NATIONAL INSTITUTE FOR HEALTH & CLINICAL EXCELLENCE

Health Technology Appraisal

Thrombophilia Testing
Scope

Objective: To appraise the clinical and cost effectiveness of thrombophilia testing in patient populations at high risk of thrombotic events and to provide guidance to the NHS in England and Wales.[1]

Background:

Thrombophilia is an acquired or inherited (genetic) defect in blood coagulation that leads to a predisposition towards intravascular coagulation (arterial and venous thrombosis). Intravascular coagulation produces a thrombus, which is a solid mass of blood constituents that can fragment and block vessels downstream (thromboembolism). Depending on the blood vessel occluded, thromboemoboli can lead to coronary artery thrombosis (myocardial infarction), stroke, or pulmonary embolism.

Venous thrombosis often occurs in normal vessels, with the majority of venous thrombi forming in the deep veins of the leg (deep vein thrombosis, DVT). Venous thrombosis is an important cause of morbidity and mortality; approximately 90% of pulmonary emboli are caused by dislodged fragments from asymptomatic DVTs. The estimated annual incidence of venous thrombosis is 1 in 1000 individuals in the general population.

Arterial thrombosis usually occurs in association with atheroma in areas of turbulent blood flow, such as the bifurcation of arteries.

Inherited (genetic) thrombophilia is caused by mutations in coagulation factors such as factor II and factor V or enzymes such as methylenetetrahydrofolate reductase. Acquired thrombophilia refers to conditions in which individuals without genetic deficiencies in coagulation factors are at increased risk of thrombosis (for example pregnancy, oestrogen therapy [oral contraceptive pill - OCP / hormone replacement therapy], obesity and major orthopaedic surgery).

The technology:

Thrombophilia testing refers to a panel of tests which are performed on individuals who are believed to be at high risk of thrombosis, the purpose being to identify those who may benefit from a more intensive or prolonged course of anticoagulant therapy and to prevent thrombosis. A blood sample is taken and a panel of diagnostic tests are performed to detect deficiencies in blood coagulation.

Diagnostic tests that are predictive for an increased risk of venous thrombosis include genetic (DNA based) tests for factor V leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase (MTHFR C677T) and functional (phenotypic) assays of clotting factors or enzymes such as antithrombin, protein C and protein S deficiencies. Diagnostic tests that are predictive for an increased risk of arterial

[1] The Department of Health remit to the Institute is " To appraise the clinical and cost effectiveness of thrombophilia testing in patient populations at high risk of thrombotic events "

thrombosis include the genetic test for MTHFR C677T, and functional assays of homocysteine, lupus anticoagulant and anti-cardiolipin antibodies.

Thrombophilia tests may be performed on individuals who present with or have a history of thrombosis.

Intervention(s)	Thrombophilia testing using genetic and/or functional tests and the resulting long-term anticoagulation therapy • Examples of genetic tests are: factor v leiden, prothrombin G20210A, MTHFR C677T • Examples of functional (phenotypic) tests are: activated protein C resistance, protein C, protein S and antithrombin deficiency, lupus anticoagulant (dilute Russell viper venom time, kaolin clotting time), anti-phospholipid antibodies and elevated homocysteine.
Population(s)	Individuals at high risk of thrombosis as follows: • with venous thrombosis (e.g. DVT) • with arterial thrombosis (e.g. stroke, myocardial infarction)
Current standard treatments (comparators)	Risk assessment based on personal and family history of thrombosis (that is, no thrombophilia testing using diagnostic tests) and the resulting long-term anticoagulation therapy
Other considerations	The outcome measures to be assessed in this appraisal include: • Mortality • Recurrence of cardiovascular events, including DVT, pulmonary embolism, stroke and myocardial infarction. • Adverse effects of anticoagulation treatment (e.g. haemorrhage) • Health-related quality of life The appraisal will therefore consider the extent to which a diagnosis of thrombophilia influences the intensity or duration of anticoagulant therapy, and the subsequent impact on outcome. Cost-effectiveness analysis will take into account the effectiveness of thrombophilia testing, the sensitivity and specificity of specific diagnostic tests, and changes in the performance characteristics of some tests (due to the effect of thrombus) when thrombophilia testing is performed before, or after anti-coagulant treatment. Where the evidence allows, consideration will be given to the • cost-effectiveness of testing with specific tests and

	combinations of tests • testing in central vs. local hospital laboratories The cost-effectiveness should be presented as the incremental cost per quality-adjusted life year. Other factors or conditions which increase the susceptibility to acquired thrombophilia (for example major orthopaedic surgery, pregnancy and oral contraception / hormone replacement therapy) have been excluded from the scope of this appraisal. Case finding (thrombophilia testing of asymptomatic family members) has also been excluded from the scope of this appraisal. The Institute recognises that these are important population groups to be considered, but it is not feasible to appraise all these within a single appraisal.