What Is the Risk of a Venous Thromboembolic Event After a Negative Computed Tomographic Pulmonary Angiography Result?

TAKE-HOME MESSAGE

Computed tomographic (CT) pulmonary angiography may exclude venous thromboembolism in patient populations with less than 40% prevalence of disease, but it is insufficient to exclude venous thromboembolism, in particular deep venous thrombosis, in patients with higher disease prevalence.

METHODS

DATA SOURCES

Investigators searched MEDLINE, EMBASE, and the Cochrane Library from January 1990 to May 31, 2017, using predefined search terms. Authors searched references of included studies and systematic reviews, meta-analyses, and other texts found during the search. They also conducted a search of conference abstracts.

STUDY SELECTION

Authors selected prospective outcome studies of patients undergoing CT pulmonary angiography and a predefined diagnostic strategy used to confirm or exclude venous thromboembolism (pulmonary embolism and deep venous thrombosis) during subsequent follow-up (within 3 months). Two investigators read the title and abstract of each study identified, eliminated studies not meeting inclusion criteria, read each study independently to determine eligibility, and settled disagreements by either consensus or discussion with a third author. Inclusion criteria were prospective outcome

EBEM Commentators
Brit Long, MD
Michael D. April, MD, DPhil
Department of Emergency Medicine, San Antonio Uniformed Services Health Education Consortium, Fort Sam Houston, TX

This review does not reflect the views or opinions of the US government, Department of Defense, US Army, US Air Force, or SAUSHEC EM Residency Program.

Jestin N. Carlson, MD, MS, and Alan Jones, MD, serve as editors of the SRS series.

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Belzile D, Jacquet S, Bertoletti L, et al. Outcomes following a negative computed tomography pulmonary angiography according to pulmonary embolism prevalence: a meta-analysis of the management outcome studies. *J Thromb Haemost.* 2018;16:1107-1120.**

Results

Results of included trials.

PE Prevalence	No. of Studies (Negative CTPA Result)	No. of VTE Events	Proportion With VTE After Negative CTPA Result* (95% CI), %	Heterogeneity (I^2), %
Overall	22 (7,863)	222	2.4 (1.3–3.8)	92
Subgroup analysis, %				
<20	5 (1,316)	25	1.8 (0.5–3.7)	78
20–29	11 (1,985)	37	1.4 (0.7–2.3)	67
30–39	13 (943)	35	1.0 (0.5–1.8)	58
≥40	4 (1,805)	70	8.1 (3.5–14.5)	88

PE, Pulmonary embolism; *CTPA*, CT pulmonary angiography; *VTE*, venous thromboembolic event; *CI*, confidence interval.
*Percentage based on random-effects model.

Authors included 22 prospective studies for analysis from the initial 3,143 publications retrieved. From the included studies, 11 used 4-detector (4 to 64 multislice) CT scanner, 4 used single-detector helical CT, 2 used single and multidetector CT, and 5 did not

studies with detailed inclusion or exclusion criteria, selection of consecutive patients, CT pulmonary angiography–based diagnostic strategy, predefined clinical follow-up, predefined diagnostic strategy to confirm or exclude venous thromboembolism during follow-up, and systematic report of symptomatic subsequent venous thromboembolism. Authors excluded studies with overlapping or duplicated patient cohorts and pediatric studies.

DATA EXTRACTION AND SYNTHESIS

Two authors extracted data independently, and if they could not obtain the necessary data directly from the publication, they attempted to contact the original trial investigators. Investigators used a random-effects model to obtain summary estimates with 95% confidence intervals of the proportion of patients with confirmed venous thromboembolism at the index visit versus follow-up after a negative CT pulmonary angiography result. To calculate the overall proportion of venous thromboembolism events that clinicians would miss by using CT pulmonary angiography as a stand-alone imaging test, the authors included deep venous thrombosis or pulmonary embolism objectively confirmed by an additional imaging test despite a negative CT pulmonary angiography result during the index event and objectively confirmed venous thromboembolism that occurred during subsequent clinical follow-up. The authors excluded from analysis specific patients with an inconclusive CT pulmonary angiography result or who received anticoagulant therapy for reasons other than venous thromboembolism during follow-up. The meta-analysis calculated the specify the CT technology used. In regard to additional imaging, 5 studies included routine venous ultrasonography, 9 used alternative imaging per protocol, and 5 included additional imaging only at the physicians' discretion. The follow-up period was 3 months for 20 studies and 6 to 36 months for the other 2 studies. The overall venous thromboembolism prevalence diagnosed at either the index or follow-up visit was 33% (3,923 of 11,872 patients), ranging from 16.4% to 74.5%. Of the 7,863 patients with negative CT pulmonary angiography results, 148 (1.9%) had venous thromboembolism according to venous ultrasonography (113), ventilation-perfusion scan (3), angiography (4), or an unspecified alternative modality during the index visit (28). An additional 74 patients (0.9%) experienced deep venous thrombosis (26), nonfatal pulmonary embolism (22), fatal pulmonary embolism (22), and unspecified venous thromboembolism (4) in follow-up. Twenty-five patients were lost to follow-up. The authors' random-effects models generated an estimated proportion of patients with venous thromboembolism at the index visit or during follow-up after negative CT pulmonary angiography results of 2.4% and CT pulmonary angiography sensitivity of 94.6% (Table). Subgroup analyses demonstrated that the probability of venous thromboembolism diagnosed after negative CT pulmonary angiography result varied significantly with the overall prevalence of venous thromboembolism, with venous thromboembolism diagnosed in 1.8% of patients with overall venous thromboembolism prevalence less than 20% versus 8.1% of patients with overall venous thromboembolism prevalence greater than or equal to 40%. All included studies demonstrated good methodological quality but high heterogeneity.

Commentary

Pulmonary embolism can lead to poor outcomes if not appropriately diagnosed, and emergency department (ED) evaluation for pulmonary embolism requires an accurate diagnostic modality to avoid delays in management.[2,3] CT pulmonary angiography is currently an integral component of the ED evaluation for suspected pulmonary embolism, which provides direct visualization of the pulmonary arterial circulation. Previous studies suggest that a negative CT pulmonary angiography result may safely exclude pulmonary embolism, with low 3-month risk of venous thromboembolism and high sensitivity.[4-7] Current guidelines recommend using CT pulmonary angiography as a stand-alone imaging test for pulmonary embolism; however, patients with high clinical probability and negative CT pulmonary angiography results present a quandary because of higher false-negative rates.[3,8,9]

This meta-analysis assessed the proportion of patients with venous thromboembolism despite a negative CT pulmonary angiography result based on pulmonary embolism prevalence. Authors calculated an overall 2.4% rate of venous thromboembolism at the index event or within 3-month follow-up despite a negative CT pulmonary angiography result, which increased as overall prevalence increased in subgroup analyses. Of the patient population

probabilities of venous thromboembolism despite negative CT pulmonary angiography results, stratified by overall venous thromboembolism prevalence subgroups (<20%, 20% to 29%, 30% to 39%, and >40%) and evaluated heterogeneity with the χ^2 and I^2 tests. Authors evaluated publication bias with funnel plot and assessed methodological quality with the Quality Assessment of Diagnostic Accuracy Studies assessment tool.[1]

with greater than or equal to 40% venous thromboembolism prevalence, the subgroup with a negative CT pulmonary angiography result at the initial evaluation had a prevalence of venous thromboembolism of 8.1% (95% confidence interval 3.5% to 14.5%). Of course, the application of test results in clinical practice does not depend on disease prevalence, which is knowable only in retrospect after the completion and interpretation of testing at the population level. Rather, clinicians must rely on pretest probability, usually informed by scoring systems or gestalt. To the extent that pretest probability accurately reflects overall prevalence of disease, the results of this meta-analysis facilitate Bayesian reasoning supported by other studies[10]: although a negative CT pulmonary angiography result may reliably exclude venous thromboembolism in patients with low to intermediate pretest disease probability, this test alone is insufficient to exclude venous thromboembolism among those with a high pretest disease probability. Unfortunately, the use of prevalence instead of pretest probability as an analytic framework makes this clinical application dubious and hence represents the single most important limitation of this meta-analysis.

This meta-analysis has several other important limitations. First, pulmonary embolism prevalence in the studied populations ranged from 16.4% to a staggering prevalence of 74.5%. These values far exceed the yield for contemporary pulmonary embolism testing in most US EDs and so may inflate the estimated risk of missed venous thromboembolism. Another factor potentially inflating these estimates is that a majority of cases of missed venous thromboembolism were due to deep venous thrombosis. Yet CT pulmonary angiography assesses for pulmonary embolism and is an inadequate modality for excluding deep venous thrombosis. Second, no information is present in regard to the clinical significance of pulmonary embolisms, especially subsegmental pulmonary embolisms. Third, CT scanning technology varied among the studies, and true accuracy may be different with newer-generation CT scanners. Fourth, there was a difference in confirmatory testing among the included studies, and more intensive screening may have introduced detection bias into the evaluation of the high-risk population. Moreover, many studies did not use a true criterion standard. For example, modalities assessing for deep venous thrombosis, such as lower extremity ultrasonography, do not assess for pulmonary embolism. Furthermore, many studies used ventilation-perfusion scan, which can lead to a false-positive test result, resulting in ambiguity in regard to which test result is actually correct. Other limitations of this meta-analysis include various follow-up periods, which can affect incidence of venous thromboembolism after negative CT pulmonary angiography results, although most used 3 months. Assessing for the presence of pulmonary embolism on follow-up CT pulmonary angiography may identify a new pulmonary embolism, rather than diagnose a missed pulmonary embolism from the index visit. There was also significant heterogeneity in regard to study methodology.

This meta-analysis suggests patient populations with less than 40% prevalence of venous thromboembolism have low risk of missed venous thromboembolism after negative CT pulmonary angiography results. Moreover, the majority of missed venous thromboemboli are deep venous thromboses, suggesting that the addition of lower extremity ultrasonographic studies to diagnostic algorithms may further decrease the probability of missed venous thromboembolism. However, the risk of missed venous thromboembolism remains high after a negative CT pulmonary angiography result in patient populations with greater than or equal to 40% disease prevalence. The clinical applicability of these findings remains unclear because physicians interpret test results according to pretest probability, not prevalence. Further studies are necessary to clarify the relationships between missed venous thromboembolism and pretest probability as defined by scoring systems or clinical gestalt. Further studies are also necessary to evaluate the effect of contemporary CT scanner technology and algorithms

incorporating lower extremity ultrasonography on the risk of missed venous thromboembolism.

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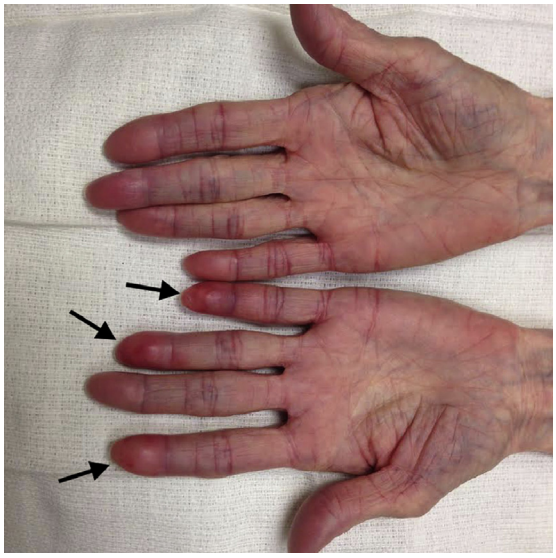

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