigated?**

Differences between the studies with similar diagnostic strategies were assessed statistically using Fisher’s exact test.

**Results of the review**

Twenty-five prospective cohort studies with more than 7,000 patients were included.

No heterogeneity in the incidence of pulmonary thromboembolism was found among similar diagnostic studies.

All referred patients (19 studies, 4,096 patients).

The strategies associated with low failure rates were: normal results on pulmonary angiography with failure rate 0.8% (upper 95% CI: 2.1%), based on 1 study with 931 patients; normal results on lung scintigraphy with failure rate 0.9% (upper 95% CI: 2.3%), based on 7 studies with 441 patients; and normal D-dimer levels combined with low clinical probability with failure rate 0.2% (upper 95% CI: 0.8%), based on 4 studies with 894 patients.

Second-round tests (20 studies with 3,376 patients).

In patients with a non-diagnostic lung scan, the strategies associated with low failure rates were: normal pulmonary angiography with failure rate 0.0% (upper 95% CI: 3.5%), based on 1 study with 105 patients; and normal serial leg testing for venous thrombosis with failure rate 1.7% (upper 95% CI: 2.8%), based on 3 studies with 779 patients.

In patients with inconclusive D-dimer tests plus clinical probability, the strategies associated with low failure rates were: normal perfusion lung scan with failure rate 0.0% (upper 95% CI: 1.1%), based on 2 studies with 343 patients; and normal results on spiral CT with failure rate 0.0% (upper 95% CI: 3.5%), based on 1 study with 105 patients.

In patients with inconclusive first-round spiral CT and compression ultrasonography, the use of normal lung scintigraphy and/or pulmonary angiography gave low failure rates 0% (upper 95% CI: 4.3%), based on 1 study with 84 patients.

Strategies after two diagnostic rounds (7 studies).

Most of the studies had small sample sizes. Three studies (130 patients) examined the same diagnostic strategy. These found that in patients with elevated D-dimer levels, non-diagnostic lung scans, and moderate to high clinical probability, normal results on compression ultrasonography and pulmonary angiography had low failure rates of 0.8% (upper 95% CI: 4.2).
The results for other combinations of tests were reported in the paper.

**Authors’ conclusions**
Many diagnostic strategies to exclude PE have been assessed in consecutive patients. Interest in a simple, fast strategy, which starts with a normal perfusion lung scan or a combination of normal D-dimer levels and low clinical probability, is likely to increase. After the initial round of testing, a reliable diagnostic method, such as angiography or lung scintigraphy, is warranted.

**CRD commentary**
The review question was clearly defined in terms of the participants, interventions and study designs. A number of sources were searched for relevant studies, but only articles in English were included. This means that studies published in languages other than English might have been missed. The review methods were not reported clearly and, therefore, it was unclear whether any steps were taken to minimise bias and errors in selecting studies for inclusion in the review. In addition, since the quality of the included studies was not assessed, it is impossible to comment on how the quality of the included studies might have impacted on the results of the review. Appropriate methods to minimise reviewer bias and errors in the data extraction process were implemented.

The studies were appropriately grouped by type of diagnostic strategy and pooled within these groups. Heterogeneity between the studies was explored statistically. The authors appropriately highlighted (in the text) that the studies examined did not directly compare different diagnostic strategies, thus inferences regarding the relative safety of one strategy compared with another needed to be made with caution. Overall, the conclusions of the review were balanced and appeared warranted.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that further studies are required to assess the safety of excluding PE with normal results on spiral CT.

**Bibliographic details**

**PubMedID**
12809450

**Original Paper URL**
http://www.annals.org/cgi/content/full/138/12/941

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Fibrin Fibrinogen Degradation Products /analysis; Follow-Up Studies; Humans; Leg /ultrasonography; Lung /radiography /radionuclide imaging; Prospective Studies; Pulmonary Embolism /diagnosis; Risk Factors; Venous Thrombosis /diagnosis

**AccessionNumber**
12003008323

**Date bibliographic record published**
Date abstract record published
31/07/2005

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.