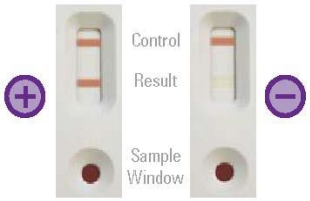
Horizon Scan Report 0005 **14 April 2009**

Diagnostic Technology:
The D-Dimer Test for ruling out Deep Vein Thrombosis in Primary Care

Clinical Question: In patients presenting in primary care with suspected DVT, does a point-of-care D-dimer assay combined with a decision rule accurately diagnose DVT compared to venous ultrasound and is this strategy cost effective.

Advantages over Existing Technology:
Current practice is to refer all patients suspected of having deep vein thrombosis (DVT) for diagnostic testing services. However, 80% to 90% of referred patients do not have DVT (1). Therefore, the ability to safely exclude DVT at initial presentation would impact on the number of referrals.

Details of Technology:
D-dimer is a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. The presence of this protein in blood is detected using a monoclonal antibody-based method. For example, the Clearview Simplify test from Inverness Medical (Bedford, UK) can be performed using a fingerprick sample and results are obtained in 10 min. (4). The test has a sensitivity of 100% (95% CI, 90.0-100%), specificity of 53% (42-64%) and a Negative Predictive Value of 100% (92-100%).



A decision rule incorporating the D-dimer assay has been developed specifically for primary care.
Decision Rule for Primary Care (1):

Variable	Points
Male	1
Use of hormonal contraceptives	1
Active cancer in past 6 months	1
Surgery in previous month	1
Absence of leg trauma	1
Distention of collateral leg veins	1
Difference in calf circumference ≥ 3 cm (measured 10 cm below the tibail tubercle)	2
Abnormal D-dimer assay result (Clearview Simplify, Inverness Medical, Bedford, UK)	6

Patients with a score ≤ 3 do not receive a referral for ultrasonography; patients with a score ≥ 4 should be referred.

Patient Group and Use:
- Patients with suspected deep vein thrombosis

Importance:
More than 140 000 patients present in primary care with signs and symptoms suggestive of deep vein thrombosis (DVT) of the leg in the UK each year (2).

Previous Research:
A systematic review determining the prevalence of DVT using clinical prediction rules either with or without D-dimer was published in 2006 (5). The review concluded patients with a low clinical probability using the predictive rule have a prevalence of DVT < 5%. The clinical prediction published by Wells et al. (3) accurately categorised patients as having low, moderate, or high clinical probability. In low-probability patients with negative D-dimer results, diagnosis of DVT could be excluded without ultrasound.

However, the Wells score was not accurate enough for primary care patients suspected of having DVT, because the prevalence of thrombosis was still 2.9% among patients with a low probability (based on the Wells score and a normal quantitative D-dimer) (7).

Due to this uncertainty a decision rule specifically for the primary care setting that includes clinical items and the D-dimer assay result has been developed and validated (1; 6). A major difference between the rules, taking into account the additional use of D-dimer for low-probability patients in the Wells rule, is the replacement of the subjective phrase "alternative diagnosis more likely" with the more objective phrase "absence of leg trauma" (1). Using this rule, the category of low probability based on the new rule had a 0.7% prevalence for thrombosis (6). A trial of 1028 patients from approximately 300 primary care practices using the rule identified 49% of patients at low enough risk to withhold imaging tests and anticoagulation treatment. In the subsequent 3 months, 1.4% (95% CI, 0.6% to 2.9%) of low-risk patients went on to have venous thromboembolism (1). For patients receiving ultrasonography 25% had DVT, and of those who had a normal ultrasonogram, 1.1% (CI, 0.3% to 2.7%) developed venous thromboembolism during the 3-month follow-up. The study concluded that patients with a score of 4 or greater based on clinical items, had a 35.9% probability of having DVT. Those with a normal D-dimer result still have a 23.5% probability of having DVT, whereas probability increases to 42.6% among those with an abnormal D-dimer result.

Health Technology Assessments:
A health technology assessment of DVT diagnosis in hospitals, published in 2006, showed that in patients with clinically suspected DVT, D-dimer had 91% sensitivity and 55% specificity for DVT, although performance varied substantially between assays and populations (8). D-dimer specificity was dependent on pretest clinical probability, being higher in patients with a low clinical probability of DVT. The report concluded that diagnostic algorithms based on a combination of Wells score, D-dimer and ultrasound were feasible at most UK hospitals and among the most cost-effective.

Research Questions:
To what extent has the D-dimer test in combination with the decision rule been implemented in primary care?

Suggested next step:
1. Systematic review of the use of D-dimer in primary care.
2. Overview and comparison of D-dimer tests currently in use.

Expected outcomes:
A point-of-care D-dimer assay combined with a decision rule validated in primary care will effectively reduce the need for patients with suspected DVT to be referred to secondary care.

Cost-effectiveness and economic impact:
A recent HTA report Goodacre et al. (8,9) presented a cost-effectiveness analysis based on a meta-analysis (10). They developed a decision analytic model to evaluate 18 different strategies for managing patients with suspected DVT, it principally applied to patients presenting as outpatients, without known co-morbidity (such as malignancy). For thresholds of willingness to pay of £10,000 or £20,000 per QALY the optimal strategy involved discharging patients with a low or intermediate Wells score and negative D-dimer, ultrasound for those with a high score or positive D-dimer, and repeat scanning for those with positive D-dimer and a high Wells score, but negative initial scan. For thresholds of £30,000 or more a similar strategy, but involving repeat ultrasound for all those with a negative initial scan, was optimal.
Comparison to other studies of cost-effectiveness: Perone and colleagues (11) used decision analysis modelling to compare four strategies, incorporating combinations of clinical risk scoring, D-dimer and ultrasound, with a 'no treatment' alternative. Although a number of differences in the methods, assumptions and parameters used exist, their results broadly concur with the HTA results, that combining clinical probability and D-dimer with a single ultrasound is probably the most cost-effective option among those tested. Other cost-effectiveness analyses have tended to focus on the cost-effectiveness of one particular non-invasive technology (12-14).

Policy Context Comments:

In recent years the Health Select Committee and the Chief Medical Officer have published reports on DVT prevention in hospitalised patients. Another area of focus has been on DVTs occurring after air travel. Both of these risk groups are relevant to primary care clinicians, as many possible post-operative and post-travel DVTs will be encountered by general practitioners.

The various Darzi-related NHS service developments are encouraging the re-location of more services (including diagnostic services) into the community. However an informal survey within East and North Yorkshire has revealed considerable variability in the service models for the delivery of DVT diagnostic services. Particular variation is seen in relation the technology used (i.e. D-Dimer (POCT or laboratory) +/- ultrasound) and the pre-test diagnostic pathway in patients presenting with possible symptoms of DVT. This has the potential to lead to significant diagnostic inefficiencies with adverse effects on health costs and key patient outcomes. The role of D-Dimer testing versus ultrasound, in conjunction with a clinical decision rule applicable to the primary care setting, needs to be clarified as a matter of urgency.

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Comments:

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