

Critical appraisal of the diagnostics of 270 consecutive cases of suspected venous thromboembolism and established consequences at a non-university center

Johannes Lukaschek, Hans-Rudolf Schmid, Christian Vorburger, Jürg H. Beer

Department of Internal Medicine, Kantonsspital Baden, Switzerland

Summary

Questions under study: Diagnostic strategies in venous thromboembolism (VTE) are subject to controversy and rapid change and are dependent on the availability of the specific tests. The aim was to critically analyse the diagnostic procedures in patients with VTE at an intermediate size, non-university hospital.

Methods: The diagnostic work up of 270 consecutive patients with suspected VTE disorders was analysed prospectively and the therapeutic decisions were monitored and compared with the actually implemented new standard evaluation which consists of a sequential application of the diagnostic tools (clinical probability, D-dimer compression ultrasound V/Q lung scan or CT). The patients were followed clinically for at least three months.

Results: 50% of the 55 patients with suspected deep vein thrombosis (DVT) and 35% of the 215 patients with suspected pulmonary embolism (PE)

were found positive and were anticoagulated. The overall number of patients being anticoagulated was not significantly changed by the new procedure but approximately 30% of the additional examinations inclusive V/Q-scans, spiral CT and compression ultrasound or phlebography could be saved. Our study and the follow up after the therapeutic decision indicate that 92% of the patients can be clearly and safely allocated, while the remainder are managed according to an essentially clinical decision.

Conclusions: The vast majority (>90%) of the patients can be clearly diagnosed as positive or negative with the strategy presently used. A minority still requires an "overall decision". Our modified approach results in considerable cost savings.

Key words: venous thromboembolism; deep vein thrombosis; pulmonary embolism; V/Q-scan; D-dimer; spiral computed tomography

Introduction

Diagnostic strategies for venous thromboembolic disease have been subject to rapid and profound changes and have been constantly modified. However, over the sequence and number of procedures remain controversial. Furthermore, some diagnostic procedures are not readily available at every hospital. For these reasons we have prospectively analysed the diagnostic work-up for all patients that presented with suspected thromboembolic disease over 7 months. The aims of the study were:

1. the critical appraisal of the diagnostic strategy;
2. the implementation, analysis and adequate use of the new diagnostic procedures locally available such as a reliable and rapid D-dimer assay and the spiral computed tomography (CT);
3. the implementation and analysis of a locally standardised approach, based on our data and the evidence from the literature.

Patients and methods

Between December 1996 and July 1997, 270 consecutive patients presenting at the emergency ward with suspected venous thromboembolic disease (VTE) were

prospectively analysed: 215 presented with suspected pulmonary embolism (PE) and 55 with suspected deep vein thrombosis (DVT). The respective numbers illustrate the

fact that a majority of DVTs are nowadays diagnosed and managed on an outpatient basis. Figure 3a illustrates the approach used for the study and figure 3b the modified procedure implemented after the study. Patient data are summarised in table 1.

The initial overall clinical probability was determined in analogy to the “pre-test probability” and was grouped into “high” – “non-diagnostic” – “low probability”. It was determined by the resident together with the attending physician on call based on the history, the clinical findings, the ECG, the chest x-ray and the blood gas analysis (which was asked for in 97 of 215 cases of PE (= 45%) as it was standard at this hospital. It is important to note that this initial overall clinical probability was determined without the knowledge of the D-dimer concentration and without additional radiological (V/Q-scan or spiral CT) or laboratory data. The ranking list of major clinical symptoms was known to clinicians [1, 2] but the overall clinical decision (high – non-diagnostic – low) was left at the discretion of the attending physician. In the meantime, a score such as proposed by Wells et al. [3] was shown to be useful.

D-dimer: Venous citrated blood was taken on arrival in the emergency room with vacutainer tubes (Becton-Dickinson, Basel) and centrifuged within 30 minutes at 1800 g for 10 minutes. D-dimer was determined within 1 hour by the D-dimer Tinaquant®-assay (Roche Diagnostics AG, Basel, Switzerland). It is a microlatex test. Immobilised mouse monoclonal antibodies on latex particles are used for turbidometric quantitative determination on a BM/Hitachi 911 autoanalyser (Roche Diagnostics (Schweiz) AG). Interassay variation coefficient at a level of 950 µg/l was 6%. The results of this assay are comparable to a goldstandard ELISA in outcome data [4–7] and the reference value in healthy donors is less than 500 µg/l.

Lung ventilation/perfusion scans (V/Q-scan): All patients with suspected PE received a ventilation perfusion scan and the results were analysed blinded and independently by the radiologist who assigned a negative, positive or non-diagnostic probability to them (according to the modified PLOPED criteria [8–10]).

Based on the initial clinical evaluation, the D-dimer, the V/Q-scan and the other clinical features, an overall interpretation was made (positive or negative) and the pa-

Table 1

Patient characteristics.

Patient characteristics	n = 270	
Sex	male (n = 134)	female (n = 136)
<i>Age (years):</i>		
Mean ± SD	65 ± 14	66 ± 15
Median / range	67 / 29–90	70 / 22–95
<i>Risk factors:</i>		
None	31 (23%)	18 (13%)
Positive family history for VTE	1 (1%)	4 (3%)
Earlier PE/DVT	24 (18%)	27 (20%)
Recent immobilisation / bed rest ≥48 h	27 (20%)	44 (32%)
Recent travel >3 h	6 (4%)	7 (5%)
Recent surgery (last 4 weeks)	7 (5%)	13 (10%)
Obesity (BMI >30 kg/m ²)	28 (21%)	41 (30%)
Varicosis	21 (16%)	46 (34%)
Oral contraceptives	–	15 (11%)
Cancer	26 (19%)	17 (13%)
Heart failure	26 (19%)	28 (21%)
Stroke / hemiparesis	6 (4%)	8 (6%)
Forced diuretic therapy	12 (9%)	7 (5%)
APC-resistance (Factor V Leiden)	21 (16%)	17 (13%)
Homocysteine >15 µmol/l	50 (37%)	42 (31%)
<i>Clinical features</i>		
None	3 (2%)	3 (2%)
Dyspnoea / tachypnoea	71 (53%)	82 (60%)
Cyanosis	5 (4%)	3 (2%)
Chest pain	47 (35%)	47 (35%)
Heart rate >100/min	43 (32%)	49 (36%)
Cough	38 (28%)	32 (24%)
Haemoptysis	5 (4%)	1 (1%)
Syncope	9 (7%)	10 (7%)
Hypotension (systolic <100 mm Hg)	2 (1%)	6 (4%)
Right heart failure (clinical)	16 (12%)	17 (13%)
Pathological chest x-ray	46 (21%)	43 (20%)
Painful calf	25 (19%)	25 (18%)
Difference in calf circumference	37 (28%)	29 (21%)

tients were anticoagulated accordingly. Patients with non-diagnostic scans who were not anticoagulated based on the other parameters or the clinical evaluation were followed clinically for at least 1.5 to maximally 2 years, in collaboration with the family physician by phone-call follow-up. The clinical follow-up in the next 3 months after diagnosis was regarded as "gold-standard" in patients who were not anticoagulated.

Compression ultrasound (CUS) and/or phlebography was performed in 82 cases. In the DVT group (55 patients) 5 received phleboographies alone and 50 CUS. In 6 cases the CUS analysis was inconclusive and phlebography was performed in addition. 27 CUS were carried out in the PE group.

Results

The initial clinical probability in patients with suspected PE was considered high in 25% of patients, non-diagnostic in 64% and low in 11%. In patients with suspected DVT the clinical suspicion was high in 59%, non-diagnostic in 32% and low in 9%.

Taken together, a high pretest probability of DVT or PE resulted in a positive overall evaluation and anticoagulation in 84% of the cases. On the other hand, a low clinical probability was finally negative in 94% of the cases. The interme-

diante range of the clinical suspicion relies particularly on additional testing, as one would expect.

The *D-dimer* values in the population with suspected PE showed values <500 µg/l in 28% (60/215 patients) and with suspected DVT in 35% (19/55 patients).

Very high levels of D-dimers >8000 µg/l were analysed for their positive predictive value. 6% of the D-dimers were >8000 µg/l (13/215) in the patients with suspected PE) and 18% (10/55) in the DVT group. 85% and 90% were finally judged positive for PE and for DVT respectively.

In 3/215 V/Q-scans (1,4%) and 3/82 CUS/phleboographies (3,6%) the D-dimer levels were <500 µg/l but were nonetheless considered positive either in the V/Q-scan, the CUS or phlebography and underwent anticoagulation (fig. 1, 2). The 3 cases in the PE group all had subsegmental positivity and therefore might have been categorised as having non-diagnostic probability by other observers. The 3 cases in the DVT group had DVT of the lower limb, which was verified by phlebography. A D-dimer of <350 µg/l was not observed in any patients with a positive V/Q-scan.

The sensitivity of 92% (95% CI = 89-95%) of the D-dimer assay used did not reach the sensitivities observed in the literature [6, 7, 11, 12]. With the above mentioned observer variability the three positive V/Q-scans with a D-dimer <500 µg/l might have been judged as having non-diagnostic probability and therefore would have increased the sensitivity up to 100%.

V/Q-scans: 28% (60/215) were considered positive, 15% (32/215) were non-diagnostic, and 57% (123/215) were judged negative (fig. 1a). In 14 patients with a non-diagnostic or low probability V/Q-scan the CUS of the legs was performed because of clinical suspicion and 1 patient with DVT was found and anticoagulated.

CUS/phlebography was positive in 51% (28/55) and negative in 49% (27/55). Figure 1b shows the results of all examinations, ie, together with the 27 CUS of the PE group in whom DVT was suspected as well.

Clinical follow-up of the 32 PE patients (15%) with a non-diagnostic probability V/Q-scan

16/32 patients were considered negative overall, 3 of them were anticoagulated for other reasons (2 with atrial fibrillation and one with car-

Figure 1

a. Overview of the diagnostic result of the patients with suspected PE analysed with V/Q-scans and D-dimer test.

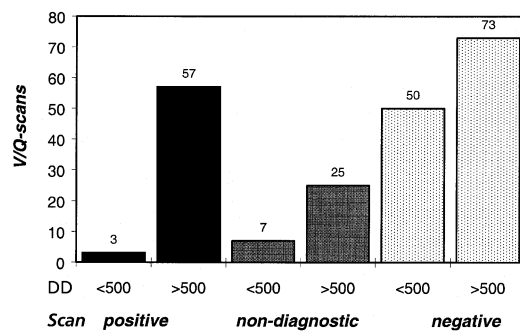


Figure 1

b. Overview of the diagnostic result of the patients with suspected DVT analysed with CUS/phlebography and D-dimer.

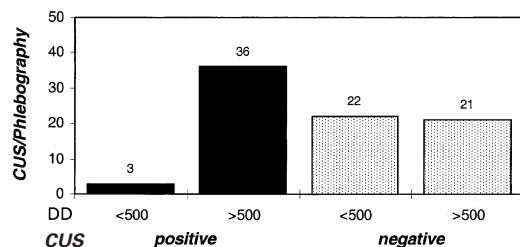
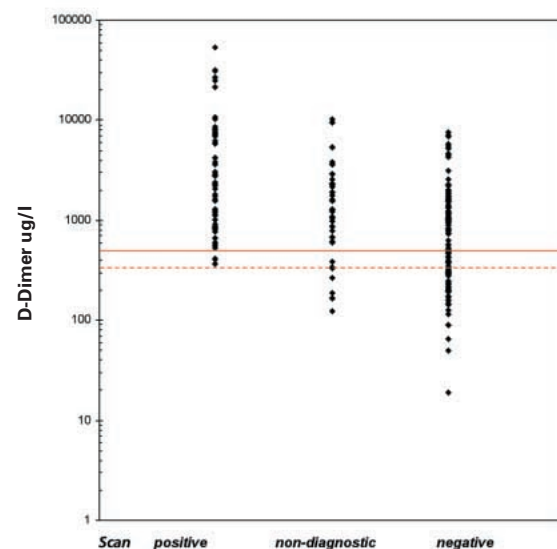


Figure 2

D-dimer concentrations are depicted on a logarithmic scale for the three different V/Q scan result groups. The red horizontal line shows the D-dimer cut off of <500 µg/l and the lower line indicates the cut off at <350 µg/l. The data demonstrate a specificity of 92% (95% confidence interval = 89-95%) for the cut-off at <500 µg/l and of 100% at 350 µg/l respectively.



diomyopathy and low ejection fraction (<25%). Three of the remaining 13 had D-dimers <500 µg/l. Therefore, in only 10 of 215 patients (=4.6%) was the decision not to anticoagulate based on clinical grounds alone. None of the 13 were found to have venous thromboembolism during the follow-up of >3 months. One patient died 2 months later at home due to lung cancer.

16/32 were considered positive overall and therefore anticoagulated. 4 of them had a D-dimer <500 µg/l. 4 died of other diseases during the hospitalisation and 2 patients died at home (none of bleeding). Interestingly, one of them suffered a

non-fatal pulmonary embolism 3 months later; anticoagulation had been stopped owing to macrohaematuria, thus suggesting a correct initial diagnosis of VTE-disease. No other severe bleeding episodes were observed.

The results of the new diagnostic protocol are summarised in figure 3b. They essentially indicate a substantial reduction in the number of investigations, namely 73V/Q-scans or CTs, which amounts to a reduction of 34%. In addition, the percentage of hospitalisations due to early negative findings could be reduced.

Discussion

According to the literature, 3/1000 persons per year present with suspected deep vein thrombosis and 1–3/1000 with suspected pulmonary embolism. The annual actual incidences of PE are ~25–70/100'000 inhabitants and about ~50–100/100'000 for DVT [13, 14]. Our data show that the incidences of PE 65/100'000 correspond with the literature. For DVT the numbers are expectedly smaller, since a large number of DVTs are treated on an outpatient basis. 50% percent of the patients with suspected DVT were diagnosed as positive, again suggesting a selection of positive or more severe cases.

Figure 3a and 3b illustrate the old and the modified new approach. The latter allows a saving on investigations and some hospitalisations by relying on clinical probability and D-dimer-levels. Furthermore, the introduction of the spiral CT scan in cases with pre-existing pulmonary pathology will exclude some false positive V/Q-scans. However, the problem of an insufficient sensitivity of approximately 70% of the CT scans remains unsolved (thus adding an unknown number of false negatives) [1].

CUS of the calf veins identifies thrombosis in approximately 10% of patients with suspected PE and a D-dimer of >500 µg/l, rendering further evaluation superfluous [2].

In contrast to the literature (30–70% [8–10]), is the relatively low percentage of non-diagnostic probability scans (15%) in our study, possibly suggesting some over-interpretation of our scans. The relatively high number of low probability scans (57%) may reflect the relatively low threshold for clinicians requesting this investigation, owing to its expediency and easy in-house availability.

Similar to reports in the literature, our 32 non-diagnostic probability V/Q-scans were categorised to 50% in each group, ie, finally judged PE-negative or positive [8, 15].

What have we learned in the past 4 years concerning diagnostics in suspected pulmonary embolism (figures 3a and 3b)?

1. The widely accepted “gold-standard” of pulmonary angiography (for patients in whom the

algorithm cannot fully settle the diagnostic question) is not applicable at an institution such as ours due to an insufficient frequency of the test being requested, its expected side effects, delays and low reading experience. A substitute gold-standard (clinical observation for 3 months following presentation) has been proposed for patients who are not anticoagulated.

2. It is critical how the V/Q-scans of non-diagnostic probability (15% of 215 PE) are handled, ie, those cases that cannot be clearly assigned to a treatment category: our data show that about 5% of all patients with suspected PE (but D-dimer >500 µg/l, a non-conclusive V/Q-scan, a negative CUS and a low or non-diagnostic clinical probability) were left without anticoagulation; these patients, however, were followed clinically and had no signs of PE over the next 18 months which may represent a substitute “gold-standard”. 7% of all 215 patients with suspected PE and with a non-diagnostic V/Q-scan (but high clinical suspicion) and a D-dimer >500 µg/l were anticoagulated. One of these suffered a major bleeding episode and promptly developed PE after cessation of the anticoagulation, thus confirming a correct initial assignment.
3. The D-dimer assay chosen at our institution is a reliable method for ruling out suspected PE in >92% of cases (95% confidence interval = 89–95%) at a cut-off <500 µg/l. The 3 patients with the D-dimer <500 µg/l who were judged positive in the V/Q-scan had only subsegmental perfusion deficits, which may be considered as indicating non-diagnostic probability; therefore they would undergo further work-up.
4. Very high levels of D-dimer (>8000 µg/l) in the absence of another plausible explanation reach a highly positive predictive value of about 90% in our study of PE as well as in DVT.
5. Only 1% of patients present with a high clinical suspicion and a D-dimer <500 µg/l. These should be (and were) further evaluated.
6. A stepwise, sequential exclusion process will save multiple examinations (in our study 73

Figure 3

Figures 3 a and 3b show the former and a new proposed diagnostic procedure for PE, our proposal is a synthesis of our data and the literature.

OAC = oral anticoagulation; V/Q-scan = lung ventilation/perfusion scan; Tx = treatment; CUS = compression ultrasound; spiral CT = spiral computed tomography; (%)= our data; numbers in italics = percentages derived from the literature and applied to our flow sheet.

* Patients with D-dimer <500 µg/l and high clinical probability for PE; † no treatment of the patients with low or non-diagnostic clinical probability; low = low suspicion for PE; high = high suspicion for PE

[a] based on reference [2]; [b] based on references [17-19]. The mean value of the non-diagnostic probabilities of V/Q-scans mentioned in the three references was taken.

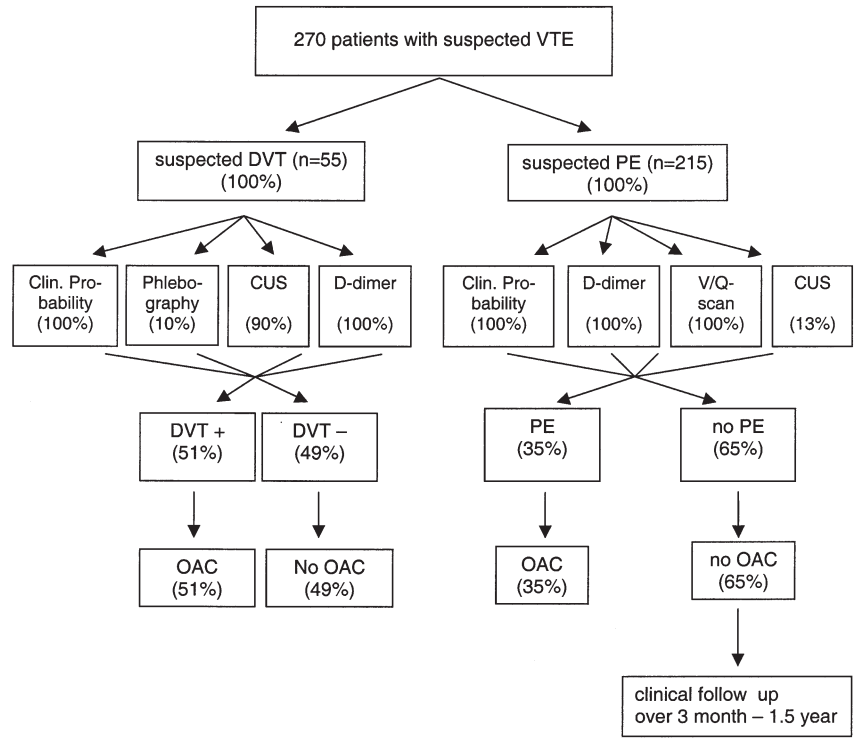
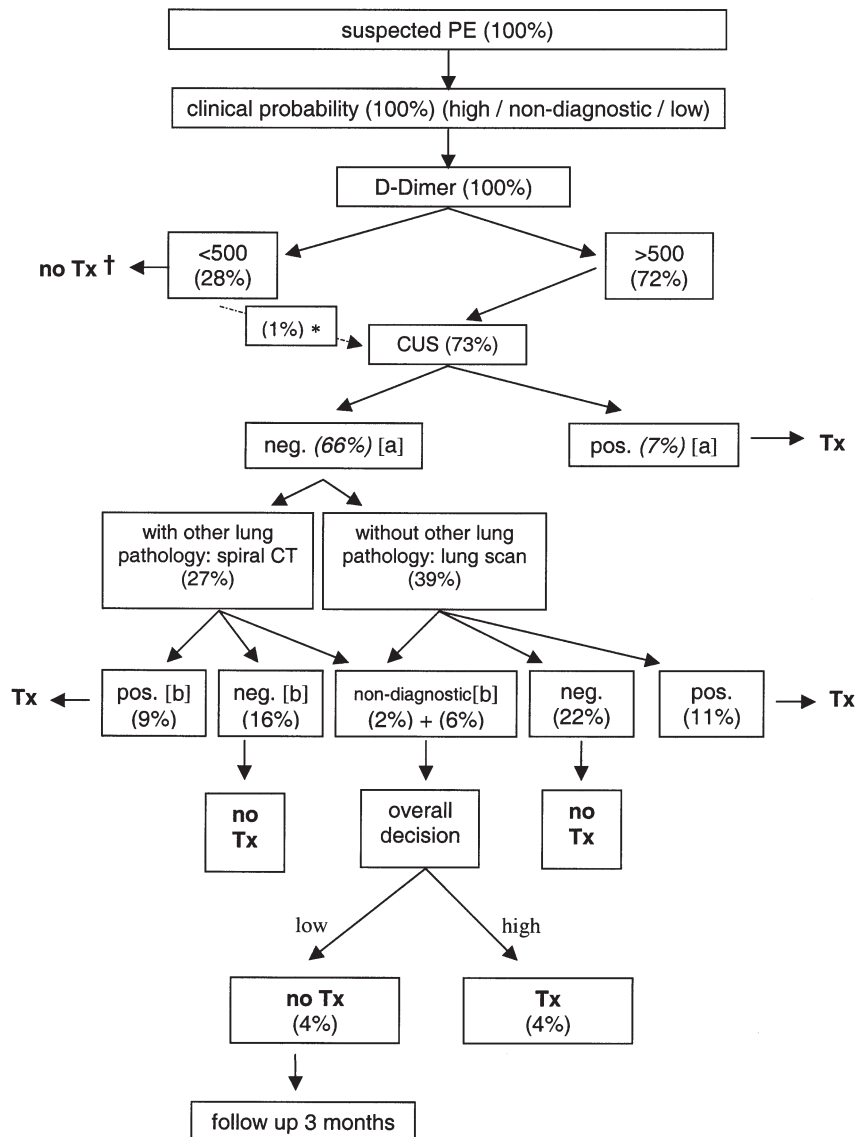


Figure 3a

Figure 3b



V/Q-scans or spiral CT), ie, 34% of these tests would have been dispensed with. In addition, the percentage of hospitalisations due to early negative findings could be reduced.

7. The introduction of the spiral CT will further help to reduce false positive diagnoses. However, its relatively low sensitivity (~70%) [1, 16] requires further evaluation and is far from being a gold-standard. In the future, a higher sensitivity with narrower CT slices might enhance the sensitivity up to 90 percent [17]. We use the CT-scan in the absence of a structural abnormality on chest x-ray.
8. In our study 76 of 215 (= 35%) patients with suspected pulmonary embolism were anticoagulated whereas 67 of 215 (= 31%) would have been anticoagulated according to the proposed flow diagram and guidelines, thus suggesting that the formerly applied procedure might have slightly overestimated the number of PE. (Since only non-anticoagulated patients

would qualify for clinical follow-up for future events, this point will be difficult to prove.)

Our data let us conclude that with the use of the flow diagram presented in figure 3b and by the application of the clinical probability, the D-dimer and the V/Q-scan or the spiral CT, (and accepting that clinically negative follow-up for the subsequent 3 months confirms the diagnosis as truly negative), at least 92% of our patients with suspected PE can be safely allocated at reduced costs to treatment or non-treatment group for PE.

Correspondence:

Prof. Dr. Jürg H. Beer, MD
Department of Internal Medicine
Kantonsspital
CH-5404 Baden
e-mail: hansjuerg.beer@ksb.ch

References

- 1 Perrier A, Howarth N, Didier D, Loubeyre P, Unger PF, de Moerloose P, et al. Performance of helical computed tomography in unselected outpatients with suspected pulmonary embolism. *Ann Intern Med* 2001;135:88–97.
- 2 Perrier A, Desmarais S, Miron MJ, de Moerloose Ph, Lepage R, Slosman D, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet* 1999;353:190–5.
- 3 Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. *Ann Intern Med* 2001;135:98–107.
- 4 Hubbuch A, Adema E, Gebert U, Herz R. Multicentre evaluation of Tina-quant® D-Dimer, a latex based reagent for BM/Hitachi Systems. *Klin Lab* 1995;41:383–6.
- 5 Adema E, Gebert U. Pooled patient samples as reference material for D-Dimer. *Thrombosis Research* 1995;41:85–8.
- 6 van Beek EJ, van den Ende B, Berckmans RJ, van der Heide YT, Brandjes DP, Sturk A, et al. A comparative analysis of D-Dimer assays in patients with clinically suspected pulmonary embolism. *Thromb Haemost* 1993;70:408–13.
- 7 Janssen MC, Heebels AE, de Metz M, Verbruggen H, Wollersheim H, Janssen S, et al. Reliability of five rapid D-dimer assays compared to ELISA in the exclusion of deep vein thrombosis. *Thromb Haemost* 1997;77:262–6.
- 8 The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. *JAMA* 1990;263:2753–9.
- 9 Freitas JE, Sarosi MG, Nagle CC, Yeomans ME, Freitas AE, Juni JE. Modified PIOPED criteria used in clinical practice. *J Nucl Med* 1995;36:1573–8.
- 10 Perrier A, Bounameaux H, Morabia A, de Moerloose P, Slosman D, Didier D, et al. Diagnosis of pulmonary embolism by a decision analysis-based strategy including clinical probability, D-dimer levels, and ultrasonography: a management study. *Arch Intern Med* 1996;156:531–6.
- 11 de Moerloose P, Desmarais S, Bounameaux H, Reber G, Perrier A, Dupuy G, et al. Contribution of a new, rapid, individual and quantitative automated D-Dimer ELISA to exclude pulmonary embolism. *Thromb Haemost* 1996;1:11–3.
- 12 Perrier A, Desmarais S, Goehring C, de Moerloose P, Morabia A, Unger PF, et al. D-dimer testing for suspected pulmonary embolism in outpatients. *Am J Respir Crit Care Med* 1997;156:492–6.
- 13 Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study 1991. *Arch Intern Med* 1991;151:933–8.
- 14 Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998;158:585–93.
- 15 Hull RD, Hirsh J, Carter CJ, Jay RM, Dodd PE, Ockelford PA, et al. Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. *Ann Intern Med* 1983;98:891–9.
- 16 Rathbun SW, Raskob GE, Whitsett Th. Sensitivity and Specificity of helical computed tomography in the diagnosis of pulmonary embolism: a systematic review. *Ann Intern Med* 2000;132:227–32.
- 17 Ost D, Rozenshtein A, Saffran L, Snider A. The negative predictive value of spiral computed tomography for the diagnosis of pulmonary embolism in patients with nondiagnostic ventilation-perfusion scans. *Am J Med* 2001;110:16–21.
- 18 Remy-Jardin M, Remy J, Deschildre F, Artaud D, Beregi JP, Hossein-Foucher C, et al. Diagnosis of pulmonary embolism with spiral CT: comparison with pulmonary angiography and scintigraphy. *Radiology* 1996;200:699–706.
- 19 Mayo JR, Remy-Jardin M, Muller NL, Remy J, Worsley DF, Hossein-Foucher C, et al. Pulmonary embolism: prospective comparison of spiral CT with ventilation-perfusion scintigraphy. *Radiology* 1997;205:447–52.

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website <http://www.smw.ch> (direct link from each SMW record in PubMed)
- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

Editorial Board

Prof. Jean-Michel Dayer, Geneva
 Prof. Peter Gehr, Berne
 Prof. André P. Perruchoud, Basel
 Prof. Andreas Schaffner, Zurich
 (Editor in chief)
 Prof. Werner Straub, Berne
 Prof. Ludwig von Segesser, Lausanne

International Advisory Committee

Prof. K. E. Juhani Airaksinen, Turku, Finland
 Prof. Anthony Bayes de Luna, Barcelona, Spain
 Prof. Hubert E. Blum, Freiburg, Germany
 Prof. Walter E. Haefeli, Heidelberg, Germany
 Prof. Nino Kuenzli, Los Angeles, USA
 Prof. René Lutter, Amsterdam, The Netherlands
 Prof. Claude Martin, Marseille, France
 Prof. Josef Patsch, Innsbruck, Austria
 Prof. Luigi Tavazzi, Pavia, Italy

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:

http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
 SMW Editorial Secretariat
 Farnsburgerstrasse 8
 CH-4132 Muttenz

Manuscripts: submission@smw.ch
 Letters to the editor: letters@smw.ch
 Editorial Board: red@smw.ch
 Internet: <http://www.smw.ch>