CHAPTER 8

DISCUSSION

Accepted (in Dutch) ‘Huisarts en Wetenschap’
On a busy Friday morning consultation hour a 35 year old woman presents with pain on the right side of her chest that started five days earlier and continued to worsen until presentation. The pain originates near her right scapula and radiates throughout her right chest. The pain is not worsening with movements of arm or shoulder but is worsening with deep inspiration. She is otherwise healthy and has no history of deep venous thrombosis or pulmonary embolism (PE), haemoptysis, recent surgery or trauma. She has not been immobilized recently, is a non-smoker and does not use hormonal anti-conceptives.

With physical examination she is not short of breath, has a tachycardia of 109 beats per minute, a blood pressure of 105/60mmHg and an oxygen saturation of 100% at pulse oximetry. She has no clinical signs of deep venous thrombosis.

An important part of the workload of the primary care physician consists of making a diagnosis or formulating a diagnostic hypothesis, including the exclusion of a severe condition in patients with a relatively low pre-test probability. The introduction stated: ‘In patients consulting their primary care physician (PCP) with symptoms suggestive of pulmonary embolism the PCP can not do anything but refer to secondary care for further evaluation’. Reality is more complicated. In daily practice the PCP has to deal with the ‘chagrin’-factor. The physician must choose between the ‘active’ and the ‘passive’ option, between admitting the patient to the hospital or leaving the patient at home. The active option carries the potential chagrin of doing something major for what turns out to be a minor problem, whereas the passive option, which involves a minor action, can produce chagrin if the clinical problem is major and has a poor outcome that might have been avoided with the active option. The potential major cause of the complaints of the 35 year old woman is pulmonary embolism; the potential minor cause is musculo-skeletal pain. The active option is to refer the patient to the hospital; the passive option to leave the patient at home and prescribe painkillers. With the active option, if the patient is diagnosed with musculo-skeletal pain, one might feel substantial chagrin about the needless fuss, fright and expenses. With the passive option, if the patient after all is diagnosed with pulmonary embolism the level of chagrin will depend on the severity and prognosis of the emboli.
In daily practice the PCP will not refer all suspected PE-patients to secondary care. If the physician regards the disease probability, as assessed with empirical clinical judgment, as very low, she/he might give preference to the passive option thereby taking the very small risk of missing PE. PCPs never exclude a diagnosis completely. If they regard a diagnosis as very unlikely the patient is reassured.³ The validated diagnostic strategy using the Wells rule and the D-dimer test offers the physician an evidence based strategy to safely manage the disease and to diminish largely the ‘chagrin’-factor. Before applying the strategy the PCP first has to include the diagnosis of PE in the differential diagnosis of patients with unexplained shortness of breath or pleuritic chest pain. With the introduction of this strategy in primary care the PCP will keep on missing pulmonary embolism occasionally but with establishing the strategy as the standard of care the fear of medico-legal risk will be largely reduced.

**What clinical features of history and physical examination predict the presence or absence of pulmonary embolism in our 35 year old patient?**

Table 8.1 shows the characteristics of suspected PE-patients finally not diagnosed with PE in comparison with suspected PE-patients finally diagnosed with PE (data AMUSE-2). Patients diagnosed with PE were on average six years older than patients not diagnosed with PE. Both immobilization or recent surgery and a history of venous thromboembolism occur significantly more often in patients diagnosed with PE. Pleuritic pain is the most common complaint in patients with pulmonary embolism (66%) but this complaint is even more frequent in patients suspected of PE who turned out not to have PE. More than half of the PE patients complain of acute dyspnoea (56%) but in patients not diagnosed with PE this symptom is as frequent. Significantly more patients diagnosed with PE complain of lower limb pain (40%). More than 75% of patients reported an acute onset of symptoms. However more than 50% had already symptoms for more than three days (average duration of symptoms of six days) before their visit to the doctor suggesting that pulmonary embolism in general practice is less an acute disease than often thought. Two studies performed in secondary care confirmed this finding with an average delay in seeking medical attention.
Tabel 8.1. Characteristics of suspected PE-patients finally not diagnosed with PE in comparison with suspected PE-patients finally diagnosed with PE (data AMUSE-2)

<table>
<thead>
<tr>
<th>Characteristics:</th>
<th>No PE</th>
<th>PE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>525</td>
<td>73 (12%)</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>72%</td>
<td>66%</td>
<td>0.28</td>
</tr>
<tr>
<td>Age in years ± SD</td>
<td>47 ± 16</td>
<td>53 ± 15</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Patient history**

<table>
<thead>
<tr>
<th>History</th>
<th>No PE</th>
<th>PE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of VTE*</td>
<td>13%</td>
<td>25%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Malignancy*</td>
<td>4%</td>
<td>7%</td>
<td>0.26</td>
</tr>
<tr>
<td>Immobilization or surgery &lt;1 month*</td>
<td>14%</td>
<td>32%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>COPD</td>
<td>9%</td>
<td>8%</td>
<td>0.91</td>
</tr>
<tr>
<td>Heart-failure</td>
<td>2%</td>
<td>3%</td>
<td>0.81</td>
</tr>
</tbody>
</table>

**Symptoms**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No PE</th>
<th>PE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleuritic pain</td>
<td>79%</td>
<td>66%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chest pain</td>
<td>65%</td>
<td>40%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Acute dyspnoea</td>
<td>55%</td>
<td>56%</td>
<td>0.83</td>
</tr>
<tr>
<td>Cough</td>
<td>31%</td>
<td>34%</td>
<td>0.58</td>
</tr>
<tr>
<td>Lower limb pain</td>
<td>13%</td>
<td>40%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Haemoptysis*</td>
<td>3%</td>
<td>7%</td>
<td>0.09</td>
</tr>
<tr>
<td>Acute onset of symptoms</td>
<td>76%</td>
<td>77%</td>
<td>0.84</td>
</tr>
<tr>
<td>Mean duration of symptoms, mean (SD) in days</td>
<td>5.9 (8.4)</td>
<td>6.4 (11.0)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

**Physical examination**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No PE</th>
<th>PE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia &gt;100/min*</td>
<td>16%</td>
<td>34%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tachypnoea &gt;20/min</td>
<td>23%</td>
<td>29%</td>
<td>0.29</td>
</tr>
<tr>
<td>DVT signs*</td>
<td>8%</td>
<td>36%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fever &gt;38.5 degrees</td>
<td>na</td>
<td>na</td>
<td></td>
</tr>
</tbody>
</table>

**Assessment primary care physician**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No PE</th>
<th>PE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism more likely than alternative diagnosis*</td>
<td>52%</td>
<td>84%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

SD = standard deviation, VTE = venous thrombo-embolism, DVT = deep venous thrombosis, *= item Wells-rule.
of three days (95% upper confidence interval (CI) 12 days), respectively eight days (median 4 days). Tachycardia and signs of DVT exist significantly more often in patients with pulmonary embolism. Both history and physical examination are neither specific nor sensitive for PE. There is no individual clinical sign or even a combination of these that can be used to confirm or safely exclude the diagnosis. In our patient tachycardia is the only positive clinical feature predicting the presence of PE.

In the application of the diagnostic strategy using the Wells rule and the D-dimer test the first step is to assess the clinical probability of pulmonary embolism.

**Is the assessment of clinical probability necessary or can we exclude PE just by a normal D-dimer test?**

Even though the negative predictive value of some quantitative D-dimer assays is very high the D-dimer test cannot be used as a standalone test. In AMUSE-2 (Chapter 4) twelve out of 339 patients were diagnosed with pulmonary embolism despite a negative qualitative point of care (POC) D-dimer test (regardless of the clinical probability assessment) giving an unacceptable failure rate of 3.5%. Eight out of 67 patients (11.9%) with a Wells score >4 and a negative qualitative POC-test were diagnosed with PE. This finding is confirmed in secondary care with nearly 10% PE in patients with a Wells score >4 and a negative quantitative D-dimer test. Therefore it is of paramount importance to first examine the patient and assess the clinical probability. If the probability for PE is considered high or likely the patient needs to be referred to secondary care for further imaging without the need for a D-dimer measurement. If the clinical probability is low or unlikely the D-dimer result can be taken into account.

**Can we assess clinical probability by means of gestalt (empirical clinical judgement of the physician) or do we need to use a standardized clinical decision rule?**

The introduction of clinical decision rules may feel as a threat to some physicians’ autonomy. They feel that the algorithmic simplicity of decision rules disrespects clinical complexity and may therefore regard decision rules as cookbook medicine. In a survey among
clinicians in the United States 72.5% of physicians said to prefer an unstructured approach to probability assessment. A majority of clinicians are familiar with at least one of the decision rules for PE yet only one half of them use a rule in more than 50% of their patients. In general, in applying their own clinical judgment physicians are more concerned about the sensitivity (proportion of patients with pulmonary embolism who are assigned a high clinical probability) than about its specificity (proportion of patients not diagnosed with pulmonary embolism who are assigned a low clinical probability). They are more afraid of missing a diagnosis than diagnosing wrongly. The meta-analysis (Chapter 3) showed that the sensitivity of gestalt and different clinical decision rules are comparable. However it is not just sensitivity that matters. The lower specificity (and thus more false-positives) of gestalt in comparison with a standardized rule increases the number of patients that are unnecessarily referred to secondary care. Physicians using gestalt are well able to correctly identify PE-patients at high risk for pulmonary embolism, but they do this at the expense of more non-PE-patients incorrectly identified at high risk.

Hence in our patient we need to apply a clinical decision rule (CDR). One of the most validated and used CDRs is the Wells rule (See Table 1.1a Introduction). The validation study (Chapter 4) showed that PCPs can accurately categorize the probability of PE using the Wells rule. Patients with a Wells score $\leq 4$ had a PE-rate of 5.0% (21 out of 422 patients). Patients with a Wells score $>4$ had a PE-rate of 30% (52 out of 176 patients) ($p<0.001$). The meta-analysis showed that a negative test result from any clinical decision rule alone is insufficient for safely excluding PE. This was confirmed in the AMUSE-2. Even patients with a Wells score of 0 still had a PE-rate of 3.2% (5 out of 157 patients).

In applying the Wells rule to our patient the score is 1.5 points for the heart rate higher than 100 beats per minute. The final result of the Wells rule score of our patient depends heavily on the second item. If the physician is of the opinion that PE is the most likely diagnosis, he will add an extra three points to the score resulting in a total score of 4.5 points, a likely probability of PE and prompting the PCP to refer the patient to secondary care. If an alternative diagnosis is as likely as PE or more likely than PE he will add zero points to the
score resulting in a total score of 1.5 points and an unlikely probability of PE. Klok and colleagues showed that a physician, when deciding on awarding 3 points for PE as the most likely diagnosis, is influenced by the other variables in the Wells rule. This finding is explained from the fact that besides haemoptysis and heart rate, all other variables are well established risk factors for PE.13

The subjective character of this criterion and its moderate reproducibility due to interobserver variability is the main point of criticism of the Wells rule. On the other hand, this criterion enables the physician to use his medical intuition.14 In our patient we assess an alternative diagnosis as more likely than PE. The total score for her will be 1.5 points: an unlikely clinical probability of PE. The next step in the diagnostic management of the patient will be the D-dimer test.

Referral to a central laboratory or performing a point of care test? D-dimer testing using a quantitative D-dimer test or a qualitative D-dimer test?

The decision to perform a point of care test or to refer the patient to a central laboratory depends partly on the easy accessibility of a central laboratory. Both point of care and laboratory based tests are available as quantitative and qualitative tests. Quantitative tests express the result in a number. Qualitative tests express the outcome in a positive or negative test result.

The use of a quantitative test in primary care, either as a point of care or as a laboratory based test, may have several advantages. Firstly, the quantitative test gives the flexibility to increase the cutoff value of the D-dimer test thereby decreasing sensitivity and increasing specificity. Douma and colleagues showed the potential of an age-adjusted D-dimer cutoff value to improve the exclusion of PE in elderly patients in secondary care.15 Secondly, the magnitude of abnormality of the test result may be an important factor in the interpretation of results, since the D-dimer level is associated with the extent of pulmonary embolism.16;17 Finally, when test results are dichotomized into normal and abnormal, important information may be lost.18 A quantitative test result might give the primary care physician the flexibility to interpret the result and even to deny borderline laboratory test results in very low probability patients (for instance Wells
score of 0 points) as he is generally used to do in assessing laboratory tests.\textsuperscript{19;20}

Quantitative point of care tests are yet available but differ from the qualitative Simplify D-dimer test as they need calibration, an expensive analyzer and they can not be performed on capillary whole blood.\textsuperscript{21}

Available qualitative tests use a less sensitive cutoff than quantitative tests (more false negatives: more patients with pulmonary embolism who incorrectly have a negative test). As a consequence the qualitative tests are more specific than quantitative tests.\textsuperscript{21} The lower sensitivity is a disadvantage but due to the lower prevalence of PE in primary care (lower pre-test probability) the negative predictive value is still acceptable. However due to the higher specificity fewer patients will be assigned as false-positive (patients without PE who incorrectly have a positive test) and thus fewer patients will be referred unnecessarily to secondary care. This makes the qualitative test feasible for use in primary care.

In our 35 year old patient we apply a qualitative D-dimer test which appeared to be negative. With both Wells clinical decision rule and qualitative D-dimer test negative we can safely exclude PE in our patient.

\textbf{Is PE safely excluded?}

In fact we are answering the question: what is an acceptable post-test probability (after applying the diagnostic strategy) below which physicians may choose to defer from further testing (in this case referral to secondary care)? In their derivation study Wells et al showed a failure rate of 2.2\% (95\% CI 1.0-4.0\%) in a three month follow-up period in patients with an unlikely Wells rule and a negative SimpliRed D-dimer test. Wells et al considered this as safe because it was similar to the PE-rate in patients with normal VQ-scans and normal angiograms.\textsuperscript{22} Subsequent outcome studies considered a three month thromboembolic risk of 4\% being the upper limit of the 95\% CI acceptable.\textsuperscript{23-25} In their systematic review of diagnostic strategies for excluding PE Kruip et al considered a strategy to be safe if the upper 95\% CI did not exceed an arbitrarily chosen 3\%.\textsuperscript{26} In the Christopher-study an upper limit of 2.7\% (pointestimate 1.7\%) was used being the upper limit of the range of recurrent VTE after a normal pulmonary angiography in a three month follow-up period.\textsuperscript{27;28}
Kline et al showed a very different approach to determine the testing threshold using the method of Pauker and Kassirer. When to decide whether or not to evaluate a low-risk patient for pulmonary embolism, one must balance the harm as a result from missing the diagnosis against the harm associated with the diagnostic evaluation and the harm induced by treatment. With this method the test threshold is calculated using different variables like test characteristics of the CT-scan (as subsequent diagnostic test in patients with a positive strategy), risk of treatment (bleeding) in patients with (true positives) and without disease (false positives), risk of the CT-scan (cancer from radiation exposure, death from anaphylaxis, mortality from contrast-induced renal failure) and benefit of treatment in patients with disease. Kline calculated a test threshold of 1.8%. The interpretation of this number is that patients with a disease probability below 1.8% should not undergo further testing because the probability of harm due to testing or treating will outweigh the probability of benefit in this patient when suffering from PE. A major drawback of this approach is that it is very difficult to calculate accurately the used variables. Moreover the weight of the variables will be different in individual patients depending for instance on co-morbidity or age.

In conclusion one can say that there is no clearly defined testing threshold but considering the above mentioned literature using a testing threshold close to 2% seems realistic in patients with an unlikely Wells rule and a negative D-dimer test. In AMUSE-2 (Chapter 4) the risk of having PE despite a negative strategy is about 1.5%.

**With the exclusion of PE the story of our patient has not ended yet.**

Our patient is relieved that she is not diagnosed with pulmonary embolism but is still suffering from her pleuritic chest pain. What is her alternative diagnosis after excluding PE? The low clinical PE-probability and the negative D-dimer test not only exclude PE but make a clinically severe alternative diagnosis less likely as well (Chapter 5 and 6). The most frequent alternative diagnoses after excluding PE are thoracic pain/dyspnoea of unknown cause (43%), pneumonia (13%) and myalgia (12%) (Chapter 5). The further management of our patient depends on the clinical judgment of the PCP. If the PCP considers a clinically severe alternative diagnosis as
very unlikely he might reassure the patient and prescribe painkillers if necessary. If she/he considers a severe diagnosis as still possible she/he might decide to order a chest X-ray, electrocardiography or an additional C-reactive protein (CRP) test. C-reactive protein blood levels rise in response to inflammation. The CRP-test is available both as a point of care and as a laboratory based test. In Chapter 6 we show that the CRP-test with using 10 mg/l as cutoff point could be of additional value in differentiating between clinically severe and clinically non-severe alternative diagnoses. In our patient the PCP decided to perform a CRP-test and with a CRP-result <10 mg/l she/he refrained from further testing. The patient was diagnosed with myalgia and reassured. Her complaints disappeared completely in 7 days.

**What are problems to expect with implementation of our diagnostic strategy?**

When a new test or strategy is evaluated the existing diagnostic pathway for the identification of the target condition (pulmonary embolism) should be considered. In evaluating the study results of AMUSE-2 (new strategy) it is suggested that the PCP refers all suspected PE-patients to secondary care (existing pathway). In fact we do not know the existing pathway. It is not known how many suspected PE-patients are referred to secondary care or how many suspected patients are managed in primary care. The PCP does not refer all suspected patients to secondary care what makes patient outcomes and cost-effectiveness of the introduction of the strategy less clear. In secondary care the introduction of non-invasive diagnostic strategies for excluding pulmonary embolism led to an increase in testing of PE. As a consequence, the number of patients who undergo investigations in order to find one case of PE increased: the PE prevalence in the tested population decreased. The availability of a diagnostic strategy in primary care may have the same consequences. The strategy will be applied to patients with a very low probability of PE in whom the GP previously excluded PE and refrained from referral to secondary care only using clinical gestalt. This might lead to a substantial number of false-positive patients also due to the relatively low specificity of the diagnostic strategy, thereby causing patients to be unnecessarily referred to secondary care. Our strategy is a two-
stage process. After applying the Wells rule the PE-probability in patients eligible for D-dimer testing (Wells score ≤ 4) is already reduced to 5%. Figure 8.1 shows that a reduction of the prevalence of PE in the suspected population below 10% is accompanied with a high number of patients who need to be further investigated to identify one PE-patient when the D-dimer result is positive (NNI = number needed to be investigated). 35

Concerns about the low specificity of the diagnostic strategy could be resolved in three ways. Firstly, one could increase the cutoff value of the Wells rule thereby increasing the specificity and at the same time decreasing the sensitivity of the strategy. The AMUSE-2-data revealed that using a Wells cutoff score < 6 points in combination with a negative qualitative D-dimer test appeared to be efficient (322 out of 598 patients with a negative strategy) but not safe enough (8 failures out of 322 patients = 2.5%).
Secondly, Douma and colleagues showed that using an age adjusted D-dimer cutoff point increased the proportion of older patients in whom PE could be safely excluded. The new D-dimer cutoff value was defined as (patient’s age x10) ug/l in patients above the age of 50 years.\textsuperscript{15} This method is only possible when a quantitative D-dimer test is applied.

Thirdly, Kline and colleagues developed a prediction rule named the PERC-rule (Figure 8.2), to support the decision not to order subsequent diagnostic tests (including D-dimer test) for PE in patients in whom the clinician already had a low suspicion for PE (a pre-test probability estimate of < 15% using gestalt).\textsuperscript{36} To be negative the PERC-rule requires the clinician to answer ‘no’ to eight questions. A systematic review showed that the PERC-rule can only be safely used in a low PE-prevalence population (PE-prevalence < 10%) excluding PE in about 20% of suspected patients.\textsuperscript{37} The PERC-rule could be a useful tool for the primary care physician in patients in whom the PCP currently decides not to refer to secondary care because the pre-test probability, as assessed with gestalt, is regarded that low that he/she dares to take the risk of missing PE. This strategy however is not yet tested in primary care.

For a negative result, the physician must answer ‘no’ to the following eight questions:

1. Is the patient older than 49 years of age?
2. Is the pulse rate above 99 beats/min?
3. Is the pulse oximetry reading <95% while the patient breathes room air?
4. Is there a present history of haemoptysis?
5. Is the patient taking exogenous oestrogen?
6. Does the patient have a prior diagnosis of venous thromboembolism (VTE)?
7. Has the patient had recent surgery or trauma? (Requiring endotracheal intubation or hospitalization in the previous four weeks.)
8. Does the patient have unilateral leg swelling? (Visual observation of asymmetry of the calves.)

\textbf{Figure 8.2.} PERC rule (Pulmonary Embolism Rule-out Criteria)
In reality the problem of a false-positive strategy might be less clinically relevant for three reasons. Firstly, the meta-analysis (*Chapter 3*) showed lower sensitivity and higher specificity with a lower prevalence of PE both in clinical decision rules and in the combination of rules and (quantitative and qualitative) D-dimer tests. In AMUSE-2 (*Chapter 4*) the sensitivity and the specificity of the qualitative D-dimer test in the Wells >4-group (PE-prevalence 30%) versus the Wells ≤ 4-group (PE-prevalence 5%) was 85% and 48%, 81% and 67% respectively, showing lower sensitivity and higher specificity with a lower PE-prevalence. If the prevalence of PE in the tested population is lower, the specificity of our strategy appears to be higher, as could be expected. Secondly, simply by using a qualitative D-dimer test with a lower sensitivity but higher specificity in comparison with a quantitative D-dimer test the number of false-positive patients will be lower. Thirdly, patients referred to secondary care because of a positive strategy, with either a likely Wells decision rule result or a positive D-dimer test, are frequently diagnosed with a clinically relevant alternative diagnosis (after excluding PE). Hence, the referral to secondary care is justified by either diagnosing pulmonary embolism or by diagnosing any other clinically relevant disease (*Chapter 5* alternative diagnoses).

### In conclusion

This thesis started by quoting the Lancet of 100 years ago: ‘pulmonary embolism is often overlooked because not considered in differential diagnosis’. The introduction of an evidence based strategy in primary care can not completely solve this problem. Before applying this strategy the doctor first has to consider the diagnosis of pulmonary embolism.

This thesis showed that the primary care physician is able to safely exclude PE in 45% of suspected primary care patients using the Wells clinical decision rule for PE and a point of care D-dimer test. After the exclusion of PE the doctor might be able to further manage the patient with the use of a (point of care) CRP-test to reduce the risk of having a clinically relevant alternative disease in patients with a CRP concentration below 10mg/l. Further prospective research should examine the additional role of the CRP-test in patients in whom the GP excluded PE.
Implementation of the strategy using the Wells rule and the D-dimer test might lead to an increase in testing for PE in primary care. This will not influence the safety of the strategy but might increase the number of unnecessary referrals to secondary care. This stresses the importance of the application of a D-dimer test with a high specificity in primary care. To ascertain whether the validated strategy will actually be used by physicians, will change or direct physicians’ decisions and will improve patient outcomes, an impact analysis should be performed. A randomized controlled trial is the ideal design for an impact analysis but due to logistic and financial reasons a ‘before-after’ analysis (measure outcomes before, during and after using the strategy) can be a good alternative.\textsuperscript{9}
Reference List


13. Klok FA, Zidane M, Djurabi RK, Nijkeuter M, Huisman MV. The physician’s estimation ‘alternative diagnosis is less likely than pulmonary embolism’ in the Wells rule is dependent on the presence of other required items. Thromb Haemost 2008; 99(1):244-245.

CHAPTER 8


