Thrombophilias: A Practical Approach

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Disclosures

- Speaker's Bureau: BMS/Pfizer (Apixaban)
- PI→ Altru Health System: EVE Trial→ Apixaban in Malignancy

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Objectives:

- Define and introduce the "Thrombophilias"
- Recognize that thrombophilia status plays a relatively minor role in the long term management of VTE
- Provide guidance on when to order testing…and when NOT to!
- Recognize the nuances of test interpretation
- Recognize the burgeoning literature RE: DAOC use in antiphospholipid syndrome (APS)

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Thrombophilia defined:

- Abnormality of blood coagulation that increases the risk of thrombosis
  - Classically, the "heritable" conditions + APS
  - VTE but in some circumstances, arterial thrombosis as well
- Hypercoagulable state vs. Thrombophilia:
  - All thrombophilias are hypercoagulable states.
  - Not all hypercoagulable states are thrombophilias
  - Hypercoagulable state = "umbrella" over anything that can potentially increase the risk of VTE
    - Thrombophilia = subtype of hypercoagulable state.

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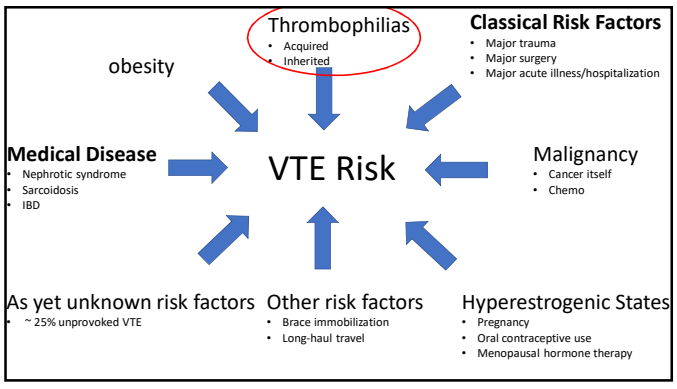

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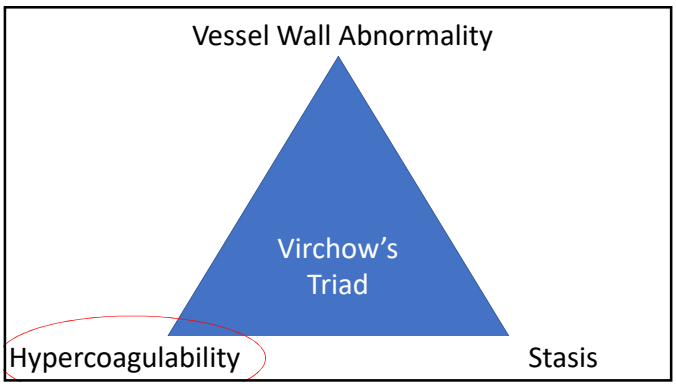

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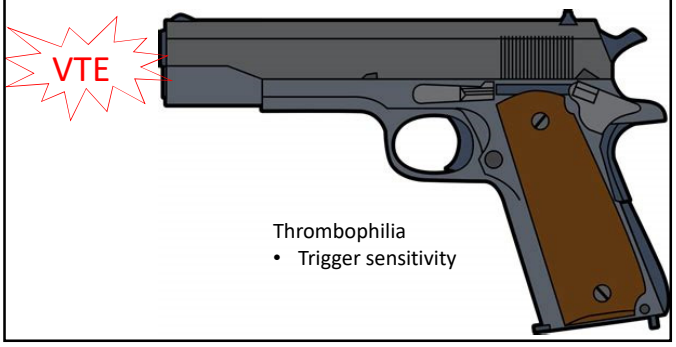
Risk Factors



Thrombophilia
- Trigger sensitivity

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Major Thrombophilias

Inherited
- Natural anticoagulant deficiencies
  - Antithrombin deficiency
    - Type I and II
  - Protein C deficiency
    - Type I, III, III
  - Protein S deficiency
    - Type I and II
- "Gain of function" mutations
  - Leiden factor five
    - Heterozygous and homozygous
  - Prothrombin gene mutation
    - Heterozygous and homozygous
  - "Double Heterozygote"

Acquired
- Antiphospholipid Antibody Syndrome
  - Anticardiolipin antibodies
  - Beta 2, Glycoprotein I antibodies
  - Lupus anticoagulant

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Inconclusive Thrombophilias

- MTHFR mutation
  - Very common
    - 45% of the world's population is heterozygous
      - 10% homozygous
  - Although mutations MAY increase Homocyst[illegible] levels, it has not been shown to increase the risk of 1st or recurrent VTE
    - Many other causes of elevated homocysteine: CKD, ETOH, hypothyroidism, drugs…
  - If Homocysteine elevated, Rx [illegible] – NO change in thrombotic risk…
- Homocystinuria: exceptionally severe dz in the young→ VTE and Vascular dz.
  - CBS deficiency→ rare!
  - Unclear clinical relevance
- Others: All either not conclusively a/w risk OR need further validation!
  - elevated FVIII, IX, XI activity, fibrinogen level
  - Anti-phosphatidyl ethanolamine/serine antibodies
  - PAI-1 elevation or 4G/5G PAI-1 promotor polymorphism

Don't order

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The Players…

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Gain of Function Polymorphisms: Factor V Leiden

- Most common thrombophilia, thus well characterized epidemiology
- Considerable variability in prevalence by ethnic origin
  - White Europeans highest; almost unheard of in Asians and sub-Saharan Africa
- Cause: mis-sense point mutation G1691A→ activated FV (a clotting factor) inactivated 10 fold SLOWER than normal by activated Pro C→ increased thrombin!!
  - Autosomal dominant→ 50% chance for 1st degree relatives to be +
- 3-5 fold increased risk of VTE throughout life (10 fold if homozygous)
- Does NOT increase risk of VTE recurrence!
- Absolute risk remains low, with only 5% having clot by age 65
- 20% of all 1st unprovoked VTE are positive
  - Up to 40% if strong FH
- Stronger risk for DVT over PE→ unclear why…
- "Multiplies" risk with concomitant OCP use
  - OCP alone= 4x increased VTE risk
  - OCP + FVL = 30x increased risk!
- NO association with arterial thrombosis or CV disease
- Weak association with late pregnancy loss

MacCallum, P et al. BMJ 2014;349:g4387
Thrombosis Canada, 2017

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Gain of Function Polymorphisms Prothrombin Gene Mutation

- 2nd Most common *inherited* thrombophilia
  - APS is 2nd most common thrombophilia overall…
- 1-2% of European Whites
- Cause: single nucleotide substitution (G20210A) in promoter region of gene for F II (prothrombin)→ Increased Prothrombin!!
  - Prothrombin increased by 30% in Hetero and 70% in homozygotes
- 2-4x increase risk of VTE throughout life
  - Slightly less than FVL
- Present in ~ 5% of people with 1st unprovoked VTE
- Like LFV, no increased risk of VTE recurrence

MacCallum, P et al. BMJ 2014;349:g4387
Thrombosis Canada, 2017

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"Double Heterozygotes" Prothrombin AND Leiden Factor V

- Long thought to have higher risk than only one
- Recent meta-analysis:
  - Similar risk to that of Leiden Factor V alone!!

MacCallum P et al. BMJ 2014;349:g4387

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Natural Anticoagulant Deficiencies Antithrombin Deficiency

- Less inhibition of FXa and thrombin→ increased thrombin generation and activity
- Rare!!→ 0.02% of population/0.5% of VTE pts
- d/t rarity, unclear risk…similar to FVL to 5x higher risk (over FVL)
  - Likely does increase risk of recurrent VTE
- *Not* a/w arterial thrombosis
- Many conditions influence levels!
  - DOACs increase; Heparin products decrease
  - Extensive acute thrombosis decrease
  - Nephrotic syndrome decrease
  - L-asparaginase chemo decrease
- Clinical clue: difficulty achieving therapeutic APTT while receiving heparin.
  - Heparin = indirect inhibitor of thrombin and FXa; *relies* on AT to be effective
- AT concentrate available… 3 requirements:
  - Bonified AT deficiency (levels < 50% of normal)
  - Previous VTE
  - Undergoing "high risk" procedure

MacCallum P et al. BMJ 2014;349:g4387
Thrombosis Canada, 2018

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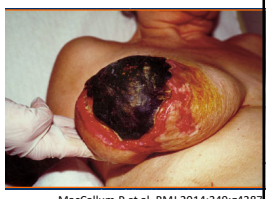
Natural Anticoagulant Deficiencies Protein C and S Deficiency

- Impaired inactivation of FVa and FVIIa→ increased thrombin generation…
- Both with various subtypes
- Pro C prevalence 0.3%; Pro S 0.1%
- Risk not well understood
  - At least on par with LFV if not higher
  - Pro S likely lower risk than Pro C
- Many conditions will influence levels…
  - Acute fresh thrombosis: decrease
  - Hyper-estrogenemic states: mild decrease Pro S
  - VKA decrease
    - Caveat: Warfarin induced skin necrosis
  - DOAC: up or down
  - Advanced liver disease: decrease



MacCallum P et al. BMJ 2014;349:g4387
Thrombosis Canada, 2018

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Antiphospholipid Syndrome (APS)

- Acquired and autoimmune
  - Autoantibodies against ag on cell membrane, assoc plasma proteins (coag) molecules
- Increase risk of BOTH venous AND arterial thrombosis
  - 2-11 fold initial VTE
  - The more antibodies, the higher the risk
- Increased risk of recurrence (unlike the heritable disorders)
  - 12% at one year, 17-26% 5 yr, 30-44% at 10 yrs
- Plays important role in risk of maternal complications→ "Obstetric APS"
  - ~ 6% of women with recurrent pregnancy loss
- Rarely: acute thrombosis in multiple vascular beds simultaneously
  - Multiorgan failure→ "catastrophic antiphospholipid antibody syndrome"
- Dx: BOTH clinical and lab abnormalities…Sapporo criteria
  - Clinical thrombosis + persistently positive antibodies
    - Lupus Anticoagulant testing (2 separate assays)
    - Anticardiolipin antibodies (IgG and/or IgM)
    - Beta 2 Glycoprotein 1 antibodies (IgG and/or IgM)
- Clinical clue: elevated baseline Aptt
  - May see other manifestations: Livedo reticularis/racemosa, low plt count, renal disease, etc.

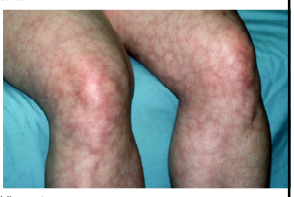

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Table 4. Diagnostic criteria for antiphospholipid antibody syndrome.[28]

Laboratory criteria[a]
- Positive lupus anticoagulant
- IgG or IgM anticardiolipin antibody
- IgG or IgM anti-β_2 glycoprotein antibody

Clinical criteria

Vascular thrombosis
- Venous or arterial thrombosis in any vascular bed not associated with vasculitis

Pregnancy complications
- Unexplained death of a normal fetus at 10 or more weeks' gestation
- Premature birth of a normal fetus before 34 weeks' gestation due to eclampsia, severe pre-eclampsia, or placental insufficiency
- Three or more unexplained, consecutive, spontaneous abortions before 10 weeks' gestation not related to chromosomal or anatomic abnormalities

At least one laboratory and one clinical criteria must be present to meet the diagnosis of antiphospholipid antibody syndrome

IgG, immunoglobulin G; IgM, immunoglobulin M.
[a]Abnormal test results must be confirmed on two different occasions, at least 12 weeks apart, to meet diagnostic criteria.

Superficial Vein Thrombosis NOT part of the criteria…

Carroll BJ, et al. Vascular Medicine. 2018

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APS Testing Pearls

- Remote from fresh thrombosis and free of AC
  - DAOC widely known to result in + LAC
    - ACL and B2G1 antibodies NOT affected by DOACs
  - Any heparin product will interfere with LAC testing…
  - Warfarin can also influence results

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APS

- More appetite for long term AC with true APS→ risk for recurrence
  - Particularly triple positive
- LAC APS will cause Aptt prolongation→ difficulty with Heparin infusion
  - Suggest UFH anti-factor Xa (heparin assay) if using heparin infusion
  - Alternatively, LMWH can be used (no need for clot-based assay monitoring)
- Obstetric APS:
  - Ante/post partum prophylactic LMWH + ASA
    - Expert consensus only, no evidence-based trials….
    - No clear guidance on optimal dose→ CHEST lower/ACOG higher
- Livedo/thrombocytopenia *without* thrombosis: no evidence suggesting Rx
- No evidence to support corticosteroids or other immunosuppressives…

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When should thrombophilia be suspected?

- VTE at young age (< 40-50)
  - VTE risk increases with age, starting in late 40s, with dramatic increase ~ 60
    - Thus, pts in whom VTE occurs at young age more likely to have thrombophilia
- Strong family history of VTE
  - Particularly VTE occurring at young age and without provoking factors
- VTE in conjunction with weak provoking factors at young age
- Recurrent VTE events
- Spontaneous VTE in unusual sites
  - CNS→ cerebral venous thrombosis
  - Splanchnic veins—> portal, SMV, splenic
- Recurrent pregnancy loss

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Easy to order, Difficult to Interpret…

- Most should NOT be tested…
- Data on clinical usefulness/benefits of testing: limited or nonexistent
  - Some authorities: "never perform"
- No validated testing guidelines have been published…
  - CHEST 2012, 2016→ no guidance…
  - ASH 2013: "Choosing Wisely"→ Do not test for thrombophilia in adults with VTE who have major transient risk factors…
  - British Committee for Standards in Haematology→ most comprehensive guideline
    - "It is not possible to give a validated recommendation as to how such pts (and families) should be selected for testing".
- No Uniformity
  - d/t indiscriminate testing practices and misconceptions regarding the role of thrombophilia status in the management of VTE

Connors, JM NEJM 377;12

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Will it change management?

- Often no
  - Unprovoked VTE and malignancy→ indefinite AC
- Contrary to popular belief, thrombophilias have either modest or no association with risk of *recurrence*
  - Thus, testing should play limited role in decisions regarding choice or duration of anticoagulation
  - Several studies: No difference in VTE recurrence whether testing had been performed or not!!
  - Several proposed prediction models out there; none include thrombophilia status in the risk calculation for recurrence!
    - DASH score→ d dimer, age, sex, hormonal Rx status
    - Vienna prediction model→ gender, location of VTE, d dimer
    - HERDOO2 score→ presence of PTS, d dimer, obesity, age, and gender

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Will it change management?

- Provoked VTE (Major sx, trauma, immobility or hospitalization for acute medical illness)
  - Low risk of recurrent VTE ***regardless*** of thrombophilia status
  - Rates of recurrence very low no matter the thrombophilia status
    - 0-1% at 2 years
  - No indication for lifelong AC with ***any*** thrombophilia status
    - Even with Homozygous LVF, Homozygous PGM, double heterozygotes!
- Unprovoked VTE
  - High risk of recurrence ***regardless*** of thrombophilia status
    - Risk of recurrence after AC stopped: 10% 1st year; 40% at 5 yrs; 50% at 10 yrs
    - Several studies showing no difference on rate of recurrence with any (heritable) factor
      - LFV and PGM HR 1.34 (95% CI 0.73-2.46)
      - LFV HR 1.3 (95% CI 0.8-2.1)
      - PGM HR 0.7 (95% CI 0.3-2)
      - Natural AC def HR 1.8 (95% CI 0.9-3.8)
  - AC failure rates no different regardless of thrombophilia status
  - Remember, guidelines suggest "extended" AC

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Beware the Pitfalls of testing…

- Best time to test:
  - Remote from acute VTE (at least 3 months later)
    - Fresh thrombosis consumes factors
  - Off all AC
    - VKA→ low pro c and s
    - Heparin→ low AT
    - DOAC→ false + LAC testing, can increase AT levels leading to false normal levels
  - Not on any estrogen containing medications or pregnant
    - Falsely low natural anticoagulants
  - Free of acute infection
    - False + LAC, + IgM ACL antibodies
- Bottomline: The hospital is no place to test!!
  - Leads to anxiety if "positive"
  - Leads to a false sense of security if all negative
  - Overwhelming in an otherwise already chaotic environment
  - Often leads to repeat testing→ discomforting/drives unnecessary expenses

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Many medical conditions can influence test results…

- Nephrotic syndrome
- Surgery/trauma
- Hemodialysis
- Liver disease
- DIC
- All with varying influence primarily on natural anticoagulant levels

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False sense of security…

- Negative test results-→ inappropriate reassurance and undertreatment or prophylaxis
- First degree relatives of pt with prior VTE *still* at higher risk for VTE even if thrombophilia testing is negative!!
- A negative thrombophilia test should never be used as the sole justification for cessation of AC
  - Unprovoked VTE: indefinite AC regardless of thrombophilia status!!

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So….Who should I test!?

- FH thrombophilia + OCP consideration
  - Estrogen containing OCP as the "compounder"*
  - Risk highest first 6 month after initiation…
    - Women without LFV and no OCP as baseline…
      - OCP use without LFV→ 4 x increased risk
      - LFV without OCP→ 7 x
      - OCP + LFV→ 35x !!
  - In women who incurred VTE while on OCP; thrombophilia increased risk **
    - OR 2.3 95% (CI 1.32-3.51)
    - Smoking = similar to having a thrombophilia; obesity = higher risk than anything!
      - Smoke→ OR 1.65 (95%CI 1.3-2.1); BMI > 35→ OR 3.46 (95%CI 1.81-7.03)
  - Some OCPs have less risk of VTE…
    - 2nd generation better than 3rd gen!
      - 3rd gen→ 3-4 x increased risk of VTE and doubling of recurrence risk if continued after event
    - Higher the estrogen dose, the higher the risk…
      - 20-30 ug = lowest risk vs > 50 = highest risk
    - Best options (for VTE risk)
      - Progestin only pill, Mirena IUD, copper IUDs→ all with no associated risk.
- Bottomline: testing (LFV) may have merit to aid in decision making on type of OCP and further risk factors…
  - Smoking status and obesity

*Vandenbroucke JP et al. Lancet 1994;344:1453-57
**Suchon P et al. Thromb Haemost 2016;115:135-42

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So….Who should I test!?

- Infertility/pregnancy risks
  - Thrombophilia a/w increased risk of early and late miscarriage.
    - All with some element of risk…
    - LFV and PGM = doubling of risk recurrent pregnancy loss..
  - ↑risk: severe pre-eclampsia, abruptio placentae, fetal growth retardation
- Bottomline:
  - Any female with h/o of recurrent miscarriage may benefit from testing.
  - May change management strategy: LMWH +/- low dose ASA

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So….Who should I test!?

- Pregnancy: multiple changes result in hypercoagulability
  - Coagulation related: increased APC resistance, more fibrinogen, FII, VII, IX, X; decreased protein S
  - Non-coagulation related: greater venous capacitance, uterine compression of pelvic veins, less mobile (late)
- Presence of a thrombophilia is additive…
- Baseline: pregnant/no thrombophilia, initial VTE risk…
  - FVL (hetero): 9 x and 34 x (homo)
  - PGM (hetero): 7 x
  - ~ 8% absolute risk VTE during pregnancy with homo FVL or "double heterozygous"*
- Bottomline: Consider *focused* testing if personal or FH of VTE
  - Absolute risk still quite low for most women…
    - 2012 Chest guidelines: "clinical vigilance" over prophylaxis with pregnancy with FVL and no h/o of VTE
  - Remember: Natural AC levels normally decrease in setting of pregnancy…Don't test!!

* Gerhardt A et al. Blood 2016;128: 2343-49

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So….Who should I test!?

- Acute Ischemic Stroke
  - Data conflicting on whether it makes any difference or changes management
    - Even those with APS + AIS: no decrease in risk of events whether on Warfarin or ASA
    - No data showing any increased risk with most thrombophilias
      - Natural AC def and gain of function mutations….
  - Conflicting data on homocysteine levels
    - Possible link with very high levels→ an exceedingly rare finding.
    - Targeted intervention does not seem in lessen thrombotic risk…

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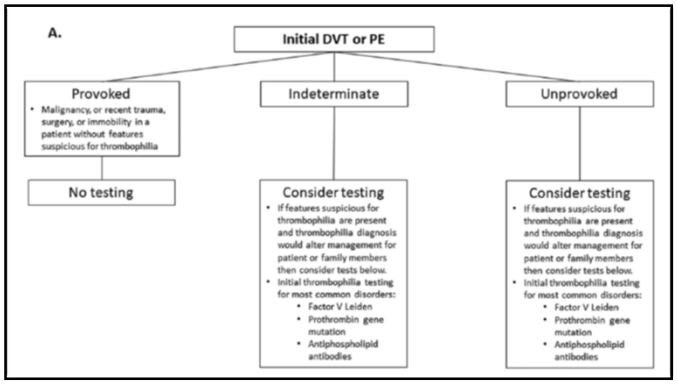

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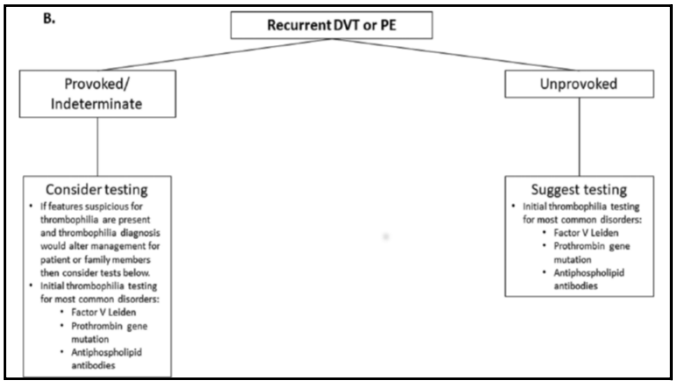

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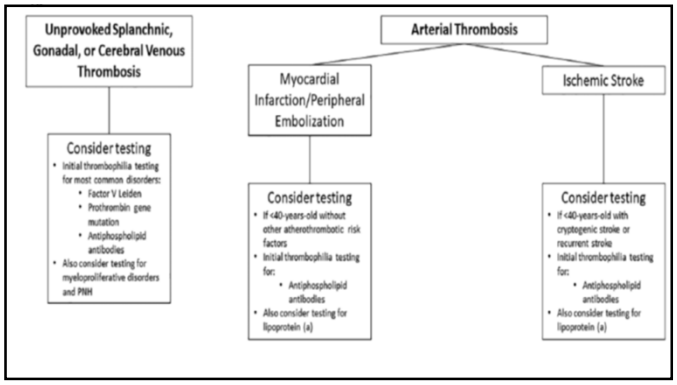

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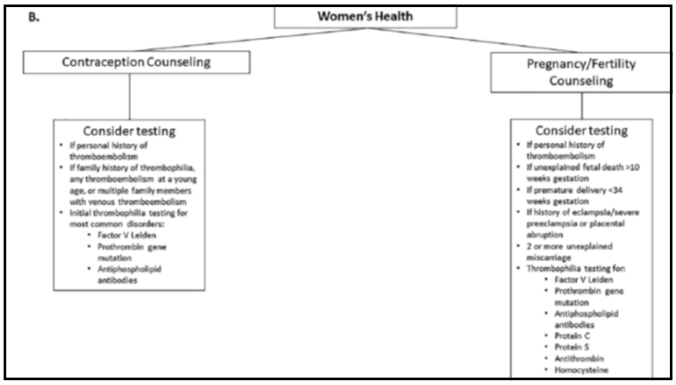

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Testing Strategy

- Acute phase:
  - LVF, PGM, APS antibodies (Not LAC)
    - Not affected by the clot itself or anticoagulants…
    - These account for the majority of known thrombophilias
    - Caveat: knowing the results really never affects initial management…
- Remote from event AND off AC (4 weeks minimum if on VKA)
    - Natural AC→ Rare, low yield
    - LAC→ should have a pretty good idea about this provided you have a baseline Aptt for review…

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Choice of Anticoagulant…

- DOACs have risen to the preferred agents in (non-cancer) VTE Rx
  - Only small numbers in the trials had known thrombophilia
  - Case series generally support the use….with one exception…
- APS
  - Growing concern that DOACs may not be as good as VKA
  - Particularly in "triple positive" APS
    - Much higher risk of thrombosis

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DOAC and APS: On the radar for years….

- 2016 Systematic Review of the Literature
  - 6 case reports; 8 case series→ majority with Rivaroxaban
- Of 122 published APS pts treated with DOAC, 19 with recurrent thrombosis while on DOAC…
  - "triple positive" status a/w 3.5 fold increased risk for recurrent thrombosis…
- "What you had is likely what you will get"
  - 89% of those with original VTE developed subsequent VTE
  - 67% of those with original arterial event developed subsequent arterial event
- If thrombosis occurred, it usually occurred *early* after switch to DOAC
- All retrospective data….

Dufrost, V et al Curr Rheumatol Rep 2016;18:74

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RAPS

- Randomized, controlled, open label, non-inferiority trial.
- Examined "endogenous thrombin potential" (ETP)
  - Surrogate "lab" marker of AC efficacy
- APS + prior VTE randomized to either VKA or full dose Rivaroxaban
  - ~55 pts in each group
- Primary outcome: % change in ETP from randomization to day 42
- Findings: ETP increased by 2 fold in Riva Rx pts vs. VKA
  - No clinical events; No difference in bleeding or ADE
    - Of note, only 25% were "triple positive"
    - Previous arterial thrombosis and recurrent VTE while on therapeutic VKA excluded
- Suggests higher thrombotic risk in comparison with VKA users

Cohen H et al. Lancet Haematol 2016;3:e426-36

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TRAPS

- ***Prospective*** randomized phase III open label non-inferiority study with blinded end point adjudication
- Adults b/t 18-75; had to be "triple positive" AND have h/o thrombosis
- Randomized to full dose Rivaroxaban vs. Warfarin (Target INR 2-3)
- Enrollment began 11/2/2014; stopped ahead of planned date (1/25/2018) by the Advisory Board
- At time of trial termination, 120 pts randomized…
  - 59 Rivaroxaban and 61 Warfarin
- Significantly higher number of *cumulative* events in Rivaroxaban group
  - 19% vs 3% HR 6.7 (95% CI 1.5-30.5) P 0.01
    - 12% arterial thrombosis + 7% major bleeding in Riva group
    - 0% either arterial or venous thrombosis and 3% major bleeding in Warfarin group
- Bottomline: Rivaroxaban does not protect high risk APS pts from arterial event and higher rate of bleeding.
- Unable to justify its use to prevent venous thromboembolism
  - No strict concordance b/t the arterial and venous sites of the qualifying event at diagnosis and that of the recurrent thrombotic event (unlike the previous finding in the 2016 systematic review)
  - 3/7 cases with an arterial outcome were originally pts with venous thromboembolism

Pengo V. et al. blood 2018;132:13

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Why doesn't Riva work in full positive APS?

- Noncompliance?
  - TRAPS→ 96% compliance via pill count in the Riva group
- Suboptimal drug concentration?
  - Animal models: need higher [drug] to prevent arterial vs venous thrombosis
  - Although pharmacological studies have demonstrated a predictable riva anticoagulant effect, high inter-individual variability may expose some patients to inadequate plasma levels of the drug
- Differences in mechanism of action?
  - Thrombin generation in APS pts Rx c Riva is different compared to warfarin
    - VKA reduced functional coagulation factors though both the intrinsic and extrinsic pathway
    - Intrinsic pathway may be critical as is demonstrated by warfarin to better attenuate thrombin generation with prosthetic material

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Summary

- Thrombophilia status and its influence on patient care is complex and often not helpful
  - May even be harmful…
- If testing, wait till the "dust settles"
  - Less false positives, little influence in acute management, less psychologically taxing
- Testing likely most helpful in:
  - assisting in risk stratification in pts with young females contemplating estrogen based therapy
  - women with maternal fetal complications
  - APS testing in unprovoked VTE where suspected
- With 1st provoked VTE, even if found to have a thrombophilia, generally do not require indefinite AC….so don't test…
- AC duration should be determined on "provoked vs. unprovoked" rather than thrombophilia status
  - Several studies→ thrombophilia status= no difference in recurrence rate
- APS (particularly "triple positive") should be treated with VKA over DOAC based on recent RCTs

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Thank You!

Questions or Concerns?

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