Effect of age on the performance of a diagnostic strategy based on clinical probability, spiral computed tomography and venous compression ultrasonography

The ESSEPs study*

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Summary
As the prevalence of PE increases with age, the effect of age on the diagnostic work-up in front of a clinical suspicion of PE deserves exploration. In this retrospective analysis, we used the data from 1041 consecutive suspected PE patients. The patients were divided into three groups according to tertiles of age: under 54 years, 54 to 73 years and above 73 years. The prevalence of PE in patients with respectively low, intermediate and high pretest clinical probability was expressed within each age group. We studied the effect of age on the results observed in three main groups of patients, after performing CT scan and ultrasonography (CUS): (1) patients with inconclusive results; (2) patients with negative findings on both exams and non high pretest clinical probability; (3) patients with positive findings. The prevalence of PE increased significantly with age, in overall, as well as in patients with low or intermediate pretest clinical probability. An analysis according to the three main diagnostic groups showed that: (1) the distribution of inconclusive spiral CT or CUS examinations was not different between age groups; (2) no thromboembolic event occurred in untreated patients with low or intermediate clinical probability aged under 54 years of age, whereas 7 events were diagnosed in patients aged over 73 years (p<0.001); (3) a higher proportion of older patients had a positive result at both spiral CT and CUS examinations. The percentage of positive CT scans in the case of negative or inconclusive CUS results was not different between age groups; conversely, in the case of a negative or inconclusive CT scan, the percentage of positive CUS was higher in older patients. In conclusion, management of elderly suspected PE patients appears to be different from both the work-up and the outcome perspectives.

Keywords
Pulmonary embolism, age, pretest clinical probability, helical computed tomography, venous compression ultrasonography of the lower limbs

Introduction
The incidence of venous thromboembolism (VTE) increases with age. Data from a community-based study conducted in Western France show that estimates of the annual incidence rate per thousand range from 0.58 in subjects aged from 20 to 39, to 12.04 in patients over 74 years (1); pulmonary embolism (PE) accounts for an increasing proportion of VTE events with increasing age, from 22% for the 20–39 age group, to 40% above 75 years (1). Register studies have identified old age as a signifi-
cant predictor of a higher mortality rate in patients with diagnosed PE (2). Several autopsy studies conducted in hospitals or in the community suggest that most fatal episodes of PE are not identified before death (3). Although considerable effort has been made to assess the pretest clinical probability of PE, the diagnosis of PE remains difficult as clinical findings can mimic various cardiopulmonary diseases, particularly in older patients. These findings have at least two implications for the future. Firstly, as the average age of the population is increasing in Western countries, the number of VTE events is expected to increase. Secondly, the need to improve diagnostic strategies in the setting of a suspected PE in older patients is challenging.

Previous studies have shown that age affects the performance of several diagnostic tests for PE. Some procedures appear to be less useful in older patients. Plasma D-Dimer testing specificity decreases markedly with age: over 70 years, less than 10% of patients have a D-Dimer level below the cut-off point (4, 5). The proportion of non-diagnostic ventilation-perfusion (V/Q) lung scanning increases with age: in the study by Righini and co-workers, the proportion of diagnostic V/Q lung scanning (e.g., normal, near normal or high probability) ranged from 68% in patients aged 39 to under 42% in patients aged 81 years and over (5). Conversely, the performance of venous CUS of the legs appears higher in older patients: one quarter of the patients suspected of PE aged 80 years and over have a positive result (5). Finally, recent data from a prospective evaluation of contrast-enhanced spiral computed tomography (spiral CT) in comparison with a validated strategy have indicated that its performance is not influenced by age (6).

The association of spiral CT and venous CUS has recently been evaluated in 1041 consecutive suspected PE inpatients and outpatients from 14 French centres (7). We have analysed the database from this study to evaluate the effect of age on this diagnostic strategy.

**Patients and methods**

The present retrospective analysis has been performed using data from the previously published ESSEP study. The main objective of this prospective multicentre outcome study was to assess the safety of withholding anticoagulant treatment in patients with low or intermediate clinical probability, negative findings on spiral CT and normal venous CUS of the lower limbs. Consecutive inpatients (n: 240) and outpatients (n: 801) with suspected PE were included. The pretest clinical probability of PE was assessed empirically by the physician in charge of the patient on the basis of risk factors for VTE, of clinical presentation and of the likelihood of another diagnosis. All patients underwent a single detector spiral CT and a venous CUS of the legs within 24 hours of enrolment. Among patients with negative findings on spiral CT and venous CUS, those who had a low or intermediate clinical probability of PE were deemed not to have PE and did not receive anticoagulant treatment; on the other hand, those with a high clinical probability of PE underwent V/Q lung scan and/or pulmonary angiography. Patients with either deep vein thrombosis (DVT) on CUS or PE on spiral CT received anticoagulant treatment. Patients with an inconclusive diagnostic algorithm (i.e., (i) non diagnostic CUS and normal spiral CT, (ii) normal CUS and non diagnostic spiral CT, (iii) isolated subsegmental thrombus on spiral CT and negative CUS) underwent V/Q lung scanning and/or pulmonary angiography. Pulmonary angiography and V/Q scanning were performed within 48 h of inclusion. All patients were followed-up for 3 months (telephone in-

<table>
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<tr>
<th>Age, years</th>
<th>Suspected PE Patients, N</th>
<th>Prevalence of PE in all patients %</th>
<th>Prevalence of PE in patients with low clinical probability %</th>
<th>Prevalence of PE in patients with intermediate clinical probability %</th>
<th>Prevalence of PE in patients with high clinical probability %</th>
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</thead>
<tbody>
<tr>
<td>&lt; 54</td>
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<td>8.1%</td>
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</tr>
<tr>
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<td>6.5%</td>
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<td>70.1%</td>
</tr>
<tr>
<td>&gt; 73</td>
<td>347</td>
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<td>19.2%</td>
<td>34.7%***</td>
<td>70.1%</td>
</tr>
<tr>
<td>All</td>
<td>1040**</td>
<td>34.6%</td>
<td>12%</td>
<td>26%</td>
<td>68%</td>
</tr>
</tbody>
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*p < 0.01, **p < 0.05, ***p = 0.001, chi-square tests, compared with patients from other tertiles of age.

**Table 1: Prevalence of pulmonary embolism according to tertiles of age and clinical probability.**
terviews 1 month and 2 months after inclusion and medical visit at the outpatient clinic at 3 months) and the following events were recorded: confirmed PE; confirmed deep vein thrombosis; deaths possibly or certainly related to PE, duly classified by the adjudication committee.

In order to evaluate the effect of age on the performance of the diagnostic strategy, patients were divided into three groups according to tertiles of age: under 54 years, 54 to 73 years and above 73 years. The overall prevalence of PE, as well as the prevalence of PE in patients with respectively low, intermediate and high pretest clinical probability were expressed within each age group. We then studied the effect of age on the results observed in three main groups of patients after performing spiral CT scan and venous CUS (Fig. 1): (i) patients with inconclusive results from this diagnostic strategy; (ii) patients with negative findings on both exams and non high pretest clinical probability; (iii) patients with positive findings.

### Results

The main steps of the flowchart in the diagnostic process of the ESSEP study and in distribution of the population under study according to this algorithm are summarised in figure 1. Table 1 shows the prevalence of PE, according to tertiles of age and to pretest clinical probability: the prevalence of PE increased significantly with age; the prevalence of PE in patients with respectivelow or intermediate pretest clinical probability also increased with age. In these two subgroups, the prevalence of PE in patients above 73 years was twofold higher than that observed in those patients under 54 years of age; in contrast, in the subgroup of patients with high pretest clinical probability, the prevalence of PE was found to be high and comparatively similar between tertiles of age (Table 1).

The diagnostic strategy was inconclusive in 95 patients (9.1%) (Fig. 1). The distribution of inconclusive spiral CT or CUS examinations did not differ in any age group (Table 2). The distribution of venous thromboembolic events which occurred during the 3-month follow-up in untreated patients with low or intermediate clinical probability and negative findings on spiral CT and CUS are shown in Table 3. No event occurred in patients under 54 years of age, whereas 7 events were diagnosed in patients over 73 years of age (p < 0.001, comparing patients over 73 years of age to others, Fisher exact test). Finally, table 4 summarises the effect of age on the percentage of positive spiral CT scans and positive venous CUS examinations. A higher proportion of older patients had a positive result at both examinations. This higher number of positive venous CUS in older patients was also observed when the analysis was restricted to those suspected PE patients free from leg symptoms at clinical examination (n: 817): 6% in the lower, 15.1% in the intermediate and 23.8% in the upper tertile, respectively (p < 0.001, data not shown in table). The percentage of positive spiral CT scans in the case of negative or inconclusive venous CUS results (that is, in those patients where VTE could not be ruled out by a CUS used as a first line test) was not different between age groups; conversely, in the case of a negative or inconclusive spiral CT scan, the percentage of positive venous CUS was higher in older patients (Table 4).

### Discussion

To the best of our knowledge, for the first time the analysis of the data from the prospective multicentre ESSEP study gives the opportunity to evaluate the effect of age on a diagnostic strategy that includes for each suspected PE patient an assessment of the pretest clinical probability, a spiral CT and a venous CUS. Two main conclusions can be drawn from this study of more than 1
000 patients with suspected PE. Firstly, the rate of VTE events observed during the three month follow up in suspected PE patients who were not given anticoagulant therapy on the basis of a low or intermediate pretest clinical probability and both negative spiral CT and venous CUS is lower in patients aged 73 years and under than in patients aged above 73 years. Secondly, although a greater percentage of suspected PE patients had positive findings on either spiral CT or venous CUS with increasing age, in accordance with the increasing prevalence of PE with increasing age, the appropriate sequence of testing appears affected by age. Venous CUS, if used as a front-line method, could prove particularly useful in older patients, thus avoiding spiral CT in nearly 30% of patients over 73 years of age (Table 4). The percentage of PE diagnosed by a further use of spiral CT in the case of inconclusive or negative venous CUS appears to be unaffected by age. As a consequence, a similar “sparring effect” is unlikely to be observed in the case of a spiral CT as a front-line test, as further testing with venous CUS in the case of an inconclusive or negative spiral CT would also diagnose a higher proportion of events in older patients.

Two arguments strengthen the clinical validity of these findings: (1) a broad range of suspected PE in- or outpatients has been included consecutively; (2) the overall frequency of confirmed PE in our studied population is 34.6%, which is similar to that of other multicentre outcome studies. However, as patients suspected of massive PE with haemodynamic instability or requiring thrombolytic therapy have not been included, our conclusion may not be applicable in this particular setting.

In published strategies which involve a sequential testing procedure including spiral CT and venous CUS, the order of these tests varies. In the study by van Strijen and co-workers, spiral CT was used as a front-line method and identified PE in 124 out of 519 suspected PE patients (24.3%) (8); the additional value of venous CUS, when performed in the case of a spiral CT examination judged as negative or indeterminate for PE and in the absence of a clear alternative diagnosis, was low. Venous CUS revealed deep vein thrombosis in only two patients. No data on the effect of age are provided in this study which includes rather young patients (mean age: 56.2 years). In the study by Perrier and co-workers, plasma D-Dimer measurement was used as the front-line method (9). PE was ruled out in patients with a D-Dimer level under 500 μg/l, irrespective of the pretest clinical probability. In patients with D-Dimer levels of 500 μg/l or over, a venous CUS was indicated; spiral CT was then performed in patients with a normal venous CUS. The overall prevalence of PE was 23% and 593 out of 965 suspected PE patients (61.4%) underwent a spiral CT examination. Our results are in accordance with this latter strategy and confirm the interest of venous CUS when used as a front-line diagnostic method in older patients. A strategy that combines spiral CT pulmonary angiography with CT venography of the lower extremities has also been recently evaluated (10–12): CT venography, performed following spiral CT pulmonary angiography without additional bolus of contrast offers the potential to detect deep venous thrombosis. This association could also prove to be efficient and effective in the elderly population.

Our study provides an opportunity to analyse the effect of age on the predictive value of pretest clinical probability. In the case of a low or intermediate clinical probability, the prevalence of diagnosed PE in older patients is twice that compared to younger ones. It remains unclear whether this may raise concerns regarding the safety of withholding anticoagulant therapy in older patients on the basis of a non invasive strategy that includes the assessment of a low pretest clinical probability. Indeed, studies including adult patients suspected of PE without any age limitation have reported an overall low rate of management failure (13). However, authors have also highlighted the occurrence of a selection bias, with a lower proportion of older suspected PE patients being included in prospective management studies (14). Therefore, the practical relevance of such findings may prove particularly important for patients who are not included in prospective studies.

The effect of age on the predictive value of pretest clinical probability has been assessed by the Geneva group in two studies which focused on outpatients (5, 15). In the first study, clinical probability was assessed empirically by the physician who saw the patient on admission (5). Although a low clinical probability was associated with a very low prevalence of PE in patients under 60 years of age, the prevalence of PE tended to increase in older patients, so that PE was diagnosed in 20% of patients with a low clinical probability over 80 years old. More recently, the same authors have evaluated the effect of age on the assessment of clinical probability of PE using two prediction rules: (i) the Geneva score with an implicit judgement overriding the rule by implicit probability assessment, in the case of a disagreement between the rule and the physician’s opinion (16); and (ii) the Wells’ score (17, 18). This analysis was conducted in 922 outpatients suspected of PE who were then divided into three age subgroups (50 and under; 51–74 years; 75 and over). The prevalence of PE in the case of a low pretest clinical probability was respectively 5.4, 8.6 and 6 percent in these three subgroups when the Geneva rule was applied. In the case of a low clinical probability, as assessed by the Wells’ score, the prevalence of PE was respectively 7.4, 9.8 and 14.9 percent in these same three subgroups. As age is included in the calculation of the Geneva score (60–79 years old being associated with a 1 point score; 80 years and over with a 2 point score), a lower proportion of patients aged 75 and over were rated as having a low pretest clinical probability. It remains unclear whether the low prevalence of PE observed in these older patients with a low pretest clinical probability is related only to this inclusion of age in the Geneva score and/or to differences in scoring clinical symptoms and risk factors, independent of age. Moreover, as the Geneva score is restricted to outpatients, a comparison with our data is difficult. However, these findings basically show that a low pretest clinical probability of PE has limited performance in older patients. Further studies among elderly suspected PE out- and inpatients should clarify at least two points: (i) does the inclusion of age in the assessment of pretest clinical probability result in higher performance? (ii) if so, what is the impact on the diagnostic work-up, especially regarding the need for invasive examinations?
Appendix

Members of the ESSEP study group:

References