Arterial thrombosis

Testing for heritable thrombophilia is not indicated in patients with arterial thrombosis.
Antiphospholipid antibodies, antibeta 2 glycoprotein 1 and anticardiolipin antibodies.

**Indications for these tests:**

- History of recurrent first trimester miscarriage (≥1 consecutive miscarriages)
- ≥1 unexplained deaths of a morphologically normal foetus at or beyond 10/40
- ≥1 premature birth of a morphologically normal neonate before 34/40 because of eclampsia/severe preeclampsia or placental insufficiency
- Young adults (<50 years) with ischaemic stroke
Secondary prevention following provoked VTE

Should thrombophilia testing be performed to help determine duration of anticoagulation following provoked VTE?

✓ Of the many factors which predict the risk of recurrent thrombosis after an initial event, the presence of provoking factors is the most important

✓ A positive thrombophilia evaluation is not a sufficient basis to offer extended anticoagulation following an episode of provoked VTE.

Do not perform thrombophilia testing following an episode of provoked VTE.
Secondary prevention following provoked VTE

Should thrombophilia testing be performed to help determine duration of anticoagulation following unprovoked VTE?

- The absolute risk for recurrent VTE among patients with unprovoked thrombosis is higher than among those with provoked VTE, with 5-year risk approaching 30% unless extended-duration anticoagulant therapy is provided.
- Current guidelines from the American College of Chest Physicians (ACCP) recommend extended duration anticoagulation after unprovoked VTE unless the risk of bleeding is high or this is contrary to the patient’s values and preferences.
- Other factors, such as the degree of post-thrombotic symptoms, D dimer levels after a minimum of 3 months of anticoagulant therapy, and residual vein thrombosis may also modify the risk of recurrence.

Do not perform thrombophilia testing in patients following an episode of unprovoked VTE.
Primary prevention in relatives of VTE patients

Should family members of patients with VTE or hereditary thrombophilia undergo thrombophilia testing?

- Except for temporary prophylaxis during certain high risk situations (during hospitalization, following major surgery, and during long distance travel), anticoagulation for primary prevention of thrombosis is not advocated regardless of the genetic defect because the risk of bleeding may be higher than the absolute risk of a first thrombotic event.

- However, a family history of thrombosis alone carries an increased risk, even in the absence of an identifiable thrombophilia.

- Therefore, negative thrombophilia screening does not equate to normal VTE risk.

- Family members who tested negative for a thrombophilic defect were less likely to use prophylaxis.

Do not test for thrombophilia in asymptomatic family members of patients with VTE or hereditary thrombophilia.
Primary prevention in female relatives of VTE patients considering estrogen

Should female relatives of patients with VTE or hereditary thrombophilia who are considering using estrogen-containing medications be tested for thrombophilia?

- Although studies have shown that it is not practical or cost-effective to screen all women for thrombophilia before they use combination oral contraceptives, for women who are first-degree relatives of patients with VTE and known inherited thrombophilia, screening may provide guidance in making informed choices about contraceptive use.

- As with screening in any patient population, however, a strong family history of VTE with negative results of thrombophilia testing does not indicate a low risk of VTE.
Do not test for thrombophilia in asymptomatic family members of patients with VTE or hereditary thrombophilia who are contemplating use of estrogen.

Family history of VTE in a first degree relative predicts an excess risk of thrombosis with estrogen use, even when thrombophilia testing is negative.
Pregnancy is a period of particularly high risk for thrombosis, causing a relative risk increase of 5–10 times baseline.

The presence of a thrombophilic defect amplifies this risk several-fold further.

Thrombophilia screening, if performed, would be most applicable to the setting of primary prevention, as women with a prior VTE that was unprovoked, or provoked by pregnancy or an OCP.

Primary prevention in female relatives of VTE patients who are contemplating pregnancy

Should female relatives of patients with VTE or hereditary thrombophilia who are contemplating pregnancy be tested for thrombophilia?
A personal history of a prior VTE provoked by surgery or trauma does not significantly increase the risk of VTE during pregnancy; and no special prophylaxis measures are indicated ante-partum.

The use of antepartum prophylaxis in women who have an inherited thrombophilia but no personal or family history of VTE is controversial, with varying recommendations because of extremely limited data.

Primary prevention in female relatives of VTE patients who are contemplating pregnancy

Should female relatives of patients with VTE or hereditary thrombophilia who are contemplating pregnancy be tested for thrombophilia?

✓ A personal history of a prior VTE provoked by surgery or trauma does not significantly increase the risk of VTE during pregnancy; and no special prophylaxis measures are indicated ante-partum.

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<table>
<thead>
<tr>
<th>Peso</th>
<th>Dose enoxaparina</th>
<th>Dose dalteparina</th>
<th>Dose tinzaparina</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 kg</td>
<td>2000 UI/die</td>
<td>2500 UI/die</td>
<td>3500 UI/die</td>
</tr>
<tr>
<td>50-90 kg</td>
<td>4000 UI/die</td>
<td>5000 UI/die</td>
<td>4500 UI/die</td>
</tr>
<tr>
<td>91-130 kg</td>
<td>6000 UI/die</td>
<td>7500 UI/die</td>
<td>7000 UI/die</td>
</tr>
<tr>
<td>131-170 kg</td>
<td>8000 UI/die</td>
<td>10.000 UI/die</td>
<td>9000 UI/die</td>
</tr>
<tr>
<td>&gt;170 kg</td>
<td>0.6 UI/kg/due</td>
<td>75 mcg/kg/die</td>
<td>75 mcg/kg/die</td>
</tr>
</tbody>
</table>

Taglio cesareo

✓ Eseguire stratificazione del rischio per scegliere la strategia di profilassi appropriata (grado 2C)

✓ EBPM o ENF a dosi profilattiche +/- calze a compressione graduata durante la degenza ospedaliera post-partum (grade 2C) da continuare fino a 6 settimane se persistono fattori di rischio importanti (grado 2C).
### Stratificazione del rischio in gravidanza e dopo il parto


<table>
<thead>
<tr>
<th>Fattori di rischio presenti</th>
<th>Punti</th>
<th>Fattori di rischio ostetrici</th>
<th>Punti</th>
<th>Fattori di rischio transitori</th>
<th>Punti</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progresso TEV escluso singolo evento post-chirurgia maggiore</td>
<td>4</td>
<td>TC in lavoro</td>
<td>2</td>
<td>Immunostatici e disinnestazione</td>
<td>1</td>
</tr>
<tr>
<td>Progresso TEV post-chirurgia</td>
<td>3</td>
<td>Paro operativi</td>
<td>1</td>
<td>Sepoli</td>
<td>1</td>
</tr>
<tr>
<td>Nota condizione trombofilica ad alto rischio</td>
<td>3</td>
<td>Pre-esistenza nelle gravidanze attuali</td>
<td>1</td>
<td>Procedura chirurgiche in gravidanza e puerperio (accettato occlusione percutanea)</td>
<td>3</td>
</tr>
<tr>
<td>Consorbidità mediche (cancer, trombopenia, cardiiti, buli, poltropie e interf diploma, maletta inf cronica intestinale, idr nefroso, diabete mellito con nefropatia, anemia falciforme, abuso stupefacenti)</td>
<td>3</td>
<td>Gravidanza ottenuta mediante PNI (se prima della nascita)</td>
<td>1</td>
<td>Sindrome da pretermolazione ovarica (oltre il terzo trimestre)</td>
<td>4</td>
</tr>
<tr>
<td>Storia familiare di TEV con provvedimento o associata terapia anticoagulante in parente di 1° grado</td>
<td>1</td>
<td>Gravidanza multiplo</td>
<td>1</td>
<td>Terapie emorragie</td>
<td>3</td>
</tr>
<tr>
<td>Libidini</td>
<td>1</td>
<td>1 se 30, 2 se 40</td>
<td>1</td>
<td>TC eletto</td>
<td>1</td>
</tr>
<tr>
<td>Parto</td>
<td>1</td>
<td>Travaglio prolungato</td>
<td>1</td>
<td>1 (≤68)</td>
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</tr>
<tr>
<td>Idoneità al fumo</td>
<td>1</td>
<td>Emorragia post-partum (≥1000ml)</td>
<td>1</td>
<td>1 (≥1000ml)</td>
<td>1</td>
</tr>
<tr>
<td>Gravidanza Vescicola sensor</td>
<td>1</td>
<td>Parto prematuro (≤3700g) settimane (≤37 e attuale)</td>
<td>1</td>
<td>Morbidi</td>
<td>1</td>
</tr>
<tr>
<td>≥20 anni</td>
<td>1</td>
<td>1 (≥1000ml)</td>
<td>1</td>
<td>Mal</td>
<td>1</td>
</tr>
<tr>
<td>Nota condizione trombofilica e basso rischio (senza TEV)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

#### Punteggio calcolato

<table>
<thead>
<tr>
<th>Rischio emorragico Alto</th>
<th>Baso</th>
<th>(prendere la cosa che interessa)</th>
</tr>
</thead>
</table>

#### Strategia di profilassi (indicare la propria scelta)

<table>
<thead>
<tr>
<th>Punteggio prima del parto</th>
<th>Livello di rischio trombotico</th>
<th>Strategia di profilassi consigliata</th>
<th>Barrare la strategia scelta</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4</td>
<td>Alto</td>
<td>Tromboprofilassi con EBM del 1° trimestre</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Intermedio</td>
<td>Tromboprofilassi con EBM della 2ª settimana</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Baso</td>
<td>Consulenza e monitorizzazione</td>
<td></td>
</tr>
<tr>
<td>2 después del parto</td>
<td>Alto</td>
<td>Consulenza e monitorizzazione</td>
<td></td>
</tr>
<tr>
<td>≤ 3 después del parto</td>
<td>Intermedio</td>
<td>Tromboprofilassi con EBM del 1° trimestre</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Baso</td>
<td>Consulenza e monitorizzazione</td>
<td></td>
</tr>
<tr>
<td>2 después del parto</td>
<td>Alto</td>
<td>Consulenza e monitorizzazione</td>
<td></td>
</tr>
</tbody>
</table>

Data: ______________________

Firma del medico: ______________________

(RCOG Green-top Guidelines n°37a)
MTHFR polymorphism test
The 5,10-methylenetetrahydrofolate reductase (MTHFR) enzyme catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the primary circulatory form of folate, and a cosubstrate for homocysteine remethylation to methionine.
✓ Reduced enzyme activity of MTHFR is a genetic risk factor for hyperhomocysteinemia, especially in the presence of low serum folate levels.

✓ Mild to moderate hyperhomocysteinemia has been identified as a risk factor for venous thrombosis.
Homocysteine and venous thromboembolism—Is there any link?

Hirmerova J, 2013
Abnormal homocysteine metabolism is linked to vascular disease, including endothelial dysfunction, but is hyperhomocysteinemia sufficient to trigger thrombosis?
The role of homocysteine in venous thrombosis has been studied less extensively than its role in arterial diseases and nowadays it seems quite controversial. It is also possible that hyperhomocysteinemia plays a role in the pathogenesis of VTE only as an additional risk factor in the presence of other thrombophilic disorders.

The results of epidemiologic studies are not so clear. Most of them found an association of hyperhomocysteinemia with venous thromboembolism (VTE) but the association was quite weak.

So far, the benefit of lowering homocysteine level in primary and secondary VTE prevention has not been clearly proven.
Currently, there is not enough evidence to support the necessity of testing homocysteine level in VTE patients, neither is sufficient evidence of the benefit of vitamin supplementation in mild or moderate hyperhomocysteinemia. Therefore, such testing and supplementation should be performed only in selected cases.
Guideline: lack of evidence for MTHFR polymorphism testing and homocysteine measurement

✓ The American Congress of Obstetricians and Gynecologists does not recommend the measurement of homocysteine or MTHFR polymorphisms in the evaluation of the etiology of venous thromboembolism.

✓ The British Committee for Standards in Haematology and the British Society for Haematology do not include MTHFR polymorphism testing as part of their clinical guidelines for heritable thrombophilia testing.

✓ The ACMG (American College of Medical Genetics and Genomics) consensus statement on factor V Leiden testing briefly references the limited clinical utility of MTHFR polymorphism testing and that homocysteine measurement may be more informative.
Do not test
Do not test

✓ Testing for heritable thrombophilia in unselected patients presenting with a first episode of venous thrombosis.
✓ Do not test if VTE is provoked by strong risk factors
✓ Testing is not recommended in unselected patients with upper limb venous thrombosis.
✓ Testing is not recommended in patients with central venous catheter (CVC)-related venous thrombosis.
✓ Testing is not indicated in patients with retinal vein occlusion.
Do not test at time of VTE event

Test at completion of anticoagulant therapy for provoked VTE; for unprovoked VTE, test after treatment for acute event if cessation of anticoagulant therapy is contemplated and test results might change management strategy.
Do not test while patient is receiving anticoagulant therapy

Test when VKA has been stopped for at least 2 wk, DOAC has been stopped for at least 2 days (preferably longer), and UFH or LMWH for antithrombin levels has been stopped for more than 24 hr.
Consider testing in patients in whom VTE occurs at a young age in association with weak provoking factors or a strong family history of VTE or in patients who have recurrent VTE.
Repeat testing

There is no benefit in repeating a normal thrombophilia screens. In the event of an abnormal result, requests for confirmatory testing should be limited to the relevant deficiency only.
If you do test

DO’S

DON'TS
Known the 4 P:

– Patient selection
– Patient counseling
– Proper test interpretation
– Provision of education and advice

✓ Don't test while the patient is on anticoagulation
✓ Don't test during an acute thrombosis
Ordering thrombophilia tests is easy….

Determining whom to test and how to use the results is not!