Diagnostic management of pulmonary embolism using clinical assessment, plasma D-dimer assay, complete lower limb venous ultrasound and helical computed tomography of pulmonary arteries

A multicentre clinical outcome study

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Summary
The objective of the study was to assess the clinical validity of a non-invasive diagnostic strategy for acute pulmonary embolism using clinical assessment combined with both ELISA D-dimer and complete lower limb ultrasound (US) examination of proximal and distal veins, before single-detector helical computed tomography (CT) of pulmonary arteries. We expected the strategy to have a high diagnostic exclusion power and to safely decrease the number of CT scans. This prospective, multicenter outcome study included 274 consecutive outpatients. All underwent a priori clinical probability, D-dimer and bilateral complete lower limb US assessments. Only patients with a high clinical probability and both tests negative, or positive D-dimer and negative US assessments, underwent CT. This was deemed necessary in 114 patients (42%). At baseline, venous thromboembolism (VTE) was detected in 110 patients (40%), either by US showing proximal (n=65) or distal (n=36) thrombosis, or by CT (n=9). Anticoagulant was withheld in the remaining patients with negative results in both D-dimer and US but a non-high clinical probability (n=59), or in both US and CT (n=90), or with negative US (n=6) and inadequate CT (n=9). All patients underwent a three-month clinical follow-up. VTE occurred in one patient with inadequate CT, yielding an incidence of 0.6% [95% confidence interval: 0.1–3.4]. No patient died from VTE or had major bleeding. Using clinical probability, ELISA D-dimer and complete US before helical CT is a safe strategy resulting in a substantial reduction in CT scans.

Keywords
Pulmonary embolism, D-dimer, ultrasound / diagnosis, helical computed tomography, clinical / epidemiological studies

Introduction
In patients with clinically suspected acute pulmonary embolism (PE), a rapid and accurate diagnosis is required in order to initiate or withhold anticoagulant treatment. In order to confirm or exclude PE, objective testing is mandatory. Various diagnostic methods such as plasma D-dimer assay, lower limb venous ultrasound assessment (US) and helical computed tomography (CT) of the pulmonary arteries are now being used instead of conventional methods like ventilation-perfusion scan and pulmonary angiography (1).
Up to now, a limited US, confined to only the popliteal and femoral veins, has been recommended in the diagnostic work-up for PE. The strategies incorporating limited US have been validated and proven to be safe in prospective management studies (2–6), but do not seem to be efficient. Performing a complete US extended from the calf veins to the inferior vena cava inclusive, is another interesting but controversial method, which has never been included in a diagnostic strategy and evaluated in clinical outcome studies. The advantage of using complete US is firstly linked to the high prevalence of residual vein thromboses which may be located below the popliteal level or in the iliac and cava veins after an embolic episode, as demonstrated in autopsy (7), US (8, 9), venography (10–12), CT (13–16) and magnetic resonance angiography (17, 18) studies. These isolated thrombi can be of clinical importance (19, 20). Secondly, complete US enables detection of deep vein thrombosis (DVT) at these sites accurately (9, 21) and reliably (21, 22). Finally, in Bayesian decision models, strategies including complete US performed better than those including limited US, and compared favorably with the latter in an economic evaluation (23).

The aim of this study was to assess the clinical effectiveness of a new non-invasive diagnostic strategy, and mainly the safety of withholding anticoagulant treatment in patients testing negative. Guided by clinical probability assessment, the strategy combined both plasma ELISA (enzyme-linked immunosorbent assay) D-dimer and complete US examination as the first step in the diagnostic work-up before helical CT scanning of the pulmonary arteries. It was expected that combined ELISA D-dimer and complete lower limb US assessments would provide a high diagnostic exclusion power, while safely decreasing the number of helical CT scans.

Methods

Study design

A prospective multicenter outcome study was performed in a cohort of consecutive outpatients recruited in two general hospitals and one teaching hospital. The participating centres were Auch general hospital, Rodez general hospital and Toulouse-Rangueil university hospital. The diagnostic strategy for PE was applied and patients were accordingly treated or not. Patients were then followed up in order to measure clinical outcome.

Patients

Consecutive outpatients with a clinically suspected acute PE were included, whether or not they presented associated clinical symptoms or signs suggestive of DVT. Non-inclusion criteria were age under 18 years, pregnancy, unstable hemodynamic status with hypotension at 80 mm Hg or less, hospitalization lasting more than 24 hours or hospitalization within the last month, need for anticoagulant treatment for other reasons, contra-indication to contrast media, impossibility of follow-up, life expectancy < 3 months, and refusal of consent by the patient or physician.

Diagnostic strategy

The diagnostic strategy was guided by clinical assessment and included a two-step diagnostic procedure as shown in figure 1.

![Figure 1: Diagnostic strategy in 274 patients with clinically suspected acute pulmonary embolism: results at baseline and clinical outcome during a three-month follow-up period. Dd+: D-dimer; US: ultrasound; CT: computed tomography; TRT: treatment; VTE: venous thromboembolism; (−): negative; (+): adequate; (+): positive. Helical CT was not performed in four patients (**) with low or intermediate clinical probability, and two patients (***, ****) with high clinical probability. Outcome was uneventful despite the absence of anticoagulant treatment. Among 164 untreated patients, **** VTE occurred in one with low clinical probability, positive D-dimer assay, negative US and inadequate CT. The incidence of VTE was 0.6% [95% confidence interval: 0.1–3.4]. Death (n = 8) was unrelated to VTE or bleeding.](983.png)

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All patients underwent a priori clinical probability, and simultaneous VIDAS D-dimer and bilateral complete US assessments. According to the results, a helical CT scan of the pulmonary arteries was performed sequentially if deemed necessary. Diagnostic tests were performed within 24 hours.

Clinical assessment was based on the analysis of clinical symptoms and context, a physical examination, an electrocardiogram, a chest X-ray and a blood gas sample. As previously done (9, 24), the clinical probability of PE was estimated in relation to the presence or absence of symptoms and signs compatible with PE, a risk factor for venous thromboembolism (VTE) and the possibility of an alternative diagnosis. Clinical probability was classified into three categories: high (compatible symptoms and signs, risk factor(s), absence of any other possible explanation), intermediate (compatible symptoms and signs, associated or not with either a risk factor or absence of any other possible explanation), low (more or less suggestive symptoms and signs, no risk factor, other possible explanation).

All patients subsequently underwent simultaneous D-dimer and bilateral US assessments. Only patients with either negative results in both tests and a high clinical probability, or a positive D-dimer assay and a negative US underwent a CT examination. PE was ruled out, and anticoagulant treatment withheld, in patients with both a negative D-dimer assay and a negative US, combined with a low or intermediate clinical probability, and in those with negative results in both US and CT assessments or with a negative result in US and an inadequate CT. Conversely, either a positive US or a positive CT assessment was considered diagnostic for PE and these patients were treated by anticoagulants.

Clinical outcome was assessed during a three-month follow-up period.

**Diagnostic tests**

VIDAS D-dimer assay, complete venous US assessment and single-detector helical CT scan of the pulmonary arteries were performed as described previously (9) and were standardized among the three centres.

The D-dimer assay used was the VIDAS DD test (BioMérieux, Marcy l’Étoile, France), a fully automated ELISA (25). The test was considered positive above the cut-off level of 500 ng/ml.

Real-time B mode colour Doppler US was performed bilaterally and included the calf veins, the popliteal and femoral veins, the iliac veins and the inferior vena cava. Study of the calf veins focused on the posterior tibial and peroneal veins, the gastrocnemius (internal and external) and soleal veins. All these venous segments were examined over their entire length in transverse and longitudinal views. The lower limit of the popliteal vein was defined as the confluence of the posterior and the peroneal veins. The criterion for DVT was the image of an endoluminal thrombus associated with vein non-compressibility (9).

In patients with a history of VTE, US diagnosis of recurrent thrombosis relied on either images of occlusive material, increased vein diameter and absence of flow, or images of non-occlusive thrombus with absence of venous reflux. Diagnosis of “chronic” thrombosis was based on hyperechoic and adherent thrombus combined with venous reflux.

CT scans were obtained after intravenous administration of a contrast agent (iohexol, Omnipaque®). The study protocol was adapted from that of Remy-Jardin (26–28). Scans were performed with a 2 mm collimation, a pitch of 2 mm and a 2 mm reconstruction interval. The main, lobar and segmental arteries were studied. Results were classified as positive if there was a partial or complete endoluminal filling defect, and as negative when all vessels including the segmental arteries were correctly opacified without any artefact or image suggesting a thrombus, and finally as inadequate if there was an artefact or when the vessels from the main to the segmental arteries were not fully and correctly analyzed.

**Three month follow-up and outcome**

All patients were followed up for three months to assess clinical outcome (incidence of VTE, bleeding and death). Patients were monitored during the hospitalization period by the medical staff and afterwards by their general practitioner. At the end of the three months, they were assessed by returning to the centre or by answering a standardized questionnaire by telephone. Patients were asked to come back to the centre before the end of the follow-up period if they experienced any event. The diagnosis of VTE was confirmed or excluded according to pre-established and recognized criteria based on objective tests: ventilation-perfusion lung scan, helical CT and/or angiography for PE, and US for DVT. Bleeding complications were classified as major if patients needed a transfusion, or when there was an intraocular or intraperitoneal hemorrhage, and were otherwise considered as minor. Death was categorized as related to PE, bleeding or to other causes. Outcome events were adjudicated independently.

**Data analysis**

Analysis of effectiveness was based on the incidence of VTE events during the follow-up period in patients who tested negative using the diagnostic strategy and had anticoagulant treatment withheld. The 95% confidence intervals (CI) were computed from the binomial distribution using a Confidence Interval Analysis software (CI software version 2.0.0, University of Southampton, UK)(29). It was estimated that 142 patients with negative testing were needed for an expected three-month incidence of thromboembolic events at 1.5% and an upper limit of the 95% confidence interval at 3.5%. The accepted limit in similar studies was 4% (2, 5, 6).

**Ethical considerations and financial support**

The study protocol was approved by the local Advisory Board and the local Ethics Committee and patients provided written informed consent. The funding sources had no role in the design and conduct of the study, collection and analysis of the data, or the decision to submit the paper for publication.

**Results**

**Patients**

From January 2001 to September 2002, 541 patients were referred for clinical suspicion of PE. Two hundred and sixty-seven patients (49%) were not included (Table). The demographic and clinical characteristics of the 274 patients included were as fol-
Results of the diagnostic strategy at baseline (Fig. 1)
At baseline, pre-test clinical probability was considered low in 58 (21%) patients, intermediate in 155 (57%) and high in 61 (22%).

D-dimer assay was negative in 65 (24%) patients, of whom 60 (22%) had a low or intermediate clinical probability and 5 (1.8%) had a high clinical probability. Despite a normal D-dimer assay, 1/60 (1.7%) patients with a non-high clinical probability and 2/5 (40%) with a high clinical probability had a diagnosis of VTE. In total, 3/65 (4.6%) patients with a negative D-dimer assay had a VTE detected at baseline (one with a negative US but a positive CT, and two with a distal DVT).

US was negative in 169 (61.7%) patients, inadequate in 4 (1.4%) and positive in 101 (36.9%). Inadequate results were related to difficulty in examining the iliac vein, obesity, problems in differentiating recurrent from chronic DVT or to a calf examination. A CT scan was required in these patients. Of all patients, a DVT was proximal in 65 (24%) and distal in 36 (13%). Proximal DVT were located in the iliac vein in 16 patients, the common femoral vein in 7, the deep femoral vein in 1, the superficial femoral vein in 24 and the popliteal vein in 17. Distal DVT were located in the main vein segments in 25 patients and the muscle (soleal) veins in 11. In patients with a non-high clinical probability, DVT was detected in 49/213 (23%). It was proximal in 26 patients (25 with intermediate clinical probability) and distal in 23 patients (all with intermediate clinical probability), located in the main segments in 15 and the muscle veins in 8. In patients with a high clinical probability, DVT was present in 52/61 (85%). It was proximal in 39 patients and distal in 13 patients with the thrombosis located in the main segments in 10 and the muscle veins in 3.

The combination of clinical probability, D-dimer assay and US showed conclusive results according to the diagnostic strategy in 160 (58.4%) patients. The diagnosis was ruled out because both D-dimer and US tests were negative and clinical probability was low or intermediate in 59 (21.5%) patients, or ruled in because US was positive in 101 (36.8%) patients. In the remaining 114 (41.6%) patients, a CT scan was required.

CT was performed in 108 patients. Six patients did not undergo the CT examination because of protocol violation in five cases (refusal of patient or physician) or because of failure to perform the test in one case. CT was negative in 90 patients (83.3%), inadequate in 9 (8.3%) and positive in 9 (8.3%). PE was located at its more proximal segment in a pulmonary artery (n=2), a lobar artery (n=2), a segmental artery (n=4) or a subsegmental artery (n=1). In these preselected patients, CT was positive in 5/7 patients (71%) with a high clinical probability, and in 4/101 (4%) with a non-high clinical probability.

No patient was further investigated by pulmonary angiography.

Overall, at baseline, VTE was present in 110 patients, corresponding to a prevalence of 40%.

Clinical outcome (Fig. 1)
All patients were followed up for three months.

On follow-up, no VTE occurred in the 59 patients with both a negative D-dimer assay and a negative US, combined with a low or intermediate clinical probability.

Of the three patients with both a negative D-dimer assay and a negative US assessment but a high clinical probability, only two underwent a CT scan and one of these had a PE. The other patient who did not undergo a CT scan was not treated with an anticoagulant. No patient in this subgroup experienced a VTE event.

Among the 111 patients with either a positive D-dimer assay and a negative US (n=107), or with an inadequate US (n= 4), 5 did not undergo a CT scan. Outcome was uneventful in these five patients, despite the absence of anticoagulant treatment. Of the 106 patients who had a CT scan, 89 patients had a negative result, none of whom experienced a VTE event, 8 patients had a PE and were accordingly treated by anticoagulants, and the other 9 patients had an inadequate scan, but did not receive anticoagulant treatment. One of these nine patients presented a VTE event on day 50 with a thrombosis located in the common femoral vein. This event occurred after two other hospital stays for pulmonary tuberculosis. At baseline, this patient had a low clinical probability, a positive D-dimer assay and a negative US, with a pulmonary fibrosis revealed by CT.

Among the 101 patients with a positive US (99 with a positive D-dimer assay and 2 with a negative D-dimer assay), one experienced a recurrent VTE event despite anticoagulant treatment.

In total, anticoagulant was withheld in 155 patients with negative test results and 9 patients with an inadequate CT scan. One of these latter patients presented a VTE event on follow-up, giving a VTE incidence of 0.0% (95% CI: 0.0–2.4) to 0.6% (95% CI: 0.1–3.4).

No patient experienced major bleeding, but one patient undergoing anticoagulant treatment for proximal DVT suffered from minor hemorrhoidal bleeding.

Eight patients died, of whom six presented a VTE at baseline. Death was unrelated to VTE or bleeding. The causes of death were as follows: suicide (n=1) and metastatic cancer (n=1) in patients with negative initial screening results, terminal cancer (n=5) and severe infection in the soft tissues (n=1), in patients with either a positive CT scan (n=1) or a positive US (n=5) showing proximal (n=4) or distal (n=1) DVT at baseline.

Overall, the incidence of VTE with 95% CI appears to be at most 0.6% (95% CI: 0.1–3.4).
Discussion

This is the first outcome study that validates the utility of a strategy incorporating complete US for the diagnosis of PE. Two previous evaluations, a diagnostic efficacy study (9) and a cost-effectiveness analysis (23), demonstrated a potential medical and economic value of using D-dimer assay and complete US, before performing a helical CT scan. The present study confirms the clinical effectiveness of such a strategy guided by clinical probability and the safety of withholding anticoagulant when screening for VTE is negative. The strategy provides a high diagnostic exclusion power with a very low thromboembolic risk on follow-up while resulting in a substantial reduction (close to 60%) of the number of CT scans required. The exclusion of patients with an inconclusive CT further improves the low incidence rate from 0.6% (95% CI: 0.1–3.4) to 0.0% (95% CI: 0.0 – 2.4%).

The role of clinical assessment was important, as shown moreover in other diagnostic management strategies (3, 6, 24, 30). In our study, VTE was detected in 2/5 patients with a high clinical probability and a normal D-dimer assay, despite the use of a highly sensitive D-dimer (31). One patient had a positive US with a calf DVT and the other patient a negative US with a positive CT. Thus, a high clinical probability associated with a negative even highly sensitive D-dimer assay might prompt caution (32, 33). Moreover, as shown in previous studies, negative tests with less sensitive D-dimer assays cannot safely rule out VTE except in patients with a low clinical probability (3, 30).

Complete US was the method used as it has shown to be accurate and reliable (9, 21). When compared with a reference standard (9), it provides higher sensitivity and global test accuracy than limited US. Nevertheless, accuracy and reliability can be achieved provided that the test can be performed by experienced operators using a standardized method, as was the case in this multicentre study. Examining the calf enables the detection of more thromboses and avoids performing further investigation. More than 90% (101/110) of all VTE events were detected by complete US. However, there is no denying that there may be a risk of over-treating more thromboses. Nevertheless, we believe the high prevalence of US-detected DVT (37%), comparable to that we obtained previously (9), is not due to an overestimation of calf thromboses. Indeed, the prevalence of proximal DVT is also high (24%), similar to that reported by Perrier et al (34), although their more recent management studies (2, 6) showed a much lower prevalence (close to 10%).

Clinical probability, D-dimer assay and complete US assessments enabled us to establish a definitive diagnosis in 58% of our study patients. Thus, the proportion of CT scans required for the strategy was reduced to 42% compared to 100% in two studies using CT scan as a primary diagnostic test (4, 5), or compared to 61% in another study using VIDAS D-dimer and limited US (6), despite a higher exclusion rate by D-dimer assay (29% versus 22% in our study).

Despite these advantages, there are some limitations in this study that should be addressed.

Clinical probability was not assessed using a validated clinical score like that used by Wells et al. (3, 24), Wicki et al. (35) or others. However, explicit assignment using predefined criteria was combined with clinical judgment which was demonstrated to improve the diagnostic accuracy (36).

In the present study all patients had to undergo bilateral lower limb ultrasound irrespective of the clinical probability of PE and the D-dimer value. The reason was that in our hands, ELISA D-dimer had a sensitivity of only 92% and a specificity of 24% as compared to a reference standard (9). In systematic reviews (31, 37, 38), better results were achieved for ELISA D-dimer. In patients with suspected PE, the combination of non-high clinical probability of PE and a negative ELISA D-dimer is safe to rule out the diagnosis (31, 38). Thus, most likely, bilateral complete lower limb ultrasound could have been avoided in 22% of the study population (59 patients with a non-high clinical probability and a negative D-dimer) thereby increasing the cost effectiveness of the applied approach.

Another important issue is the use of complete instead of limited US scan. There may be as a consequence two limitations. Firstly, a risk of false positive results. Being aware of this potential pitfall, we paid careful attention in order to avoid diagnostic errors. Rigorous US criteria were required for the diagnosis of calf vein thromboses which relied on both compression test and thrombus image. Recurrent vein thromboses were also differentiated from old thromboses as described in the method section. Secondly, the unknown clinical significance of calf thromboses in patients with clinically suspected PE raises the question of over-diagnosing and over-treating patients, which could increase bleeding risk and cost. Actually, many data suggest that the thromboembolic risk largely outweighs the bleeding risk (39). In this study, bleeding seemed to be extremely low and did not exceed the risk reported with strategies using limited US. In addition, as mentioned above, in a cost-effectiveness analysis taking into account the bleeding and the thromboembolic risks even in patients with false positive results, incorporating complete US is more effective in terms of three-month survival at an acceptable incremental cost (23). The results were consistent across countries. A more formal randomized study of complete versus limited US imaging is needed in a management study format that also includes the use of a highly sensitive D-dimer test and multi-detector helical CT scan.

Another limitation in our study is the use of single-slice CT scan which provides an overall low sensitivity and a high proportion of inadequate tests. None of the patients who had inadequate CT in our study underwent pulmonary angiography as it is invasive and needs to be performed in optimal conditions. Serial compression US of the popliteal and femoral veins has been suggested to replace and avoid angiography but seems to have limited additional value after CT (5, 40). The same applies to CT venography (13–16) and resonance magnetic imaging of the pulmonary arteries (41) and the veins of the lower limbs (17, 18), the utility of which needs to be further evaluated. To sum-up, the utility of further investigations after inconclusive CT (in 3% of all patients under this strategy) needs to be assessed, as our study was not powered to answer this question. Replacing single-detector by multi-detector helical CT might be an effective option (42).

A high proportion of patients (49%) in our study were not included according to predefined criteria. This proportion is comparable with that reported by the ANTELOPE study group (43)
and remains within the wide variation of the percentage of patients excluded from similar studies. The prevalence of VTE in our study was also high (40%) but similar to that reported in some recent series (4, 34, 44). In a systematic review (44), the reported prevalence in outcome studies of diagnostic strategies for excluding PE varied from 10 to 49%.

Our results can be applied to the diagnostic management of PE within the same conditions as in our study, namely in outpatients, by using the same diagnostic methods. Caution should be exercised if adopting our strategy to all patients with suspected PE. It may not be suitable for “hemodynamically unstable” patients. The diagnostic management (echocardiography) and treatment are different. Patients may need aggressive measures and intensive care and any strategy used should not delay the initiation of therapy. Similarly, in hospitalized patients, as the specificity of the D-dimer assay decreases, its utility becomes questionable (45, 46). In this situation, using only complete US before CT is potentially an interesting and effective option (23), but needs to be assessed in terms of clinical outcome.

In conclusion, when guided by clinical assessment, a strategy that includes ELISA D-dimer and complete lower limb venous US before helical CT of the pulmonary arteries, can safely exclude the diagnosis of PE and greatly reduces the need for CT scans.

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Appendix

Trial registry information: Délégation Régionale à la Recherche Clinique (DRRC), Centre Hospitalier Universitaire (CHU) de Toulouse, Hôtel Dieu, Toulouse, France. Registration Number: 00–21–H. Institutional review board approval: CCPPRB (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) – Toulouse II. Registration Number: 2–00–16.

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