Clinical validity of a negative computed tomography scan in patients with suspected pulmonary embolism: a systematic review

CRD summary
This review investigated the use of computed tomography (CT) in ruling out the diagnosis of a pulmonary embolism. The authors concluded that a CT scan was comparable to conventional pulmonary angiography, that withholding anticoagulant therapy after a negative CT seemed safe, and additional imaging was not warranted. Considering the limitations of the review, these conclusions should be treated with caution.

Authors' objectives
To assess the validity of computed tomography (CT) to rule out a diagnosis of pulmonary embolism (PE).

Searching
MEDLINE, PubMed, EMBASE, CRISP, the meta Register of Controlled Trials and the Cochrane Library were searched from January 1990 to May 2004; the search terms were reported. The search was restricted to English language papers. The authors handsearched journals (number and titles not specified) and contacted experts in the field. The Science Citation Index was used to cross-reference articles that met the inclusion criteria. Reviews and editorials were excluded.

Study selection
Study designs of evaluations included in the review
Reviews, editorials and studies with a quality score of less than 5 were excluded. Studies with a minimum of 3 months appropriate follow-up (i.e. office visits, telephone interviews or questionnaires) were eligible for inclusion. Studies that did not report, or inappropriately reported, follow-up or VTE events were excluded. The follow-up in the included studies ranged from 3 to 12 months.

Specific interventions included in the review
Studies evaluating contrast-enhanced chest CT were eligible for inclusion. The CT modalities used in the included studies were single-slice CT, multidetector-row CT and electron-beam CT. Studies that included D-dimer testing as an initial triage tool were excluded.

Reference standard test against which the new test was compared
There were no clear inclusion criteria regarding the reference standard. It seems that diagnosis during a follow-up period of at least 3 months was the reference standard used.

Participants included in the review
Studies of more than 30 people with suspected PE were eligible for inclusion.

Outcomes assessed in the review
No inclusion criteria for the outcomes were specified. The primary outcome reported was the number of cases of venous thromboembolism (VTE), defined as either symptomatic or asymptomatic PE or deep vein thrombosis. The number of false-negative CT results was recorded, and negative likelihood ratios (NLRs) were calculated and reported for each included study.

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 criteria for assessing quality were publication in a peer-reviewed journal, prospective design, description of the imaging technique, patient demographics collected, follow-up, and the reporting of recurrences and mortality. Studies with a quality score below 5 (the maximum score attainable was not specified; however, it appeared to be 7) were excluded. The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

**Data extraction**
Two reviewers independently performed the data extraction, with any disagreements resolved by a third reviewer. The number of cases of PE and deep vein thrombosis were extracted for each study at 3, 6 and 12 months and used (together with the number of false-negative CT results) to calculate the overall NLR. Prevalences of PE from each study were used as estimates of pre-test probability to calculate negative predictive values (NPVs).

**Methods of synthesis**
How were the studies combined?
Pooled NLRs and 95% confidence intervals (CIs) for VTEs and deaths related to PE were calculated using both fixed-effect and DerSimonian and Laird random-effects meta-analyses. Patients who received anticoagulant therapy for reasons other than VTE were excluded from the analysis. The prevalence of PE from each study was used to estimate prior probability. Post-test probability of a VTE was defined as the product of the prior odds and the pooled NLR. The authors investigated publication bias using funnel plots.

How were differences between studies investigated?
Heterogeneity was evaluated statistically using the chi-squared statistic. Meta-regression was used to investigate the impact of additional imaging tests, CT modality used and the duration of follow-up on VTE. The influence of individual studies was investigated by omitting one study at a time and recalculating the summary statistic.

**Results of the review**
Fifteen studies (n=3,500) were included in the review.

The overall NLR of a VTE after a negative chest CT scan was 0.07 (95% CI: 0.05, 0.11), and the NPV was 99.1% (95% CI: 98.7, 99.5). The NLR was 0.08 (95% CI: 0.05, 0.13) after a negative single-slice CT and 0.15 (95% CI: 0.05, 0.43) after a negative multidetector-row CT. The overall NLR for mortality attributed to PE was 0.01 (95% CI: 0.01, 0.02), and the NPV was 99.4% (95% CI: 98.7, 99.9).

The relative risk (RR) of VTE was not significantly reduced when additional imaging techniques were used in comparison with chest CT alone (RR 0.51, 95% CI: 0.22, 1.17). The RR of VTE was not significantly increased when single-slice CT was compared with multidetector-row CT (RR 1.66, 95% CI: 0.47, 5.94), or when the follow-up extended beyond 3 months (RR 1.05, 95% CI: 0.43, 2.52).

The authors stated that the meta-regression did not reveal a significant source for the heterogeneity seen between the studies, and that there was no indication of publication bias.

**Authors' conclusions**
The clinical validity of using a CT scan to rule out PE was similar to that reported for conventional pulmonary angiography.

**CRD commentary**
The review question was clear in terms of the index test, population and outcomes, but the inclusion criteria relating to the reference standard were less clear. The authors restricted the review to data published in English in peer-reviewed journals, therefore publication and language bias could not be ruled out. The authors investigated publication bias and discussed other possible sources of bias in detail. Although the data extraction was performed in duplicate, it was
unclear whether similar measures to reduce error and bias were utilised in the study selection or quality assessment processes. No results of the chi-squared test for heterogeneity were given for any of the subgroup analyses. Given the limitations of the review, the conclusions and implications for practice should be treated with caution.

Implications of the review for practice and research
Practice: The authors stated that withholding anticoagulant therapy after a negative CT scan appeared safe, and that additional imaging for ruling out PE was not warranted.

Research: The authors did not state any implications for further research.

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