

Critical Review Form Therapy

[Freund Y, Chauvin A, Jimenez S, et al. Effect of a Diagnostic Strategy Using an Elevated and Age-Adjusted D-Dimer Threshold on Thromboembolic Events in Emergency Department Patients With Suspected Pulmonary Embolism: A Randomized Clinical Trial. JAMA. 2021 Dec 7;326\(21\):2141-2149.](#)

Objectives: “to determine whether in emergency department (ED) patients with suspicion of PE that was not excluded by the PERC rule, a strategy that combines the YEARS rule and the age-adjusted D-dimer cutoff can safely rule out the diagnosis... Whether this strategy decreased the use of chest imaging was also determined.” (p. 2142)

Methods: This cluster-randomized, crossover, [noninferiority trial](#) was conducted in 18 EDs from France (n = 16) and Spain (n = 2) affiliated with the [Improving Emergency Care Research Federation](#). Recruitment occurred between October 1, 2019, and October 8, 2020, but was paused during the first COVID-19 wave and resumed after 4 to 6 weeks.

Patients included were adults presenting with clinical suspicion of PE and either a low subjective probability (< 15%) with one or more PERC score elements or an intermediate subjective probability of PE (16-50%). Exclusions included high subjective probability (> 50%), severe illness, current anticoagulant treatment, current thromboembolism diagnosis, pregnancy, being a correctional facility inmate, or symptoms related to other causes than PE. Randomization was computer-generated and stratified by country and ED size, with each ED assigned to either a control or intervention strategy period for four months, separated by a two-month washout.

In the intervention strategy, patients with no [YEARS criteria](#) and a D-dimer level below 1000 ng/mL, or with one or more YEARS criteria and a D-dimer level below the [age-adjusted threshold](#), were ruled out for PE. During the control period, all patients underwent age-adjusted D-dimer testing based on current guidelines. A D-dimer above the relevant threshold in either group triggered chest imaging. Outcomes were analyzed at the individual patient level, with the primary outcome being VTE diagnosis within three months after initial exclusion of PE, determined by telephone interview. The noninferiority margin for this outcome was set at 1.35%. There were several secondary outcomes, including use of chest imaging (CTPA or V/Q scan), ED length of stay, hospital admission, anticoagulant administration, all-cause mortality, and all-cause readmission at 3 months.

The trial enrolled 1414 patients, with 726 in the intervention group and 688 in the control group. After excluding 106 patients due to ineligibility or protocol deviations, 1271 were included in the per-protocol analysis. The mean patient age was 55 years, and 58% were female. PE was diagnosed in 100 patients in the ED: 54 (7.4%) in the intervention group and 46 (6.7%) in the control group.

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Guide	Comments
Are the results valid?	
Did experimental and control groups being the study with a similar prognosis?	
Were patients randomized?	Sort of. This was a cluster randomized trial . "Each ED was randomized to either the control strategy period for 4 months, followed, after a 2-month washout period, by the intervention strategy period for 4 months, or to the reverse order. The randomization ratio was 1:1. Randomization was stratified by country and ED size (small vs large defined as <50,000 or ≥50,000 patients per year), using 4 blocks of 4 and 1 block of 2." (p. 2143)
Was allocation concealed? Was it possible to subvert the randomization to ensure a patient would be "randomized" to a particular group?	Yes. "The randomization sequence was computer generated by a statistician who was not otherwise involved in the trial using PROC PLAN (SAS version 9.4; SAS Institute). This was concealed until the center was instructed by the global project manager to begin the study." (p. 2143) It would not have been possible to influence the allocation of study sites.
Were patients analyzed in the groups to which they were randomized?	No. "Because this was a noninferiority study, the primary end point was assessed in the per-protocol population to avoid favoring the noninferiority hypothesis." (p. 2144)
Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar in regards to age, gender, medical comorbidities, history of active cancer, prior VTE, symptoms, vital signs, PE risk factors, and presence of signs of DVT.
Did experimental and control groups retain a similar prognosis after the study started?	
Were patients aware of group allocation?	Maybe. There was no blinding of patients or clinicians, however it is unlikely many patients are aware of PE risk stratification tools or their use. It is unlikely that performance bias on the part of patients would have influenced outcomes.
Were clinicians aware of group allocation?	Yes. There was no blinding of clinicians. This awareness could have influenced their interpretation of aspects of risk scores or assessment of pre-test probability.
Were outcome assessors aware of group allocation?	No. "The primary outcome was adjudicated by 3 clinicians with expertise in thromboembolic disease, had no other involvement in the study, worked independently, and were blinded to study period. (p. 2143)
Was follow-up complete?	Mostly yes. The primary endpoint was missing in 37 patients (2.6%) which were replaced by zero in the as-randomized population.
What are the results?	
How large was the treatment effect?	- In the per-protocol population 6 PEs not found during the index ED visit were diagnosed at 3 months, 1 in the intervention group and 5 in the control group. The failure rate was therefore 0.15% (95% CI, 0.00% to 0.86%) in the intervention group and 0.80% (95% CI, 0.26% to 1.86%) in the control group. - The adjusted difference in the failure rate between the 2 groups was -0.64% (1-sided 97.5% CI, -∞ to 0.21%), the upper bound of which is less than the noninferiority margin of 1.35%. - In the as-randomized population, chest imaging was performed less often in the intervention group (30.4%) compared to the control group (40.0%); adjusted difference -8.7%, 95% CI -13.8% to -3.5%.

	- The median ED length of stay was lower in the intervention group (6.0 hours) compared to the control group (6.0 hours); adjusted difference -1.6 hours, 95% CI -2.4 to -0.9. - None of the other outcomes differed with any statistical significance between groups.
How precise was the estimate of the treatment effect? (i.e. what 95% CIs were associated with the results?)	See above.
How can I apply the results to patient care?	
Were the study patients similar to my patient?	Uncertain. This study was conducted at multiple sites in France and Spain, where some differences in diet, ethnicity, and medical history could influence risk of PE and affect the results (external validity).
Were all clinically important outcomes considered?	Yes. The authors considered the failure rate, proportion of patients undergoing chest imaging, ED length of stay, mortality, and need for hospital admission. They did not assess for episodes of major or minor bleeding or long-term consequences of radiation exposure.
Are the likely treatment benefits worth the potential harm and costs?	Yes. It would appear that the use of the YEARS criteria in conjunction with an age-adjusted d-dimer, when appropriate, does not result in a higher miss rate for PE that use of an age-adjusted d-dimer alone. Additionally, this algorithm resulted in decreased use of chest imaging and shorter ED length of stay.

Limitations:

- 1. There was, understandably, no blinding of clinicians. This awareness could have influenced their interpretation of aspects of risk scores or assessment of pre-test probability ([performance bias](#)).**
- 2. This study was conducted at multiple sites in France and Spain, where some differences in diet, ethnicity, and medical history could influence risk of PE and affect the results ([external validity](#)).**
- 3. The primary endpoint was missing in 37 patients (2.6%) which were replaced by zero in the as-randomized population.**

Bottom Line:

In this multicenter, cluster randomized study conducted in France and Spain, the use of the YEARS criteria in conjunction with an age-adjusted d-dimer, when appropriate, does not result in a higher miss rate for PE that use of an age-adjusted d-dimer alone (adjusted difference -0.64%; 1-sided 97.5% CI, $-\infty$ to 0.21%). Additionally, this algorithm resulted in decreased use of chest imaging by nearly 10% and shorter ED length of stay.