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Challenging Topics in Anticoagulation

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1. Discuss managing techniques for challenging patient types including alcoholism, pregnancy, and patients with Antiphospholipid Antibodies Syndrome
2. Discuss the evidence for 12 week follow up visits and how to determine which patients are appropriate
3. Evaluate anticoagulation therapy for selected challenging cases

Alcoholism

JT is 67yo male recently diagnosed with atrial fibrillation. He currently takes lisinopril, HCTZ, simvastatin, doxazosin, diltiazem. He has a PMH of hypertension, hyperlipidemia, BPH, obesity, pre-diabetes, and alcoholism.

- JT has been in your clinic for 6 wks with occasional INR levels above 3 resulting in multiple dose changes.

Question 1

Alcoholism

A. Is a labeled contraindication to warfarin
B. Warfarin interaction has been well studied
C. Should be discussed openly with patients
D. All of the above

Alcoholism

- Alcohol metabolized primarily by alcohol dehydrogenase.
- Minor activity with CYP2E1, CYP3A4, CYP1A2
  - S warfarin metabolized by CYP2C9
  - R warfarin metabolized by CYP3A4
- Other things in alcohol may effect pharmacokinetics/dynamics of warfarin
  - Hops, flavonoids, flavor additives

Pharmacotherapy 2005:25(2):303-307

Alcoholism

- Few clinical trials have been conducted
- Enhanced Antithrombotic Effect of Warfarin Associated with Low Dose Alcohol Consumption. *Pharmacotherapy* 2005:25(2):303-307
  - Case study
- In general, studies conducted indicate a lack of effect with moderate intake, no studies on heavy drinking or binge drinking identified.

Alcoholism

- Anecdotal experience
  - Binge drinking generally greatly increases the INR
  - Steady intake has no noticeable effect

Counseling advice:

- Be open and non-judgmental
- Moderate intake likely to have no effect
  - May decrease cardiovascular risk!
- Binge drinking should be avoided for multiple reasons.
  - Non-compliance, fall/injury risk, vomiting
  - Beware of self-management
- Alcoholism is a significant risk factor for GI bleeding.

CHEST. 2008;133(6_suppl):257S-298S

Alcoholism

Management

- Counsel based on healthy lifestyle choices
- Treat like other drug-drug interactions
- Encourage reporting of changes in intake
- Consider increase in monitoring frequency
- Track effects over time

Question 2

JL is a 32 yo female receiving long term warfarin after her second DVT occurred 2 years ago. She calls the clinic to report an unplanned positive pregnancy test.

- What do we do now?
- What do we do later?
- Is warfarin ever indicated during pregnancy?
- Yes OR No

Anticoagulation and Pregnancy

- Warfarin therapy during the 6^{th}-12^{th} week of pregnancy is associated with a 14%-56% risk of miscarriage and 6-30% risk of congenital abnormalities.
- Warfarin embryopathy
  - Variable degree of malformations, nasal hypoplasia, cleft lip, stippling of bones.
- Exposure later in pregnancy has been linked to minor developmental slowing.

CHEST. 2012;141(2_suppl):e691S-e736S.

Anticoagulation and Pregnancy

Goals

- Need to treat/prevent thrombosis during the pregnancy.
- Rapidly remove anticoagulation at time of birth to prevent adverse bleeding events.
- In most cases, stop warfarin and change to LMWH.

Anticoagulation and Pregnancy

CHEST 2012 Guidelines:

- For pregnant women receiving long term vitamin K antagonists, we suggest adjusted dose LMWH or 75% of a therapeutic dose of LMWH throughout pregnancy followed by resumption of long-term anticoagulants postpartum rather than prophylactic-dose LMWH (Grade 2C) .
- For pregnant women with acute VTE, we recommend therapy with adjusted-dose subcutaneous LMWH over adjusted-dose UFH (Grade 1B) .
- (check Anti-Xa levels every 10-14 days in 3^{rd} trimester)

CHEST. 2012;141(2_suppl):e691S-e736S.

Anticoagulation and Pregnancy

Atrial fibrillation: European Society of Cardiology Task Force for the Management of Atrial Fibrillation 2010

- Change to adjusted dose LMWH in first trimester.
- Resume warfarin until the last month of pregnancy.
- Change to LMWH prior to birth.

Europace 2010:12; 1360–1420

Anticoagulation and Pregnancy

Mechanical heart valves

- Use of UFH or LMWH
  - Risk of valve thrombosis or maternal thromboembolism 7.2-33%
- Warfarin
  - 2.9-3.9% thrombosis risk
- Much tougher risk/benefit decision!

CHEST. 2012;141(2_suppl):e691S-e736S.

Anticoagulation and Pregnancy

CHEST 2012 Guidelines

- Adjusted-dose bid LMWH throughout pregnancy, with doses adjusted to achieve the manufacturer's peak anti-Xa LMWH 4 h postsubcutaneous injection (Grade 1A).
- Adjusted-dose UFH throughout pregnancy administered subcutaneously every 12 h in doses adjusted to keep the midinterval aPTT at least twice control or attain an anti-Xa heparin level of 0.35-0.70 units/mL (Grade 1A).
- UFH or LMWH (as above) until the 13th week with substitution by vitamin K antagonists until close to delivery when UFH or LMWH is resumed (Grade 1A).
- For women judged to be at very high risk of thromboembolism in whom concerns exist about the efficacy and safety of UFH or LMWH as dosed above (eg, older-generation prosthesis in the mitral position or history of thromboembolism), vitamin K antagonists throughout pregnancy with replacement by UFH or LMWH (as above) close to delivery (Grade 2C).

CHEST. 2012;141(2_suppl):e691S-e736S.

Anticoagulation and Pregnancy

Birthing time

- If receiving LMWH, discontinue 24hrs prior to induction.
- If at high risk, convert to UFH infusion and discontinue 6 hours prior to induction.
- For spontaneous labor:
  - Monitor aPTT, Anti Xa levels.
  - Consider protamine administration
- Caution with epidural administration

CHEST. 2012;141(2_suppl):e691S-e736S.

Anticoagulation and Pregnancy

- Re-initiate LMWH/UFH 12-24hours post delivery or epidural removal.
- Warfarin can be restarted immediately

- Breast feeding
  - LMWH- OK
  - Warfarin- OK

CHEST. 2012;141(2_suppl):e691S-e736S.

Question 3

ST is a 42 yo female with a history of multiple miscarriages and DVT post a major MVA 6 wks ago. She has recently been diagnosed with Antiphospholipid Antibodies Syndrome. A colleague reviewing her case in your POC clinic notices that it has been difficult keeping her INR in range and has required a wide variation in weekly warfarin dosing. You should…

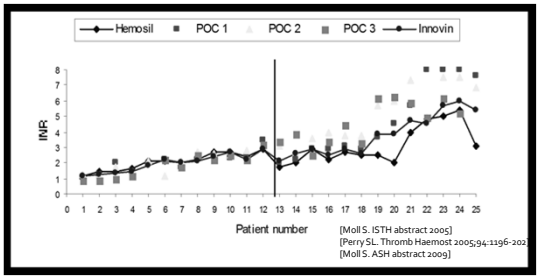
A. Continue to adjust her warfarin based on the POC values
B. Keep the dose the same for 2 weeks and hope it stabilizes
C. Try a different monitoring method.

Antiphospholipid Antibody Syndrome

- Autoimmune disease with a persistent presence of antibodies against specific phospholipid-binding proteins.
  - Anticardiolipon antibody
  - Lupus anticoagulant
  - Anti-β_2-glycoprotein I antibody
- Antibodies cause a pro-thrombotic state, and…
- Interfere with PT/INR measurements

AM Journal of Hematology. 2012;87:S75-S81

Antiphospholipid Antibody Syndrome



Moll, S Antiphospholipid Antibody Syndrome and Thrombosis. Webinar archived at http://www.standingstoneinc.com/Webinars/WebinarArchive.aspx Accessed 1/2/13

Antiphospholipid Antibody Syndrome

Expert opinion:

- INR determination in pts with APLA can be unreliable regardless of the method.
- Use alternative test method (factor II or X) in every patient with APLA on warfarin: obtain a correlation of factor II or X and INR at some point.
- INR 2-3 correlates with
  - Factor II 15-40% of normal = INR 1.8-3.3
  - Factor X 24-45% of normal = INR 2-3

Moll, S Antiphospholipid Antibody Syndrome and Thrombosis. Webinar archived at http://www.standingstoneinc.com/Webinars/WebinarArchive.aspx Accessed 1/2/13

Antiphospholipid Antibody Syndrome

- Do not use POCs in APLA pts, unless clearly established o.k.
- Correlate the POC to factor II, X; phlebotomy INR to ensure similar results
- Be aware- the APAs fluctuate over time.
  - Is the current dose is unexpected?
- Re-correlate every 6 months or so.
- (differing POC devices may yield different effects)

Moll S. APS Foundation of America, inc. Newsletter Spring 2007 vol 5

Question 4

SS is a 68yo female with a prosthetic mechanical atrial valve. She has been therapeutic with no dose changes for the past 5 months and asks if she still needs to return in 4 weeks. ("the cost of gas is ridiculous! Coming her cuts into my bingo kitty, you just want more of my money too")

- You respond with:

A. It's dangerous to go >4 weeks without testing
B. Testing every 4 weeks is the standard
C. It may be safe for you to go >4 weeks, let's discuss this further.

Testing Frequency

CHEST Guidelines

- 2008: For patients who are receiving a stable dose of oral anticoagulants, we suggest monitoring at an interval of no longer than every 4 weeks (Grade **2C**)
- 2012: For patients taking VKA therapy with consistently stable INRs, we suggest an INR testing frequency of up to 12 weeks rather than every 4 weeks (Grade **2B**) .
- Was something new and groundbreaking published?
- 3 randomized controlled trials have been conducted to examine extended duration follow-up
- (yes, only 3)
- Observational studies have shown, worse, better, and no difference in outcomes.
- Standard in US is 4 wks, up to 3 months has been recommended in UK

Testing Frequency

- Fihn SD , McDonell MB , Vermes D , et al ; National Consortium of Anticoagulation Clinics . A computerized intervention to improve timing of outpatient follow-up: a multicenter randomized trial in patients treated with warfarin . *J Gen Intern Med . 1994 ; 9 (3): 131 - 139 .*
  - *May not actually exist*
- Pengo V , Barbero F , Biasiolo A , Pegoraro C , Cucchini U , Iliceto S . A comparison between six- and four-week intervals in surveillance of oral anticoagulant treatment . *Am J Clin Pathol . 2003 ; 120 (6): 944 - 947 .*

Testing Frequency

- Warfarin Dose Assessment every 4 weeks versus every 12 weeks in patients with stable International Normalized Ratios. *Ann Intern Med* 2011;155:653-659

	4 wk group (126)	12 wk Group (124)
TTR	71.6	74.1
Any dose change	55.6%	37.1%
INR ≥ 4.5	11.9%	6.5%
INR ≤ 1.5	9.5%	8.9%
Major bleeding event	1	2
VTE Event	1	0

Testing Frequency

Inclusion criteria
- INR Range of 2-3 or 2.5-3.5
- Managed for at least 6 months
- No change in maintenance dose of at least 6 months (single day changes permitted)

Exclusions
- Younger then 18, "deemed unsuitable"- psychiatric disorder, history of poor adherence, geographically inaccessible.

Testing Frequency

Design
- All patients were tested and contacted at least every 4 wks. The 12 wk group had 'sham' values reported to the clinician outside of the 12 wk schedule.

Editors comments:
- "Extending the warfarin dosing assessment interval from every 4 weeks to every 12 weeks is probably safe for patients receiving stable doses of warfarin if they continue to have supportive contact with anticoagulation clinic staff every 4 weeks. The findings should not be interpreted to mean that extending INR monitoring to every 12 weeks is proven safe"

Testing Frequency

So is it safe?
- These studies combined represent 313 patient years of experience.
- Major modern trials still use every 4 week monitoring.
- Superior TTR results seen in self-testing trials were done with weekly testing.
- No definitive answer.

Testing Frequency

Final Thoughts…
- Should we be trying to make warfarin as convenient as [safely] possible?
  - Follow up intervals
  - Not changing dose +/- 0.5 INR
  - Venipuncture confirmations
  - Increased self testing/dosing