Blood Day for Primary Care

When is a hypercoagulable work up indicated?

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Disclosures

1. Non relevant to this presentation
Objectives

Thrombophilia testing

1. To understand the various tests done with a “thrombophilia work up”

2. To understand that the results of a “thrombophilia work up” rarely has meaningful impact on the management of the patient

3. To appropriately select and refer the patients that may benefit from thrombophilia testing for counseling and perhaps testing
Referral to Hematology: Case 1

49 Male, without risk factor, presented with left MCA stroke

Consultation Form

Key Features Relevant to Question:
Thank you for seeing this young previously healthy 49 y.o. Left handed male with left MCA stroke affecting his right side and speech in Oct. 2012. All tests and stroke w/in to date have been negative. Please see re: possible hypercoaguable cause for his stroke. Enclosed

Thank you in advance, [Assessment or Nurse Clinician for Dr. O. Bas Stroke Clinic HSC]
Interactive Question

Case 1: stroke in young person

• What “thrombophilia work up” is indicated in this patient?
  A) No thrombophilia work up is required
  B) Lupus inhibitor and antiphospholipid IgG and IgM
  C) Factor V Leiden, prothrombin mutation, Protein C, S, AT levels
  D) Both B & C
Referral to Hematology: Case 2

22 year old who is currently 24 weeks pregnant; tested + Factor V Leiden R506Q. Please see ASAP for management in pregnancy.
Case 2: Known thrombophilia during pregnancy

- What type of prophylaxis should she receive based on the result of her Factor V Leiden mutation (FVL)?
  A) None – she should not have been tested for FVL
  B) Unclear but consider 6 weeks post partum prophylaxis with LMWH
  C) She requires both antepartum and postpartum prophylaxis
Introduction

• Venous or arterial thrombosis is encountered commonly in a clinical setting

• Epidemiological studies have identified many phenotypic and genotypic hemostatic variables and demonstrated their association with cardiovascular thrombotic events (both arterial and venous thrombosis)

• *Thrombophilia (or hypercoaguability) refers to increased tendency for the occurrence of thrombosis*

Lowe et al, bjh 2006;133:232-250
Risk factors for arterial thrombosis

• Atherosclerosis
  – Age, smoking, hypertension, hypercholesterolemia, diabetes, calcified aorta (CT or MR angiogram) etc...

• Cardio-embolic
  – Arrhythmia (Holter), structural cardiac disease, left ventricular clot (ECHO)

• Others
  – Heparin induced thrombocytopenia (HIT), paroxysmal hemoglobinuria, myeloproliferative disorders, vasculitis or vascular aneurysm, medications, etc

Antiphospholipid syndrome (APS)

- **Diagnosis:** Needs both clinical & laboratory criteria (Sydney update on Sapporo criteria)
  
  1. **Vascular thrombosis or Pregnancy complications**
     - One or more unexplained fetal deaths at >10 weeks gestation
     - One or more premature births at <34 weeks gestation due to severe preeclampsia, eclampsia, or placental insufficiency
     - Three or more unexplained consecutive spontaneous abortions at <10 weeks gestation (excluding anatomic or chromosomal causes)
  
  2. **Laboratory:** positive on at least 2 occasions and >12 weeks apart
     - Lupus inhibitor
     - Antiphospholipid antibodies
     - Anti-beta 2 GPI antibodies
Controversy exists about treating patients with stroke and APS with ASA vs warfarin.

However, if anticoagulation is stopped, high incidence of VTE seen (up to 70% of patients in some series).

Typically, patients are considered for long term therapy.
“Thrombophilia work up”

Table 1  Thrombophilic conditions and associations

<table>
<thead>
<tr>
<th>Primary (inherited)</th>
<th>Secondary (acquired)</th>
</tr>
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<tbody>
<tr>
<td>Antithrombin deficiency</td>
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<td>Immobility</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>Trauma</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>Postoperative state</td>
</tr>
<tr>
<td>Prothrombin 20210 mutation</td>
<td>Oral contraceptive pill</td>
</tr>
<tr>
<td>Disorders of plasmin generation</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>Dysfibrinogenaemia</td>
<td>Antiphospholipid syndrome</td>
</tr>
<tr>
<td>Hyperhomocysteinaemia*</td>
<td>Hyperhomocysteinaemia</td>
</tr>
<tr>
<td>Increased plasma concentration of fibrinogen and coagulation factors*</td>
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</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
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<tr>
<td></td>
<td>Myeloproliferative disorders</td>
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<td></td>
<td>Haemoglobinuria</td>
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<tr>
<td></td>
<td>Behçet’s disease</td>
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<tr>
<td></td>
<td>Risk of VTE increases with age</td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism.  
*Partly determined by environment.

Thrombophilic defects:
1. Increased plasma levels of coagulation factors (FVL, prothrombin mutation etc)
2. Low plasma levels of coagulation inhibitors (Deficiencies in AT, PrC, PrS)
# Prevalence of inherited thrombophilia

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>% general population</th>
<th>% patients with thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein C deficiency</td>
<td>0.2–0.4</td>
<td>3</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>Not known</td>
<td>1–2</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>0.02</td>
<td>1</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Prothrombin 20210A</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

*Rosendaal et al, Lancet 1999;353:1167-1173*
Current practice: Why order thrombophilia testing?

- Referral laboratory (questionnaires)
- N=2000 (63% returned)
- N=1134 evaluable
  - 60% of testing request is for VTE-related
  - 77% result of test did NOT alter management of tested patient

**Table 1** Reasons for testing for inherited thrombophilia and therapeutic

<table>
<thead>
<tr>
<th>Reasons for testing</th>
<th>%</th>
</tr>
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<tr>
<td>Patients with VTE</td>
<td>41.7</td>
</tr>
<tr>
<td>Single VTE</td>
<td>20.2</td>
</tr>
<tr>
<td>Single VTE + familial predisposition</td>
<td>4.1</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>8.3</td>
</tr>
<tr>
<td>VTE at unusual location</td>
<td>3.7</td>
</tr>
<tr>
<td>Calf vein thrombosis or thrombophlebitis</td>
<td>0.8</td>
</tr>
<tr>
<td>Suspected VTE (before objective testing)</td>
<td>0.8</td>
</tr>
<tr>
<td>VTE + arterial CVD</td>
<td>2.7</td>
</tr>
<tr>
<td>VTE + pregnancy related vascular events</td>
<td>1.1</td>
</tr>
<tr>
<td>Patients with arterial CVD</td>
<td>23.2</td>
</tr>
<tr>
<td>Only arterial cardiovascular event</td>
<td>22.6</td>
</tr>
<tr>
<td>Art CVD + familial predisposition</td>
<td>0.4</td>
</tr>
<tr>
<td>Arterial CVD + pregnancy-related vascular event</td>
<td>0.2</td>
</tr>
<tr>
<td>Patients with pregnancy-related vascular events</td>
<td>17.0</td>
</tr>
<tr>
<td>Pregnancy loss (single or recurrent)</td>
<td>8.7</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>5.6</td>
</tr>
<tr>
<td>Pre-eclampsia or HELLP syndrome</td>
<td>2.2</td>
</tr>
<tr>
<td>Intrauterine growth retardation</td>
<td>0.5</td>
</tr>
<tr>
<td>Asymptomatic individuals with familial predisposition</td>
<td>16.0</td>
</tr>
<tr>
<td>Known family carrier</td>
<td>9.5</td>
</tr>
<tr>
<td>Only familial thrombotic disease</td>
<td>6.5</td>
</tr>
<tr>
<td>Reason not remembered</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*Coppens et al, J Thromb Haemost 2007;5(9):1979*
Thrombophilia testing: in the *symptomatic* patients – why do it?

1. To establish the pathologic basis for their VTE
2. To influence duration of therapy based on the predicted risk of recurrent VTE (secondary prevention)
3. To identify a heritable condition within the family (family screening)

*Lowe et al*, bjh 2006;133:232-250
1. Thrombophilia testing: To establish the pathologic basis for their VTE:

VTE is *multi-causal* disease (Virchow’s triad)

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<tr>
<td>Heparin-induced thrombocytopenia</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Paroxysmal nocturnal haemoglobinuria</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Behçet’s disease</td>
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VTE, venous thromboembolism.

*Partly determined by environment.
2. **Thrombophilia testing: To predict risk of recurrent VTE (and to extend anticoagulation to reduce recurrent clot)**

- Clinical setting is the **best** predictor for VTE recurrence
  
  *Baglin et al*, Lancet 2003;362:523-526

- Thrombophilia status did **not** influence the risk of recurrent VTE after discontinuation of anticoagulation
  
  *Christiansen et al*, JAMA 2005;293:2352-61
Clinical setting is the **best** predictor for VTE recurrence

- Prospective, unselected cohort of patients with 1st VTE (excluded APS, cancer, unusual site thrombosis)
  - N = 520
    - 137/487 (28%) had identifiable defects and 40 patients (7.7%) with a “strong” defect (AT, PrC, PrS deficient)
    - Divided into 4 groups:
      - **Group A**: major transient risk factor
      - **Group B**: Pregnancy related
      - **Group C**: idiopathic
      - **Group D**: non-surgical RF (cast, OCP, immobilization/travel/hospitalization)
  - All stopped warfarin at median of 6 months
  - Follow up = 2 years
  - No recurrence in Group B (pregnancy related)

*Idiopathic* 19%

*Non-surgical RF*

*Major transient RF*

*Baglin et al, Lancet 2003;362:523-526*
Thrombophilia status did NOT influence the risk of recurrent VTE after discontinuation of anticoagulation

Thrombophilia status did NOT influence the risk of recurrent VTE after discontinuation of anticoagulation

- Prospective, unselected cohort of patients with 1\textsuperscript{st} VTE (excluded cancer, age>70)
- N = 474 patients with longer follow up (mean 7.3 years)
  - 329/474 (67%) had at least “some” lab abnormality (25% with FVL, prothrombin and 5% had “strong” defects)

*Christiansen et al, JAMA 2005;293:2352*
Common thrombophilias do NOT predict risk of recurrent VTE

- **Conclusion based on *prospective* studies:**
  - Common heritable thrombophilia do not greatly influence risk of VTE recurrence

- **Limitations:**
  1. No RCTs to directly answer this question
  2. Short follow up (incidence of VTE recurrence continues to increase up to 10 years)
  3. Patients with rare defects but stronger thrombophilic potential were too small in numbers (~5%; i.e., not powered to detect a difference)
     - Homozygous FVL
     - Compound heterozygous (FVL/G20210A mutation)
     - Deficiencies in AT/PC/PS
Thrombophilia testing in asymptomatic individuals to identify a heritable condition within the family

- **Advantages:**
  - Knowledge leads to heightened awareness → seek medical advice earlier with symptoms
  - Opportunity to avoid risk factors: estrogen, immobilization
  - Opportunity to receive primary prophylaxis for unavoidable risk factors (surgery, pregnancy)

- **Disadvantages**
  - **Proband:**
    - May result in over-investigation, prophylaxis and treatment of the proband
  - **Relatives:**
    - Result in general unwellness (“unchangable”)
    - Denied insurance for predisposing condition
    - May result in over-investigation, prophylaxis and treatment of the asymptomatic relatives if tested positive
    - May result in false “reassurance” if tested negative
Asymptomatic carrier – OCP-associated VTE is avoidable but at the increased risk of pregnancy-associated VTE

Table 3. Comparison of thrombosis outcome in women with factor V Leiden or prothrombin G20210A, or a combination of these defects (including homozygosity)

<table>
<thead>
<tr>
<th>Defects</th>
<th>COC</th>
<th>LNG-IUD</th>
<th>Copper IUD (380 mm²)</th>
<th>Condom*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of first VTE per 100 pregnancy-years</td>
<td>0.55†</td>
<td>0.25‡</td>
<td>0.25‡</td>
<td>0.25‡</td>
</tr>
<tr>
<td>Cases of VTE per 100 000 pregnancy-years</td>
<td>550</td>
<td>250</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>Contraceptive failure rate, per 100 women-years§</td>
<td>0.2</td>
<td>0.7</td>
<td>1.4</td>
<td>12</td>
</tr>
<tr>
<td>Unintended pregnancies per 100 000 pregnancy-years</td>
<td>200</td>
<td>700</td>
<td>1400</td>
<td>12 000</td>
</tr>
<tr>
<td>Incidence of VTE per 100 pregnancy-years¶</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Additional cases of VTE</td>
<td>6</td>
<td>20</td>
<td>40</td>
<td>336</td>
</tr>
<tr>
<td>Total number of VTE</td>
<td>556</td>
<td>270</td>
<td>290</td>
<td>586</td>
</tr>
</tbody>
</table>

Vlijmen et al, Blood 2011;25:2055
Can antepartum prophylaxis reduce risk?

Multi-centre RCT included patients with:
(1) known thrombophilia (including APS)
(2) High risk for pregnancy related complications (including prior history of provoked VTE, APS or positive family history)
• All patients received postpartum prophylaxis for 6 weeks
Outcome assessments:
(1) Primary composite outcomes: symptomatic VTE, preeclampsia/eclampsia, loss
(2) Secondary outcomes: major and minor bleeding
Can antepartum prophylaxis reduce risk?

- Primary composite outcome
  - No difference (17% vs 19%)

- Bleeding
  - No difference in major bleeding but increased minor bleeding in the antepartum prophylaxis arm (19% vs 9%, p=0.01)

Rodger et al, Lancet July 2014
When is THROMBOPHILIA TESTING (HYPERCOAGULABLE WORK-UP) Indicated?

**Practice Points:** Thrombophilia testing = Hypercoagulable work-up (estimated cost $1000.)
- Acquired: lupus inhibitor, antiphospholipid antibodies (IgG, IgM) = APLA, +/- high FVIII levels?
- Inherited: Factor V Leiden, Prothrombin mutation, Protein C, S and antithrombin deficiency

**When is Thrombophilia Testing Indicated?**
1. When the results will influence the management of the patients or their family OR
2. Patients’ preference for knowledge (after informed consent)

**Unprovoked or Idiopathic:** indicates that no alternative explanation for clot AFTER appropriate history, physical and work up has been completed (depending on the clinical situation) – see examples of possible explanations/risk factors as listed below

**Recognized Causes of Arterial Clot:**
- Atherosclerosis (age, smoking, hypertension, hypercholesterolemia, diabetes, calcified aorta etc)
- Cardiogenic (arrhythmia, left ventricular clot, structural cardiac disease)
- Other secondary causes (heparin induced thrombocytopenia, paroxysmal hemoglobinuria, vasculitis, OCP, etc)

**Recognized Causes of Venous Clot:**
- Major provoked events: post operative state or trauma (within 4 weeks), immobilization (casting, hospitalization, bed ridden), active cancer/chemotherapy drugs (esp. estrogen containing contraception, HRT)
- Recurrent pregnancies lost: > 3 first trimester losses or 1 or more stillbirth (spontaneous, normal anatomy, no chromosomal anomalies or infection)

**Flowchart:***
- Has the patient had an arterial or venous clot?
  - Yes, Was the clot unprovoked?
    - Yes, Antiphospholipid syndrome (APS)
    - No, Testing not indicated
  - No, Any history of unexplained* recurrent lost pregnancies?
    - Yes, Antiphospholipid syndrome (APS)
    - No, Any family history of idiopathic* arterial/venous clot or both? Or known thrombophilia?
      - Yes, Referral to CCMB Hematology for counseling & decide if testing should change patient management or be done based on patients’ preference
      - No, No thrombophilia testing
        - Was the event(s) arterial or venous or both?
          - Yes, Is there consideration for estrogen therapy or pregnancy?
            - Yes, No thrombophilia testing. Need to screen/optimize risk factors for arterial clot or venous clot
            - No, Referral to CCMB Hematology for counseling & decide if testing should change patient management or be done based on patients’ preference
          - No, Referral to CCMB Hematology for counseling regarding ASA + peripartum heparin
          - Venous Clot or both or known thrombophilia
            - No, Referral to CCMB Hematology for counseling & decide if testing should change patient management or be done based on patients’ preference
            - Yes, Antiplatelet
          - Arterial Clot

Pathways are subject to clinical judgment and actual practice patterns may not always follow the proposed steps in this pathway.
Rationale for Referral and Decisions Made for THROMBOPHILIA TESTING

Estrogen associated venous clot?

- Test for acquired defects: lupus inhibitor & APLA
- If #1 positive → Must repeat testing 12 weeks later

Unprovoked venous clot?

- Any high risk features?
  1. Males OR
  2. Females with 2 or more of the following:
     - Hyperpigmentation, edema, redness,
     - positive D-dimer, age >65, BMI >30

Any high risk features?

- Yes
- No

Antiphospholipid syndrome (APS)

1. 30% risk of recurrence clot if discontinued anticoagulation
2. Consider indefinite anticoagulation

1. Intermediate risk of 2nd recurrence (~10%)
2. Anticoagulate for 3 months and stop if estrogen can be safely discontinued. If not, consider referral for advice to balance the risk of clotting/bleeding/unwanted pregnancy, etc

1. Variable risk of recurrence clot if discontinued anticoagulation (5-20%)
2. Consider patient's preference to decide regarding duration of anticoagulation (6 months versus indefinite)
3. Do inherited thrombophilia work up if the results will aid in patient's decision making or due to patients' preference

Problems “false reassurance” - still at increased risk compared to general population (~0.1% VTE per year)

Absolute risk is dependent on the actual defect found
- FVL/prothrombin mutation: 0.4% VTE per year
- Protein C or S deficiency: 1% VTE per year
- Antithrombin deficiency: 4% VTE per year

If above defects found AND starting OCP – increase RR 2-4
- **~300 women need to avoid OCP in order to prevent 1 VTE (at cost of other complications such as unwanted pregnancy/pregnancy associated VTE)
- **As such, thrombophilia is NOT an absolute contraindication for OCP but requires counselling

All pregnant women with a family history of unprovoked thrombosis or thrombophilia should be considered for postpartum prophylaxis for 6 weeks

Family history of Unprovoked arterial/venous clot or both OR known thrombophilia?

AND

- Consideration for estrogen therapy or pregnancy?
- Consider testing for inherited thrombophilia to decide avoidance of OCP and/or peripartum thrombophylaxis
- NO

- YES
49 Male without any risk factor presented with left MCA stroke

Choice: A – no thrombophilia work up is required
22 years old who is currently 24 weeks pregnant, tested + Factor V Leiden R506Q. Please see ASAP for management in pregnancy.

Choice B: Unclear but consider 6 weeks post partum prophylaxis with LMWH
Take Home Messages

Thrombophilia testing: *who to refer and why?*

1. Patients with **unexplained** arterial clot $\rightarrow$ test for APS and refer for advice regarding antiplatelet versus anticoagulant therapy

2. Patients with **unprovoked** venous clot $\rightarrow$ refer for counseling regarding optimal duration of anticoagulation and whether testing should influence this decision

3. **Asymptomatic** patients with a strong family history of clotting disorder or known thrombophilia: an **informed decision** needs to be made regarding OCP/pregnancy
Questions?

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