The diagnostic and therapeutic management of pulmonary embolism

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CHAPTER 3

Wells rule and D-dimer testing to rule out pulmonary embolism - a systematic review and individual-patient data meta-analysis -

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ABSTRACT

Background

The performance of different diagnostic strategies for pulmonary embolism (PE) in patient subgroups is unclear.

Purpose

To evaluate and compare the efficiency and safety of the Wells rule with fixed or age-adjusted D-dimer testing overall and in inpatients and persons with cancer, chronic obstructive pulmonary disease, previous venous thromboembolism, delayed presentation, and age 75 years or older.

Data Sources

MEDLINE and EMBASE from 1 January 1988 to 13 February 2016.

Study Selection

6 prospective studies in which the diagnostic management of PE was guided by the dichotomized Wells rule and quantitative D-dimer testing.

Data Extraction

Individual data of 7268 patients; risk of bias assessed by 2 investigators with the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool.

Data Synthesis

The proportion of patients in whom imaging could be withheld based on a "PE-unlikely" Wells score and a negative D-dimer test result (efficiency) was estimated using fixed (≤500 µg/L) and age-adjusted (age × 10 µg/L in patients aged >50 years) D-dimer thresholds; their 3-month incidence of symptomatic venous thromboembolism (failure rate) was also estimated. Overall, efficiency increased from 28% to 33% when the age-adjusted (instead of the fixed) D-dimer threshold was applied. This increase was more prominent in elderly patients (12%) but less so in inpatients (2.6%). The failure rate of age-adjusted D-dimer testing was less than 3% in all examined subgroups.

Limitation

Post hoc analysis, between-study differences in patient characteristics, use of various D-dimer assays, and limited statistical power to assess failure rate.

Conclusion

Age-adjusted D-dimer testing is associated with a 5% absolute increase in the proportion of patients with suspected PE in whom imaging can be safely withheld compared with fixed D-dimer testing. This strategy seems safe across different high-risk subgroups, but its efficiency varies.

INTRODUCTION

The diagnosis of pulmonary embolism (PE) cannot be based on clinical features alone because the signs and symptoms of PE are not specific [1]. Objective imaging tests, including computed tomography pulmonary angiography (CTPA), are therefore warranted to confirm or refute the presence of PE [2]. Only 15% to 25% of presenting patients have PE [3], so CTPA is not an appropriate first-line test because of radiation exposure, costs, and risk for contrast-induced nephropathy.

To guide decisions about who should be referred for imaging, various diagnostic algorithms have been developed over the past 2 decades. They aim to identify patients at low risk for PE in whom imaging and anticoagulant treatment can be safely withheld. One frequently used algorithm consists of the sequential application of the dichotomized Wells rule [4], which estimates the clinical probability of PE, and D-dimer testing. Pulmonary embolism can be considered ruled out in patients with a Wells score of 4 or less and a negative D-dimer test result (conventionally ≤500 µg/L) [5]. This combination is present in approximately 30% to 40% of those with suspected PE [3]. The latter proportion is commonly called the "efficiency" of the algorithm. The proportion of these patients with symptomatic venous thromboembolism (VTE) during 3-month follow-up (the failure rate) is less than 1% [3]. It has recently been shown that the efficiency can be safely increased by applying an age-adjusted D-dimer positivity threshold, which is defined as the age of patients multiplied by 10 µg/L in those older than 50 years [6].

Although many studies have validated the clinical utility and safety of the dichotomized Wells rule combined with D-dimer testing in excluding PE, an individual-patient data (IPD) meta-analysis can address important questions with greater precision and power. First, what is the overall efficiency and safety of the Wells rule and fixed D-dimer testing? Second, what is the performance of this strategy in clinically important subgroups? Third and most important, how do the efficiency and safety of age-adjusted D-dimer testing compare with fixed D-dimer testing?

To answer these questions, we did a systematic review and IPD meta-analysis combining patient-level data from 6 large, prospective outcome studies in which diagnostic management of clinically suspected PE had been guided by the Wells rule and D-dimer testing. Using the fixed and age-adjusted D-dimer thresholds, we estimated the efficiency and failure rate of this diagnostic algorithm overall; in inpatients; and in persons with cancer, chronic obstructive pulmonary disease (COPD), age 75 years or older, previous VTE, and delayed presentation.

METHODS

We developed a protocol (Appendix, all appendixes are available at www.annals.org) and followed the guidance of the PRISMA-IPD (Preferred Reporting Items for Systematic reviews and Meta-Analyses of individual participant data) Statement [7].

Data Sources and Searches

We searched MEDLINE and EMBASE from 1 January 1998 (the year in which the Wells score was introduced) [8] to 13 February 2016. The search was based on a previously published search strategy [3], which included terms for "pulmonary embolism" and "D-dimer", and an adapted search filter for diagnostic and prognostic studies [9]. We restricted the search to original studies in adults. No language restrictions were applied. The full search strategy is provided in Appendix Table 1. Two authors (N.E. and T.H.) independently screened the titles and abstracts of the identified articles and independently assessed the full-text articles for eligibility. Conflicts were resolved by discussion.

Study Selection

Eligible studies included those that had prospectively enrolled, consecutive, hemodynamically stable adults presenting in a secondary care setting (emergency department or inpatient ward) with signs and symptoms suggestive of acute PE. At the individual level, the clinical probability of PE had to be assessed by the Wells rule and followed by quantitative D-dimer testing in patients with a Wells score of 4 or less (indicating "PE unlikely"). According to the study protocol, patients with a PE-unlikely Wells score and a negative D-dimer test result were to be managed without imaging and anticoagulant therapy but prospectively followed for 3 months to document the occurrence of VTE (Appendix Figure). By applying these criteria, we aimed to identify all studies that prospectively evaluated the current diagnostic management of patients with suspected PE in a secondary care setting.

Data Extraction and Quality Assessment

Authors of studies fulfilling the inclusion criteria were invited to provide IPD, and all agreed. We sought study-level information on D-dimer assays used; imaging tests done to confirm PE; and definitions of the outcomes, regardless of whether outcome measures were adjudicated by an independent committee. Patient-level data collected at baseline included information on demographics, risk factors for VTE, Wells score items, D-dimer levels (converted to µg/L), and results of imaging tests. We also collected follow-up data about anticoagulant treatment for reasons other than VTE, symptomatic VTE, mortality, or loss to follow-up. We followed the subgroup definitions used in each study without any adjustments and ascertained these definitions by the case report forms of the studies and variable labels in the study databases.

Two authors who were not involved in the original studies independently assessed each study for potential sources of bias and applicability concerns using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool [10].

Data Synthesis and Analysis

Our analysis focused on the efficiency and failure rate of the diagnostic strategy. Efficiency was defined as the number of patients with a Wells score of 4 or less and a negative D-dimer test result relative to the total number of patients. We evaluated the efficiency of 2 D-dimer positivity thresholds: the conventional, fixed threshold of 500 µg/L and an age-adjusted threshold, which was defined as the age of patients multiplied by 10 µg/L in patients older than 50 years. For example, the age-adjusted strategy in a patient aged 75 years would lead to a D-dimer positivity threshold of 750 µg/L. To evaluate age-adjusted D-dimer testing in our study, we reclassified patients enrolled in studies that evaluated fixed D-dimer testing according to the age-adjusted D-dimer threshold post hoc.

The failure rate was defined as the proportion of patients with symptomatic deep venous thrombosis, nonfatal PE, or fatal PE during 3-month follow-up or objectively confirmed PE at baseline that was previously ruled out on the basis of a Wells score of 4 or less and a negative D-dimer test result. Death was considered to be caused by PE if it was confirmed by autopsy, if an imaging test for PE yielded positive results just before death, or in the case of sudden death due to unknown reasons.

The efficiency and failure rates were calculated overall and in clinically important high-risk subgroups, including inpatients and patients with cancer, COPD, age 51 to 74 years, age 75 years or older, previous VTE, and symptoms lasting more than 7 days.

Statistical Analysis

To avoid bias associated with excluding missing data [11], we used multiple imputation separately within each study (10 times). The proportion of missing values is reported in Appendix Table 2. Results across the multiply imputed data sets were combined by using the Rubin rule [12] (Appendix).

A single-stage meta-analytic approach was used [13, 14] to analyze the efficiency and failure rates. The overall efficiency (the proportion of patients in whom imaging could be withheld) was estimated using a multilevel logistic regression model (also called a generalized linear mixed-effects model), with the combination of a Wells score of 4 or less and a negative D-dimer test result as the outcome variable. To account for the clustering of observations within studies, we specified a random effect for the intercept. For the analysis in subgroups, we used a full random-effects model [13] by adding the subgroup indicator as a covariate and allowing a study-specific random effect. From these models,

we calculated the marginal probabilities (with 95% CIs) of having a PE-unlikely Wells score and a negative D-dimer test result, both overall and in the different subgroups (Appendix).

Differences in efficiency between subgroups were tested by using the Wald test statistic with the significance level set at 0.05. The absolute difference in the efficiency of the fixed and age-adjusted D-dimer testing strategies was calculated by subtracting the point estimates of the marginal probabilities from the 2 models. The 95% CIs around these estimates were obtained by repeating the analyses in 500 bootstrap samples (Appendix).

Using similar methods, we estimated the failure rate: the proportion of patients with symptomatic VTE during 3-month follow-up in whom the Wells score and D-dimer test result had ruled out PE at baseline. The outcome variable in this multilevel logistic regression model was a final diagnosis of VTE. The analysis was restricted to patients with a Wells score of 4 or less and a negative D-dimer test result. Patients receiving anticoagulant treatment for reasons other than VTE and those lost to follow-up were excluded from this analysis. Failure rates in the subgroups were estimated using full random-effects models, with the subgroup indicator as the covariate. We calculated estimates of the marginal probabilities of the failure rates with 95% CIs.

Heterogeneity among the studies was assessed by calculating 90% prediction intervals around the estimates for the efficiency and failure rate based on the random intercept variance [13]. Because the proportion of missing baseline variables was higher in the REPEAD study [15] than in the other studies (from 1% for duration of symptoms to 21% for cancer) (Appendix Table 2), we did a sensitivity analysis in which REPEAD was excluded.

To better understand and illustrate the association between age and the efficiency and associated failure rate for the fixed and age-adjusted D-dimer thresholds, we extended the base models by adding age as a continuous variable. Age was then plotted against the predicted proportions from these models. This analysis was restricted to patients older than 50 years because the age-adjusted D-dimer threshold, by definition, applies only to them.

Because patients with clinically suspected PE often have more than 1 risk factor for PE, the conditional effect of the potential predictors of a difference in efficiency was also evaluated with a multilevel, multivariable, logistic regression model in which all predefined subgroup indicators were included as covariates.

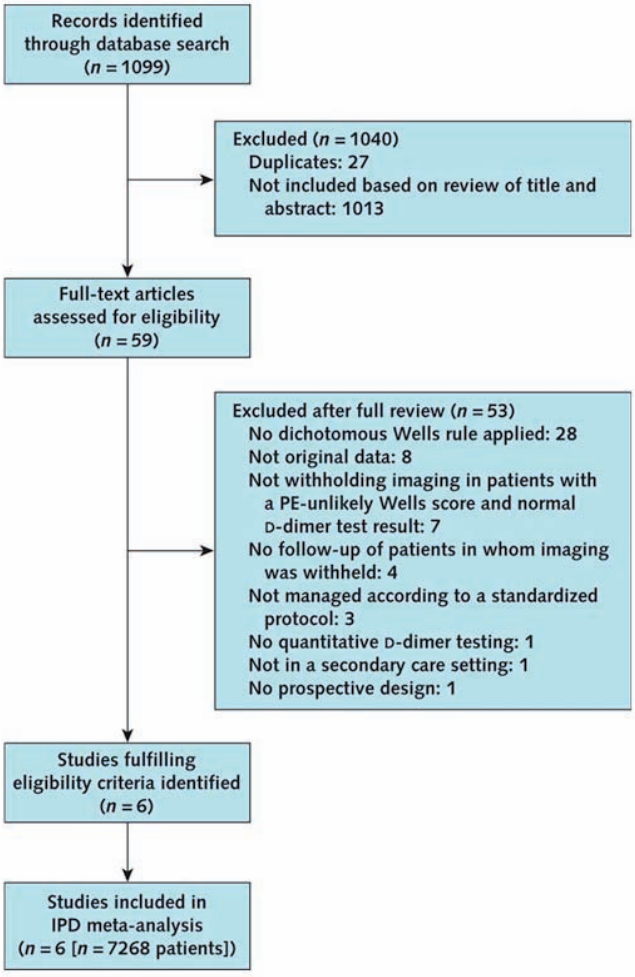
All statistical analyses were performed in R, version 3.2.2 (R Foundation for Statistical Computing; www.R-project.org), by using the mice package (version 2.22) for multiple imputation, the lme4 package (version 1.1-10) for multilevel logistic regression modeling, and the boot package (version 1.3-18) for bootstrapping. Specifications of all models used are provided in Appendix Table 3.

RESULTS

Our search identified 1099 articles, 59 of which were assessed for eligibility (**Figure 1**). Exclusion criteria are provided in Appendix Table 4. Six studies fulfilled the eligibility criteria [5, 6, 15–18], and IPD for all 7268 patients were obtained.

Basic characteristics and outcomes of the 6 included studies are summarized in **Table 1**. These studies used a diagnostic strategy consisting of the Wells rule and subsequent D-dimer testing to guide the management of patients with suspected PE. Three studies enrolled both inpatients and outpatients [5, 15, 16].

Figure 1. Systematic search and study selection.



Note: IPD: individual-patient data; PE: pulmonary embolism.

Table 1. Characteristics of Included Studies.

Study	Primary study goal	Study period	D-dimer assay	Diagnostic imaging test	Outcome adjudication	Total number of patients	Number of patients with VTE at baseline or during follow-up (%)	Number of patients managed without imaging (%)	Number of patients managed without imaging and anticoagulation with VTE during follow-up (%)
Christopher study (2006) [5]	Evaluation of Wells rule combined with D-dimer testing (threshold 500 µg/L) in in- and outpatients	November 2002 – September 2004	VIDAS or Tina-quant	CTPA	Yes	3306	700 (21%)	1057 (32%)	5 (0.5%)
Goekoop et al. (2007) [17]	Evaluation of Wells rule combined with D-dimer testing (threshold 500 µg/L) in outpatients	March 2002 – March 2004	VIDAS	CTPA or VQ-scan	No	879	110 (13%)*	450 (51%)	2 (0.4%)
Prometheus study (2008) [15]	Evaluation of 4 clinical decision rules (including dichotomized Wells rule) combined with D-dimer testing (threshold 500 µg/L) in in- and outpatients	July 2008 – November 2009	VIDAS, Tina-quant, STA Liatest, or Innovance	CTPA	Yes	807	192 (24%)	169 (21%)†	1 (0.6%)
Galipienzo et al. (2012) [18]	Evaluation of dichotomized Wells rule combined with D-dimer testing (cut-off 500 µg/L) in outpatients	May 2007 – December 2008	VIDAS	CTPA	No	241	64/241 (27%)	57 (24%)	0 (0%)
ADJUST study (2014) [6]	Evaluation of dichotomized Wells rule combined with D-dimer testing (age-adjusted cut-off) in outpatients older than 50 years	January 2010 – February 2013	VIDAS, Tina-quant, STA Liatest, D-Dimer HS or Innovance	CTPA	Yes	1753‡	345 (20%)	523 (30%)	2 (0.4%)

Table 1. Characteristics of Included Studies. (continued)

Study	Primary study goal	Study period	D-dimer assay	Diagnostic imaging test	Outcome adjudication	Total number of patients	Number of patients with VTE at baseline or during follow-up (%)	Number of patients managed without imaging (%)	Number of patients managed without imaging and anticoagulation with VTE during follow-up (%)
REPEAD study (2014) [16]	Evaluation of dichotomized Wells rule combined with D-dimer testing (cut-off 500 µg/L) in in- and outpatients with previous PE	November 2002 – November 2009	VIDAS, Tina-quant, STA Liatest, or Innovance	CTPA	Yes	282‖	117 (42%)	47 (17%)	0 (0%)

Note: CDR: clinical decision rule; CTPA: computed tomography pulmonary angiography; PE: pulmonary embolism; VQ: ventilation-perfusion scan

* Follow-up was not planned for patients with a Wells score >4 points or with the combination of a Wells score ≤4 points and a negative D-dimer (threshold 500 µg/L).

† Patients were managed without imaging when all 4 clinical decision rules classified the patient as "PE unlikely" combined with a negative D-dimer (threshold 500 µg/L).

‡ Individual patient data was obtained only from patients that were assessed with the Wells rule.

‖ Patients that were enrolled both in the Christopher and REPEAD studies were excluded from the analysis.

Subgroup definitions were homogeneous across the studies. The definitions of cancer and previous VTE followed those as per the Wells score in all studies. Chronic obstructive pulmonary disease was defined as disease requiring treatment in 4 of 5 studies that captured this variable and as disease with or without treatment in one. The fixed D-dimer threshold of 500 µg/L was applied in 5 studies, whereas the age-adjusted D-dimer threshold was used in one. D-Dimer testing was done using the locally available method: a quantitative latex-based assay or an enzyme-linked immunosorbent assay. In each study, imaging and anticoagulant therapy were withheld in patients with a Wells score of 4 or less and a negative D-dimer test result. They were followed prospectively for 3 months by telephone contact or a scheduled outpatient visit.

We identified potential sources of bias. Suspected venous thromboembolic events during 3-month follow-up were not centrally adjudicated in 2 studies [17, 18]. Quantitative D-dimer testing was not done in 104 of 5202 patients (2.0%) with a Wells score of 4 or less, and 11 patients (0.4%) in whom imaging was withheld at baseline were lost to follow-up. In all studies, the risk of bias with respect to patient selection, Wells scores, and D-dimer test results was judged to be low. Of note, concern for limited applicability in all domains was low (complete QUADAS-2 results are provided in the appendix).

Baseline patient characteristics are summarized in Appendix Table 5. The mean age was 56 years; 42% were men. The proportion of missing values for the baseline characteristics and Wells score items ranged from 0% to 6%. Among patients across the studies with a PE-unlikely Wells score, 0% to 10% had missing quantitative D-dimer test results. When we checked the IPD, no other concerns were identified. At baseline, PE was diagnosed in 1527 patients (21%).

The overall efficiency of the diagnostic strategy when the fixed D-dimer threshold of 500 µg/L was applied was 28% (95% CI, 21% to 37%) (**Table 2**). The summary estimate of the failure rate was 0.65% (CI, 0.38% to 1.11%) (**Table 3**), without any fatal events, among patients with a PE-unlikely Wells score and a negative D-dimer test result (without imaging). Five percent of patients with a PE-unlikely Wells score had D-dimer levels between 500 µg/L and the age-adjusted threshold. This resulted in an overall efficiency of 33% (CI, 25% to 42%) when the age-adjusted D-dimer threshold was applied. The failure rate among patients in whom imaging was withheld based on a Wells score of 4 or less and a D-dimer level below the age-adjusted threshold was 0.94% (CI, 0.58% to 1.5%), with 1 fatal event.

The efficiency of the diagnostic algorithms in the prespecified subgroups of patients is presented in **Table 2**. When the fixed D-dimer threshold is applied, the efficiency varied from 7% in inpatients to 25% in persons having symptoms for more than 7 days. The efficiency of age-adjusted D-dimer testing varied from 10% in inpatients to 32% in persons with COPD. Compared with fixed D-dimer testing, age-adjusted testing increased the efficiency ranging from 12% in elderly patients to 2.6% in inpatients.

Table 2. Efficiency* of the Wells Rule and D-Dimer Testing in Excluding PE Overall and in Clinically Important Subgroups.

		Active cancer		Chronic obstructive pulmonary disease		Age			Previous venous thromboembolism		Duration of symptoms		Hospitalization status	
	Overall (n=7,268)	Yes n=938)	No (n=6,264)	Yes (n=856)	No (n=6,017)	≥ 75 years (n=1,200)	51-74 years (n=3,398)	≤ 50 years (n=2,661)	Yes (n=1,116)	No (n=6,143)	> 7 days (n=1,322)	≤ 7 days (n=5,476)	Inptient (n=804)	Outpatient (n=6,455)
D-dimer threshold 500 µg/L, %	28.0	9.1	30.4	21.3	29.8	8.4	22.4	45.1	16.5	31.9	25.2	29.9	7.0	30.1
95% CI	20.5-37.0	6.8-12.0	23.0-39.1	16.6-26.8	20.2-41.5	6.3-11.0	17.5-28.2	34.9-55.7	13.8-19.6	23.5-41.6	16.8-35.8	20.8-40.6	2.5-17.3	22.4-39.1
90% PI	14.3-47.4	4.3-18.3	16.7-48.6	9.7-40.2	12.8-54.5	2.6-23.9	10.9-40.1	25.8-65.9	9.3-27.4	16.9-51.6	8.3-54.6	13.8-52.7	1.3-27.6	15.9-49.3
Age-adjusted D-dimer threshold, %	32.6	13.1	35.2	31.5	33.4	20.3	28.0	45.1	19.0	36.9	29.7	34.1	9.9	34.7
95% CI	24.6-41.7	10.6-16.1	27.3-43.9	26.5-37.0	23.2-45.2	15.9-25.5	20.7-36.5	34.7-55.8	16.4-21.8	28.7-45.8	21.1-39.9	24.5-45.2	5.3-17.4	26.8-43.5
90% PI	17.8-51.8	7.4-22.1	20.4-53.3	16.8-51.1	15.2-57.9	7.6-43.9	14.0-47.6	25.7-66.0	12.1-28.4	22.1-54.4	11.3-57.9	16.7-56.9	2.7-28.8	19.9-52.9
Absolute increase in efficiency, %	4.6	3.8	4.7	10.2	3.6	12.1	5.6	0	2.5	5.2	4.6	4.2	2.6	4.6
95% CI	4.3-4.8	3.1-4.4	4.5-5.0	9.4-10.9	3.4-3.7	11.4-12.7	5.2-6.2	NA	2.0-2.9	4.8-5.7	4.2-5.0	4.0-4.4	1.9-3.1	4.4-4.8

Note: CI: confidence interval; PI: prediction interval.

*The efficiency is defined as the probability of having an unlikely Wells score combined with a negative D-dimer test result. All subgroup differences (e.g. cancer vs. no cancer) were statistically significant (P<0.05), except for chronic obstructive pulmonary disease in the analysis of age-adjusted D-dimer testing (P=0.89).

Table 3. Failure Rate* of the Wells Rule and D-Dimer Testing in Excluding PE Overall and in Clinically Important Subgroups.

		Active cancer		Chronic obstructive pulmonary disease		Age			Previous venous thromboembolism		Duration of symptoms		Hospitalization status	
	Overall (n=7,268)	Yes (n=938)	No (n=6,264)	Yes (n=856)	No (n=6,017)	≥ 75 years (n=1,200)	51-74 years (n=3,398)	≤ 50 years (n=2,661)	Yes (n=1,116)	No (n=6,143)	> 7 days (n=1,322)	≤ 7 days (n=5,476)	Inpatient (n=804)	Outpatient (n=6,455)
D-dimer threshold 500 µg/L	0.65	2.6	0.57	0.74	0.64	NA	NA	NA	1.3	0.56	0.88	0.62	NA	NA
95% CI	0.38-1.11	0.57-11.0	0.31-1.0	0.11-4.7	0.37-1.1	NA	NA	NA	0.12-13.3	0.29-1.1	0.28-2.7	0.33-1.1	NA	NA
90% PI	0.42-0.99	0.77-8.3	0.36-0.91	0.15-3.5	0.40-1.0	NA	NA	NA	0.16-10.0	0.33-0.95	0.34-2.2	0.37-1.0	NA	NA
Age-adjusted D-dimer threshold	0.94	1.4	0.89	1.2	0.90	2.1	0.83	0.59	1.2	0.90	1.3	0.87	1.2	0.93
95% CI	0.58-1.5	0.15-12.6	0.57-1.4	0.03-25.3	0.54-1.5	0.71-5.9	0.15-4.3	0.22-1.6	0.12-11.6	0.56-1.4	0.53-3.1	0.44-1.7	0.17-8.1	0.61-1.4
90% PI	0.64-1.4	0.21-9.3	0.62-1.3	0.03-23.5	0.57-1.4	0.81-5.2	0.22-3.1	0.26-1.3	0.18-7.8	0.62-1.3	0.81-2.1	0.40-1.9	0.26-0.54	0.67-1.3

Note: CI: confidence interval; COPD: chronic obstructive pulmonary disease; PI: prediction interval; VTE: venous thromboembolism.

*The failure rate is defined as the probability of VTE in patients with an Wells score <=4 combined with a negative D-dimer test result.

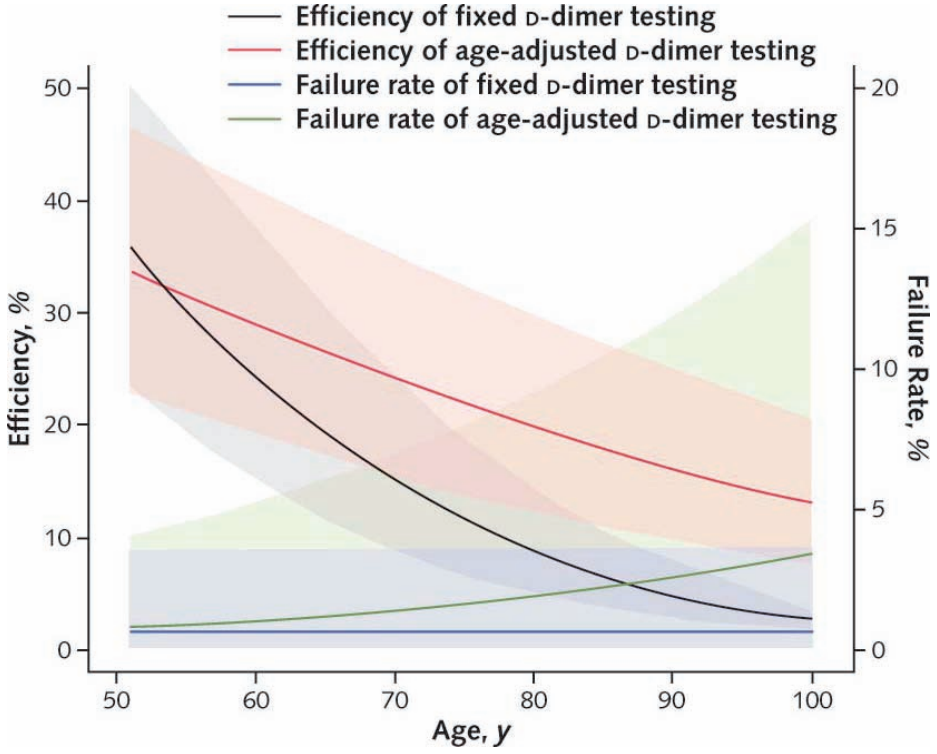
Patients who received anticoagulants for other reasons than VTE and those lost to follow-up were excluded from this analysis. The failure rate could not be estimated in the age subgroups and in inpatients when applying the fixed D-dimer threshold due to zero events.

The failure rate of the diagnostic algorithms was greatest in patients with active cancer (2.6% [CI, 0.57% to 11.0%] when the fixed D-dimer threshold is applied) and those aged 75 years or older (2.1% [CI, 0.71% to 5.9%] when the age-adjusted D-dimer threshold is applied) (**Table 3**). However, none of these subgroup differences reached statistical significance.

In the sensitivity analysis in which the REPEAD study was excluded because of a relatively higher proportion of missing baseline variables, the point estimates for efficiency were slightly higher than in the main analysis owing to the high PE prevalence and low efficiency in REPEAD (Appendix Table 6). The sensitivity analysis yielded similar results to the main analysis with respect to the failure rates (Appendix Table 7). In the exploratory analysis, the absolute difference in efficiency between the age-adjusted and fixed D-dimer thresholds increased with age from approximately 4% in patients aged 60 years to 11% in patients aged 80 years, whereas the difference in failure rate increased from 0.4% in patients aged 60 years to 1.3% in patients aged 80 years (**Figure 2**).

In the multivariable analysis, all risk factors, except COPD status, were significantly associated with a lower chance of ruling out PE based on the Wells rule and fixed D-dimer

Figure 2. Association between age and the efficiency and failure rate of the Wells rule and D-dimer testing using the fixed or age-adjusted thresholds.



testing (Appendix Table 8). Strong predictors of limited efficiency were age 75 years or older (adjusted odds ratio [OR], 0.12), inpatient status (adjusted OR, 0.21), and active cancer (adjusted OR, 0.30). In these 3 subgroups, the adjusted ORs for a Wells score of 4 or less and a D-dimer level below the age-adjusted threshold were 0.33, 0.24, and 0.34, respectively.

DISCUSSION

This large IPD meta-analysis of 7268 patients with clinically suspected PE shows that the proportion of those managed without imaging and who have no need for anticoagulation can be safely increased from 28% to 33% by applying the age-adjusted D-dimer threshold in those with a PE-unlikely Wells score. This absolute increase is more prominent in patients with COPD and elderly patients presenting with suspected PE but is less prominent in inpatients or patients with cancer, previous VTE, or delayed presentation.

A strength of our study is that it includes IPD from many persons with clinically suspected PE, which enabled robust subgroup analysis. In addition, our results pertain to the current evidence-based standards of the diagnostic management of PE [2, 19] because all patients were managed prospectively according to a widely used, uniform, and well-validated algorithm. This homogeneity in design of the included studies increased the precision of the efficiency and safety outcomes.

Our results are based in part on post-hoc analyses. The age-adjusted D-dimer threshold had been prospectively evaluated in only one study [6], whereas the efficiency and failure rate associated with this threshold were recalculated for the other studies. Therefore, we have failure rates defined from both imaging and follow-up that are not fully interchangeable. As a consequence, we may have overestimated the failure rate because most patients with a Wells score of 4 or less and a D-dimer level between the fixed and age-adjusted thresholds had imaging, which may have led to the detection of clots with less clinical significance [20].

We observed considerable between-study heterogeneity as illustrated by the relatively wide prediction intervals around the estimates. Because the included studies had a similar design, this heterogeneity was most likely due to differences in the patient population and, as a consequence, between-study differences in PE prevalence.

On average, 22% of the patients in our analysis had confirmed PE, which is substantially higher than proportions reported in most North American studies [21–23]. Therefore, the efficiency will likely be greater in settings with a lower PE prevalence. We restricted inclusion to studies conducted in secondary care; therefore, caution is warranted when extrapolating our results to, for example, primary care.

Various D-dimer assays were used in the studies. Although these widely available quantitative latex-based and enzyme-linked immunosorbent assays have a high sensitivity for diagnosing PE, their specificity may be somewhat different [24]. At present, evidence on the performance of the age-adjusted threshold with each assay is lacking [25]. Because patient-level information on the D-dimer testing method was not available for most studies, we could not compare the performance of the 2 assays. Yet we believe that this use of different D-dimer assays reflects clinical practice.

Overall, our findings are in line with previous studies that evaluated the performance of the age-adjusted D-dimer threshold. In a retrospective analysis by Douma and colleagues [26], the age-adjusted D-dimer threshold was associated with a 5% to 6% absolute increase in efficiency in the 3 cohort studies not included with the present analysis. Similarly, in a post hoc analysis of 3 cohort studies, Penaloza and colleagues [27] found a 4.6% absolute increase in the proportion of patients with a low or moderate pretest probability and a negative D-dimer test result when the age-adjusted threshold was applied. The 5% overall increase in efficiency in our study was not offset by an increase in the failure rate. Hence, when the age-adjusted (instead of the fixed) D-dimer threshold is used in clinical practice, it is expected that PE can be safely ruled out in an additional 1 of 20 patients.

This meta-analysis supports the findings of previous evaluations of the performance of clinical decision rules in combination with D-dimer testing in subgroups of patients with clinically suspected PE. We now know that such a diagnostic algorithm can safely rule out PE in patients with cancer [28, 29], COPD [30], age 76 years or older [30, 31], previous VTE [32, 33], and delayed presentation [34] as well as inpatients [31, 35]. However, the algorithm is less efficient in these subgroups than in the general population presenting with suspected PE. In most of these subgroups, the efficiency can be increased to more than 10% by applying the age-adjusted D-dimer threshold, which corresponds to a number needed to test of fewer than 10 patients to withhold 1 CTPA. For inpatients only, the efficiency of the diagnostic algorithm remains poor (10%). This is supported by the multivariate analysis, which indicated that inpatient status is the strongest predictor of a low efficiency when the age-adjusted D-dimer threshold is applied.

It is widely accepted that a diagnostic strategy for PE is considered safe if a failure rate of 3% can be excluded based on the upper limit of the 95% CI because even pulmonary angiography cannot detect all cases [36]. In our analysis, the point estimate of the failure rate was less than 3% across all subgroups and we found no evidence for a difference in failure rate between the subgroups. The statistical power was limited because of the low number of events, which was also reflected by the wide CIs.

On the basis of this analysis, we recommend using age-adjusted (rather than fixed) D-dimer testing with the Wells rule because it increases efficiency without jeopardizing safety in all studied subgroups. The improved efficiency is most pronounced in patients

with COPD and elderly patients and is considerable in those with cancer, previous VTE, or a delayed presentation. Although age-adjusted D-dimer testing increases the efficiency among inpatients from 7% to 10%, its clinical utility in this subgroup remains limited given the corresponding number needed to test of 10 patients to withhold 1 CTPA. Whether to rely on the Wells rule and D-dimer testing in these patients becomes a matter of judgment. It may still be valuable to avoid the risk for contrast-induced nephropathy in ill patients who often already have multiple comorbidities; however, based on the clinical presentation, physicians may decide to proceed to imaging directly without calculating a Wells score or ordering D-dimer testing.

Among patients with clinically suspected PE, the Wells rule combined with age-adjusted D-dimer testing is associated with a 5% absolute increase in the proportion of those in whom imaging can be safely withheld compared with fixed D-dimer testing. This diagnostic approach seems to be safe across various subgroups, but its clinical utility may be limited for some, particularly inpatients.

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