NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Health Technology Appraisal

Thrombophilia Screening
Draft scope

Objective: To appraise the clinical and cost effectiveness of thrombophilia screening 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 myocardial infarction, stroke, coronary artery thrombosis, 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 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.

Genetic or inherited thrombophilia is caused by mutations in coagulation factors such as factor II, factor V and methylenetetrahydrofolate reductase. Acquired thrombophilia refers to environmental conditions in which individuals without genetic deficiencies in haemostasis 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 screening 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 due to either acquired or genetic thrombophillia. A blood sample is taken and a panel of diagnostic tests are performed to detect inherited and acquired deficiencies in haemostasis.

Diagnostic tests that are predictive for an increased risk of venous thrombosis include genetic tests for factor V leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase (MTHFR C677T) and functional (phenotypic) assays for antithrombin, plasminogen, protein C and protein S deficiencies.

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

Diagnostic tests that are predictive for an increased risk of arterial thrombosis include the genetic test for MTHFR C677T, and functional assays of homocysteine, lupus anticoagulant and anti-cardiolipin antibodies.

Thrombophilia screening may be performed in individuals thought to be at high risk of developing thromboses such as those who present with or have a family history of thrombosis and women with complications of pregnancy (including severe pre-eclampsia, recurrent miscarriage, severe growth restriction, late foetal loss and unexplained neonatal thrombosis).

Intervention(s)	Thrombophilia screening using genetic and/or functional tests, to include all or some of the following: • Genetic tests: factor v leiden, prothrombin G20210A, MTHFR C677T • Functional (phenotypic) tests: 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 to include individuals: • with a history of thrombosis, • presenting with symptomatic thrombosis, • with a family history of thrombosis, <u>The scope of this appraisal is potentially large. In order to focus the appraisal, the Institute is minded to exclude groups of individuals that are susceptible to acquired thrombophilia (for example individuals undergoing major orthopaedic surgery, pregnant women and women taking oral contraception).</u> The Institute seeks the views of consultees on which are the most appropriate high risk populations to be included in this appraisal.
Current standard treatments (comparators)	Individual risk assessment based on personal and family history of thrombosis (i.e. no thrombophilia screening using diagnostic tests)
Other considerations	The outcome measures to be assessed in this appraisal include: • Mortality • Incidence of symptomatic and asymptomatic DVT, arterial thrombosis, venous disease, pulmonary embolism, stroke and myocardial infarction. • Adverse effects of treatment (e.g. haemorrhage) • Health-related quality of life Cost-effectiveness analysis will take into account 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 screening is performed before, or after anti-coagulant treatment. There is currently no evidence of the effectiveness of anticoagulant prophylaxis, and the risk of fatal bleeding in patients receiving extended anti-coagulation therapy. 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. Where the evidence allows, consideration will be given to the following: • the cost-effectiveness of screening with specific tests • testing in central vs. local hospital laboratories Ideally, the cost-effectiveness should be presented as the incremental cost per quality-adjusted life year.