

ORIGINAL ARTICLE

A simplified decision rule to rule out deep vein thrombosis using clinical assessment and D-dimer

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Abstract

Background: Current clinical decision rules to exclude deep vein thrombosis (DVT) are underused partly because of their complexity. A simplified rule that can be easily applied would be more appealing to use in clinical practice.

Methods: We used individual patient data from prospective diagnostic studies of patients suspected of DVT to develop a new clinical decision rule. The primary outcome was presence of DVT either at initial testing or during follow-up. DVT was considered safely excluded if the upper 95% confidence interval (CI) of DVT prevalence was <2%.

Results: Four studies and 3368 patients were eligible for this analysis. Overall prevalence of DVT was 17%. In addition to D-dimer, two variables, calf swelling and DVT as the most likely diagnosis, are included in the new rule. Based on these two variables, two clinical pretest probability (CPTP) groups were defined; low (none of the two items present) and high (at least one of the items present). DVT can be safely excluded in patients with low CPTP with a D-dimer <500 ng/mL (prevalence = 0.1%; 95% CI, 0.0–0.8), low CPTP with a D-dimer between 500 ng/mL and 1000 ng/mL (prevalence = 0.3%; 95% CI, 0.0–1.7), and D-dimer <500 ng/mL in patients with high CPTP (prevalence = 0.3%; 95% CI, 0.0–1.0).

Conclusions: The combination of D-dimer and Wells items resulted in a simple clinical decision rule with 3 items. The results suggest that the rule can safely exclude DVT. Prospective validation is required.

KEYWORDS

deep vein thrombosis, diagnosis, venous thromboembolism, ultrasonography, fibrinogen

Essentials

- Decision rules to rule out DVT are under used partly due to their complexity.
- A new simplified decision rule was developed using individual patient data from four studies.
- Rule consists of D-dimer, calf swelling and whether DVT is the most likely diagnosis.
- Rule has high negative predictive value, however, prospective validation is required.

1 | INTRODUCTION

Patients commonly present with symptoms of lower limb deep vein thrombosis (DVT) (e.g., swelling, pain, redness of the affected leg) to family physicians and emergency departments. The standard approach to diagnosing and excluding acute DVT involves clinical pretest probability (CPTP) estimate followed by D-dimer testing if appropriate.^{1,2} This reduces the need for ultrasound imaging, which is important to reduce testing time,³ reduce costs, and avoid false-positive diagnoses.⁴

CPTP stratifies the patient's probability of having acute DVT.^{2,5} The probability of having DVT also increases with D-dimer levels. CPTP and D-dimer levels both have predictive value for the presence of acute DVT; therefore, combining them yields a better estimate of the probability of acute DVT than either alone. Because D-dimer levels are usually increased in patients with acute DVT, a low or normal D-dimer level is associated with a low probability of having DVT. A low D-dimer level and a low CPTP combination can safely exclude DVT in patients with symptoms of possible DVT, thereby avoiding the need for additional diagnostic testing such as ultrasound imaging.²

The Wells DVT clinical score (with nine clinical items) is commonly used to assess CPTP.⁶ There are then a number of ways that these CPTP categories are combined with D-dimer categories to exclude DVT. However, literature has shown that the Wells score for DVT is not always used and is even miscalculated in clinical practice.⁷⁻¹¹ One reason for this might be the complexity of the rule and the time required to accurately calculate the CPTP.

We sought to develop a simplified clinical decision rule that would be easier to apply and therefore enable decision making in time-constrained environments such as an emergency department. Our analysis aimed to develop a new rule using some of the Wells score items in combination with D-dimer, using individual patient data (IPD) from studies evaluating the Wells rule and D-dimer in patients with suspected acute DVT.

2 | METHODS

2.1 | Construction of individual patient dataset

The details of study identification, study selection, and construction of the individual patient dataset have been previously published.¹² Briefly, principle investigators of published studies on the diagnosis of DVT provided their original datasets with anonymous IPD.¹³⁻¹⁵ All studies included patients presenting with symptoms of possible acute lower limb DVT. To be eligible for the current analysis, D-dimer had to have been measured quantitatively (i.e., as a continuous measure). Data from one additional study, published after the initial IPD was completed and conducted by our group, was added to the IPD dataset for this analysis.¹⁶ Data extracted from each dataset included: Wells-rule items⁶ (Table 1); D-dimer levels (ng/mL); and presence or absence of DVT (at the initial assessment or during follow-up in those not diagnosed with DVT at the initial assessment). The current analyses included all patients (i.e., patients with low, moderate, or high Wells CPTP).

2.2 | Derivation of new decision rule

Our goal was to develop a clinical decision rule that could guide decision making in time-constrained environments such as the emergency department or busy family practice clinic. We aimed to develop a rule with fewer Wells score items combined with D-dimer, while maintaining a high negative predictive value (NPV). Variable selection for the rule was done using 1000 bootstrap samples using total IPD data, whereas one study was iteratively excluded to increase the variety of bootstrap samples as well as to address the heterogeneity between studies. Each bootstrap sample randomly selects patients with replacement from the original dataset from which one of the studies has been excluded. Within each bootstrap sample, we built a logistic regression model with presence of DVT as the outcome, with the nine original Wells Score items and continuous D-dimer level as the independent variables. Then, to obtain a parsimonious model, each model was reduced using fast backward elimination using the Akaike Information Criterion for inclusion of the variables in the model. The Akaike Information Criterion measure is an alternative to significance criteria for variable selection which focuses on model fit and penalizes model complexity (greater number of variables in the model), and may improve the model fit. The variables were then ranked according to the frequency of the 1000 bootstrap models in which they were included. To develop the simplest model, we only included variables present in at least 60% of the final model for all iterations (i.e., exclusion of one study at a time).¹⁷

We then defined patient risk groups based on combinations of the selected variables. Based on recent evidence that a D-dimer level <1000 ng/mL excludes venous thromboembolism in patients with low CPTP, and that a D-dimer level <500 ng/mL excludes venous thromboembolism in patients with moderate CPTP,^{16,18} we predefined that D-dimer levels would be expressed as three categories: <500 ng/mL; 500 to 999 ng/mL; and ≥1000 ng/mL. Then the predefined D-dimer thresholds were applied to the risk groups. The combination of CPTP and D-dimer was considered safe if the upper bound of the 95% confidence interval (CI) of the overall DVT prevalence in those categorized as "DVT excluded" was less than 2%, which is considered acceptable.¹

2.3 | Decision rule performance

The overall performance of the new decision rule was assessed within each study and using all the study data combined. Performance was expressed as sensitivity, specificity, NPV, positive predictive value, and utility (defined as the proportion of all patients who were classified by the decision rule as having had DVT excluded).

Analyses were done within each study and the 95% CIs for estimates were calculated using the Wilson score method. Pooled estimates across all studies were done using random effects meta-analyses.¹⁹ Analyses were performed using the *rms*²⁰ package in R 3.6.1.²¹

TABLE 1 Characteristics of the studies

Characteristic	Study (First Author)				Overall (n = 3368)
	Schutgens (n = 814)	Toll (n = 791)	Elf (n = 325)	Linkins (n = 1438)	
Age: mean (SD)	59 (17)	60 (17)	60 (18)	61 (16)	60 (17)
Sex: n (%)					
Male	307 (38)	301 (38)	128 (39)	530 (37)	1266 (38)
Female	507 (62)	490 (62)	197 (61)	908 (63)	2102 (62)
Active cancer: n (%)	86 (11)	38 (5)	12 (4)	78 (5)	214 (6)
Bedridden: n (%)	75 (9)	105 (13)	16 (5)	116 (8)	312 (9)
Paresis: n (%)	35 (4)	112 (14)	14 (4)	39 (3)	200 (6)
Calf swelling: n (%)	353 (43)	323 (41)	93 (29)	218 (15)	312 (29)
Leg swelling: n (%)	169 (21)	353 (45)	47 (14)	148 (10)	717 (21)
Tenderness: n (%)	541 (66)	572 (72)	161 (50)	663 (46)	1937 (58)
Pitting edema: n (%)	419 (51)	490 (62)	97 (30)	383 (27)	1389 (41)
Dilated vein: n (%)	127 (16)	155 (20)	39 (12)	73 (5)	394 (12)
Alternative diagnosis: n (%)	217 (27)	300 (38)	114 (35)	548 (38)	1179 (35)
CPTP: n (%)					
Low	195 (24)	95 (12)	151 (46)	693 (48)	1134 (34)
Moderate	322 (40)	348 (44)	123 (38)	627 (44)	1420 (42)
High	297 (36)	348 (44)	51 (16)	118 (8)	814 (24)
Prevalence of DVT: n (%)	318 (39)	126 (16)	52 (16)	87 (6)	583 (17)
D-dimer assay	Tinaquant	VIDAS / Tinaquant	Auto Dimer	Triage	–
D-dimer (ng/mL): median (min, max)	1000 (0, 23500)	1078 (0, 35000)	740 (0, 16280)	530 (0, 42900)	742 (0, 42900)
Country	Netherlands	Netherlands	Sweden	Canada	–
Care setting	Secondary	Primary	Secondary	Secondary	–
Imaging modality	US	US	VG/US	US	
Whole leg or proximal imaging	Proximal	Proximal	Whole leg	Proximal	
Follow-up duration	3 months	NA	3 months	3 months	

Abbreviations: CPTP, clinical pretest probability using the Wells criteria; DVT, deep vein thrombosis; NA, not available; SD, standard deviation; US, ultrasound; VG, venography.

3 | RESULTS

3.1 | Patients

Of the 13 studies included in the original IPD, 10 were excluded as they did not measure quantitative D-dimer. Overall, four studies (three from the original IPD and one study published after the IPD) with a total of 3368 patients were included in the analysis. The overall DVT prevalence was 17%, with 34% low, 42% moderate, and 24% high CPTP as assessed by the original Wells score. The baseline characteristics of the four studies are summarized in Table 1.

3.2 | Variable selection

The bootstrap-derived estimates for each variable as well as the frequency of inclusion of each variable in the bootstrap models for each iteration (i.e., excluding one study at a time) is shown

in Table 2. The D-dimer value, calf swelling of 3 cm or greater in diameter and DVT as the most likely diagnosis (the inverse of “another diagnosis more likely than DVT”) were included ranked within the top three among all variables in the bootstrap samples in all of the iterations and therefore were selected for the decision rule.

Based on the two Wells items, we identified two patient subgroups; those with none of the items present (low CPTP, 27% of patients) and those with at least one item present (high CPTP, 73% of patients).

3.3 | Low CPTP (none of the items present)

Of the 920 patients with low CPTP, 63 (6.8%) patients had DVT. Of the patients with low CPTP, the DVT prevalence for patients with D-dimer <500 ng/mL was 0.1% (95% CI, 0.0–0.8) and 0.3% (95% CI, 0.0–1.7) for patients with D-dimer between 500 and 999 ng/mL (Table 3). Therefore, because the upper bounds of the 95% CIs are

TABLE 2 Results of variable selection using logistic regression and bootstrap methodology (outcome is DVT)

Variable	Excluding Schutgens		Excluding Toll		Excluding Elf		Excluding Linkins	
	OR (95% CI)	Frequency (%)	OR (95% CI)	Frequency (%)	OR (95% CI)	Frequency (%)	OR (95% CI)	Frequency (%)
D-dimer (mg/L) ^b	1.7 (1.5, 2.0)	100	2.1 (1.7, 2.5)	100	1.8 (1.6, 2.1)	100	1.9 (1.7, 2.1)	100
Calf swelling	2.5 (1.8, 3.5)	99.7	2.5 (1.8, 3.4)	100	2.6 (2.0, 3.3)	100	2.0 (1.5, 2.6)	99.0
DVT most likely ^a	1.6 (1.0, 2.2)	63.1	2.1 (1.5, 3.0)	99.1	1.9 (1.4, 2.6)	98.5	1.7 (1.0, 2.3)	84.7
Tenderness	1.0 (1.0, 1.6)	10.1	1.8 (1.0, 2.4)	96.4	1.5 (1.0, 1.9)	73.3	1.0 (1.0, 1.7)	19.4
Paresis	1.0 (1.0, 1.7)	5.5	1.0 (1.0, 2.2)	9.7	1.0 (0.5, 1.0)	8.5	1.0 (0.4, 1.0)	16.6
Active cancer	1.0 (1.0, 2.6)	23.6	1.0 (1.0, 2.2)	33.7	1.0 (1.0, 2.2)	40.2	1.0 (1.0, 2.0)	11.6
Bedridden	1.0 (0.4, 1.0)	15.0	1.0 (1.0, 2.2)	42.0	1.0 (0.5, 1.0)	13.5	1.0 (0.6, 1.0)	5.9
Pitting edema	1.0 (0.7, 1.0)	4.0	1.6 (1.0, 2.1)	86.7	1.0 (1.0, 1.5)	14.3	1.0 (1.0, 1.4)	4.2
Dilated vein	1.0 (1.0, 1.7)	7.3	1.0 (0.3, 1.0)	35.1	1.0 (1.0, 1.7)	17.0	1.0 (1.0, 1.0)	2.9
Leg swelling	1.6 (1.0, 2.3)	62.2	1.0 (1.0, 2.0)	47.8	1.0 (1.0, 1.4)	8.5	1.0 (1.0, 1.0)	2.7

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; frequency, percent of bootstrap models in which the variable was retained; OR, odds ratio.

^aThe inverse of “another diagnosis more likely than DVT.”

^bIncluded as a continuous variable.

TABLE 3 Prevalence of DVT by items present in the new rule and D-dimer categories

D-dimer (ng/ml)	Study (First Author)				
	Schutgens (n = 814)	Toll (n = 791)	Elf (n = 324)	Linkins (n = 1438)	Overall ^a (n = 3368)
	n / N Prevalence (95% Confidence Interval)				
0 items					
<500	1/57 1.8 (0.1-9.3)	1/79 1.3 (0.1-6.8)	0/42 0 (0-8.4)	0/258 0 (0-1.5)	2/436 0.1 (0.0-0.8)
500-<1000	2/30 6.7 (1.8-21.3)	1/42 2.4 (0.1-12.3)	0/32 0 (0-10.7)	0/120 0 (0-3.1)	3/224 0.3 (0.0-1.7)
≥1000	25/59 42.4 (30.6-55.1)	16/75 21.3 (13.6-31.9)	7/26 26.9 (13.7-46.1)	10/100 10.0 (5.5-17.4)	58/260 24.5 (11.1-37.8)
At least 1 item					
<500	4/159 2.5 (1.0, 6.3)	0/140 0 (0-2.7)	1/67 1.5 (0.1-8.0)	1/423 0.2 (0-1.3)	6 / 789 0.3 (0.0-1.0)
500-<1000	15/105 14.3 (8.9-22.2)	6/111 5.4 (2.5-11.3)	1/55 1.8 (0.1-9.6)	11/255 4.3 (2.4-7.6)	33 / 526 5.8 (1.9-9.7)
≥1000	271/404 67.1 (62.4-71.5)	102/344 29.7 (25.1-34.7)	43/103 41.7 (32.7-51.4)	65/282 23.0 (18.5-28.3)	481 / 1133 40.4 (17.9-62.8)

^aOverall estimates are pooled estimates of the individual studies using random effects meta-analyses

less than 2%, in patients with low CPTP, DVT can be safely excluded in patients with D-dimer <1000 ng/mL.

high CPTP, DVT can only be safely excluded in patients with D-dimer <500 ng/mL.

Based on these results, the new rule was formed, which we refer to as the DAYS rule (Figure 1).

3.4 | High CPTP (at least one of the items present)

Of the 2448 patients with high CPTP, 520 (21.2%) patients had DVT. Of the patients with high CPTP, the prevalence of DVT for patients with D-dimer <500 ng/mL was 0.3% (95% CI, 0.0-1.0) whereas it was 5.8% (95% CI, 1.9-9.7) for patients with D-dimer between 500 and 999 ng/mL (Table 3). Therefore, for patients with

3.5 | Diagnostic accuracy

The overall diagnostic performance of the rule in all patients is shown in Table 4. The NPV is 99.3 (95% CI, 98.3-100), specificity of 49.4 (95% CI, 39.3-59.5), and utility of 40.6 (95% CI, 27.2-54.0).

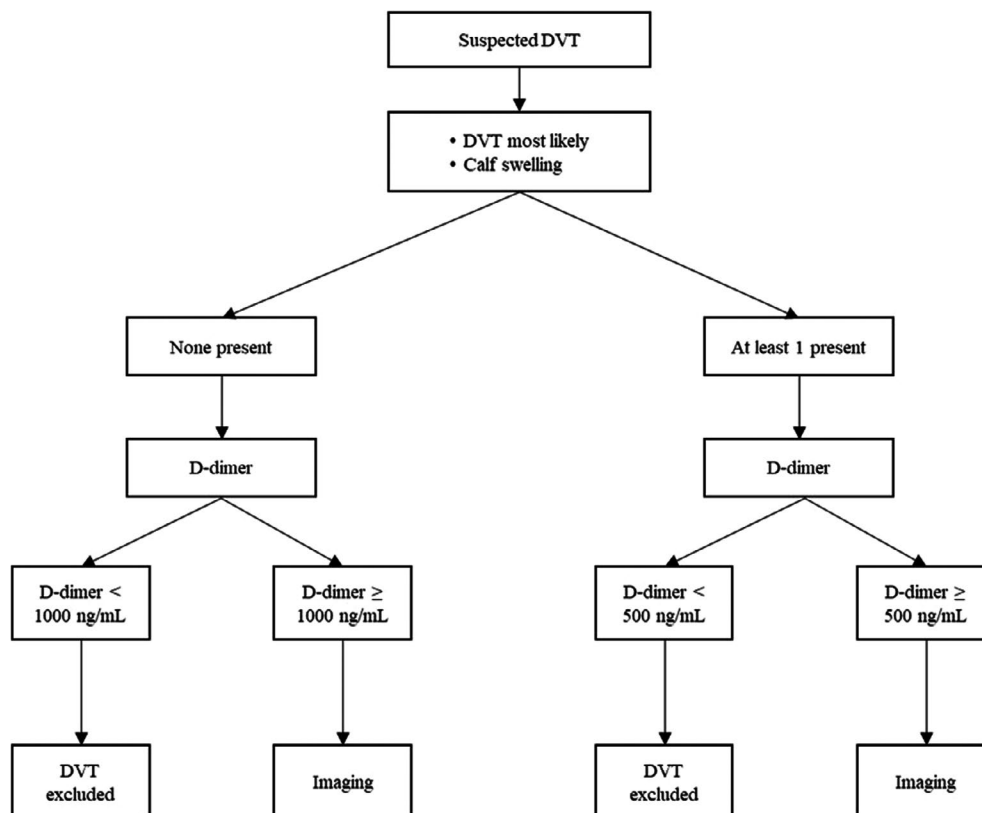


FIGURE 1 Diagnostic workup for suspected DVT using the DAYS rule. DVT, deep vein thrombosis

TABLE 4 Diagnostic properties of new rule

Diagnostic Indices	Study (First Author)				Overall ^a (n = 3368)
	Schutgens (n = 814)	Toll (n = 791)	Elf (n = 324)	Linkins (n = 1438)	
	n / N % (95% Confidence Interval)				
Sensitivity	311/318 97.8 (95.5-98.9)	124/126 98.4 (94.4-99.6)	51/52 98.1 (89.9-99.9)	86/87 98.9 (93.8-99.9)	572/583 98.1 (96.9-99.4)
Specificity	239/496 48.2 (43.8-52.6)	259/665 38.9 (35.3-42.7)	140/273 51.3 (45.4-57.2)	800/1351 59.2 (56.6-61.8)	1438/2785 49.4 (39.3-59.5)
Negative predictive value	239/246 97.2 (94.2-98.6)	259/261 99.2 (97.2-99.8)	140/141 99.3 (96.1-100)	800/801 99.9 (99.3-100)	1438/1449 99.3 (98.3-100)
Positive predictive value	311/568 54.8 (50.6-58.8)	124/530 23.4 (20.0-27.2)	51/184 27.7 (21.8-34.6)	86/637 13.5 (11.1-16.4)	572/1919 29.8 (11.4-48.3)
Utility	246/814 30.2 (27.2-33.5)	261/791 33.0 (29.8-36.3)	141/325 43.4 (38.1-48.8)	801/1438 55.7 (53.1-58.3)	1449/3368 40.6 (27.2-54.0)

^aOverall estimates are pooled estimates of the individual studies using random effects meta-analyses.

4 | DISCUSSION

We used IPD to develop a simple diagnostic decision rule (DAYS rule) for testing patients with symptoms of possible lower limb DVT. This rule consists of only three variables: calf swelling, DVT the most likely diagnosis, and D-dimer. The rule safely excludes DVT in this dataset in 43% of patients.

Our derived rule is similar to the YEARS clinical decision rule for PE, which incorporates three clinical findings: clinical signs of DVT, hemoptysis, and PE as the most likely diagnosis. For none of the items present, a D-dimer of <1000 ng/ml rules out PE, and for at least 1 item present, a D-dimer of <500 ng/ml rules out PE.²² A D-dimer of less than 1000 ng/ml excludes DVT in patients with low CPTP and D-dimer of less than 500 ng/ml excludes DVT in high

CPTP patients. We were unable to verify the safety of excluding DVT with a D-dimer threshold of 500 or 999 ng/ml in high CPTP patients, which constituted 16% of the population in this analysis. The order of CPTP assessment and D-dimer result is of importance in the rule. Although it is possible to interpret the rule as requiring CPTP assessment only in patients with D-dimer between 500 and <1000 ng/mL, we recommend assessing CPTP first followed by the D-dimer to avoid the result of the D-dimer influencing the CPTP assessment, particularly in this group of patients.

We found our new rule excluded DVT in a similar proportion of patients as the Wells Score CPTP-adjusted D-dimer strategy²³; however, there are several compelling reasons why this new rule might have a greater clinical utility. First, the Wells score has nine items, some of which consist of multiple components. For example, either a history of recent surgery within 12 weeks or having been bedridden for a minimum of three days. Another example is having paralysis, paresis, or being immobilized in a cast. Not only are there many components, but the physician requires to remember which component makes up which item. The advantage of this simple new rule is that it uses only two clinical items. Second, points are not assigned uniformly in the Wells score, with another diagnosis being more likely than DVT requiring a deduction of two points and all other items earning 1 point. The availability of cell phones and medical apps helps to standardize practice; however, there is evidence that physicians often do not use the Wells score opting instead for ultrasound or Gestalt estimate of CPTP.¹¹ This is in part, to reduce to the cognitive load of calculating a score in an often busy and overcrowded environment.²⁴ Third, five of the Wells score items are based on examination findings which benefit from experience of treating DVT; for example, the definition of dilated superficial veins or tenderness in the distribution of the deep veins can be interpreted differently between physicians. In contrast, our newly derived score has the advantage of having fewer items, each with only one component.

We opted to develop a decision algorithm rather than a prediction rule because of the clinical utility of an algorithm over absolute predicted estimates of DVT prevalence. Even though the overall accuracy and predictive performance of a predictive rule might be better, we believe the proposed clinical decision rule has optimal sensitivity and NPV to be used in clinical practice.

Our research does have some limitations. Of the 13 studies in the original IPD, we were unable to include 10 studies because they did not measure a quantitative D-dimer (rather, they mainly used qualitative D-dimer assays). The patients were recruited into four studies from three countries between 2000 and 2010. Although inclusion of studies from different settings should improve the generalizability of our findings, the indication to investigate patients for DVT may have changed over time and may vary by country. We have previously identified additional heterogeneity between studies resulting from differences in prevalence of DVT and distribution of patients who had low and moderate Wells CPTP.²³ Given that we have used the same data to develop the

rule, and estimate the diagnostic performance of the rule, we recommend interpreting the diagnostic performance of the rule with caution. External validation and prospective evaluation should be carried out to assess the diagnostic performance of the rule. The performance of our rule may vary by setting, with higher efficiency and negative predictive values in settings with a lower threshold to test for DVT.

A controversial component of the Wells rules is the incorporation of physician gestalt estimation, because of its subjective nature. In the case of Wells DVT score, this is captured with the question on an alternative diagnosis being more likely than DVT. In our analysis, we included the converse of the response to the original question, "DVT is the most likely diagnosis." Despite the criticism of this item, it was retained with high frequency in the variable selection bootstrap approach and therefore, included it in our decision rule. Last, these results are not applicable to pregnant women suspected of acute DVT.

In conclusion, we have derived a simplified clinical decision rule for the diagnosis of DVT (the DAYS rule). This rule may be more appealing to use compared with standard approaches such as the Wells score because there are fewer items to apply. Prospective validation will be required to establish the safety and efficacy of this new clinical decision rule.

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CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

Concept and design: Sameer Parpia, Keying Xu, Kerstin de Wit, Geert-Jan Geersing, Toshihiko Takada, and Clive Kearon; acquisition, analysis, or interpretation of data: Sameer Parpia, Keying Xu, Kerstin de Wit, Geert-Jan Geersing, Toshihiko Takada, and Clive Kearon; drafting of manuscript: Sameer Parpia, Keying Xu, Kerstin de Wit, and Clive Kearon; critical revision of manuscript for important intellectual content: all authors; and statistical analysis: Keying Xu and Sameer Parpia.

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