Improving efficiency of the diagnostic management of pulmonary embolism

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Chapter 7

Combination of pulmonary embolism rule-out criteria (PERC) and YEARS algorithm in a European cohort of patients with suspected pulmonary embolism

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Thrombosis and Haemostasis 2018 Mar; 118(3): 547-552

ABSTRACT

Background

Both the YEARS algorithm and the pulmonary embolism (PE) rule-out criteria (PERC) were created to exclude PE with limited diagnostic tests. A diagnostic strategy combining both scores might save additional computed tomography pulmonary angiography (CTPA) scans, but they have never been evaluated in conjunction.

Aim

The aim of this study was to determine the safety and efficiency of combining YEARS and PERC in a single diagnostic strategy for suspected PE.

Methods

The PERC rule was assessed in 1,316 consecutive patients with suspected PE who were managed according to YEARS. We calculated the absolute difference (with 95% confidence interval [CI]) in failure rate and the number of 'saved' CTPAs for the scenario that PE would have been ruled out without CTPA in the absence of all PERC items.

Results

Using the YEARS algorithm, PE was diagnosed in 189 patients (14%), 680 patients (52%) were managed without CTPA and the 3-month rate of venous thromboembolism in patients in whom PE was ruled out was 0.44% (95% CI: 0.19–1.0). Only 6 of 154 patients (3.9%; 95% CI: 1.4–8.2) with no YEARS items who were referred for CTPA would have been PERC negative, of whom none were diagnosed with PE at baseline or during follow-up (0%; 95% CI: 0–64). Applying PERC before YEARS in all patients would have led to a failure rate of 1.42% (95% CI: 0.87–2.3%), 0.98% (95% CI: 0.17–1.9) more than shown in patients managed by YEARS.

Conclusion

Combining YEARS with PERC would have yielded only a modest improvement of efficiency in patients without a YEARS item and an unacceptable failure rate in patients with ≥1 YEARS item.

INTRODUCTION

The diagnostic management of suspected pulmonary embolism (PE) remains challenging, due to the nonspecific clinical presentation of acute PE in combination with the potential harmful imaging test that is required in most cases of suspected PE to rule out the disease (1). It has been widely demonstrated that PE can be ruled out in patients with an unlikely clinical probability in combination with a normal high-sensitive D-dimer test, without any imaging tests (1, 2, 3). The best validated and most widely used clinical decision rules are the Wells rule and revised Geneva score (4, 5). The YEARS algorithm, designed to further decrease the number of required imaging tests that includes parallel D-dimer and pretest probability assessment, was recently evaluated in a large outcome trial (Figure 1) (6). It was shown to safely rule out acute PE with a low failure rate of 0.61% (95% confidence interval [CI]: 0.36–0.96). Only 52% of all patients were referred for computed tomography pulmonary angiography (CTPA), a reduction of 14% points compared with the traditional diagnostic algorithm (6).

The PE rule-out criteria (PERC) are based on eight criteria (age < 50 years, heartbeat < 100/min, SaO_2 > 94%, no unilateral leg swelling, no haemoptysis, no recent trauma or surgery, no hormone use and no previous venous thromboembolism) and patients are considered to be negative when all these criteria were met (Table 1). This rule was designed to identify patients with respiratory or chest symptoms who have a very low risk of PE and do not need further

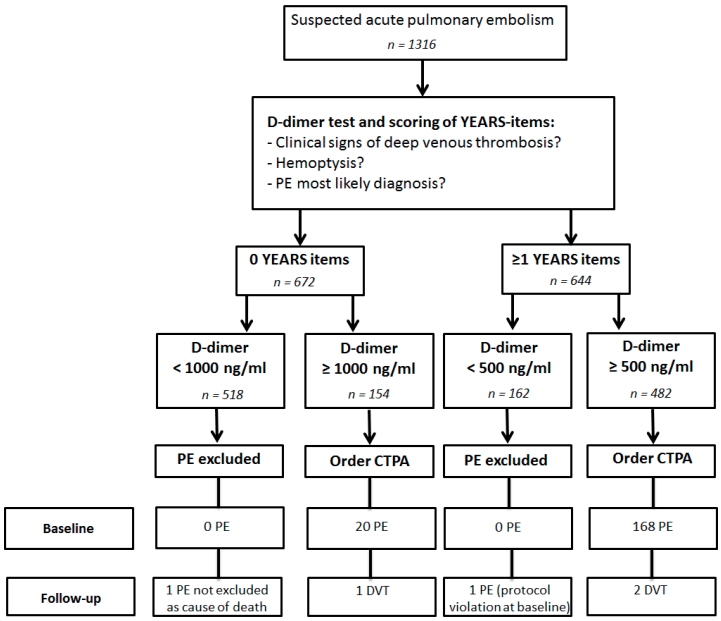

Figure 1. The YEARS algorithm with numbers of patients analyzed in this study. CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 1: The pulmonary embolism rule-out criteria (PERC)

Age < 50 years
Heartbeat < 100 beats per minute
SO_2 > 94%
No hemoptysis
No estrogen use
No surgery or trauma requiring hospitalization in the last four weeks
No unilateral leg swelling
No previous venous thrombo-embolism

clinical evaluation with clinical prediction rule, D-dimer test or imaging (7). The most recent American College of Physicians guideline suggests application of PERC in all patients judged to be at low risk for PE after initial clinical evaluation (Class II recommendation) (8).

The aim of this study was to evaluate whether the PERC rule has incremental diagnostic value to the YEARS algorithm, that is, whether the application of PERC as a standard test before the YEARS items are assessed and D-dimer levels are measured, further reduces the number of necessary CTPA examinations without compromising the safety of the algorithm.

METHODS

Study Population

This study is a post hoc analysis of the YEARS study in which consecutive in- and outpatients with clinically suspected PE were included if they were aged 18 years or older (6). All patients were managed according to the YEARS diagnostic algorithm for suspected PE (Figure 1). Patients who were referred for CTPA without an indication following the YEARS algorithm were regarded as protocol violations. Only outpatients who presented at the emergency department were included in this post hoc analysis. Exclusion criteria were allergy to intravenous contrast, pregnancy, treatment with anticoagulants initiated $\geq$ 24 hours before eligibility assessment, geographic inaccessibility precluding follow-up and life expectancy less than 3 months. All patients who were hospitalized at date of inclusion or in patients in whom the PERC items were not available were also excluded from this analysis. The follow-up consisted of a 3-month period for the occurrence of recurrent and/or fatal venous thromboembolism.

The current analysis was restricted to two of the participating hospitals of the YEARS study, that is, the Leiden University Medical Center (Leiden, the Netherlands) and the Haga Teaching Hospital (The Hague, the Netherlands) because PERC items were prospectively assessed along with the YEARS items by an independent researcher for all patients. Results of the PERC score were not registered in the patient charts and these results were therefore not used for initial management decisions.

Study Objectives

The primary aim of this study was to investigate the safety of applying the PERC rule before the YEARS algorithm in our cohort. The secondary aim of this study was to determine the efficacy of applying the PERC rule before the YEARS algorithm in our cohort. Our primary outcome was the absolute difference in the hypothetical failure rate of the algorithm when PERC would have been applied before the YEARS algorithm and the actual observed failure rate. The secondary outcome was the absolute difference in the number of required CTPA examinations between the combination of PERC and YEARS and the YEARS algorithm alone.

Statistical Analysis

The total score of the PERC rule was calculated for all patients. The PERC rule was negative when none of the eight items were present. If one or more items were present, the PERC rule was scored positive. After categorizing all patients as PERC negative or positive, the hypothetical number of diagnostic failures and required CTPAs were calculated. Diagnostic failures were defined as patients with confirmed PE at baseline or during 3-month follow-up. The proportion of required CTPAs and the 3-month venous thromboembolism (VTE) failure rate of the algorithm were calculated. The absolute differences and 95% CIs between the combination of PERC and YEARS and YEARS alone were calculated. All analyses were performed using SPSS, version 23.0 (Chicago, Illinois, United States).

RESULTS

Study Population

A total number of 1,443 patients with suspected PE were included in the YEARS study in the two hospitals. Of these patients, 111 patients were excluded because they were hospitalized at the moment of inclusion, as were 16 patients in whom the PERC rule could not be calculated due to missing data. After exclusion of these patients, 1,316 patients were entered in the current analysis. PE was confirmed in 188 patients for a PE prevalence of 14%. The mean age was 53 years (standard deviation [SD]: 18.8), the majority of patients were female (64%), 11% of the patients were known with a prior VTE, 9% were diagnosed with a malignancy before inclusions and 12% underwent surgery in the last 4 weeks or immobilization for more than 3 days (Table 2).

YEARS Algorithm

According to the YEARS algorithm, 672 patients had no YEARS items and 644 patients had a least one YEARS item. CTPA was required in 636 patients (48%) to confirm or rule out the diagnosis of PE, of whom 188 patients were diagnosed with PE at baseline (Figure 1).

Table 2 Demographical characteristics

	All patients	PERC negative patients	PERC positive patients
Number of patients (n)	1316	250	1066
Age (years), mean ± SD	53.4 ± 18.8	36.7 ± 9.4	57.4 ± 18.3
Women, n (%)	838 (63.7)	159 (63.6)	679 (63.7)
Pulmonary embolism confirmed, n (%)	188 (14.3)	11 (4.4)	178 (16.7)
Risk factors			
Previous PE, n (%)	144 (10.9)	0 (0)	144 (13.5)
Active malignancy, n (%)	119 (9.0)	11 (4.4)	108 (10.1)
Use of exogenous hormones, n (%)	127 (9.7)	0 (0)	127 (11.9)
Immobilization or surgery in last 4 weeks, n (%)	156 (11.9)	0 (0)	156 (14.6)
YEARS-score			
D-dimer < 1000 ng/ml and 0 items, n (%)	518 (39.4)	156 (62.4)	362 (34.0)
D-dimer > 1000 ng/ml and 0 items, n (%)	154 (11.7)	6 (2.4)	148 (13.9)
D-dimer < 500 ng/ml and ≥ 1 item, n (%)	162 (12.3)	37 (14.8)	125 (11.7)
D-dimer > 500 ng/ml and ≥ 1 item, n (%)	482 (36.6)	51 (20.4)	431 (40.4)

Abbreviations: PERC: pulmonary embolism rule-out criteria; SD: standard deviation; PE: pulmonary embolism

During 3-month follow-up, five patients suffered from VTE (three with deep vein thrombosis (DVT), one PE diagnosed at baseline due to protocol violation and one patient in whom PE could not be excluded as cause of death; Figure 1]. The 3-month VTE failure rate of the algorithm was 0.44% (5 out of 1,128, 95% CI: 0.19–1.0).

Applying PERC before YEARS

Of all patients, 250 (19%) would have been PERC negative. The mean age of this PERC-negative cohort was 36.7 years (SD: 9.4) and 159 patients were female (64%). PE was confirmed in 11 of these 250 patients at baseline by CTPA for a prevalence of 4.4%. A total of 1,066 patients were PERC positive. PE was confirmed in 178 of these patients at baseline (16.7%). Their mean age was 57.4 years (SD: 18.3), 64% were female and 14% was known with a history of VTE (Table 2).#

PERC-Negative Patients

From the PERC-negative patients, 162 had zero YEARS item and 88 patients had one to three YEARS items (Figure 2a; Table 2). Of the 162 patients without YEARS items, 156 patients had a D-dimer < 1,000 ng/mL and 6 patients had a D-dimer ≥ 1,000 ng/mL and were referred for CTPA (3.7%, 95% CI: 1.7–7.8). None of these PERC-negative patients without YEARS items were diagnosed with PE at baseline or during follow-up for a failure rate of 0.0% (95% CI: 0.0–2.3). From the 88 PERC-negative patients with at least one YEARS item, 37 patients had

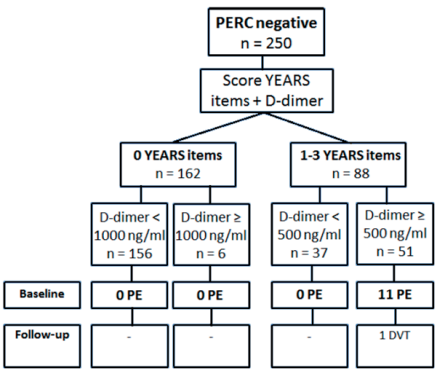

Figure 2a

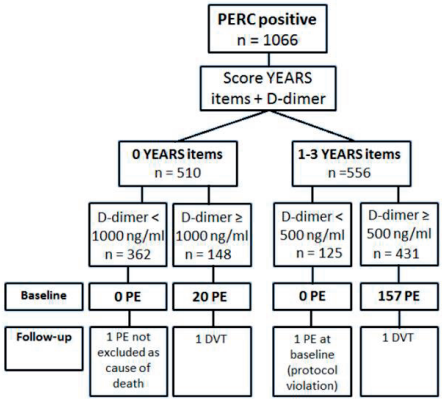

Figure 2b

Figure 2. Outcome of hypothetical situation of the application of PERC before YEARS, with (a) PERC-negative patients and (b) PERC-positive patients. PERC, pulmonary embolism rule-out criteria.
Abbreviations: PE = pulmonary embolism, DVT = deep venous thrombosis

a D-dimer < 500 ng/mL, none of these patients was diagnosed with PE at baseline and there were no events during follow-up in this group. A total of 51 patients had a D-dimer ≥ 500 ng/mL and were referred for CTPA. PE was diagnosed in 11 of these latter patients at baseline and 1 patient suffered from DVT during follow-up (Figure 2a). In patients who were PERC negative, the absolute difference in the number of required CTPAs was 2.4% (95% CI: −9.6 to 4.8) lower than by using the YEARS algorithm at the cost of a failure rate of 4.8% (12 out of 250, 95% CI: 2.8–8.2).

PERC-Positive Patients

From all PERC-positive patients, 510 patients had no YEARS item and 556 patients had at least one YEARS item (Figure 2b). In the group of PERC-positive patients without YEARS items, 362 patients had a D-dimer < 1,000 ng/mL. None of these patients was diagnosed with PE at baseline and in one patient, PE could not be excluded as a cause of death during follow-up. A total number of 148 patients had a D-dimer ≥ 1,000 ng/mL and were referred for CTPA, PE was confirmed in 20 patients at baseline. One patient was diagnosed with a DVT during follow-up. In the group of patients with at least one YEARS item, 125 patients had a D-dimer < 500 ng/mL of which 1 patient was diagnosed with PE at baseline as protocol violation in YEARS; 431 patients had a D-dimer ≥ 500 ng/mL and were referred for CTPA, 157 patients were diagnosed with PE at baseline (Figure 2b). During 3-month follow-up, one patient was diagnosed with DVT.

Combination of PERC and YEARS

Compared with the YEARS diagnostic strategy, the absolute difference in 3-month VTE failure rate of the combination of PERC and YEARS was 0.98% (95% CI: 0.17–1.9) higher compared with YEARS alone (Table 3). When PERC would have been applied before YEARS, only 579 patients (44%) would have been referred for CTPA for an absolute difference of 4.3% (0.52–8.1) in favour of the PERC/YEARS combination (Table 3).

Table 3 Overview of primary and secondary study outcome.

	Failure rate	Number of required CTPAs
YEARS, n **% (95%CI)**	5/1128, 0.44 (0.19-1.0)	636/1316, 48 (46-51)
PERC + YEARS, n **% (95%CI)**	16/1128, 1.4 (0.87-2.3)	579/1316, 44 (41-47)
Absolute difference compared to YEARS, n % (95%CI)	11/1128 + 0.98 (0.17-1.9)	57/1316 - 4.3 (0.52-8.1)

Abbreviations: CTPA: computed tomography pulmonary angiography; CI: confidence interval; PERC: pulmonary embolism rule-out criteria

DISCUSSION

In this post hoc analysis of the YEARS study, we demonstrated a modest decrease in the number of required CTPAs when the PERC rule would have been applied before the YEARS algorithm. The small 4.3% (95% CI: 0.52–8.1) increase in efficiency came at the cost of a higher failure rate of 0.98% (95% CI: 0.17–1.9). PERC was designed for patients who have a low suspicion on PE according to the treating physician's gestalt. In our analysis, we hypothetically applied PERC to all patients with suspected PE as initial diagnostic test. With all diagnostic failures by PERC at baseline in patients with at least one YEARS item, it could be argued that these failures did not occur in the patient category for which PERC was developed. Nevertheless, when we would apply PERC as extension to YEARS in patients without any YEARS items, the efficacy improvement was very modest, thus supporting our conclusion that PERC has no added value to YEARS in diagnostic management of patients with suspected PE in a Western European emergency ward setting.

The PERC rule was derived with the intention of defining a group of patients who have such a low risk of PE that PE can be ruled out without further diagnostic tests (7). One of the largest performed studies to evaluate the PERC rule was performed in the United States by Kline et al. A total number of 8,183 patients were enrolled in this study, with a PE prevalence of 6.3% at baseline. The PERC rule was found to be negative in 20% of all patients. In this subgroup, only 1.0% of patients suffered VTE during a 45-day follow-up, with an upper limit

of the 95% CI of 1.6% (9). These findings were confirmed in other studies from the North American continent (7, 10, 11).

Clearly, the reported low failure rate justified implementation of PERC in the U.S. emergency setting. Nevertheless, the reported PE prevalence is lower in the United States than in countries outside the United States (12). However, the specificity of the PERC rule appears to increase as the risk of PE in the population decreases, in accordance with Bayes' theorem (13). In other words, PERC rule can be safely applied in a population with a low to very low baseline pretest probability of PE, but may be unsafe in populations with higher PE prevalence (14). This hypothesis was confirmed in our analysis as well in several previous European studies (15-17). Hugli et al demonstrated a PE prevalence of 5.4% (95% CI: 3.1–9.3) in patients who were PERC negative in a cohort with a PE prevalence of 21.3% (16). Righini et al evaluated the use of the PERC rule as well in a cohort with a high PE prevalence of 25.6% (95% CI: 23–39) (17). Of all the PERC-negative patients in this study, 6.7% (95% CI: 3–14) were diagnosed with PE and would have been missed by the PERC rule. Moreover, these studies demonstrated that only a small proportion of patients was PERC negative, ranging from 7.7 to 13.2%, in contrast to the prevalence of 20% PERC-negative patients with a low false-negative rate of 1.0% (95% CI upper limit of 1.6%) in the U.S. studies (9, 15, 16).

A recent report of a large European study focusing on the safety of PERC concluded that PERC can exclude acute PE with a low percentage of false-negative results (18). Importantly, as in our study, PERC was not used as a primary diagnostic test but as a second test in patients with an estimated low clinical probability of PE based on assessment by the physician and calculation of the revised Geneva score. In these patients with a very low PE prevalence of 4.7% and no PERC item, the 3-month risk of symptomatic VTE was 1.2% (95% CI upper limit of 2.9%). From this study, the overall accuracy of a negative PERC score ruling as single test could not be extracted. A current prospective study in France is recruiting patients to implement and evaluate the PERC rule in a cluster randomized trial in 15 different hospitals (NCT02375919) (19). Each centre will be randomized for the sequence of a 6-month intervention period (using the PERC strategy), followed by a control period of 6 months where usual care will be applied. Awaiting the results of this trial, current evidence does not allow standard application of the PERC rule in an emergency setting in European countries.

Recently, the combination of the age-adjusted D-dimer threshold and the YEARS algorithm was analysed to reduce the number of required CTPAs further (20). Different scenarios, even in subgroup populations of patients aged 50 years and older, showed, however, no safe reduction in the number of required CTPAs. It is therefore possible that the limit of required CTPAs has been reached with YEARS.

Strengths of this post hoc analysis are the large sample size, the accurate follow-up of the included patients as well as the adjudication of the end points by an independent committee. The PE prevalence in our cohort was representable and comparable to other European cohorts of patients with suspected PE. The main limitation of our analysis is that this is a post

hoc analysis and patients were not managed according to the hypothetical scenario of using PERC before YEARS. Also, despite our large sample size of the total study cohort, a relatively small number (250 patients) would have been PERC negative. In our opinion, our results of this analysis do not justify a further prospective study to answer the research question more precise.

In conclusion, applying PERC before the start of the YEARS algorithm would have yielded a modest decrease in the proportion of required diagnostic tests at the cost of a higher failure rate of the algorithm.

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