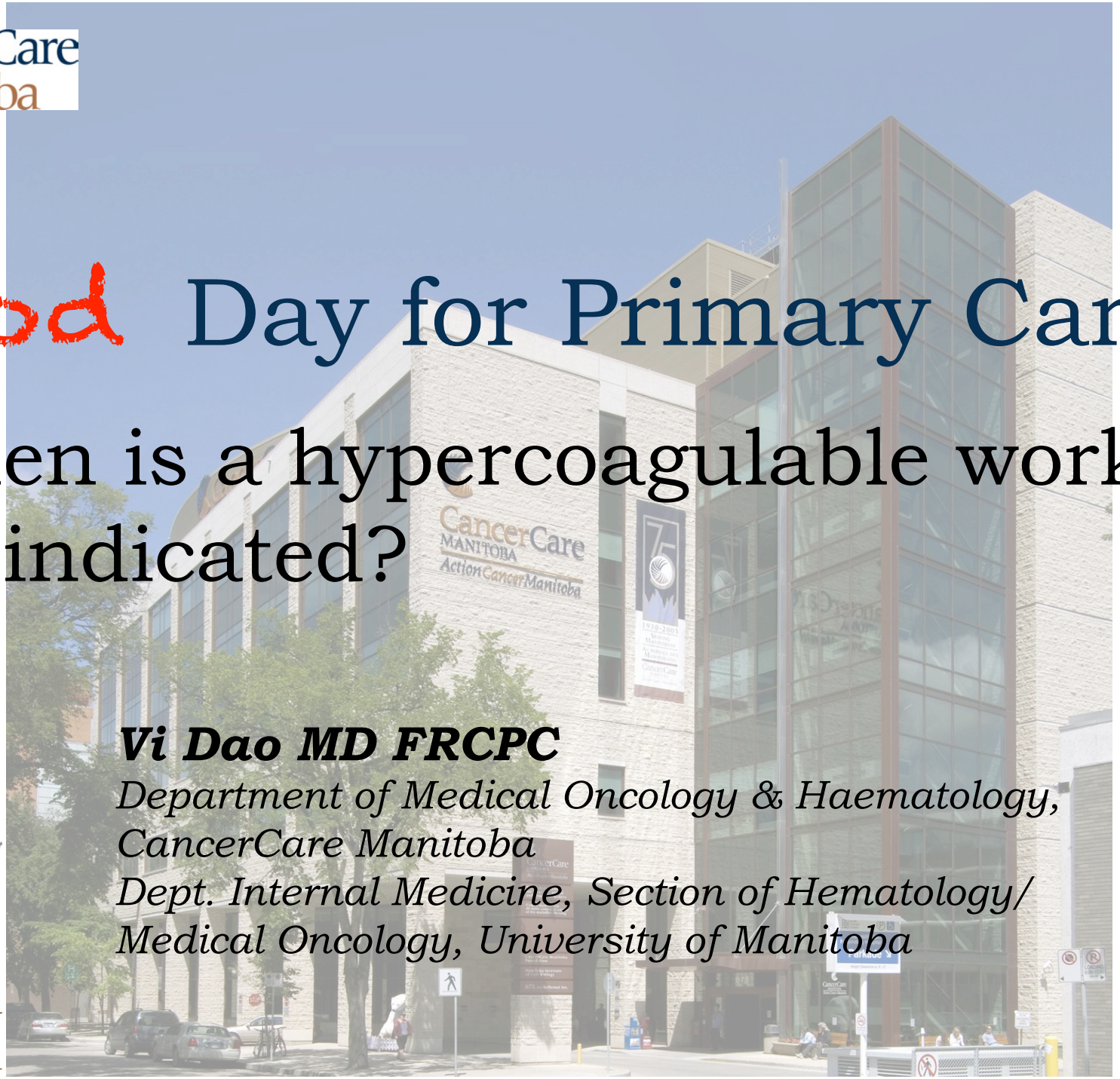


Blood Day for Primary Care

When is a hypercoagulable work up indicated?

Vi Dao MD FRCPC
Department of Medical Oncology & Haematology, CancerCare Manitoba
Dept. Internal Medicine, Section of Hematology/ Medical Oncology, University of Manitoba

Disclosures

1. Non relevant to this presentation

Objectives

Thrombophilia testing

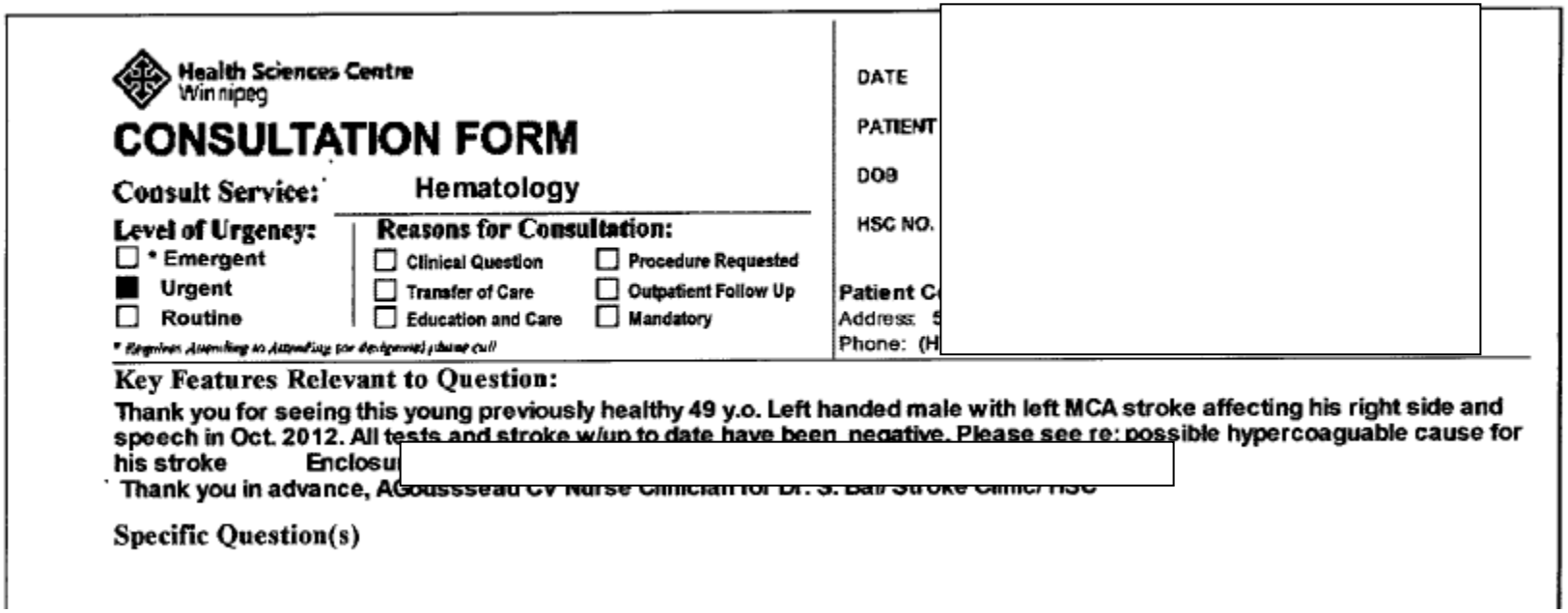
1. To understand the various tests done with a "thrombophilia work up"

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



Health Sciences Centre
Winnipeg

CONSULTATION FORM

Consult Service: Hematology

Level of Urgency:
- ☐ * Emergent
- ■ Urgent
- ☐ Routine

Reasons for Consultation:
- ☐ Clinical Question
- ☐ Procedure Requested
- ☐ Transfer of Care
- ☐ Outpatient Follow Up
- ☐ Education and Care
- ☐ Mandatory

DATE

PATIENT

DOB

HSC NO.

Patient C
Address: 5
Phone: (H

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/up to date have been negative. Please see re: possible hypercoaguable cause for his stroke Enclosu

Thank you in advance, A

Specific Question(s)

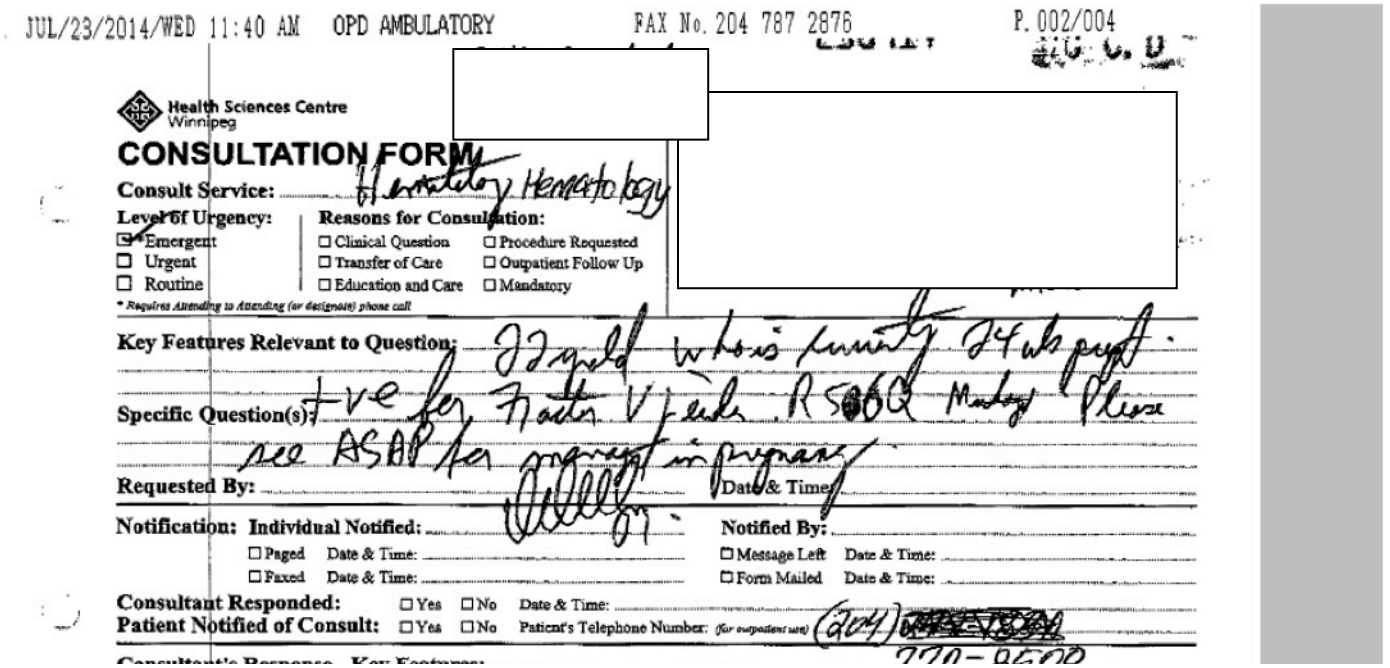
Interactive Question

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.



JUL/23/2014/WED 11:40 AM OPD AMBULATORY FAX No. 204 787 2876 P. 002/004

Health Sciences Centre Winnipeg

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* Requires Attending to Attending (or designate) phone call

Key Features Relevant to Question: 22 yr old who is currently 24 wks preg.

Specific Question(s): +ve for Factor V Leiden R506Q Mutation Please see ASAP for management in pregnancy

Requested By: Date & Time:

Notification: **Individual Notified:** **Notified By:**
- ☐ Paged Date & Time:
- ☐ Faxed Date & Time:
- ☐ Message Left Date & Time:
- ☐ Form Mailed Date & Time:

Consultant Responded: ☐ Yes ☐ No Date & Time:

Patient Notified of Consult: ☐ Yes ☐ No Patient's Telephone Number: (For outpatient use) (204)

Interactive Question

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

Allen, Int J Stroke, 2008

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

Stroke & antiphospholipid 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

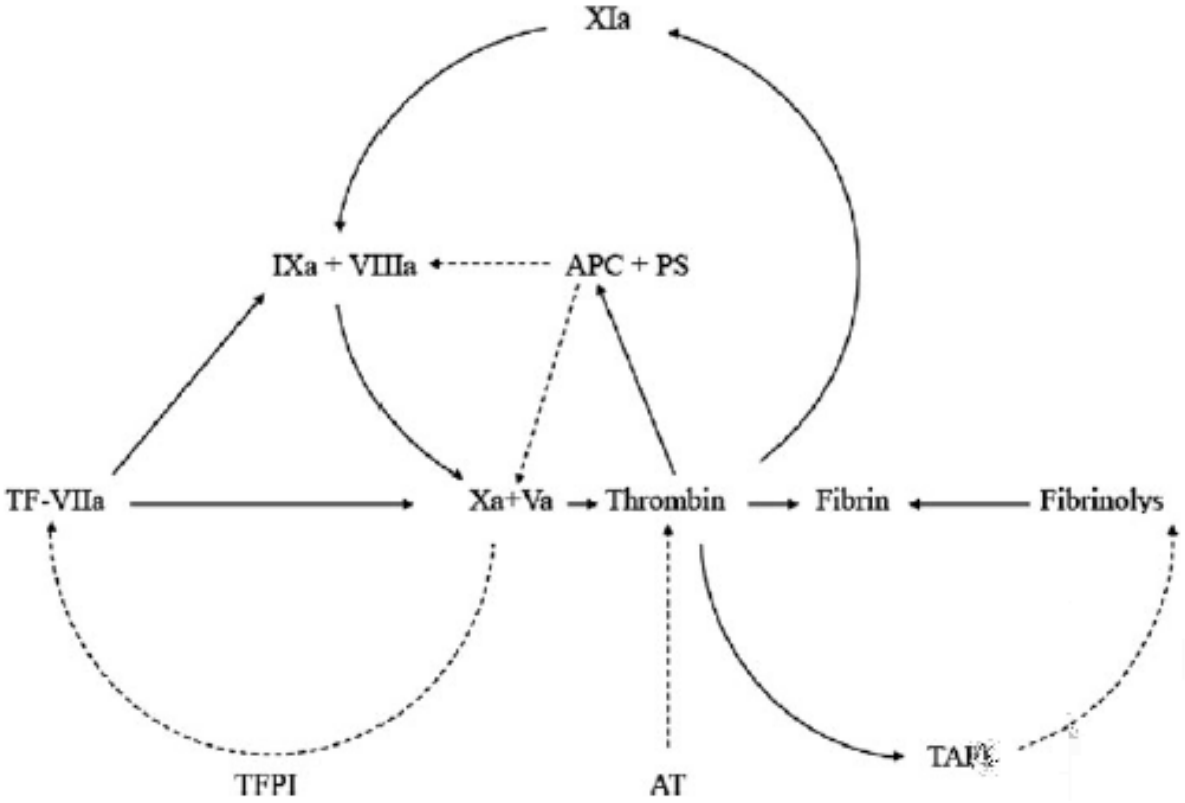
Primary (inherited)	Secondary (acquired)
Antithrombin deficiency	Pregnancy
Protein C deficiency	Immobility
Protein S deficiency	Trauma
Factor V Leiden	Postoperative state
Prothrombin 20210 mutation	Oral contraceptive pill
Disorders of plasmin generation	Hormone replacement therapy
Dysfibrinogenaemia	Antiphospholipid syndrome
Hyperhomocysteinaemia*	Hyperhomocysteinaemia
	Malignancy
Increased plasma concentration of fibrinogen and coagulation factors*	Nephrotic syndrome
	Myeloproliferative disorders
	Heparin-induced thrombocytopenia
	Paroxysmal nocturnal haemoglobinuria
	Behçet's disease
	Risk of VTE increases with age

VTE, venous thromboembolism.
*Partly determined by environment.

High FVIII levels

Merriman et al, Postgrad Med J 2006;82:699-704

Simplified scheme of coagulation & fibrinolysis



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

Risk factor	% general population	% patients with thrombosis
Protein C deficiency	0·2–0·4	3
Protein S deficiency	Not known	1–2
Antithrombin deficiency	0·02	1
Factor V Leiden	5	20
Prothrombin 20210A	2	6

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

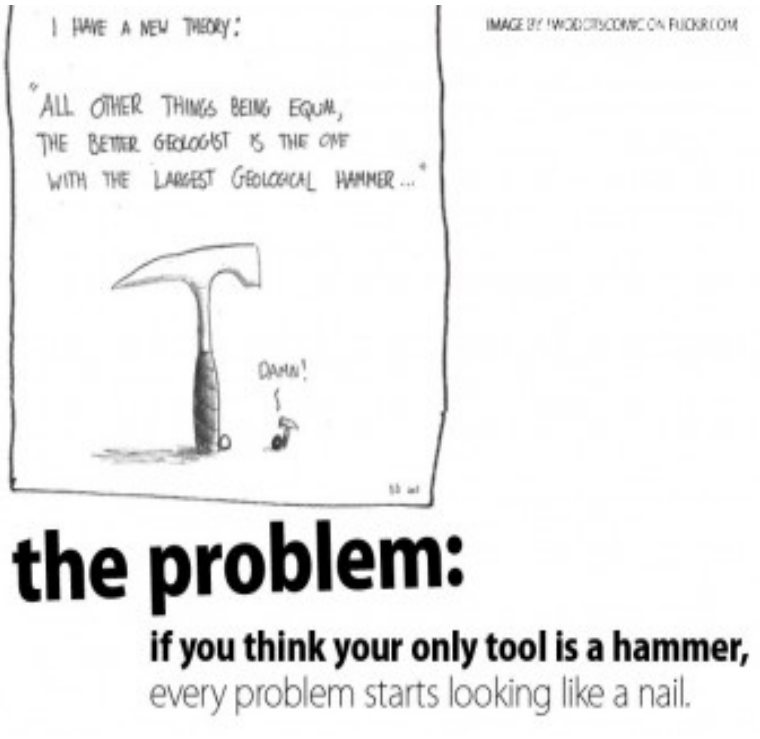
Table 1 Reasons for testing for inherited thrombophilia and therapeutic

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

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 identified 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)

Table 1 Thrombophilic conditions and associations

Primary (inherited)	Secondary (acquired)
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Protein C deficiency	Immobility
Protein S deficiency	Trauma
Factor V Leiden	Postoperative state
Prothrombin 20210 mutation	Oral contraceptive pill
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	Behçet's disease
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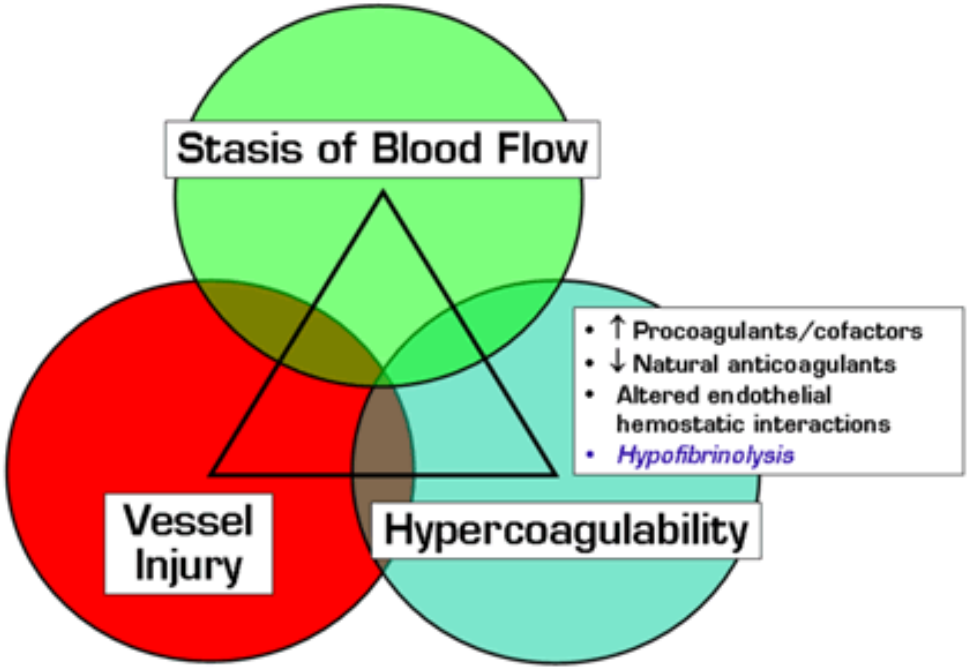
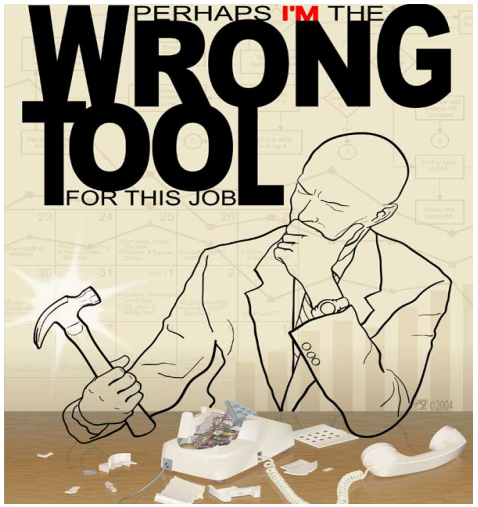


2. *Thrombophilia testing: To predict risk of recurrent VTE (and to extend anticoagulation to reduce recurrent clot)*

P-M469.

Cohn 2008

Cohn DM, Middeldorp S. Early termination of the multicentre randomised clinical trial to evaluate the benefit of testing for thrombophilia following a first venous thromboembolism: the NOSTRADAMUS study. *Nederlands Tijdschrift Voor Geneeskunde* 2008;**152**(38): 2093–4.



- Clinical setting is the best predictor for VTE recurrence

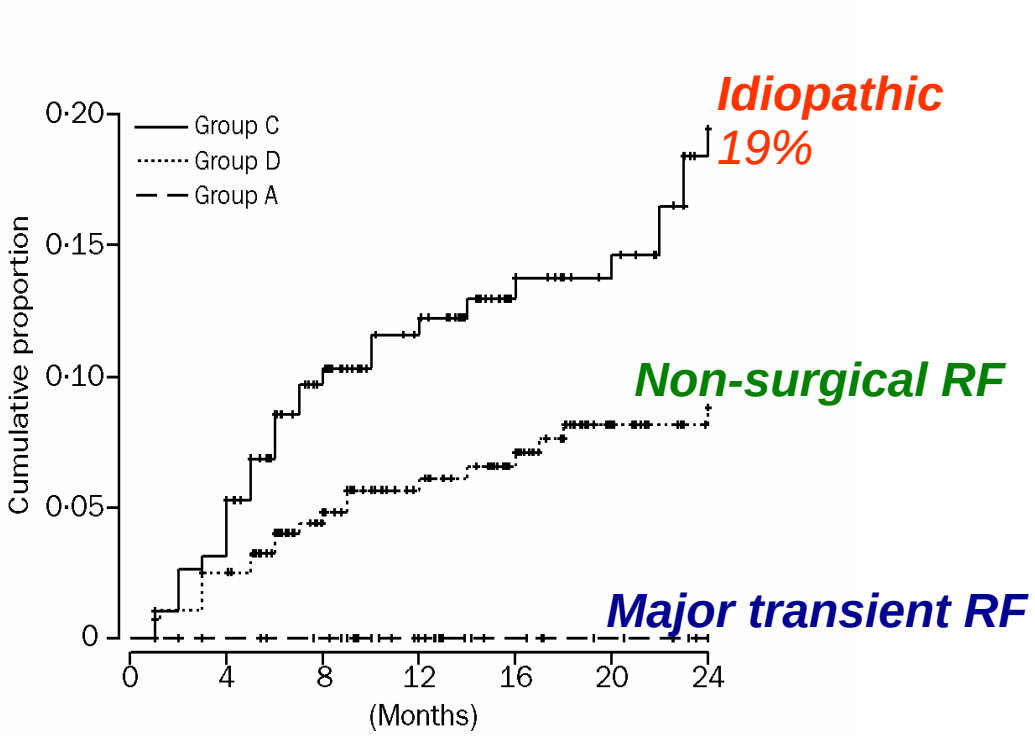
  Baglin et al, Lancet 2003;362:523-526

- 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)



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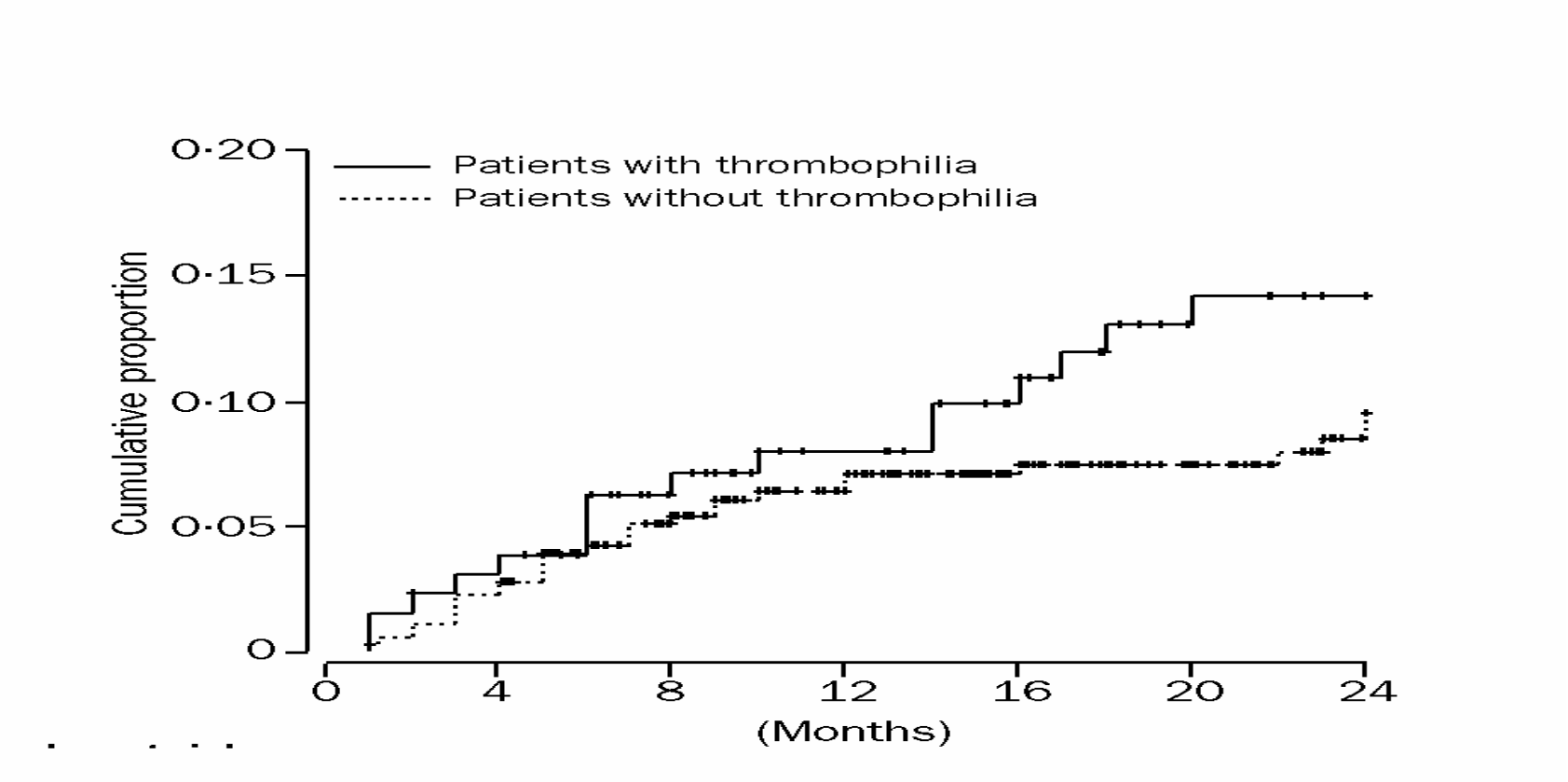
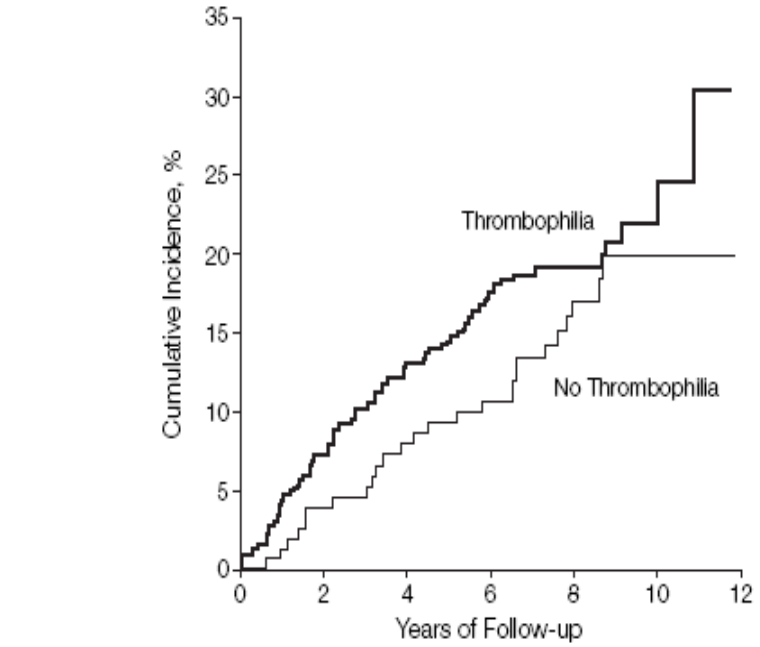


Baglin et al, Lancet 2003;362:523-526

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

- Prospective, unselected cohort of patients with 1st 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)

	Defects				No defects			
	COC	LNG-IUD	Copper IUD (380 mm²)	Condom*	COC	LNG-IUD	Copper IUD (380 mm²)	Condom*
Incidence of first VTE per 100 pregnancy-years	0.55†	0.25‡	0.25‡	0.25‡	0.19	0.09	0.09	0.09
Cases of VTE per 100 000 pregnancy-years	550	250	250	250	190	90	90	90
Contraceptive failure rate, per 100 women-years§	0.2	0.7	1.4	12	0.2	0.7	1.4	12
Unintended pregnancies per 100 000 pregnancy-years	200	700	1400	12 000	200	700	1400	12 000
Incidence of VTE per 100 pregnancy-years¶	2.8	2.8	2.8	2.8	0.7	0.7	0.7	0.7
Additional cases of VTE	6	20	40	336	2	5	10	84
Total number of VTE	556	270	290	586	192	95	100	174

Vlijmen et al, Blood 2011;25:2055

Can antepartum prophylaxis reduce risk?

Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial

Marc A Rodger, William M Hague, John Kingdom, Susan R Kahn, Alan Karovitch, Mathew Sermer, Anne Marie Clement, Suzette Coat, Wee Shian Chan, Joanne Said, Evelyne Rey, Sue Robinson, Rshmi Khurana, Christine Demers, Michael J Kovacs, Susan Solymoss, Kim Hinshaw, James Dwyer, Graeme Smith, Sarah McDonald, Jill Newstead-Angel, Anne McLeod, Meena Khandelwal, Robert M Silver, Gregoire Le Gal, Ian A Greer, Erin Keely, Karen Rosene-Montella, Mark Walker, Philip S Wells, for the TIPPS Investigators

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)

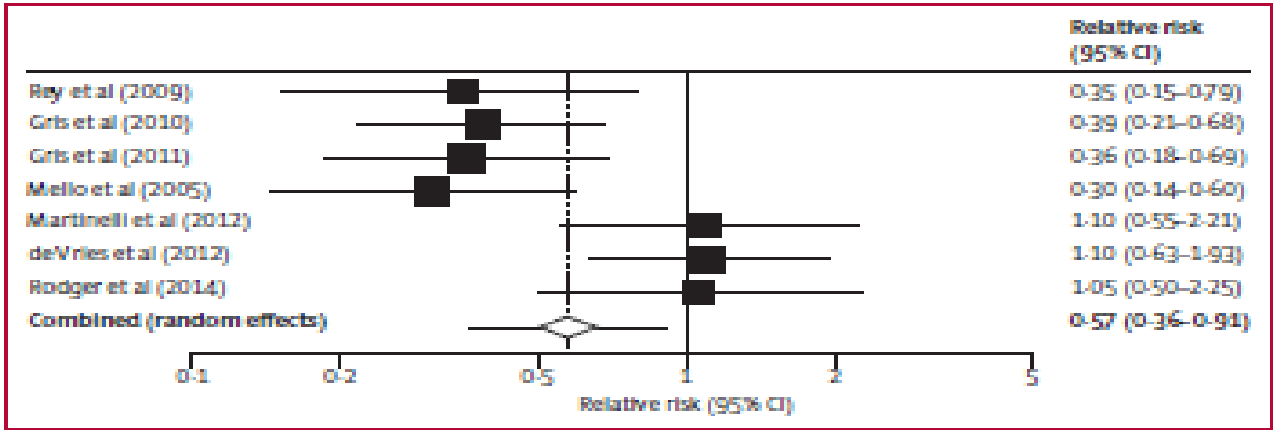


Figure 3: Meta-analysis of published randomised trials assessing the relative risk reduction (random effects) of recurrent placenta-mediated pregnancy complications with low-molecular-weight heparin in women with previous placenta-mediated pregnancy complications

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

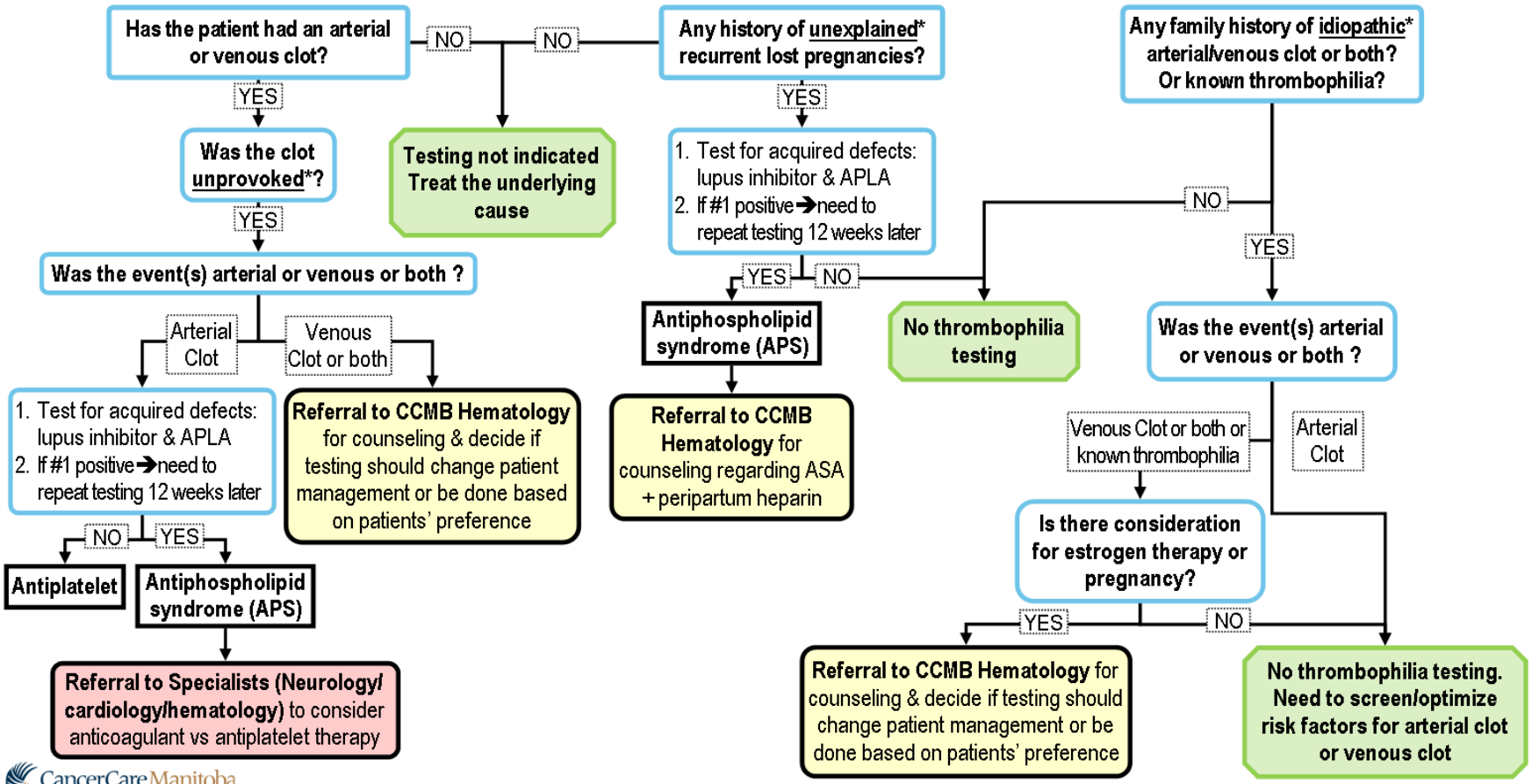
Recognized Causes of Arterial clot:

- atherosclerosis (age, smoking, hypertension, hypercholesterolemia, diabetes, calcified aorta etc)
- cardioembolic (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)

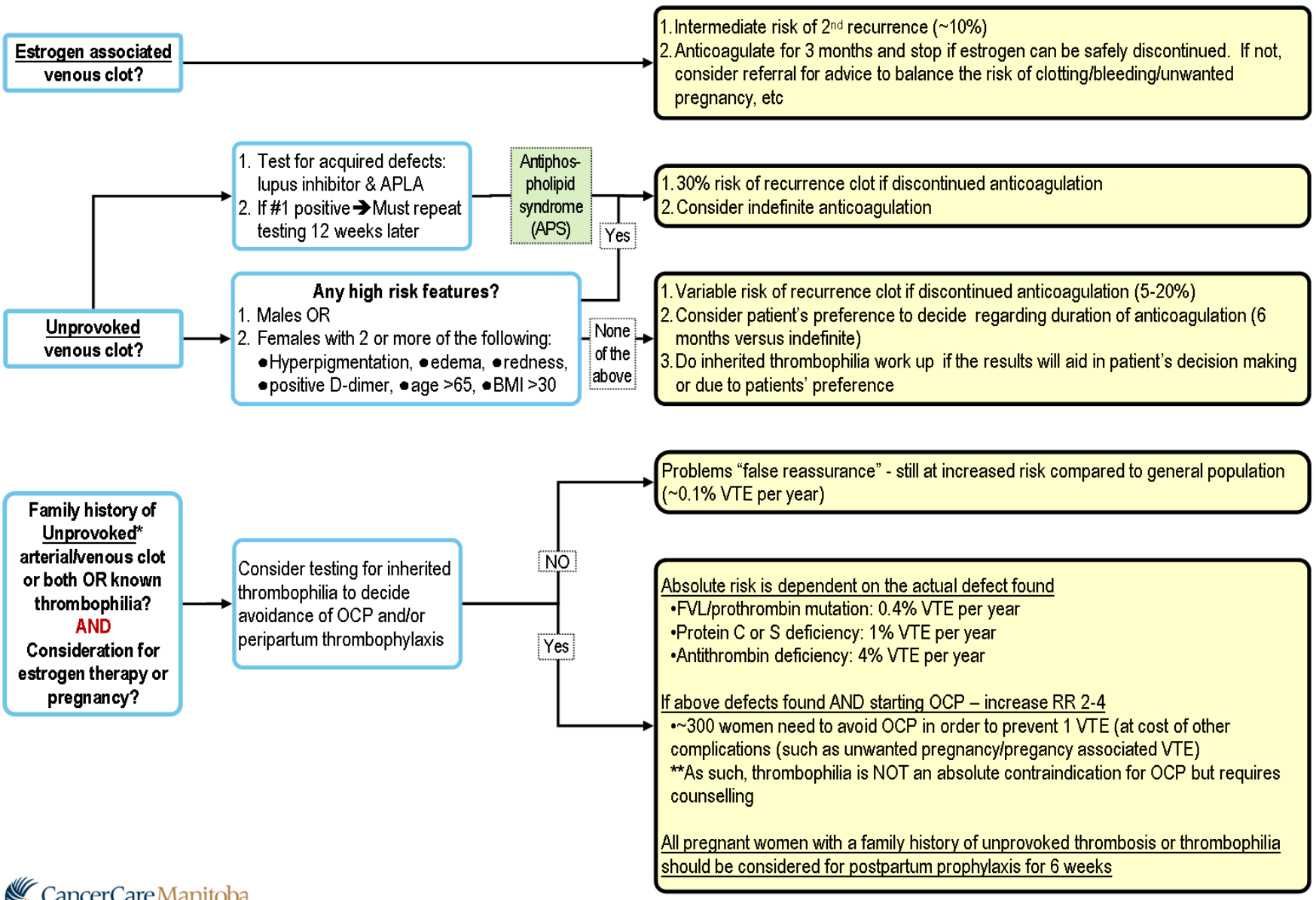


CancerCare Manitoba
ActionCancerManitoba

Feb.6, 2015: ©Hematology DSG FINAL (Dao)

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



CancerCare Manitoba
ActionCancerManitoba

Referral to Hematology: Case 1

49 Male without any risk factor presented with left MCA stroke

Choice: A – no thrombophilia work up is required

Health Sciences Centre
Winnipeg

CONSULTATION FORM

DATE

PATIENT

DOB

HSC NO.

Consult Service: Hematology

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- ☐ Education and Care
- ☐ Mandatory

Patient C
Address:
Phone: (H

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/up to date have been negative. Please see re: possible hypercoaguable cause for his stroke Enclosu

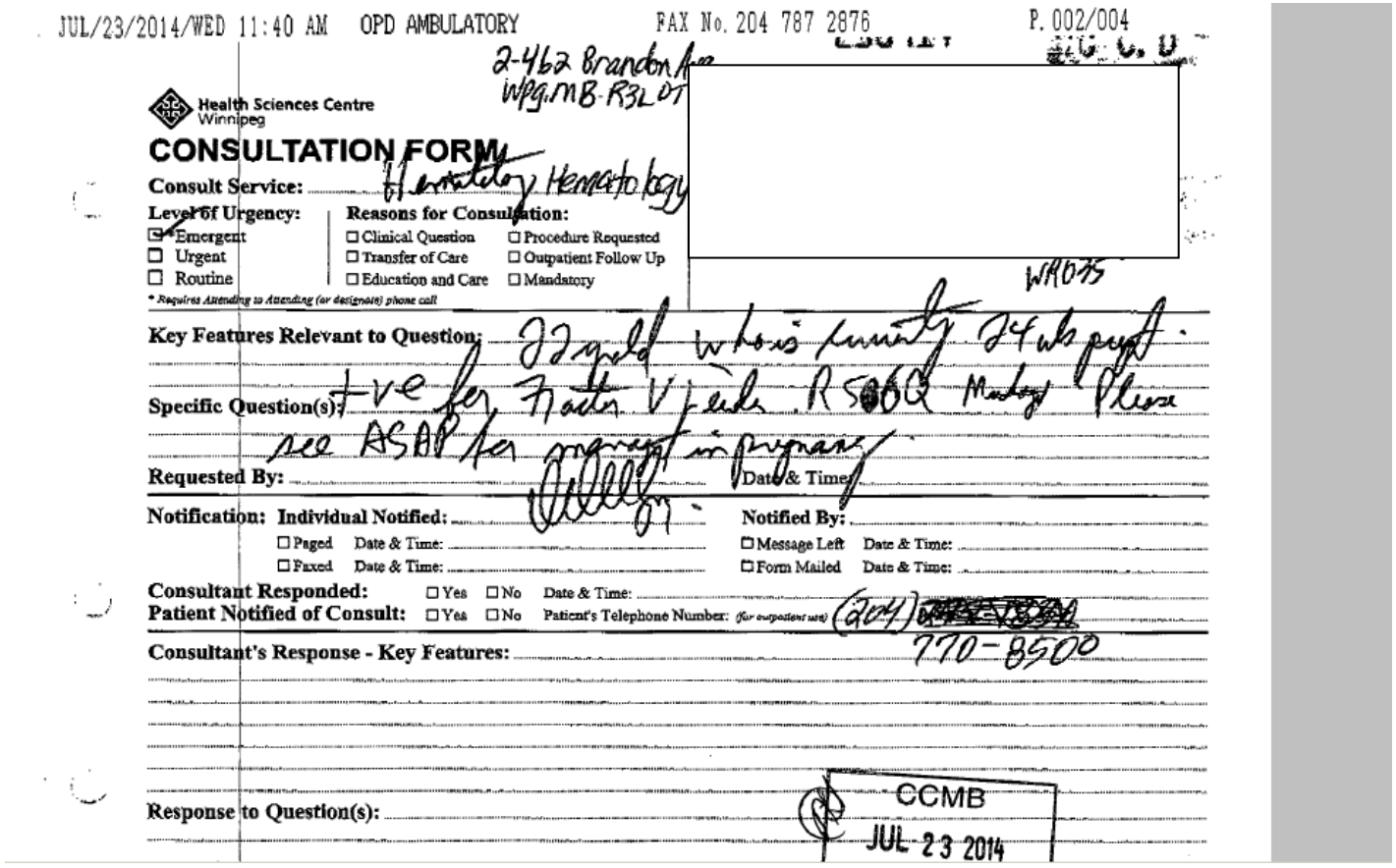
Looking at his CT angiogram I presume the mechanism of his stroke could be cervical artery dissection. The calibre of the cervical internal carotid artery is very small on the left side in comparison to the right side although there are no signs to suggest double lumen or other features. The other possibility could be vascular abnormality affecting the internal carotid artery. In view of absence of hypertension, other associated systemic symptoms or significant past history it is difficult to ascertain this cause. I would review this CT angiogram with radiologist and would plan an MRI with MR angiogram which may give us a better idea about the cross sectional lumen of the Internal Carotid artery. The small caliber of the

Photo / image caption in a differentiated font, placed under image box.

Referral to Hematology: Case 2

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



JUL/23/2014/WED 11:40 AM OPD AMBULATORY FAX No. 204 787 2876 P. 002/004

2-462 Brandon Ave
Winnipeg MB R3L 0T

Health Sciences Centre Winnipeg

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WHOSS

* Requires Attending to Attending (or designate) phone call

Key Features Relevant to Question: 22 yr old who is currently 24 wks pregnt.

Specific Question(s): +ve for Factor V Leiden R506Q Mutation Please see ASAP for management in pregnancy.

Requested By: Date & Time:

Notification: **Individual Notified:** **Notified By:**
- ☐ Paged Date & Time:
- ☐ Faxed Date & Time:
- ☐ Message Left Date & Time:
- ☐ Form Mailed Date & Time:

Consultant Responded: ☐ Yes ☐ No Date & Time:

Patient Notified of Consult: ☐ Yes ☐ No Patient's Telephone Number: (for outpatient use) (204) [redacted] 770-8500

Consultant's Response - Key Features:

Response to Question(s):

CCMB
JUL 23 2014

Take Home Messages

Thrombophilia testing: *who to refer and why?*

1. Patients with unexplained arterial clot → test for APS and refer for advice regarding antiplatelet versus anticoagulant therapy

2. Patients with unprovoked venous clot → 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 thrombophiliad: an informed decision needs to be made regarding OCP/pregnancy

Questions?

Vi Dao
v.dao@cancercare.mb.ca