[Pulmonary Vascular Original Research]

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Safety of Age-Adjusted and Clinical Probability-Adjusted D-Dimer Cutoffs in Suspected Pulmonary Embolism

A Systematic Review and Meta-Analysis

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BACKGROUND: Adaptive D-dimer strategies for ruling out pulmonary embolism (PE) have been proposed to improve the efficiency of conventional fixed 500 D-dimer thresholds. Validations of adaptive D-dimer strategies post hoc in cohorts managed according to the fixed D-dimer threshold seem to question their safety.

RESEARCH QUESTION: What is the proportion of diagnostic failures in patients with suspected PE managed according to an adaptive strategy who have a D-dimer level of > 500 ng/mL, but less than the adaptive threshold, defined as the *adaptive window*?

STUDY DESIGN AND METHODS: We conducted a systematic review and meta-analysis of prospective diagnostic management studies that recruited at least 50 patients with suspected PE and in which an adaptive D-dimer threshold was used to guide chest imaging. Diagnostic failure was defined as VTE or PE-related or unexplained death occurring within 3 months. Exclusion criteria were: (1) data required to calculate the primary outcome were unavailable or (2) the study included only children or pregnant patients. Study-specific proportions were pooled using a random-effects meta-analysis.

RESULTS: Six studies (12,194 patients) were included, with a PE prevalence ranging from 7.0% to 19.2%. Among all patients in whom PE was ruled out without CT pulmonary angiography using adaptive D-dimer strategies, failure rates ranged from 0.00% to 0.27%, with a pooled overall failure rate of 0.12% (95% CI, 0.06%-0.26%; $I^2 = 0\%$). The pooled failure rate in the adaptive D-dimer window was 0.50% (95% CI, 0.20%-1.11%; $I^2 = 0\%$). Pooled algorithm-based efficiency was 60.8% (95% CI, 49.2%-71.2%; $I^2 = 99.3\%$).

INTERPRETATION: Our results show that the diagnostic failure rate of adaptive strategies for the diagnosis of acute PE is acceptably low, and also is in patients with a D-dimer in the adaptive window.

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KEY WORDS: algorithms; D-dimer; diagnosis; pulmonary embolism

ABBREVIATIONS: AADD = age-adjusted D-dimer; CTPA = CT pulmonary angiography; DVT = deep vein thrombosis; IQR = interquartile range; PE = pulmonary embolism

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Take-Home Points

Research Question: Are age-adjusted and clinical probability-adjusted D-dimer strategies safe for ruling out pulmonary embolism (PE) in patients with suspected acute PE?

Results: Adaptive D-dimer strategies were associated with a very low pooled diagnostic failure rate (0.12%), including a 0.50% failure rate among patients within the adaptive D-dimer window, while avoiding imaging in approximately 61% of patients.

Interpretation: Validated adaptive D-dimer strategies safely reduce unnecessary chest imaging and support their broader implementation in the diagnostic workup of suspected PE.

The diagnosis of acute pulmonary embolism (PE) is challenging because signs and symptoms are nonspecific.[1] To reduce the use of CT pulmonary angiography (CTPA) and its associated risks and costs, guidelines recommend diagnostic algorithms that combine a clinical decision rule with D-dimer testing.[2-4] In patients with nonhigh clinical probability, a D-dimer less than a fixed prespecified threshold (typically 500 ng/mL) allows PE to be ruled out without imaging. In prospective studies, this approach has avoided CTPA in > 30% of outpatients with suspected PE.[5,6] However, the proportion of patients with a confirmed diagnosis of PE remains low in many settings, and diagnostic performance is influenced by the characteristics of the evaluated population and the prevalence of disease.[7-9]

To increase efficiency of the algorithm further, adaptive D-dimer strategies have been proposed. An age-adjusted D-dimer threshold has been validated prospectively and is associated with an additional approximately 10% to 12% absolute reduction in chest imaging, mainly CTPA, use for patients ≥ 50 years of age and with a nonhigh pretest probability of PE.[10,11] Clinical probability-adjusted strategies (eg, YEARS, PEGeD) apply higher thresholds conditional on the pretest probability aiming to increase efficiency compared with the fixed 500 cutoff across all age categories.[10,12-14]

Although prospective management studies have proven the safety of adaptive D-dimer strategies, these have not been compared directly with the conventional D-dimer threshold in randomized trials. In meta-analyses in which different strategies are applied post hoc to historical cohorts, the failure rate of adaptive D-dimer strategies seems higher, feeding ongoing debate on the optimal diagnostic approach.[5,6] To assess the safety of the modern diagnostic algorithm for suspected acute PE accurately, we conducted a systematic review and meta-analysis of studies that prospectively ruled out PE by the use of adaptive D-dimer thresholds. We estimated the incidence of potentially preventable failures in patients who had a D-dimer of > 500 ng/mL, but less than the adaptive threshold (the so-called adaptive window); these potentially were preventable failures if a fixed 500-ng/mL strategy had been applied and these patients had been subjected to imaging at baseline.

Study Design and Methods

Search Strategy

We searched MEDLINE, Embase, Web of Science, and Cochrane library from January 1, 1995, through January 1, 2026, to retrieve all diagnostic studies that prospectively evaluated diagnostic strategies for acute PE. The prespecified protocol for this review was registered in the International Prospective Register of Systematic Reviews. This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines for diagnostic test accuracy study.[15] Details of the search strategy are provided in e-Appendix 1.

Study Selection

For the articles published after January 1, 2021, 2 independent investigators (M.G. and B.A.) independently screened the titles and abstract and independently screened the full text of eligible studies. Any differences between the 2 independent searches were resolved through discussion. For the articles published between

Hemostasis (B. A., T. E. v. M., and F. A. K.), Department of Medicine, Leiden University Medical Center, Leiden; the Julius Center for Health Sciences and Primary Care (G.-J. G.), University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; the Emergency Department (Y. F. and H. B.), Sorbonne Université, Hopital Pitié-Salpêtrière, Assistance Publique - Hôpitaux de Paris, Paris, France; and the Division of Angiology and Hemostasis (M. R.), Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland.

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January 1, 1995, and January 1, 2021, we took advantage from the search and study selection as performed in a previous individual-patient data meta-analysis and its prespecified protocol.[5,16]

Inclusion Criteria

Eligible studies were prospective diagnostic management studies enrolling ≥ 50 patients and applying an adaptive D-dimer strategy to select patients with suspected acute PE for imaging. As prespecified in the International Prospective Register of Systematic Reviews protocol, adaptive D-dimer strategies were classified as age-adjusted D-dimer thresholds or clinical probability-adjusted D-dimer thresholds (eg, YEARS and PEGeD), applied in conjunction with a clinical prediction rule. Furthermore, a clinical follow-up of at least 1 month to identify any missed PE at baseline had to be scheduled. Studies were excluded if available data, either reported in the primary publication or supplied by the authors on request, did not allow determination of whether patients in each of the diagnostic failure categories would have undergone CTPA at baseline if a fixed D-dimer cutoff had been used. Furthermore, studies were required to provide a clear description of the source of patient enrolment or clinical health care setting. Studies including only children or pregnant patients were not eligible for inclusion, nor were studies not available as full reports.

Risk of Bias Assessment

The risk of bias was assessed independently by 2 reviewers (B. A. and M. G.). For all studies, we used the Quality Assessment of Diagnostic Accuracy Studies 2 tool.[17] Each potential source of bias was judged as low, high, or unclear, and an overall risk of bias was assigned accordingly. Disagreements were resolved by discussion with the other 2 reviewers (C. B. and F. A. K.).

Study Outcomes

The primary study outcome was diagnostic failure. Overall diagnostic failure was defined as the composite of objectively confirmed proximal DVT, PE, or PE-related or unexplained death occurring within 3 months among all patients in whom PE was ruled out without CTPA (or other imaging tests) at baseline according to an adaptive D-dimer strategy. Diagnostic failure in the adaptive window was defined as the composite outcome occurring within 3 months in patients having a D-dimer of between 500 ng/mL and the adaptive D-dimer cutoff who did not undergo CTPA (or other imaging tests) at baseline. These patients would have undergone imaging had a conventional fixed D-dimer threshold of 500 ng/mL been applied. Patients who were lost to follow-up, did not adhere to the prespecified diagnostic strategy, or initiated anticoagulation for an indication other than PE during follow-up were excluded from the analyses. Algorithm-based efficiency was defined as the number of patients managed without imaging as a proportion of all patients enrolled.

Statistical Analysis

For each study, outcomes were summarized as proportions with exact binomial 95% CIs. For the overall failure rate, the numerator was the number of patients in whom PE was ruled out without CTPA (or other imaging tests) at baseline according to an adaptive D-dimer strategy who experienced objectively confirmed proximal DVT, PE, or PE-related or unexplained death within 3 months. The denominator was the total number of patients in whom PE was ruled out without baseline imaging.

For the failure rate in the adaptive window, the numerator was the number of patients with a D-dimer level of > 500 ng/mL, but less than the adaptive D-dimer cutoff who did not undergo baseline imaging and who experienced the same composite outcome within 3 months. The denominator was the total number of patients within the adaptive window in whom imaging was withheld at baseline.

Prespecified subgroup analyses were planned in patients with cancer and in older patients, using the age cutoff prespecified in each included study. Study-specific proportions were pooled using random-effects meta-analysis after logit transformation. Zero-event cells were handled by adding 0.5 to studies with no observed events (continuity correction). As a sensitivity analysis, all meta-analyses of proportions were repeated using the Freeman-Tukey double-arcsine transformation to assess the robustness of the pooled estimates to the choice of transformation.

Pooled estimates are reported with 95% CIs and between-study heterogeneity is quantified by τ^2, I^2, and Cochran's Q (P value for heterogeneity). Algorithm-based efficiency was defined as the number of patients managed without imaging as a proportion of all patients enrolled. All analyses were conducted in R software (R Foundation for Statistical Computing) using the meta package.

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Results

Overall, 17,426 studies published after January 1, 2021, were retrieved by electronic searches. After title and abstract review, 43 studies were selected for full-text review. An additional 40 studies published before January 1, 2021, were selected for full-text review from a previously conducted meta-analysis.[5] Of these 83 studies, 6 studies (12,194 patients) were included.[10,12-14,18,19] The flow diagram showing study selection is reported in e-Figure 1.

An overview of the diagnostic strategies and the corresponding studies included in the meta-analysis is provided in Figure 1 and e-Figure 2. One study included patients from 2 different routes; only patients included through the prospective management route (n = 107) of this study were deemed eligible for the meta-analysis.[18] Overall, the risk of bias was judged to be low across most Quality Assessment of Diagnostic Accuracy Studies 2 domains. Some concerns were identified in selected domains in a minority of studies, related mainly to reference standard, flow, and timing (e-Tables 1, 2).

Data to assess the primary outcome was available in the primary publication in 3 studies and was supplied by the authors of the remaining 3 studies on request.[10,12-14,18,19] The clinical settings ranged from referred secondary care to inpatients and primary care. In all studies, CTPA was by far the most common imaging method applied. High-sensitivity quantitative D-dimer assays from several validated platforms (such as VIDAS, Tinaquant, STA-Liatest, Innovance, HemosIL, and Triage) were used across the studies. PE prevalence at baseline ranged from 7.0% to 19.2%, with an overall pooled prevalence of 9.5% (95% CI, 6.3%-14.1%; $I^2 = 98\%$) (Table 1).

Failure Rates

Among patients in whom PE was ruled out without CTPA using adaptive D-dimer strategies, the overall proportion of diagnostic failures was consistently low across studies: 0.09% (1 of 1,141) in ADJUST-PE,[10] 0.25% (4 of 1,589) in YEARS,[12] 0.0% (0/1,316) in PeGED,[13] 0.0% (0 of 83) in PECAN,[18] 0.22% (1 of 451) in the YEARS arm and 0.27% (1 of 365) in the age-adjusted D-dimer arm of MODIGLIANI,[14] and 0.0% (0 of 753) in MODS[19] (Table 2). The pooled overall failure rate was 0.12% (6 studies, 5,698 patients, and 7 events; 95% CI, 0.06%-0.26%; $I^2 = 0\%$) (Fig 2A).

When stratified by strategy, the pooled overall failure rate was 0.24% (95% CI, 0.10%-0.56%; pooled baseline prevalence of 12% [95% CI 4%-29%]; $I^2 = 98\%$) for YEARS-like strategies and 0.13% (95% CI, 0.03%-0.53%; pooled baseline prevalence of 11% [95% CI 10%-12%];

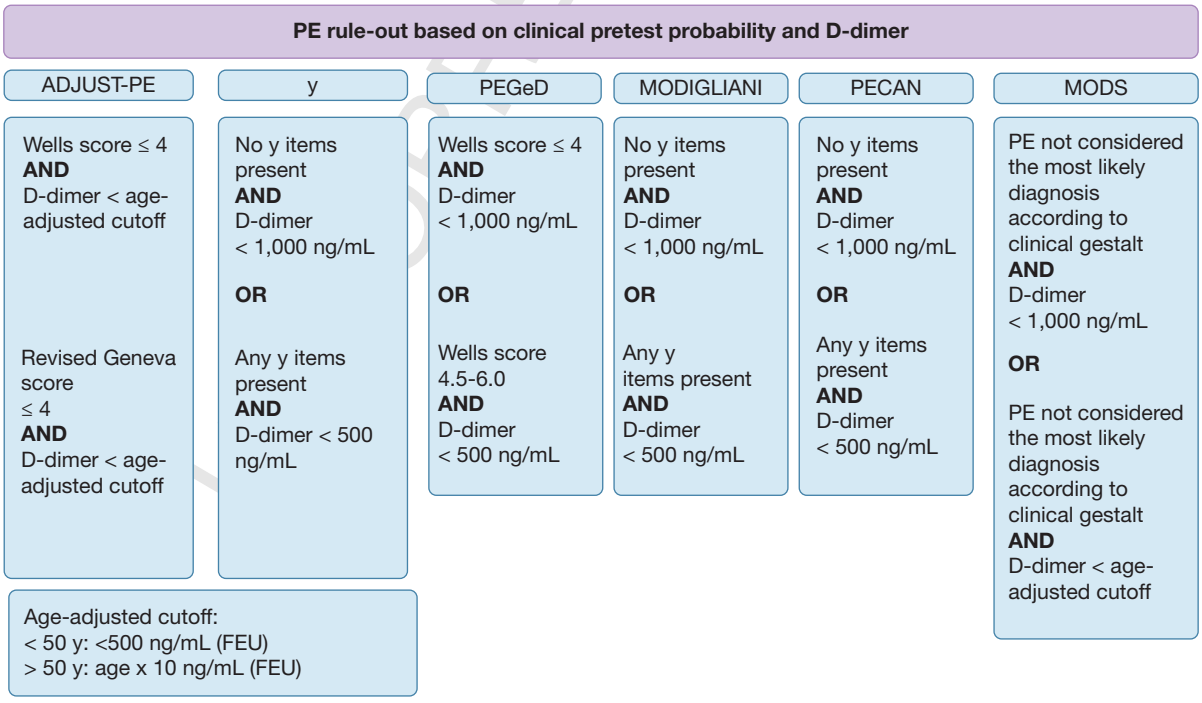


Figure 1 – *Flow diagram showing diagnostic strategies adopted in the included studies. PE = pulmonary embolism.*

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TABLE 1] Characteristics of the Included Studies

Variable	Study (Authors, Year)					
	ADJUST-PE (Righini et al, 2014)[10]	YEARS (Van Der Hulle et al, 2017)[12]	PeGED (Kearon et al, 2019)[13]	MODIGLIANI (Freund et al, 2021)[14]	PECAN (Van Maanen et al, 2025)[18]	MODS (Roussel et al, 2025)[19]
Proportion of included vs eligible patients	75.2%	95.8%	64.4%	Not available	Not available	89.5%
No. of patients	3,324	3,465	2,017	1,414	753 (prospective route n = 107)	1,221
Years of enrolment	2010-2013	2013-2015	2015-2018	2019-2020	2018-2022 prospective route, 2021-2023 learning health care	2024
Setting	Referred secondary care	Referred secondary care and inpatients	Referred secondary care and inpatients	Referred secondary care, PERC+	Primary care	Secondary care, PERC+
D-dimer assays	VIDAS (n = 1,345 [46%]); COBAS (n = 13 [0.4%]); Tinaquant (n = 128 [4.4%]); STA-Liatest (n = 389 [13%]); Innovance (n = 838 [29%]); HemosIL (n = 185 [6.3%])	VIDAS, Tinaquant, STA-Liatest, Innovance	STA-Liatest (n = 1,250 [71%]), HemosIL (n = 329 [19%]), Innovance (n = 124 [7%]); Triage (n = 31 [2%]); other (n = 18 [1%])	Not reported	Innovance D-dimer (n = 75 [100%])	NA
Imaging method	CTPA	CTPA	CTPA or V̇/Q̇ scan[a]	CTPA or V̇/Q̇ scan	CTPA	CTPA
Follow-up, mo	3	3	3	3	3	3
CDR and management strategies	Wells 2 levels, simplified-Geneva	YEARS algorithm	Wells 2 levels	PERC followed by YEARS	YEARS algorithm	Clinical judgement
Age, y	63.0 (53.0-74.0)	53 (18)	52 (18)	55 (19)	55 (41.8-66); 55 (42-66), prospective route	55 (19)
Female sex	1,887 (56.8%)	2,154 (62.2%)	1,335 (66.2%)	823 (58.0%)	521 (69.7%)	727 (60.0%)
History of venous thromboembolism	466 (14.0%)	359 (10.4%)	164 (8.1%)	110 (7.8%)	Not available	98 (8.0%)
Surgery or immobilization < 4 wk	392 (11.8%)	407 (11.8%)	149 (7.4%)	60 (4.2%)	Not available	63 (5.0%)

(Continued)

TABLE 1] *(Continued)*

Variable	Study (Authors, Year)					
	ADJUST-PE (Righini et al, 2014)[10]	YEARS (Van Der Hulle et al, 2017)[12]	PeGED (Kearon et al, 2019)[13]	MODIGLIANI (Freund et al, 2021)[14]	PECAN (Van Maanen et al, 2025)[18]	MODS (Roussel et al, 2025)[19]
Hemoptysis	134 (4.1%)	Not available	93 (4.6%)	Not available	39 (5.2%); prospective route, n = 33 (5.1%)	41 (3.0%)
Active cancer	429 (12.9%)	336 (9.8%)	187 (9.3%)	71 (5.0%)	0 (0.0%); not available (prospective route)	89 (7.0%)
Clinical signs of deep vein thrombosis	Not available	Not available	138 (6.8%)	72 (5.1%)	20 (2.7%); prospective route, n = 5 (2.3%)	64 (5.0%)
PE at initial testing	631 (19.0%)	456 (13.1%)	149 (7.4%)	100 (7.1%)	41 (5.5%); prospective route, n = 8 (7.5%)	80 (7.0%)

Data are presented as No. (%),median (interquartile range), or mean (SD). CDR = clinical decision rule; CTPA = CT pulmonary angiography; PE = pulmonary embolism; PERC = pulmonary embolism rule-out criteria. Q26

[a]Only 4% of imaging performed was $\dot{V}/\dot{Q}$ scanning.

TABLE 2] Diagnostic Failures of Adaptive D-Dimer Strategies

Variable	Study (Authors, Year)					
	ADJUST-PE[a] (Righini et al, 2014)[10]	YEARS (Van Der Hulle et al, 2017)[12]	PeGED[a] (Kearon et al, 2019)[13]	MODIGLIANI (Freund et al, 2021)[14]	PECAN[b] (Van Maanen et al, 2025)[18]	MODS (Roussel et al, 2025)[19]
Overall proportion of failures						
Patients ruled out without CTPA	1/1,141 (0.09)	4/1,589 (0.25)	0/1,316 (0.0)	1/451 (0.22)[c] 1/365 (0.27)[d]	0/83 (0.0)	0/753 (0.0)
Proportion of failures in the adaptive window						
Patients with D-dimer in adaptive window	1/331 (0.30)	4/477[b] (0.84)	0/315 (0.0)	1/124 (0.81)[c] 1/49 (2.04)[d]	Not available	0/172 (0.0)

Data are presented as No./Total No. (%). CTPA = CT pulmonary angiography. Q27

[a]Also includes patients who had the diagnostic strategy incorrectly applied.

[b]Also includes patients who had the diagnostic strategy incorrectly applied and patients who started with anticoagulation.

[c]YEARS arm.

[d]Age-adjusted D-dimer arm.

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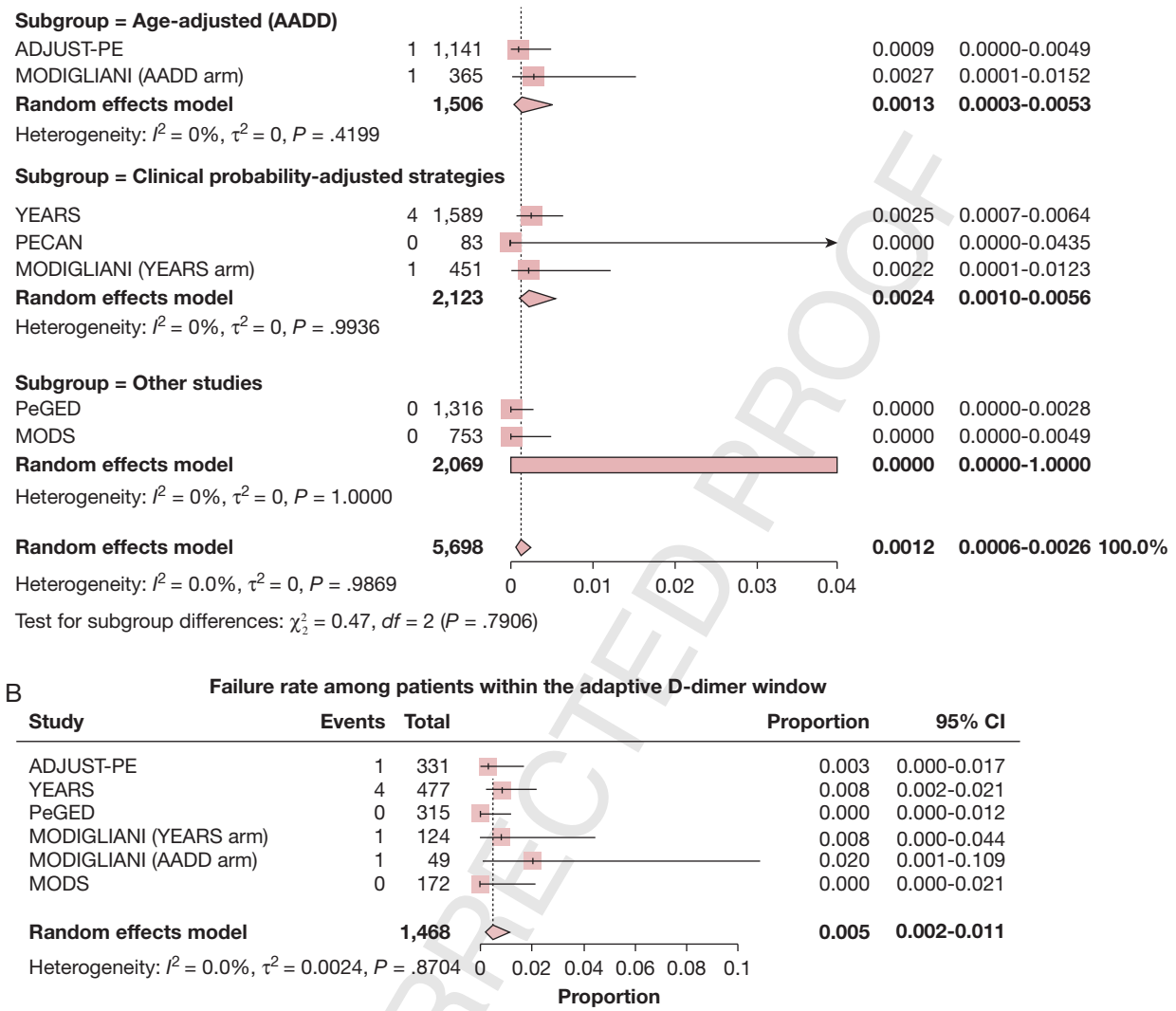


Figure 2 – *Forest plots showing failure rates in patients managed according to adaptive strategies. A, Overall failure rate among patients with PE ruled out by adaptive D-dimer strategies. B, Failure rate among patients within the adaptive D-dimer window. AADD = age-adjusted D-dimer; PE = pulmonary embolism.*

I^2 = 94.7%) for age-adjusted D-dimer strategies. PeGED and MODS were excluded from these analyses because their diagnostic algorithms could not be classified clearly as either age-adjusted D-dimer or YEARS-like strategies (Fig 2A).

Among patients with D-dimer values in the adaptive window, failure rates were 0.30% in ADJUST-PE (1 of 331),[10] 0.84% in YEARS (4 of 477),[12] 0.0% in PeGED (0 of 315),[13] 0.81% in the YEARS arm (1 of 124) and 2.04% (1 of 49) in the age-adjusted D-dimer arm of MODIGLIANI,[14] and 0.0% (0 of 172) in MODS.[19] The pooled failure rate in patients qualifying for the adaptive window was 0.50% (5 studies, 1,468 patients, and 7 events; 95% CI, 0.20%-1.11%; I^2 = 0%) (Fig 2B).

Proportion of Failures for Individual Events

ADJUST-PE reported 1 nonfatal PE (0.30%) 40 days after baseline.[10] YEARS reported 1 nonfatal PE (0.06%) 18 days after baseline, 1 proximal DVT (0.06%) 49 days after baseline, and 2 unexplained deaths (0.13%) on day 11 and day 54 after baseline.[12] MODIGLIANI reported 1 unexplained death in the YEARS arm (0.22%) and 1 unexplained death in the age-adjusted D-dimer arm (0.27%); for this study, the number of days between

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baseline and death was not available.[14] In PeGED, MODS, and PECAN, no events were observed (Table 3).[13,18,19]

Efficiency of Adaptive D-Dimer Strategies

Algorithm-based efficiency was consistently high across studies. The proportion of patients in whom the adaptive strategy did not indicate CTPA was 1,154 of 3,324 patients (34.7%) in ADJUST-PE[10], 1,651 of 3,465 patients (47.6%) in YEARS,[12] 1,325 of 2,017 patients (65.7%) in PeGED,[13] 83 of 107 patients (77.6%) in PECAN,[18] 833 of 1,217 patients (68.4%) in MODS,[19] and 505 of 726 patients (70%) for the YEARS arm and 413 of 688 patients (60%) for the age-adjusted D-dimer arm of the MODIGLIANI study,[14] corresponding to a pooled algorithm-based efficiency of 60.8% (95% CI, 49.2%-71.2%; $I^2 = 99.3\%$) (Table 4, Fig 3). Analyses repeated after removal of 1 study at a time did not show substantial reduction of between-study heterogeneity.

Subgroup Analyses in Older Patients and Patients With Cancer

Subgroup analyses were limited by the availability of stratified data. In ADJUST-PE, among 195 patients $\geq$ 75 years of age in whom PE was ruled out without CTPA under the age-adjusted D-dimer strategy and who did not receive anticoagulation therapy during follow up, no diagnostic failures occurred during the 3-month follow-up.[10] Data by age class were not available in the other studies. Similarly, separate data for patients with cancer were not available. Thus, subgroup analyses were not feasible.

Sensitivity Analyses

Sensitivity analyses using the Freeman-Tukey double-arcsine transformation supported the robustness of the main findings: the pooled overall failure rate was 0.03% (95% CI, 0.00%-0.16%; $I^2 = 18.7\%$), the failure rate within the adaptive D-dimer window was 0.23% (95% CI, 0.00%-0.73%; $I^2 = 29.4\%$), and efficiency was 60.5% (95% CI, 49.4%-71.1%; $I^2 = 99.3\%$) (e-Figs 3, 4).

Discussion

Our study, also including unpublished outcome data, showed that among patients in whom PE was ruled out without CTPA, integrating clinical decision rules with adaptive D-dimer thresholds is associated with low rate of diagnostic failure; similarly low failure rates were observed among patients within the adaptive window, with upper 95% confidence limits close to 1%.

The rationale for starting diagnostic process for acute PE has changed over recent decades. Over time, the concept moved from confirming highly suspected PEs to excluding PE in patients with compatible symptoms. This led to a significant increase in the use of CTPA, translating to potential overexposure to radiation and contrast medium.[20,21] To reduce the need for CTPA in this setting, prospective management studies have proven the safety of adaptive D-dimer strategies. However, validation studies and meta-analyses in which adaptive strategies were applied post hoc to historical cohorts suggested higher failure rates compared with prospective studies, raising concerns regarding their safety.[5,6] Indeed, these studies and meta-analyses may suggest wrongly a relevant difference in sensitivity of conventional vs modern D-dimer thresholds for several reasons: differences in baseline PE prevalence, differences in prevalence of potentially irrelevant subsegmental PE, evolving imaging techniques, and differences in study design and definition of fatal PE during follow-up.[5]

When pooling failures from individual studies, the summary estimate was 0.12% (95% CI, 0.06%-0.26%), confirming the excellent global safety profile of adaptive strategies. The failure rate among patients in the adaptive window, which has been introduced in our study as a different approach to reporting outcomes, was low as well.[22] These findings are consistent with the notion that the absolute number of missed clinically relevant events remains low when management is guided by validated adaptive algorithms. A recent multinational, prospective real-world study further supports the safety of these approaches, reporting no failures among 1,507 patients managed according to the age-adjusted D-dimer strategy.[23] Because this study was published as a Letter to the Editor, we decided not to include it into our systematic review. The scientific community should concentrate efforts and resources to run an international, randomized clinical trial comparing adaptive vs fixed D-dimer strategies to close the debate and solve such a clinically relevant issue. Whether this trial would be feasible remains to be considered because of the low observed rates of failure.

The discrepancy between our findings and those of previous meta-analyses suggesting higher failure rates associated with the use of adaptive D-dimer strategies may have several explanations. First, adaptive D-dimer strategies are probably less sensitive for potentially irrelevant subsegmental PE.[24,25] Because the latter were captured in historical diagnostic studies, these

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TABLE 3] Secondary Outcomes: Individual Components of Diagnostic Failure Among Patients Who Avoided CTPA

Variable	Study (Authors, Year)					
	ADJUST-PE[a] (Righini et al, 2014)[10]	YEARS (Van Der Hulle et al, 2017)[12]	PeGED[a] (Kearon et al, 2019)[13]	MODIGLIANI (Freund et al, 2021)[14]	PECAN[b] (Van Maanen et al, 2025)[18]	MODS (Roussel et al, 2025)[19]
Overall proportion of failures by study outcome event						
PE at 3 mo	1/1,141 (0.09)	1/1,589 (0.06)	0/1,316 (0.0)	0/451 (0.0)[c] 0/365 (0.0)[d]	0/83 (0.0)	0/753
DVT at 3 mo	0/1,141 (0.0)	1/1,589 (0.06)	0/1,316 (0.0)	0/451 (0.0)[c] 0/365 (0.0)[d]	0/83 (0.0)	0/753
PE-related or unexplained death at 3 mo	0/1,141 (0.0)	2/1,589 (0.13)	0/1,316 (0.0)	1/451 (0.22)[c] 1/365 (0.27)[d]	0/83 (0.0)	0/753
Individual proportion of failures by study outcome event in the adaptive window						
PE at 3 mo	1/331 (0.30)	1/477 (0.21)	0/315 (0.0)	Not available	Not available	Not available
DVT at 3 mo	0/331 (0.0)	1/477 (0.21)	0/315 (0.0)	Not available	Not available	Not available
PE-related or unexplained death at 3 mo	0/331 (0.0)	2/477 (0.42)	0/315 (0.0)	Not available	Not available	Not available

Data are presented as No./Total No. (%). CTPA = CT pulmonary angiography; DVT = deep vein thrombosis; PE = pulmonary embolism.
[a]Also includes patients who had the diagnostic strategy incorrectly applied.
[b]Also includes patients who had the diagnostic strategy incorrectly applied and patients who started with anticoagulation.
[c]YEARS arm.
[d]Age-adjusted D-dimer arm.

TABLE 4] Secondary Outcome: Efficiency of the Adaptive D-Dimer Strategy vs a Fixed D-Dimer Strategy as the Proportion of Patients Without Indication for CTPA After CDR

Variable	Study (Authors, Year)					
	ADJUST-PE (Righini et al, 2014)[10]	YEARS (Van Der Hulle et al, 2017)[12]	PeGED (Kearon et al, 2019)[13]	MODIGLIANI[a] (Freund et al, 2021)[14]	PECAN (Van Maanen et al, 2025)[18]	MODS (Roussel et al, 2025)[19]
Efficiency (adaptive strategy vs fixed)	AADD: 1,154/3,324 (34.7) Fixed: 817/3,324 (24.6)	YEARS: 1,651/3,465 (47.6) Fixed: 1,174/3,465 (33.9)	Adapted: 1,325/2,017 (65.7) Fixed: 970/2,017 (48.1)	Adapted: 505/726 (69.6)[b] 413/688 (60)[c] Fixed: not available	Adapted: 83/107 (77.6) Fixed: not available	Adapted: 833/1,217 (68.4) Fixed: 606/1,215 (49.9)

Data are presented as No./Total No. (%). AADD = age-adjusted D-dimer; CDR = clinical decision rule; CTPA = CT pulmonary angiography.
[a]Only reported for the per-protocol population.
[b]YEARS arm.
[c]AADD arm.

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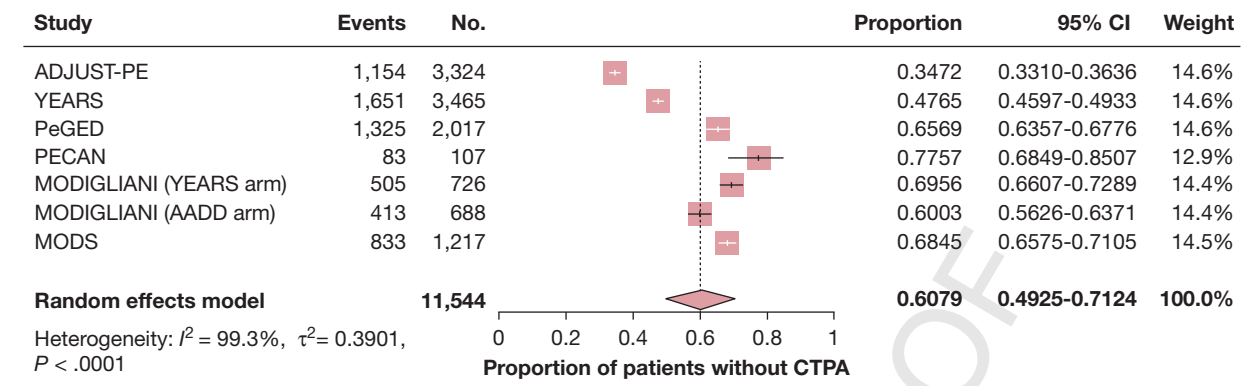


Figure 3 – *Forest plot showing the efficiency of adaptive D-dimer strategies. CTPA = CT pulmonary angiography.*

subsegmental PEs are accounted for as failures of adaptive D-dimer strategies in previous meta-analyses. Second, 4 of 7 of the failures observed in the pooled studies occurred as PE-related or unexplained death. Although these are the most feared events in this setting, whether these actually can be considered acute PE in the absence of autopsy confirmation remains questionable, and whether these were preventable deaths also is questionable. Third, current D-dimer assays are more sensitive than those used in earlier diagnostic studies; when modern diagnostic strategies are applied post hoc to historical cohorts, this difference in assay sensitivity may lead to the identification of thromboembolic events that would not have been detected at the time of cohort construction, thereby inflating the apparent failure rate of contemporary algorithms. Fourth, retrospective application of clinical decision rules may lead to misclassification of unrelated events, such as flow artifacts or chronic thromboemboli, as missed diagnoses. Of note, a certain proportion of unexplained deaths are likely not caused by a missed PE.[26,27] Moreover, it remains unknown if all VTE that occurred during follow-up are indeed missed PEs at baseline or perhaps newly developed thromboemboli. For instance, among the patients with treatment failure in the studies included in this meta-analysis is a patient with a provoked DVT diagnosed more than 1 month after the baseline presentation. The scientific community should consider revising the definition of diagnostic failure by using a shorter, 30-day follow-up window in future studies on the diagnosis of acute PE.

The implications for efficiency and use of resources are substantial. Efficiency was markedly improved with adaptive D-dimer strategies, despite a substantial heterogeneity. Heterogeneity can be explained by several factors. First, differences across algorithms probably led to different study populations. Although in age-adjusted algorithms D-dimer is tested only after clinical probability assessment, in the YEARS algorithm, all patients receive D-dimer testing before clinical probability assessment. This led to different prevalence of PE based on different algorithms and partially could contribute to heterogeneity. Second, in hospital-based cohorts, roughly one-third to two-thirds of patients with suspected PE could be managed without CTPA, and in primary care settings, this was up to 80%. Although the estimate from primary care may have been inflated by the relatively small sample size, these findings suggest that adaptive D-dimer algorithms offer a highly favorable balance between safety and efficiency, maintaining very low rates of adverse outcomes while substantially reducing the need for CTPA and unnecessary exposure to radiation and contrast media.[28,29]

Several features of our review strengthen the robustness of these conclusions. All included studies were prospective diagnostic management studies, with standardized follow-up of at least 3 months and objective confirmation of recurrent VTE, which has allowed us to avoid intrinsic biases that arise when clinical decision rules are applied retrospectively.[5,30] We covered a broad range of health care settings—from referred secondary care to primary care—and a spectrum of D-dimer assays, enhancing generalizability. Importantly, by concentrating on failures occurring in the D-dimer range of between 500 ng/mL and the adaptive threshold, we provide an upper-bound estimate of events that might have been avoided under a fixed 500 cutoff, focusing on the subgroup most informative for evaluating the safety implications of adaptive thresholds. Nonetheless, some limitations must be acknowledged. First, D-dimer assays, cutoffs, and

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clinical prediction rules varied among studies, and some domains were judged to be at unclear or high risk of bias. Second, reporting of subgroup data was incomplete, leading us to rely on descriptive rather than comparative analyses. Given that older patients and those with cancer are precisely those in whom both PE prevalence and competing risks are higher and in whom imaging can be more burdensome, future studies should oversample and report these groups prospectively to define better the risk-benefit profile of adaptive strategies in high-risk populations.[31] In addition, evidence regarding other clinically relevant subgroups remains limited. Notably, a secondary analysis of the prospective ADJUST-PE study suggested that the age-adjusted D-dimer strategy remains safe in patients with obesity who have suspected PE.[32]

Third, the analysis restricted to the D-dimer range between 500 ng/mL and the adaptive threshold provides an upper-bound estimate of failures that theoretically might be avoided under a fixed 500-ng/mL cutoff, based on classification differences, rather than direct within-study comparisons. This approach does not account for events arising de novo during follow-up or for unexplained deaths, and therefore potentially overestimates the true excess failure attributable to adaptive thresholds. Fourth, data on the number of patients with protocol deviations, anticoagulation during follow-up, or both was not available for some studies, likely resulting in a slight underestimation of the failure rate. Because this applies only to a very small proportion of patients, we deem the potential difference to be negligible.

From a clinical standpoint, our findings support the continued use and broader implementation of validated adaptive D-dimer strategies in the diagnostic workup of suspected PE. These strategies can avoid imaging safely in a large proportion of patients, with only a very small increase in potentially clinically relevant missed events compared with a fixed 500-ng/mL threshold. In higher-prevalence settings, including hospitalized and patients of very advanced age, adaptive thresholds still are appropriate, although the efficiency in such settings is only marginally better than that of a conventional fixed D-dimer threshold.[33] We excluded studies with pregnant patients. However, one prospective diagnostic study in pregnant patients showed that a modified YEARS algorithm was applied safely in pregnant patients with suspected PE, a finding confirmed in an individual patient-level meta-analysis.[5]

Interpretation

Our study showed that, across a range of healthcare settings, age-adjusted D-dimer and probability-based D-dimer strategies were associated with very low diagnostic failure rates, including among patients within the adaptive window, while substantially improving efficiency compared with fixed D-dimer cutoffs. These findings support the safety of adaptive D-dimer thresholds and provide a quantitative benchmark for future diagnostic models and prospective management trials aiming to personalize the diagnostic workup of suspected PE further.

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Additional information: The e-Appendix, e-Figures, and e-Tables are available online under "Supplementary Data."

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