

Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomised non-inferiority trial

Marc Righini*, Grégoire Le Gal*, Drahomir Aujesky, Pierre-Marie Roy, Olivier Sanchez, Franck Verschuren, Olivier Rutschmann, Michel Nonent, Jacques Cornuz, Frédéric Thys, Cédric Petit Le Manach, Marie-Pierre Revel, Pierre-Alexandre Poletti, Guy Meyer, Dominique Mottier, Thomas Perneger, Henri Bounameaux, Arnaud Perrier

Summary

Background Multislice CT (MSCT) combined with D-dimer measurement can safely exclude pulmonary embolism in patients with a low or intermediate clinical probability of this disease. We compared this combination with a strategy in which both a negative venous ultrasonography of the leg and MSCT were needed to exclude pulmonary embolism.

Methods We included 1819 consecutive outpatients with clinically suspected pulmonary embolism in a multicentre non-inferiority randomised controlled trial comparing two strategies: clinical probability assessment and either D-dimer measurement and MSCT (DD-CT strategy [n=903]) or D-dimer measurement, venous compression ultrasonography of the leg, and MSCT (DD-US-CT strategy [n=916]). Randomisation was by computer-generated blocks with stratification according to centre. Patients with a high clinical probability according to the revised Geneva score and a negative work-up for pulmonary embolism were further investigated in both groups. The primary outcome was the 3-month thromboembolic risk in patients who were left untreated on the basis of the exclusion of pulmonary embolism by diagnostic strategy. Clinicians assessing outcome were blinded to group assignment. Analysis was per protocol. This study is registered with ClinicalTrials.gov, number NCT00117169.

Findings The prevalence of pulmonary embolism was 20·6% in both groups (189 cases in DD-US-CT group and 186 in DD-CT group). We analysed 855 patients in the DD-US-CT group and 838 in the DD-CT group per protocol. The 3-month thromboembolic risk was 0·3% (95% CI 0·1–1·1) in the DD-US-CT group and 0·3% (0·1–1·2) in the DD-CT group (difference 0·0% [–0·9 to 0·8]). In the DD-US-CT group, ultrasonography showed a deep-venous thrombosis in 53 (9% [7–12]) of 574 patients, and thus MSCT was not undertaken.

Interpretation The strategy combining D-dimer and MSCT is as safe as the strategy using D-dimer followed by venous compression ultrasonography of the leg and MSCT for exclusion of pulmonary embolism. An ultrasound could be of use in patients with a contraindication to CT.

Funding Swiss National Research Foundation, Projets Hospitaliers de Recherche Clinique (France), Pneumologie Développement (France).

Introduction

The contemporary diagnostic approach of pulmonary embolism is based on the combination of clinical probability assessment of disease with sequential diagnostic tests such as plasma D-dimer measurement, venous compression ultrasonography of the leg, and helical CT.^{1–3} CT of the chest has emerged as a new way to directly visualise the clot in pulmonary arteries.⁴ First-generation single-slice spiral CT had a low sensitivity (about 70%) for pulmonary embolism,^{5,6} restricting its use as a stand-alone test. Emergence of multislice CT (MSCT) has renewed hope that it could replace pulmonary angiography because of better visualisation of the segmental and subsegmental vessels and thinner collimation. Although the overall sensitivity of MSCT was only 83% in the large Prospective Investigation on Pulmonary Embolism Diagnosis II (PIOPED II) study,³ the negative predictive value of MSCT was 95% in patients with a low clinical probability

of pulmonary embolism and 89% in those with an intermediate clinical probability.

To increase the diagnostic yield, the PIOPED II study also investigated the added value of undertaking CT venography of the legs during the same procedure. Although the sensitivity of the combined examination was higher (90%) than it was with chest CT alone, the negative predictive value was only marginally increased (97% vs 95%).³ This finding is compounded by data from two large studies assessing MSCT.^{1,2} In the first, which included 756 consecutive patients who were referred to the emergency department for clinically suspected pulmonary embolism,¹ the proportion of patients in whom a proximal deep-venous thrombosis was detected by venous compression ultrasonography of the leg despite a negative MSCT was only three of 324 (0·9% [95% CI 0·3–2·7]). In the second study,² the 3-month thromboembolic risk was low (1·3% [0·7–2·0]) in patients who were left untreated because of a negative chest CT,

Lancet 2008; 371: 1343–52

See [Comment](#) page 1312

*These authors contributed equally

Division of Angiology and Hemostasis (M Righini MD, Prof H Bounameaux MD), Division of General Internal Medicine (O Rutschmann MD, Prof A Perrier MD), Department of Internal Medicine, Department of Radiology (P-A Poletti MD), and Clinical Epidemiology (Prof T Perneger MD), Geneva University Hospital and Faculty of Medicine, Geneva, Switzerland; Department of Internal Medicine and Chest Diseases, EA 3878 (GETBO), Brest University Hospital, Brest, France (G Le Gal MD, M Nonent MD, Prof D Mottier MD); Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (D Aujesky MD, Prof J Cornuz MD); Emergency Department, Saint-Luc University Hospital, Bruxelles, Belgium (F Verschuren MD, F Thys MD); Emergency Department, Angers University Hospital, Angers, France (P-M Roy MD, C Petit Le Manach MD); and Service of Pneumology (O Sanchez MD, Prof G Meyer MD) and Service of Radiology (M-P Revel MD), Hôpital Européen Georges-Pompidou, Paris, France

Correspondence to: Dr Marc Righini, Division of Angiology and Hemostasis, Department of Internal Medicine, Geneva University Hospital and Faculty of Medicine, 24 rue Micheli-du-Crest, CH-1211 Geneva 14, Switzerland Marc.Righini@hcuge.ch

	Points
Risk factors	
Age >65 years	+1
Previous deep-venous thrombosis or pulmonary embolism	+3
Surgery or fracture within 1 month	+2
Active malignancy	+2
Symptoms	
Unilateral leg pain	+3
Haemoptysis	+2
Clinical signs	
Heart rate (bpm)	
75–94	+3
≥95	+5
Pain on leg deep-vein palpation and unilateral oedema	+4
Clinical probability	
Low	0–3
Intermediate	4–10
High	≥11
bpm=beats per min.	

Table 1: Revised Geneva clinical prediction rule

despite the fact that venous ultrasonography was not undertaken.

Collectively, these results suggest that MSCT might be safe as a stand-alone test and that the added value of venous ultrasonography is questionable. To assess this notion, we compared two strategies: clinical probability assessment and either ELISA D-dimer measurement and MSCT (DD-CT strategy) or ELISA D-dimer measurement, venous compression ultrasonography of the leg, and MSCT (DD-US-CT strategy).

Methods

Study setting

The study was designed as a multicentre, randomised, prospective, non-inferiority trial. Data were collected from Jan 10, 2005 to Aug 30, 2006, at six participating medical centres that serve as general and teaching hospitals (Switzerland: Centre Hospitalier Universitaire Vaudois, Lausanne; Geneva University Hospital, Geneva. France: Hôpital Européen Georges-Pompidou, Paris; CHU Angers, Angers; CHU de la Cavale Blanche, Brest. Belgium: Saint Luc University Hospital, Brussels). All patients provided written informed consent before enrolment. The study was approved by the ethics committees of the Geneva and Lausanne University Hospitals for Switzerland, of the Brest University Hospital for France, and of Saint-Luc University Hospital for Brussels.

Patients

Consecutive patients who presented to the emergency department of the participating institutions were eligible if they had a clinical suspicion of pulmonary embolism, defined as acute onset of new or worsening shortness of breath or chest pain without another obvious cause. In the

2684 screened patients, 865 (32%) were excluded from the study because of a contraindication to CT (known allergy to iodine contrast agents or at risk for allergic reaction [n=72]); impaired renal function, defined as a creatinine clearance below 30 mL/min, as calculated by the Cockcroft-Gault formula (173);⁷ pregnancy (35); age less than 18 years (10); anticoagulant therapy in progress (144); diagnosis of pulmonary embolism already established before admission (143); unavailability for follow-up (7); inability to give informed consent (197); refusal to participate in the study (77); and other reasons (7). Hence, 1819 patients were included in the trial and randomly assigned.

Procedures

After assessment of the clinical probability of pulmonary embolism with the revised Geneva score (table 1),⁸ eligible patients were randomly assigned to one of two diagnostic strategies: either ELISA D-dimer measurement and CT (DD-CT strategy) or ELISA D-dimer measurement, venous compression ultrasonography of the leg, and MSCT (DD-US-CT strategy). Inclusion and exclusion criteria and the intervention in the reference strategy (DD-US-CT) were similar to that used in a previous study, confirming the safety of the reference strategy.¹ Figure 1 shows the compared strategies. Randomisation was undertaken in computer-generated blocks, with a block size of 6, 8, or 10 selected at random, and with stratification according to centre. The allocation sequence was generated in Geneva (coordinating centre). The randomisation assignments were concealed in opaque numbered envelopes that were opened by investigators at each site only after the patient-consent form had been signed and the clinical probability of pulmonary embolism had been established.

In the DD-US-CT strategy, D-dimer was measured only in patients with a low or intermediate clinical probability (0–3 and 4–10 points on the revised Geneva score, respectively). In these patients, pulmonary embolism was ruled out by a negative D-dimer test without further testing. When the D-dimer concentration was greater than 500 ng/mL, the next test we did was venous compression ultrasonography of both legs, and patients with a proximal deep-venous thrombosis were given anticoagulant drugs without further testing. Patients without proximal deep-venous thrombosis proceeded to MSCT and were treated if MSCT was positive for pulmonary embolism. Patients with a negative MSCT were not given anticoagulant drugs. Patients with a high clinical probability of pulmonary embolism (≥11 points) had ultrasonography as the initial test, followed by MSCT when negative for proximal deep-venous thrombosis, and were treated if MSCT showed a pulmonary embolism. In case of a negative MSCT, they proceeded to ventilation-perfusion (V/Q) scintigraphy or pulmonary angiography, or both. V/Q scan or pulmonary angiography was also deemed necessary in case of a non-conclusive MSCT for technical reasons or in case of isolated subsegmental pulmonary embolism, irrespective of the clinical probability. Patients with a

normal V/Q scan were not treated, and those with a high probability V/Q scan were given anticoagulant therapy.⁹ Patients with a non-diagnostic V/Q scan proceeded to pulmonary angiography.

The DD-CT strategy was similar to the DD-US-CT strategy apart from the omission of venous

ultrasonography of both legs. Therefore, patients with a raised D-dimer concentration and those with a high probability of pulmonary embolism in whom D-dimer was not measured proceeded directly to MSCT. In patients with a low or an intermediate clinical probability and abnormal D-dimer, a normal MSCT ruled out

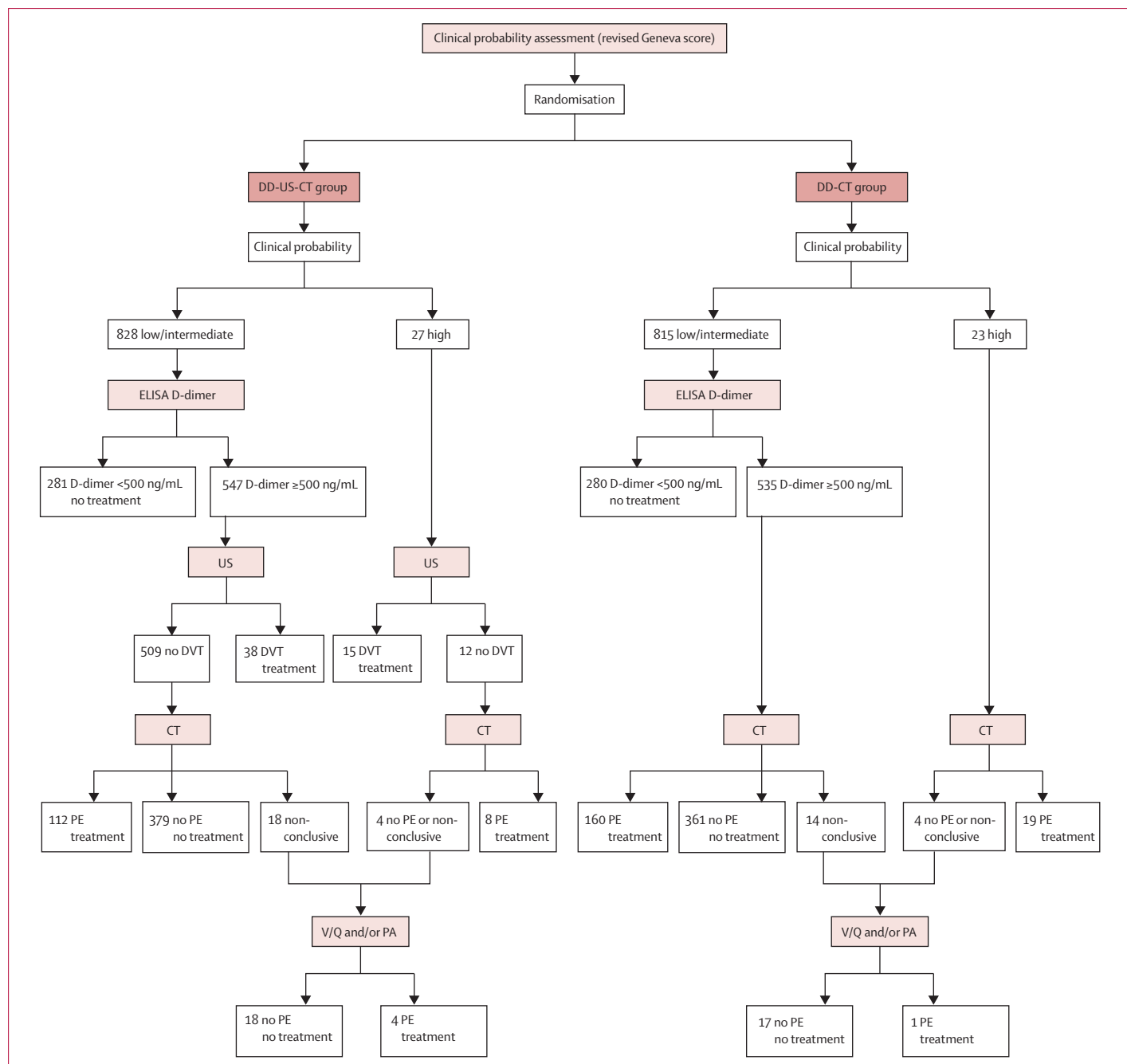


Figure 1: Diagnostic work-up of the study population

CT findings were considered to be non-conclusive in case of technical problems and if the only finding was isolated subsegmental pulmonary embolism. Numbers shown correspond to the number of patients included in the per-protocol analysis. DD-US-CT=ELISA D-dimer measurement, venous compression ultrasonography of the leg, and MSCT. DD-CT=ELISA D-dimer measurement and MSCT. DD=D-dimer. US=proximal venous compression ultrasonography of the leg. MSCT=multislice CT. DVT=proximal deep vein thrombosis. PE=pulmonary embolism. V/Q=ventilation-perfusion lung scintigraphy. PA=pulmonary angiography.

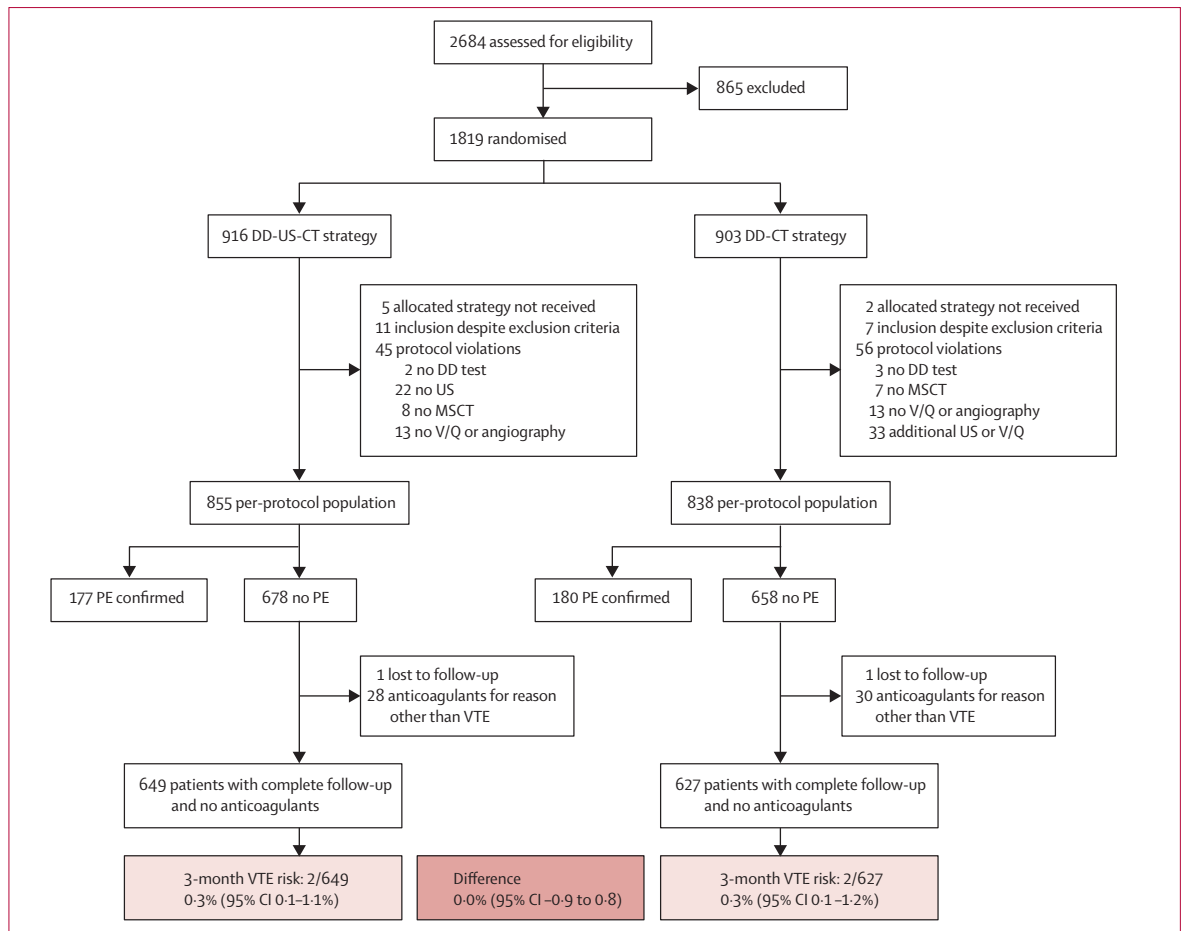


Figure 2: Trial profile for the per-protocol analysis

DD-US-CT=ELISA D-dimer measurement, venous compression ultrasonography of the leg, and CT. DD-CT=ELISA D-dimer measurement and CT. DD=D-dimer. US=proximal venous compression ultrasonography of the leg. MSCT=multislice CT. PE=pulmonary embolism. VTE=venous thromboembolism. V/Q=ventilation-perfusion lung scintigraphy. PA=pulmonary angiography.

pulmonary embolism, and these patients were not given anticoagulant therapy.

We assessed clinical probability (table 1) before the realisation of any specific test for pulmonary embolism.⁸ Plasma D-dimer was assayed by an automated quantitative analyser (rapid ELISA assay, Vidas DD, BioMérieux, Marcy-l'Étoile, France).¹⁰ B-mode venous compression ultrasonography of both legs was undertaken within 24 h after admission by a trained staff member who was blinded to the results of the clinical probability assessment. The examination consisted of a real-time B-mode examination of the common femoral and popliteal veins. The criterion for diagnosis of deep-venous thrombosis was incomplete compressibility of a proximal deep vein.¹¹

The protocol for MSCT consisted of an assessment of the pulmonary arteries up to and including the subsegmental vessels. Patients were examined while holding their breath or breathing shallowly, depending on the degree of dyspnoea. A clot was considered present if contrast material outlined an intraluminal defect or if a

vessel was totally occluded by low-attenuation material. We used only multidetector-row CT (number of detectors 16–64). The acquisition parameters for MSCT were injection of a total volume of 100–120 mL of non-ionic contrast material (iodine concentration 300–350 mg/mL) with a power injector at 3–5 mL per second; imaging 9–20 seconds after initiation of the contrast-material injection on the basis of bolus tracking; collimation 0.625 mm or 1.25 mm with a pitch of 0.9–1.75, 120 KV, and 115–260 mA/s; and 0.6–0.8 second per gantry rotation, allowing reconstruction of images that were 0.625 or 1.25 mm thick at 0.6–1.0 mm intervals. For patients who were obese, slice thickness was sometimes increased to 2.5 mm. MSCTs were interpreted by staff radiologists as part of their daily clinical work. Previous studies have described the technique for undertaking and interpreting lung scanning and pulmonary angiography.^{12,13}

All patients underwent follow-up at 3 months. Both patients and physicians in charge of these patients were instructed to go back to see the investigators or telephone

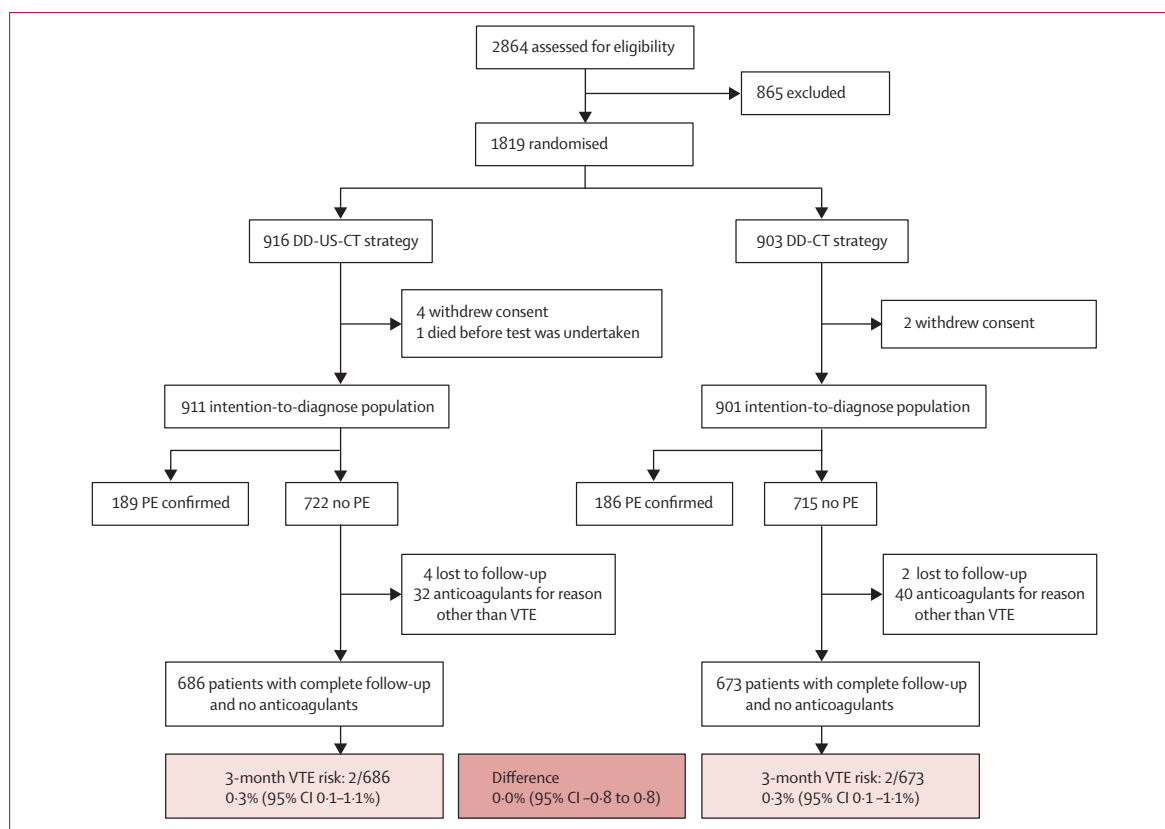


Figure 3: Trial profile for the intention-to-diagnose analysis

PE=pulmonary embolism. VTE=venous thromboembolism. DD-US-CT=ELISA D-dimer measurement, venous compression ultrasonography of the leg, and CT. DD-CT=ELISA D-dimer measurement and CT.

them in case of recurrent symptoms of the respiratory system or legs. At the end of follow-up, all patients included in the study were interviewed by telephone by one of the study coordinators who was blinded to the study group. Patients were asked to disclose all health-related events since their hospital discharge (any consultation with a physician, admission to hospital, change of treatment, investigation, or haemorrhagic complication). The family physician was contacted whenever a possible event was disclosed by the interim history, and charts were reviewed if a patient was readmitted to hospital for any cause or died during follow-up. The follow-up and assessment of the outcome in our study was similar to that used in a previous study, confirming the safety of the reference strategy.¹

The primary outcome was the proportion of venous-thromboembolic events in the 3-month follow-up period in each group in patients who were left untreated on the basis of the exclusion of pulmonary embolism by the diagnostic strategy. Diagnoses of venous thromboembolic events during follow-up were established on the basis of abnormal results on ultrasonography for deep-vein thrombosis, and on the basis of V/Q lung scan showing a high-probability pattern or CT or angiography showing intraluminal defects for pulmonary embolism. Deaths

were adjudicated as related, possibly related, or unrelated to pulmonary embolism. Death was judged to be related to pulmonary embolism if it was confirmed by autopsy, or if it followed a clinically severe pulmonary embolism, either initially or after a recurrent event that was objectively confirmed. Death in a patient who died suddenly or unexpectedly was classified as possibly related to pulmonary embolism. Unrelated deaths were due to an obvious cause other than pulmonary embolism. Three independent experts who were blinded to the allocation group adjudicated the outcome events.

We calculated the mean cost per patient of diagnostic testing for both diagnostic strategies. Tests included in this analysis were D-dimer measurement, venous compression ultrasonography of the leg, MSCT, V/Q lung scan, and pulmonary angiography. We did not include in the analysis costs of testing for alternative diagnoses in patients in whom pulmonary embolism was excluded, costs of treatment, and costs of hospital stay for patients who were admitted. We did the analysis between randomisation and until a final diagnosis was obtained. We used direct costs of the year 2007 from the institutions that participated in the study. Costs in Euros (€) and in Swiss Francs (CHF) were converted in US dollars as follows: €1=US\$1.44; CHF1=US\$0.74.

Statistical analysis

In a recent study,¹ the rate of thromboembolic events during a 3-month follow-up in patients who were left untreated on the basis of a low or intermediate clinical probability, absence of deep-venous thrombosis on a 4-point proximal ultrasonography, and a negative multidetector CT was 1.3% (95% CI 0.5–3.1). Thus, we assumed a 3-month thromboembolic event rate of 1.5% in the DD-US-CT group. We postulated that the strategy using MSCT without ultrasonography (DD-CT) would be non-inferior to the combined strategy. To be regarded as non-inferior, we stated that the 3-month thromboembolic risk in the DD-CT group should not be higher than the usually reported upper limit of the CI for diagnostic strategies for pulmonary embolism (about 3%).¹⁴ We calculated that a study with 810 patients per group would have an 80% power with a one-sided type error of 0.05 to reject the hypothesis that the thromboembolic event-rate in the DD-CT group would be 1.5% higher than that in the DD-US-CT group (3% vs 1.5%).

In accordance with good statistical practice, we did not compare the groups statistically at baseline.¹⁵ We undertook two sets of analyses for both outcome and cost. The main analysis was per-protocol to avoid favouring the non-inferiority hypothesis.¹⁶ In that analysis, all patients who were included wrongly (n=25) or whose diagnostic work-up did not strictly adhere to the study protocol (n=101) were not included. We also did an intention-to-diagnose analysis in which we analysed all patients in their original randomisation group (including crossovers), apart from those who withdrew consent or died before diagnostic tests could be undertaken. We used the Newcombe method,¹⁷ as

implemented on the Confidence Interval Analysis software programme (version 2.1.2),¹⁸ to compute a 95% CI on the difference of proportions. We used a two-sided CI approach.

This study is registered with ClinicalTrials.gov, number NCT00117169.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figures 2 and 3 show the trial profile in the per-protocol and intention-to-diagnose populations, respectively. During the study period, 1819 patients with clinically suspected pulmonary embolism were randomly assigned: 916 in the DD-US-CT group and 903 in the DD-CT group. Six patients withdrew consent and one died before any test could be undertaken, leaving 1812 patients in the intention-to-diagnose analysis. Table 2 shows the baseline characteristics of the two groups. In the intention-to-diagnose population, the overall prevalence of pulmonary embolism was 20.6% (189 cases in DD-US-CT group and 186 in DD-CT group) and did not differ between the two groups (p=0.74).

The proportions of patients who were excluded because of a diagnostic work-up that was not in accordance with study protocol were much the same between both groups (45/916 [4.9%] in the DD-US-CT group and 56/903 [6.2%] in the DD-CT group; p=0.23). Therefore, 855 patients were in the per-protocol population in the DD-US-CT group and 838 in the DD-CT group. Figure 1 details the diagnostic work-up in these patients. With only venous-thromboembolic events that were objectively confirmed and fatal events regarded as related to pulmonary embolism considered, the 3-month thromboembolic risk in patients who were left untreated on the basis of the exclusion of pulmonary embolism by the diagnostic strategy (primary outcome) was two of 649 (0.3% [95% CI 0.1–1.1]) in the DD-US-CT group and two of 627 (0.3% [0.1–1.2]) in the DD-CT group, as analysed per protocol (figure 2). The difference in the 3-month risk between the two strategies was 0.0% (–0.9 to 0.8). Recurrent events were identical in the two groups: one non-fatal pulmonary embolism and one proximal deep-venous thrombosis in each group. Addition as unfavourable outcomes of all deaths possibly related to pulmonary embolism did not change the results: the 3-month risk was six of 649 (0.9% [0.4–2.0]) in the DD-US-CT group and three of 627 (0.5% [0.2–1.4]) in the DD-CT group (difference –0.4% [–1.6 to 0.6]).

In the intention-to-diagnose analysis, patients who had one or more exclusion criteria or in whom the diagnostic work-up was not in accordance with study protocol were classified according to diagnosis at discharge. The 3-month

	DD-US-CT group (n=911)	DD-CT group (n=901)
Men	408 (44.8%)	410 (45.7%)
Age (years)	59.3 (18.6)	59.5 (18.8)
Personal history of VTE	166 (18.2%)	171 (19.0%)
Familial history of VTE	129 (14.2%)	121 (13.5%)
Active malignancy	74 (8.1%)	72 (8.0%)
Surgery within 1 month	48 (5.3%)	59 (6.5%)
Contraceptive use	45 (5.0%)	44 (4.9%)
Hormone replacement therapy	33 (3.6%)	30 (3.3%)
Chest pain	632 (69.5%)	604 (67.2%)
Dyspnea	659 (72.4%)	642 (71.3%)
Syncope	186 (20.5%)	206 (22.9%)
Haemoptysis	43 (4.7%)	47 (5.2%)
Heart rate (bpm)	86.6 (18.8)	88.3 (20.3)
Respiratory rate (bpm)	20.6 (6.4)	20.7 (6.3)
Symptoms of DVT	124 (13.6%)	116 (12.9%)
Clinical signs of DVT	88 (9.7%)	96 (10.7%)
Varicose veins	206 (22.7%)	180 (20.1%)

Data are number (%) or mean (SD). DD-US-CT=ELISA D-dimer measurement, venous compression ultrasonography of the leg, and CT. DD-CT=ELISA D-dimer measurement and CT. VTE=venous thromboembolism. DVT=deep-venous thrombosis. bpm=beats per min.

Table 2: Characteristics of included patients

thromboembolic risk in the DD-CT group was not worse than that of the DD-US-CT—two of 673 (0·3% [0·1–1·1]) versus two of 686 (0·3% [0·1–1·1]; absolute difference 0·0% [–0·8 to 0·8]; figure 3).

22 patients allocated to the DD-US-CT group did not have a venous compression ultrasonography of the leg (two with a high and 20 with an intermediate/low clinical probability). Conversely, 32 patients in the DD-CT group had an ultrasound (one with a high and 31 with an intermediate/low clinical probability). All had a negative MSCT and two had a proximal deep-venous thrombosis and were given anticoagulant drugs. If we consider these two patients as failures of the DD-CT strategy, the thromboembolic risk at 3 months increased to 0·6% (0·2–1·6), but the strategy remained non-inferior to the DD-US-CT strategy.

Table 3 shows the contribution of the various tests in both groups of the study. The proportion of negative D-dimer results was much the same in both groups of the study (table 3), and follow-up was uneventful in all these patients in either group (data not shown). In the DD-US-CT group, compression ultrasonography of the legs showed a deep-venous thrombosis in 53 of the 177 patients (30% [24–37]) who were diagnosed as having pulmonary embolism. Hence, the diagnostic yield of ultrasonography in patients with a raised D-dimer concentration or a high clinical probability was 53 of 574 (9% [7–12]). Ultrasonography was positive in 30 of 464 patients (7% [4·6–9·1]) without signs and symptoms of deep-vein thrombosis compared with 23 of 110 patients (21% [14·4–29·5]) with such findings. In the 299 patients whose MSCT showed a pulmonary embolism, the most proximal-clot level was the main pulmonary artery in 77 (26%), the lobar artery in 117 (39%), the segmental artery in 98 (33%), and the subsegmental level in seven (2%). Of the 1079 patients who underwent MSCT in the per-protocol population, 33 (3%) had an inconclusive MSCT (30 for technical reasons and three because of the presence of an isolated subsegmental image).

We recorded no difference in the rates of adverse events between the two study groups. Overall, few adverse events that were related to the undertaking of the MSCT occurred in the study. Three patients presented with contrast medium extravasation injury but had only mild and transient oedema (one in the DD-CT strategy, two in the DD-US-CT strategy). Three patients had a cutaneous rash which did not need treatment (one in DD-US-CT, two in DD-CT). We recorded no anaphylactic reaction or Quincke oedema. One patient (DD-CT) had severe nausea and vomiting at the time of CT scan. Contrast-induced nephropathy due to CT angiography was not systematically searched for by repeated measurement of creatinine. However, we noted no cases of acute renal failure or of patients requiring haemodialysis. In patients given anticoagulant treatment for confirmed pulmonary embolism, four major bleedings (two intracranial haemorrhages [one in DD-CT

	DD-US-CT group (n=855)	DD-CT group (n=838)
Pulmonary embolism diagnosed		
Total	177 (20·7%)	180 (21·5%)
Low or intermediate clinical probability		
Proximal deep-venous thrombosis on ultrasonography	38 (21·5%)	..
Positive MSCT	112 (63·3%)	160 (88·9%)
Inconclusive MSCT	4 (2·3%)	1 (0·6%)
High probability V/Q scan	1 (2·5%)	..
Positive pulmonary angiogram	3 (7·5%)	1 (100%)
High clinical probability		
Proximal deep-venous thrombosis on ultrasonography	15 (8·5%)	..
Positive MSCT	8 (4·5%)	19 (10·6%)
Pulmonary embolism excluded		
Total	678 (79·3%)	658 (78·5%)
Low or intermediate clinical probability		
Negative D-dimer	281 (41·4%)	280 (42·5%)
Negative MSCT*	379 (55·9%)	361 (54·9%)
Inconclusive MSCT	14 (2·1%)	13 (2·0%)
Normal V/Q scan	6 (42·9%)	3 (23·1%)
Low probability V/Q scan	8 (57·1%)	5 (38·5%)
Normal pulmonary angiogram	..	5 (38·5%)
High clinical probability		
Negative MSCT* and normal V/Q scan	4 (0·6%)	3 (0·4%)
Inconclusive MSCT* and normal V/Q scan	..	1 (0·2%)

Data are number (%). DD-US-CT=ELISA D-dimer measurement, venous compression ultrasonography of the leg, and CT. DD-CT=ELISA D-dimer measurement and CT. MSCT=multislice CT. V/Q=ventilation-perfusion lung scintigraphy. *In the DD-US-CT group, all patients with a negative MSCT also had a negative leg compression ultrasonography.

Table 3: Diagnostic contribution of tests in each group in the per-protocol analysis

and one in DD-US-CT], two digestive bleedings needing transfusion [one in DD-CT and one in DD-US-CT]), and five minor bleedings (one thigh haematoma [DD-CT], one flank haematoma [DD-CT], three haemorrhoidal bleedings [two in DD-US-CT, one in DD-CT]) were reported. One patient not receiving anticoagulant treatment developed a cerebral aneurysm rupture with consequent intracranial haemorrhage (DD-CT).

In the per-protocol analysis, we recorded 37 deaths in the DD-US-CT group. 14 patients with a confirmed pulmonary embolism died because of recurrent confirmed pulmonary embolism (n=2), probable recurrent pulmonary embolism (4), possible recurrent pulmonary embolism (1), cancer (5), cardiovascular disease (1), and other reasons (1). 23 patients without pulmonary embolism died because of possible pulmonary embolism (4), cancer (12), haemorrhagic complications (2), respiratory disease (3), and other reasons (2). We recorded 22 deaths in the DD-CT group. Seven patients with confirmed pulmonary embolism died (recurrent confirmed PE [2] and cancer [5]). 15 patients without pulmonary embolism died of possible recurrent pulmonary embolism (1), cancer (7), cardiovascular disease (3), respiratory disease (2), and other reasons (2).

Comparison of the mean cost per patient confirmed that the DD-CT strategy was 24% (95% CI 19–30) less expensive

	DD-US-CT group	DD-CT group	Mean difference
Intention to diagnose*			
All (n=1812)	248 (235 to 260)	194 (184 to 204)	53 (37 to 70)
France (n=867)	228 (216 to 240)	153 (143 to 162)	76 (60 to 91)
Belgium (n=249)	147 (128 to 166)	143 (128 to 159)	-3 (-28 to 21)
Switzerland (n=696)	309 (282 to 336)	264 (243 to 284)	45 (11 to 79)
Per protocol			
All (n=1693)	246 (233 to 259)	187 (177 to 197)	59 (43 to 76)
France (n=807)	228 (215 to 241)	146 (137 to 156)	82 (66 to 98)
Belgium (n=230)	147 (126 to 167)	140 (124 to 156)	-7 (-32 to 19)
Switzerland (n=656)	304 (276 to 333)	252 (232 to 272)	52 (18 to 87)

Data are mean (95% CI). DD-US-CT=ELISA D-dimer measurement, compression ultrasonography of the leg veins, and CT. DD-CT=ELISA D-dimer measurement and CT. *The intention-to-diagnose analysis takes into account all tests undertaken in each strategy, including those that were done in violation of the study algorithm (for instance, venous ultrasound done in the DD-CT group). The mean cost per patient was calculated from direct costs in the various study centres.

Table 4: Mean cost (US\$) per patient for both diagnostic strategies in per-protocol and intention-to-diagnose analyses

in the per-protocol analysis and 21% (17–27) less expensive in the intention-to-diagnose analysis than was the DD-US-CT strategy, including costs for venous ultrasonography of the leg (table 4).

Discussion

This randomised, multicentre, non-inferiority trial has shown that a strategy combining ELISA D-dimer measurement and MSCT was non-inferior to a similar strategy using D-dimer followed by venous compression ultrasonography of the leg and MSCT for exclusion of pulmonary embolism. The 3-month thromboembolic risk in both groups of the study was similar to that recorded in patients who were left untreated on the basis of a negative pulmonary angiography.¹⁹ The study included a large number of patients covering a wide range of presentations of suspected pulmonary embolism and their characteristics, and risk factors were comparable with those of other multicentre studies.^{1–3,20,21}

The prevalence of pulmonary embolism that we recorded was similar to that of a European trial^{12,20} and to that of the recent North American PIOPED II study.³ Therefore, we believe that our findings can be applied to a broad population with suspected pulmonary embolism, and they lend support to the hypothesis that a negative MSCT or ELISA D-dimer measurement safely excludes pulmonary embolism in patients with a low or intermediate clinical probability of pulmonary embolism.

Two previous prospective management studies¹² reported 3-month thromboembolic risks less than 1.5% when a strategy based on assessment of clinical probability, D-dimer, and helical CT was used. In the first study,¹ which included 756 consecutive patients referred to the emergency department with a clinical suspicion of pulmonary embolism, all patients with either a high clinical probability or a non-high clinical probability and a positive ELISA D-dimer test had both a leg ultrasound and an MSCT.¹ The proportion of patients in whom a proximal deep-venous

thrombosis was detected on ultrasound, despite a negative MSCT, was only three of 324 (0.9% [95% CI 0.3–2.7]), suggesting that the added value of ultrasonography was very low. Moreover, the 3-month thromboembolic risk in patients not given anticoagulant drugs would have been only 1.5% (0.8–3.0) if the D-dimer assay and MSCT had been the only tests that were used to exclude pulmonary embolism and ultrasonography had not been undertaken. In a Dutch study,² all patients who were classified as likely to have pulmonary embolism by the dichotomised Wells' score and those with a positive D-dimer test underwent a chest CT (90% of MSCT). The 3-month thromboembolic risk in patients who were left untreated because of a negative CT was low (1.3% [0.7–2.0]). Collectively, these results suggest that a strategy combining ELISA D-dimer test and MSCT might be safe. However, these studies were not randomised and investigators of both studies suggested that this type of diagnostic strategy should be compared with diagnostic strategies for suspected pulmonary embolism that are well validated.

In this study, we assessed clinical probability with the revised Geneva score, which was initially derived in a cohort of patients in whom a diagnostic algorithm for pulmonary embolism²² was assessed and retrospectively validated in a distinct cohort testing another strategy.¹ The derivation and retrospective validation were published together.⁸ Noteworthy, patients in the validation cohort originated largely from centres that were different from those of the derivation sample. Although this validation was not prospective, we believed that the data were robust enough to allow use of the revised Geneva score as the assessment instrument in this randomised study. Since the method was used in both study groups, it could not bias the finding that one strategy was non-inferior to the other. The revised Geneva score has been recently retrospectively validated in an independent cohort of 300 consecutive patients.²³ This study showed that it retained the same accuracy as in the derivation and retrospective validation samples. Moreover, it had a diagnostic accuracy that was comparable with that of the Wells score, which was also assessed in that trial.

The results of our study accord with those from the prospective Christopher study,² but both trials have a few differences in design. First, our randomised trial assessed the clinical usefulness of ultrasonography of leg veins in an MSCT-based diagnostic strategy for pulmonary embolism. Because the Christopher study was an outcome study, and although the 3-month thromboembolic risk was acceptable in patients who were left untreated on the basis of a negative MSCT, the investigators could not exclude that the risk might have been even lower if they had undertaken an ultrasound in patients who had a negative MSCT. Our results compared these two strategies directly and showed no difference in outcome.

Second, by contrast with the Christopher study, we considered that a negative MSCT (or a negative MSCT and a negative leg ultrasound in the DD-US-CT group) did not

safely exclude pulmonary embolism in patients who had a high clinical probability, since the negative predictive value of MSCT is expected to be lower in these patients than in those with a low or intermediate clinical probability. This notion is supported by the results of the recent PIOPED II study in which six of the 15 patients with a high clinical probability and a negative MSCT had a pulmonary embolism.³ In our cohort, additional testing did not disclose a pulmonary embolism in the seven patients with a high clinical probability and a negative MSCT. Moreover, clinicians were reluctant to follow protocol in that situation and they undertook no further tests or incomplete tests in the remaining 19 patients with high clinical probability and a negative MSCT, of whom 18 were not treated and had an uneventful follow-up. In the Christopher study,² patients with a negative MSCT were not treated irrespective of their clinical likelihood of pulmonary embolism, and the overall 3-month thromboembolic risk was acceptable. Therefore, from our data we are unable to make a firm recommendation for the most effective diagnostic algorithm for patients with a high clinical probability of pulmonary embolism.

The use of MSCT as the main diagnostic imaging technique raises two other issues. New generation CT scans are able to visualise subsegmental and sub-subsegmental arteries,²⁴ and therefore diagnosis of small peripheral and clinically insignificant clots that might be left untreated could be a concern. Indirect evidence exists—mainly from the gap between accuracy and outcome studies—that many small peripheral clots are clinically insignificant and might be left untreated.²⁵ Indeed, if that were not the case, the uneventful follow-up in patients who were left untreated because of a negative MSCT would be difficult to explain given that the sensitivity of MSCT is only 83% according to the PIOPED II study.³ In our study, only three patients in the per-protocol analysis had an isolated subsegmental pulmonary embolism. Six additional patients had a similar finding but were not included in the per-protocol analysis because they had no further explorations. Hence, isolated subsegmental pulmonary embolism remained a rare finding, and MSCT does not seem to entail the risk of overdiagnosing pulmonary embolism. Furthermore, MSCT was non-conclusive for technical reasons in around 3% of patients in both groups of the study, confirming that MSCT is better than single-detector CT, which has a rate of inconclusive results between 4% and 10%.⁶ But there were also a number of protocol violations, indicating that clinicians are reluctant to undertake further tests after MSCT. Many physicians probably do not recognise that the probability of pulmonary embolism after a non-conclusive MSCT remains the same as the pretest probability, which might be an important target for education.

What was the diagnostic yield of compression ultrasonography of leg veins in the DD-US-CT group? Our results show that ultrasound is no longer required as a safety net for the identification of clots that might have

been missed by MSCT. Nevertheless, an abnormal ultrasonography indicating deep-venous thrombosis occurred for about a tenth of patients who could have been spared a CT scan, which would be favourable in those with a contraindication to CT. Ultrasound showed a proximal deep-venous thrombosis in 30% of patients who were classified as having a pulmonary embolism, which is consistent with previous studies,²⁶ and in 9% of patients with a raised D-dimer concentration or a high clinical probability. Thus, the number needed to test—ie, the number of patients in whom an ultrasound should be undertaken to diagnose one clot and avoid an MSCT—is around 11. Patients with symptoms and signs of deep-venous thrombosis were almost four times as likely to have a positive ultrasound as were asymptomatic patients (20·9% vs 6·5%; OR 3·8 [95% CI 2·1–6·9]).

We have undertaken a model-based cost-effectiveness analysis comparing four different diagnostic strategies, which included or excluded venous compression ultrasonography of the leg.²⁷ This real-life study showed that the strategy including ultrasonography of the leg veins is about 20% more expensive than are other methods, even in the intention-to-diagnose analysis in which all tests including those that were not necessary according to protocol were considered (table 4). Therefore, our data do not support the routine use of ultrasound. However, ultrasonography might still be an attractive alternative in patients with renal failure or those who have an allergy to contrast dye, especially in the presence of symptoms and signs of deep-venous thrombosis.

Our study has some limitations. First, the exclusion rate (32%) in eligible patients might seem high, but the exclusion criteria were straightforward and most of those who were excluded had a contraindication to MSCT. However, we acknowledge that chronic renal failure and an allergy to contrast dye are relative contraindications, and that many of the excluded patients had an MSCT outside the study is possible. However, there is no reason to believe that the diagnostic yield and in particular the risk of a false negative MSCT would have been higher in that group than in those who we included. Second, since the population consisted of outpatients and the prevalence of cancer was only 8%, our results might not be directly applicable to suspected pulmonary embolism in patients admitted to hospital or those with cancer. Third, the adherence to the proposed diagnostic strategy was high in both groups (around 95%). Nevertheless, we recorded a number of protocol violations, especially in patients with a high clinical probability and a negative MSCT and those with a non-conclusive result irrespective of clinical probability. Fourth, almost all patients with high clinical probability had a pulmonary embolism and were given anticoagulant drugs, and those with a negative MSCT or an ultrasonography and MSCT combination were further investigated to rule out pulmonary embolism. Therefore, our study design does not allow any conclusion about the safety of withholding anticoagulant drugs in such

patients on the basis of a negative MSCT alone. Furthermore, 32 (8%) of the 396 patients with a negative MSCT in the DD-CT group had a leg ultrasound, and deep-venous thrombosis was recorded in two. These patients might constitute a particular subgroup in which clinicians were uncomfortable with ruling out pulmonary embolism by MSCT alone because of prominent symptoms or signs of deep-venous thrombosis. However, the frequency of symptoms and signs of deep-venous thrombosis in that subgroup did not differ from those in the entire cohort, and thus that explanation is unlikely. Finally, we limited our cost analysis to diagnostic tests and we did not measure other resources that were used by patients who were randomly assigned to the competing management strategies. Although our results show that the costs of diagnostic testing are lower in the simpler DD-CT strategy than in the DD-US-CT strategy, we cannot affirm that this finding translates into significant overall cost savings.

In summary, we conclude that ultrasound is not needed to rule out pulmonary embolism when MSCT is used. An ultrasound could still be of interest in patients with a contraindication to MSCT, although it would allow avoiding that test in only one of every 11 patients.

Contributors

MR and GLG were co-principal investigators, designed research, undertook research, collected data, analysed data, and wrote the paper. DA, OR, MN, JC, FT, CPLM, M-PR, PAP, DM, and TP undertook research, collected data, analysed data, and wrote the paper. P-MR, OS, FV, GM, HB, and AP designed research, undertook research, collected data, analysed data, and wrote the paper.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

We thank all the residents and physicians from the emergency departments, radiology units, and ultrasonography units of all participating centres; all study nurses, secretaries, and clinical research associates for their invaluable help: in Angers—Béatrice Gable, Béatrice Delasalle, and Catherine Hue; in Brest—Isabelle Pichon, Morgane Six, Solenn Le Quellec, and Ghislaine Kermagoret; in Brussels—Anne Danthée; in Geneva—Louise Riberdy; in Lausanne—Yolande Bangala; and in Paris—Daniel Pontal; members of the adjudication committee: Philippe Girard, Christophe Leroyer, and Florence Parent, for their important contribution; the staff of the Délégation à la Recherche Clinique, Brest University Hospital: Céline Dolou, Marie-Hélène Lallier, Maëlle Ningre, and Jaqueline Peguet-Menard; and the patients who made the study possible by accepting to participate to the trial. The study was supported by a grant from the Swiss National Research Foundation (grant number 3200B0-105988), a grant from the Projets Hospitaliers de Recherche Clinique (PHRC 2005-08-08), and a grant from Pneumologie Développement.

References

- Perrier A, Roy PM, Sanchez O, et al. Multidetector-row computed tomography in suspected pulmonary embolism. *N Engl J Med* 2005; **352**: 1760–68.
- Van Belle A, Buller HR, Huisman MV, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA* 2006; **295**: 172–79.
- Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med* 2006; **354**: 2317–27.
- Rémy-Jardin M, Rémy J, Wattinne L, Giraud F. Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single-breath-holds technique. Comparison with pulmonary angiography. *Radiology* 1992; **185**: 381–87.
- Mullins MD, Becker DM, Hagspiel KD, Philbrick JT. The role of spiral volumetric computed tomography in the diagnosis of pulmonary embolism. *Arch Intern Med* 2000; **160**: 293–98.
- Rathbun SW, Raskob GE, Whitsett TL. Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism: a systematic review. *Ann Intern Med* 2000; **132**: 227–32.
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.
- Le Gal G, Righini M, Roy PM, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann Intern Med* 2006; **144**: 165–71.
- The PIOPED Investigators. Value of the ventilation-perfusion scan in acute pulmonary embolism. *JAMA* 1990; **263**: 2753–59.
- de Moerloose P, Desmarais S, Bounameaux H, et al. Contribution of a new, rapid, individual and quantitative automated D-dimer ELISA to exclude pulmonary embolism. *Thromb Haemost* 1996; **75**: 11–13.
- Lensing AWA, Prandoni P, Brandjes D, et al. Detection of deep-vein thrombosis by real-time B-mode ultrasonography. *N Engl J Med* 1989; **320**: 342–45.
- Bounameaux H, Cirafici P, de Moerloose P, et al. Measurement of D-dimer in plasma as diagnostic aid in suspected pulmonary embolism. *Lancet* 1991; **337**: 196–200.
- Perrier A, Bounameaux H, Morabia A, 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**: 531–36.
- Kruij MJ, Leclercq MG, van der Heul C, Prins MH, Buller HR. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies. A systematic review. *Ann Intern Med* 2003; **138**: 941–51.
- Senn S. Testing for baseline balance in clinical trials. *Stat Med* 1994; **13**: 1715–26.
- Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006; **295**: 1152–60.
- Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med* 1998; **17**: 873–90.
- Altman D, Machin D, Bryant T, Gardner S. *Statistics with confidence* (2nd edn). London: BMJ Books, 2000.
- van Beek EJ, Brouwerst EM, Song B, Stein PD, Oudkerk M. Clinical validity of a normal pulmonary angiogram in patients with suspected pulmonary embolism—a critical review. *Clin Radiol* 2001; **56**: 838–42.
- Ghanima W, Almas V, Aballi S, et al. Management of suspected pulmonary embolism (PE) by D-dimer and multi-slice computed tomography in outpatients: an outcome study. *J Thromb Haemost* 2005; **3**: 1926–32.
- Kearon C, Ginsberg JS, Douketis J, et al. An evaluation of D-dimer in the diagnosis of pulmonary embolism: a randomized trial. *Ann Intern Med* 2006; **144**: 812–21.
- Perrier A, Roy PM, Aujesky D, et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. *Am J Med* 2004; **116**: 291–99.
- Klok FA, Kruisman E, Spaan J, et al. Comparison of the revised Geneva score with the Wells rule for assessing clinical probability of pulmonary embolism. *J Thromb Haemost* 2008; **6**: 40–44.
- Schoepf UJ, Holzknicht N, Helmberger TK, et al. Subsegmental pulmonary emboli: improved detection with thin-collimation multi-detector row spiral CT. *Radiology* 2002; **222**: 483–90.
- Le Gal G, Righini M, Roy PM, et al. Diagnosis and management of subsegmental pulmonary embolism. *J Thromb Haemost* 2006; **4**: 724–31.
- Turkstra F, Kuijter PMM, van Beek EJR, Brandjes DPM, ten Cate JW, Buller HR. Diagnostic utility of ultrasonography of leg veins in patients suspected of having pulmonary embolism. *Ann Intern Med* 1997; **126**: 775–81.
- Righini M, Nendaz M, Le Gal G, Bounameaux H, Perrier A. Influence of age on the cost-effectiveness of diagnostic strategies for suspected pulmonary embolism. *J Thromb Haemost* 2007; **5**: 1869–77.