Hemostasis Update

Tom DeLoughery, MD MACP FAWM
Oregon Health and Sciences University
DISCLOSURE

Relevant Financial Relationship(s)
Speaker Bureau - None
Consultant/Research – none
What I am Talking About

• Therapy of VTE
• Duration of anticoagulation
• Thrombophilia work-ups
Don’t Use Standard Heparin!
Heparin

- LMWH was shown in the 90’s to be superior to standard heparin
  - Better outcomes
  - Instantly therapeutic
  - > 50% UFH not at goal at 24 hrs
  - No need for the inaccurate PTT
  - Much less HIT
  - Much easier
  - Cheap ~ $20/day
  - Reversible with protamine
<table>
<thead>
<tr>
<th>Recurrent DVT day 1-15</th>
<th>LMWH</th>
<th>SH</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/365 (0.8)</td>
<td>12/371 (3.2%)</td>
<td>RR 76%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrent DVT day 16 -90</th>
<th>LMWH</th>
<th>SH</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/365 (1.9%)</td>
<td>12/371 (3.2%)</td>
<td>RR 61%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bleeding</th>
<th>LMWH</th>
<th>SH</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/394 (3.0%)</td>
<td>27/402 (6.7%)</td>
<td>RR 58%</td>
</tr>
</tbody>
</table>
LMWH vs UFH: Therapy of Pulmonary Embolism
Analysis of PTT in Patients With PE First 48 Hours of Anticoagulation With UFH

Academic Emergency Medicine, 27: 117-127, 2020
Renal Disease

- Enoxaparin adjustment FDA approved
  - Decreased clearance of drug with decreased creatinine clearances
- Renal dosing (< 30ml/min)
  - Therapy: 1 mg/kg q 24 hrs
  - Prophylaxis: 20-30 mg/day
- For therapy check level after third dose
- No difference in major bleeding compared to UFH
Procedures

• No issues with IR procedures for PE
• Not that much difference in half-life

J Vasc Interv Radiol. 2020 Apr;31(4):537-543
Conclusion

• Standard heparin should be used only on rare occasions
Post-Thrombotic Syndrome

• Common complication of DVT
• 20-50% of all patients
• 5-10% severe
• Can be disabling
PTS: Risk Factors

- Common femoral or iliac vein thrombosis
- Previous DVT
- High BMI
- Older age
- Inadequate initial anticoagulation
Prevention

- Prevent thrombosis!
- Knee-high compression stockings – controversial but…
  - Apply within 24 hours
  - 20-30mmHg
  - At least 6 months
- Keep the patient active
- DOACs
  - 4 studies show less PTS
Post-PE Syndrome?

- 50% of patients with PE report dyspnea 6 months later
- 20-70% state health status worse
- Seemingly not related to clot residual or scarring
- Chest pain/discomfort very common
- Warn/reassure patients
- “Cardiac” rehab
Duration of Therapy

Idiopathic versus provoked thrombosis is the biggest determinant of risk of recurrent thrombosis.
Duration of Therapy

• Not all thrombosis are the same
• Can stratify patients by:
  – Site of thrombosis
  – Circumstances of thrombosis
    • Most important!
Upper Extremity Thrombosis

• Mechanical defects
  – Catheter
    • PICC 3-5%
  – Local venous trauma

• Prophylaxis ineffective

• Low risk of serious sequela
Upper Extremity Thrombosis

• Therapy: PICC Catheter
  • Key is removing catheter
  • No new one for at least 10 days
  • Benefit of anticoagulation uncertain
    –25% rate of bleeding
• Remember many are superficial thrombosis
Upper Extremity Thrombosis

• Therapy: Non-PICC Catheter
  • Line can be removed
    – Assess need for anticoagulation
    – Substantial rate of bleeding
      » 5% major bleeding
  • Line cannot be removed
    – 3 months anticoagulation
    – High rates of serious bleeding
Upper Extremity Thrombosis

• “Spontaneous”
  • 3 months anticoagulation
  • Look for underlying vascular defects
  • Consider thrombolytic therapy
    —~75% with underlying lesions
Portland Portal Vein Protocol
Portal Vein: Cirrhosis

- Incidental
  - SMV negative – no treat
  - SMV involved – treat
- Symptomatic – treat
Noncirrhotics: Symptomatic

- Provoked
  - Surgery
  - Infection, etc.
    - Treatment: 3 months
    - Work-up: not recommended

- Unprovoked
  - PNH, MPS, APLA
  - Indefinite anticoagulation
2017 Meta-Analysis

- 8 studies with 353 patients

- Recanalization
  - 71% vs 42%

- Complete recanalization
  - 53% vs 33%

- PVT progression
  - 9% vs 33%

- Bleeding
  - 11% vs 11%

- Gastro 153:480, 2017
2021 Update: DOAC & PVT

- **DOAC vs Warfarin**
  - Increased PVT recanalization – RR = 1.67
  - Decreased progression – RR = 0.14

- **Anticoagulation in PVT**
  - Increased PVT recanalization – OR 4.29
  - Decreased progression – OR 0.26
  - Bleeding slightly up – OR 1.16

Dig Liver Dis 2022 Jan;54(1):56-62
Hepatol Int 2021 Dec;15(6):1356-1375
DOAC in PVT

• Increasing data on safety in liver disease
  – Easier to use
  – Less bleeding

• Drug of choice: apixaban

• Exception Child C
  – Case by case basis
Calf Vein Thrombosis

• High risk of progression
  – Up to 10% progression
  – PE rate 2-3%

• 12 weeks therapy for most patients
Calf Vein Thrombosis Therapy

### Study or Subgroup

<table>
<thead>
<tr>
<th>Anticoagulation</th>
<th>No anticoagulation</th>
<th>Odds Ratio</th>
<th>M-H, Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Randomized controlled trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barrellier, 2010 [44]</td>
<td>3</td>
<td>144</td>
<td>9</td>
</tr>
<tr>
<td>Horner, 2010 [28]</td>
<td>0</td>
<td>35</td>
<td>4</td>
</tr>
<tr>
<td>Lagerstedt, 1985 [29]</td>
<td>0</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td>Righini, 2016 [27]</td>
<td>4</td>
<td>122</td>
<td>8</td>
</tr>
<tr>
<td>Schwarz, 2010 [6]</td>
<td>2</td>
<td>54</td>
<td>2</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>378</td>
<td>387</td>
<td>22.4%</td>
</tr>
<tr>
<td>Total events</td>
<td>9</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $t^2 = 0.00$; $\chi^2 = 3.99$, d.f. = 4 ($P = 0.41$); $I^2 = 0$

Test for overall effect: $Z = 2.57$ ($P = 0.01$)

### Cohort studies

<table>
<thead>
<tr>
<th>Anticoagulation</th>
<th>No anticoagulation</th>
<th>Odds Ratio</th>
<th>M-H, Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Brateanu, 2016 [43]</td>
<td>6</td>
<td>141</td>
<td>24</td>
</tr>
<tr>
<td>Dorr, 2007 [41]</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Kazmers, 1999 [37]</td>
<td>9</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Labropoulos, 2002 [39]</td>
<td>2</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Lautz, 2010 [40]</td>
<td>36</td>
<td>236</td>
<td>36</td>
</tr>
<tr>
<td>Lohr, 1995 [36]</td>
<td>3</td>
<td>23</td>
<td>38</td>
</tr>
<tr>
<td>Masuda, 1998 [31]</td>
<td>0</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>Pellegrini, 1993 [42]</td>
<td>0</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Sales, 2010 [33]</td>
<td>10</td>
<td>76</td>
<td>7</td>
</tr>
<tr>
<td>Schwarz, 2001 [30]</td>
<td>1</td>
<td>52</td>
<td>13</td>
</tr>
<tr>
<td>Sharpe, 2002 [38]</td>
<td>0</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Solis, 1992 [34]</td>
<td>3</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Sule, 2009 [32]</td>
<td>0</td>
<td>17</td>
<td>0</td>
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<tr>
<td>Utter, 2016 [10]</td>
<td>8</td>
<td>243</td>
<td>13</td>
</tr>
<tr>
<td>Wang, 2007 [35]</td>
<td>2</td>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>989</td>
<td>1182</td>
<td>77.6%</td>
</tr>
<tr>
<td>Total events</td>
<td>80</td>
<td>157</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $t^2 = 0.47$; $\chi^2 = 25.70$, d.f. = 12 ($P = 0.01$); $I^2 = 53$

Test for overall effect: $Z = 2.97$ ($P = 0.00$)

### Total (95% CI)

<table>
<thead>
<tr>
<th>Anticoagulation</th>
<th>No anticoagulation</th>
<th>Odds Ratio</th>
<th>M-H, Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1367</td>
<td>1569</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>89</td>
<td>188</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $t^2 = 0.36$; $\chi^2 = 30.26$, d.f. = 17 ($P = 0.02$); $I^2 = 44$

Test for overall effect: $Z = 2.97$ ($P = 0.003$)

Test for subgroup differences: $\chi^2 = 0.71$, d.f. = 1 ($P = 0.40$); $I^2 = 0$

Journal of Thrombosis and Haemostasis, 15: 1142–1154
### Calf Vein Thrombosis Therapy

#### Figure 6

Recurrent venous thromboembolism in patients receiving anticoagulant treatment for > 6 weeks versus 6 weeks. CI, confidence interval; d.f., degrees of freedom; M-H, Mantel-Haenszel. [Color figure can be viewed at wileyonlinelibrary.com]

#### Table

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events &gt; 6 weeks</th>
<th>Total &gt; 6 weeks</th>
<th>Events 6 weeks</th>
<th>Total 6 weeks</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrara, 2006 [18]</td>
<td>7</td>
<td>96</td>
<td>27</td>
<td>96</td>
<td>35.4%</td>
<td>0.20 [0.08, 0.49]</td>
<td></td>
</tr>
<tr>
<td>Li, 2014 [46]</td>
<td>1</td>
<td>303</td>
<td>2</td>
<td>97</td>
<td>10.2%</td>
<td>0.16 [0.01, 1.75]</td>
<td></td>
</tr>
<tr>
<td>Pinede, 2001 [17]</td>
<td>3</td>
<td>92</td>
<td>2</td>
<td>105</td>
<td>15.9%</td>
<td>1.74 [0.28, 10.62]</td>
<td></td>
</tr>
<tr>
<td>Schulman, 1995 [45]</td>
<td>10</td>
<td>171</td>
<td>20</td>
<td>176</td>
<td>38.6%</td>
<td>0.48 [0.22, 1.07]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>662</strong></td>
<td><strong>474</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>100.0%</strong></td>
<td>0.39</td>
<td><strong>0.39 [0.17, 0.90]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 5.54$, d.f. = 3 ($P = 0.14$); $I^2 = 46%$

Test for overall effect: $Z = 2.20$ ($P = 0.03$)
Distal DVT Trial

- Rivaroxaban 6 vs 12 weeks
- N = 400
- rDVT 6: 15%  12:8%
- No major bleeding
- BMJ. 2022 11 23; 379:e072623
Duration of Therapy: Proximal DVT

• 3 months
  – Provoked DVT
    • Especially estrogen related
• No benefit with 6 months except more bleeding
• Obtain scan at end of therapy for new baseline
Proximal DVT

Duration of Therapy

• What is an Idiopathic Thrombosis?
  – No trauma, surgery or hospital stay for 1-3 months
  – No estrogens
  – No long travel (> 4 hours)
  – No cancer or major risk factors
  – Exact definition controversial
1st Idiopathic VTE

- High rates (30-40%) of recurrence off anticoagulation
- Multiple RCTs show benefit of long term anticoagulation
  - Marked increase in recurrence when stopping anticoagulation
<table>
<thead>
<tr>
<th>Year</th>
<th>Risk</th>
<th>Cumulative Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Year</td>
<td>10.3%</td>
<td>-</td>
</tr>
<tr>
<td>2 year</td>
<td>6.3%</td>
<td>16%</td>
</tr>
<tr>
<td>3-5 years</td>
<td>3.8%/year</td>
<td>25% 5 years</td>
</tr>
<tr>
<td>6-10 years</td>
<td>3.1/year</td>
<td>36% 10 years</td>
</tr>
</tbody>
</table>

Case fatality rate for recurrence 4%
Distal thrombosis 1/10th of risk
BMJ 2019: 366:4364
Extended Therapy

Treating 1,000 patient-years with extended anticoagulation following acute VTE may result in:

**DOAC**
- ≈ 5 (95% CI, 1 to 9) fewer deaths
- ≈ 4 (95% CI, 1 to 6) fewer VTE-related deaths
- ≈ 70 (95% CI, 41 to 99) fewer VTE recurrence
- ≈ 3 (95% CI, -2 to 8) more major bleeding
- ≈ 67 (95% CI, 39 to 94) net clinical benefit (absence of VTE recurrence or major bleeding)

**VKA**
- ≈ 78 (95% CI, 40 to 117) fewer VTE recurrence
- ≈ 14 (95% CI, 02 to 29) more major bleeding
- ≈ 63 (95% CI, 20 to 107) net clinical benefit (absence of VTE recurrence or major bleeding)

*Chest 155:1199-1216, 2019*
Two Phases of VTE Therapy

• Active phase (3 months)
  – Prevents reactivation of initial thrombosis

• Secondary prevention (> 3 months)
  – Prevents new thrombosis
  – Need to identify patients who will benefit

D-Dimers

• D-dimers checked off therapy to predict risk
• Meta-analysis
  – 7 studies
  – Positive D-Dimer: 10%/yr
  – Negative D-Dimer: 2.9 - 4.0%/yr
• Unclear if repeat testing helps
• Most recent study showed high rates of recurrence with negative D-dimer 5%/yr
Idiopathic VTE

• No good prediction rules
  – Negative D-dimer - NOT predictive
  – Thrombus resolution – NOT predictive

• Still need better prediction rules!

• Safer anticoagulants is shifting balance toward longer treatment
Duration of Therapy

- Indefinite
  - >1 DVT (except upper ext)
  - Acquired hypercoagulable states
  - Idiopathic unusual site
  - Idiopathic severe pulmonary embolism

- 3 months
  - Provoked pulmonary embolism
3 months

Common iliac

External iliac

Femoral

IVC

Great saphenous

Popliteal

Peroneal

Posterior tibial

3 months - ∞

14 days (prophylactic dose)

3 months - ∞

3 months

3 months - ∞
What about Hypercoagulable States?

- Testing not recommend
  - Provoked thrombosis
  - Arterial thrombosis (inherited thrombophilia)
  - Upper extremity
  - Distal thrombosis
  - Superficial thrombosis
DOACs

• Robust randomized trial data for all new anticoagulants
• Now recommend by ACCP/ASH first line over warfarin
• Irreversibility = Myth
  – Less need to reverse
  – No difference in bleeding outcomes in multiple studies
DOAC in VTE

- Recurrent VTE: 0.90 (0.77-1.06)
- Major bleeding: 0.74 (0.59-0.85)
- ICH: 0.37 (0.21-0.68)
- Fatal bleeding: 0.36 (0.15-0.84)

# Venous Thrombosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Heparin First?</th>
<th>Thrombosis</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>No*</td>
<td>Equal</td>
<td>Safer</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Yes</td>
<td>Equal</td>
<td>Equal</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Yes</td>
<td>Equal</td>
<td>Safer</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>No*</td>
<td>Equal</td>
<td>Safer</td>
</tr>
</tbody>
</table>

*Apixaban 10mg bid x 7 days then 5mg BID
*Rivaroxaban 15mg bid x 21 days then 20mg daily
**Vitamin K Antagonist**

**Dabigatran**
- LMWH: 5 days
- Dabigatran 150 mg BID

**Rivaroxaban**
- 15 mg BID: 21 days
- 20 mg daily: 6 months
- 10 mg daily
- *Must take with food*

**Apixaban**
- 10 mg BID: 7 days
- 5 mg BID: 6 months
- 2.5 mg BID

**Edoxaban**
- LMWH: 5 days
- Edoxaban 60 mg daily (CrCl 30-50, <60 kg: 30 mg daily)
Lower Dose DOACs?

- Older data for lower doses in chronic therapy of VTE
  - LMWH
  - Ximelagatran
  - Did not work for warfarin
Low Dose DOAC

• Two trials
  – Rivaroxaban 20mg vs 10mg
  – Apixaban 5mg vs 2.5 mg
• Start 6-12 months after VTE
• No difference in VTE or bleeding
  – Trend toward reduce major bleeding
Lower Dose Therapy

• Only for chronic venous thrombosis!!

• NOT
  – Atrial fibrillation
  – Cancer
  – Bad thrombophilia
  – Visceral vein thrombosis
DOAC VTE Stepped Care

Acute
A 10mg BID x 7 Days
R 15 mg bid x 21 days

6-12 Months
A 5.0 mg BID x 6-12 M
A 2.5 mg BID x 6-12 M

> 6-12 Months
R 20 mg qD x 6-12 M
R 10 mg qD
DOACs in Cancer

• Advantages
  – Few drug no food interactions
  – Short half-life
  – Not a shot

• Warfarin inferior to LMWH
  – Increase thrombosis

• Less than 33% of cancer patients on LMWH
Cancer

- 4 RCT: DOAC vs LMWH
- Recurrence: HR 0.62 (sig)
- Major Bleeding: HR 1.33 (NS)
- Relevant bleeding: HR 1.58 (sig)

- Tao DL, Eur J Haem 2020
Cancer

- DOACs now front line
- Reserve LMWH for break through thrombosis
- GI bleeding issue
  - Less with apixaban
Who NOT to use New Anticoagulants

- Triple positive APLA
- Mechanical Valves
- Rheumatic Valvular disease
- < 50 or > ??? kg
TRAPS
Randomized controlled trial of Rivaroxaban vs Warfarin in APS

High-risk APS patients
- LA positive
- aCL positive
- aB2GPI positive

Rivaroxaban N=59

Events on Rivaroxaban: 19%

Warfarin N=61

Events on Warfarin: 3%

1.5 years

Stopped early for excess of events on Rivaroxaban
Direct Oral Anticoagulants

- First line therapy for VTE
- Simplified management
- But
  - Patients still need close follow-up
  - Still need to manage anticoagulants
  - Expense an issue
Thrombophilia

- MTHFR
- APLA
METHIONINE SYNTHASE

THF

N⁵ N¹⁰ MTHF

N⁵ MTHF

ADOMET

CH₃

ADOHCY

HOMOCYSTEINE

CYSTATHIONINE B-SYNTHASE

CYSTATHIONINE

5,10 METHYLENE TETRAHYDROFOLATE REDUCTASE
<table>
<thead>
<tr>
<th>Genotype</th>
<th>Hcy (nmol/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-/-</td>
<td>11.04</td>
</tr>
<tr>
<td>+/-</td>
<td>11.03</td>
</tr>
<tr>
<td>+/+</td>
<td>13.28*</td>
</tr>
</tbody>
</table>

*P<0.01
<table>
<thead>
<tr>
<th>Study Group†</th>
<th>n</th>
<th>Ala/Ala, %</th>
<th>Ala/Val, %</th>
<th>Val/Val, %</th>
<th>Val Allele, %†</th>
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</thead>
<tbody>
<tr>
<td>Peripheral vascular disease</td>
<td>247</td>
<td>114 (46)</td>
<td>111 (45)</td>
<td>22 (9)</td>
<td>31</td>
</tr>
<tr>
<td>Healthy blood donors</td>
<td>170</td>
<td>65 (38)</td>
<td>77 (45)</td>
<td>28 (17)</td>
<td>39</td>
</tr>
<tr>
<td>Canadian neonates</td>
<td>293</td>
<td>125 (43)</td>
<td>122 (42)</td>
<td>46 (15)</td>
<td>36</td>
</tr>
<tr>
<td>Hospital/laboratory control subjects</td>
<td>133</td>
<td>50 (38)</td>
<td>63 (47)</td>
<td>20 (15)</td>
<td>39</td>
</tr>
</tbody>
</table>
But.........

- RCT of lower homocysteine uniformly negative
- Good studies show no relationship between MTHFR and thrombosis
- Hcy more of reflection of inflammation and endothelial damage
MTHFR not Associated with VTE

OR for 1st VTE for CT and TT vs nl MTHFR genotype

<table>
<thead>
<tr>
<th>MTHFR genotype</th>
<th>Homocysteine; geometric mean* (±SE) (mmol/l)</th>
<th>Cases n = 507</th>
<th>Controls n = 1430</th>
<th>OR†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC (wild type)</td>
<td>13.69 (±1.01)</td>
<td>255 (50)</td>
<td>726 (51)</td>
<td>1</td>
<td>reference</td>
</tr>
<tr>
<td>CT (heterozygote)</td>
<td>14.34 (±1.01)</td>
<td>208 (41)</td>
<td>582 (41)</td>
<td>1.01</td>
<td>0.81–1.25</td>
</tr>
<tr>
<td>TT (homozygote)</td>
<td>16.35 (±1.04)</td>
<td>44 (9)</td>
<td>122 (8)</td>
<td>1.02</td>
<td>0.70–1.49</td>
</tr>
</tbody>
</table>

*Calculated in the controls.
†Adjusted for age (5-year age bands) and sex.

“polymorphisms” not “mutations”

HUNT2: prospective case control of 66,140 Norwegians
505 VTE cases identified, 1458 matched controls
Serum homocysteine level and MTHFR C677T genotype
not associated with VTE

Also: Bezemer, Arch Int Med 2007
Naess, BJH 2008
A call to action: MTHFR polymorphisms should not be a part of inherited thrombophilia testing

Thomas G. Deloughery MD, MACP, FAWM1 | Beverley J. Hunt OBE2 | Geoffrey D. Barnes MD, MSc3 | Jean M. Connors MD4 | The WTD Steering Committee

Bottom Line

• Hcy not a part of thrombophilia work-ups
• NEVER check MTHFR
How do We Test for APLA?

- Screening aPTT inadequate
- Different APLA behave differently in tests
- Only 60% of ACLA and lupus inhibitors overlap
ACLA

LUPUS INHIBITORS

SYMPTOMS
Testing for APLA

- Anticardiolipin antibodies
  - ELISA assay

- Anti\(\beta_2\)glycoprotein antibodies
  - ELISA

- Coagulation based test:
  - All based on demonstrating phospholipid dependent antibodies
Anticardiolipin Antibodies

- Based on observation of false positive VDRL
- Laboratory dependent
- Common in older patients
- Low titer ACLA very common (~20-30%)
- High titers predictive of recurrent events
  - How high > 40 units (>99th percentile)
- Anti-β2 glycoprotein antibodies more predictive??
Testing Strategy

• Get total set
  – dRVVT
    • Ratio is key number
  – Hexagonal
  – Anticardiolipin antibody
  – Antiβ2glycoprotnien
Need to Repeat Test

- Triple positive – 98% confirmed
- Double positive – 84% confirmed
- Single positive – 40% confirmed
- Note
  - No LA only confirmed
    - Can be falsely high due to CRP
  - ACLA and Aβ2GP same isotype
Is The APLA Significant?

- More significant if:
  - Good history
  - Younger patient
  - Lupus inhibitor
  - High titer ACLA
  - Positive dRVVT
  - Multiple tests positive
Triple Positive

• LA, ACLA and $\alpha \beta 2$GP positive
  – Same isotype (IgG, etc)
• High risk of recurrance
• High risk of first event
• Higher risk of warfarin refractoriness
Burn Point #1

- Diagnosis is based on 99\textsuperscript{th} percentile and not lab listed as “abnormal”
- Labs have wildly different 99\textsuperscript{th} percentile and reference ranges
- Know you lab!
### Cardiolipin IgA Antibody:
- 0 - 19 CU Negative
- >=20 CU Positive
- Cardiolipin IgG Antibody:
  - 0 - 19 CU Negative
  - 20 - 94 CU Low Positive
  - >= 95 CU Moderately to High Positive

### Cardiolipin Antibody, IgG

<table>
<thead>
<tr>
<th>Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=14 GPL</td>
<td>Negative</td>
</tr>
<tr>
<td>15-19 GPL</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>20-80 GPL</td>
<td>Low to Moderately Positive</td>
</tr>
<tr>
<td>81 GPL or above</td>
<td>High Positive</td>
</tr>
</tbody>
</table>

Effective November 15, 2021

### Reference Values

- Negative < or =30.0 U
- Borderline 30.1-40.0 U
- Positive > or =40.1 U
AB2GP

Negative <20 CU
Positive >=20 CU

<15.0 U/mL (negative)
15.0-39.9 U/mL (weakly positive)
40.0-79.9 U/mL (positive)
> or =80.0 U/mL (strongly positive)

Results are expressed in arbitrary units. Reference values apply to all ages.
Burn Point #2

• Persistent
  – Need to demonstrate APLA persists over time (same test)
Burn Point #3

- Direct Oral Anticoagulants
  - All will mess up lupus inhibitors!
  - Many labs do not screen for!
  - Increasing cause of false positive APLA
What I Talked About

- Therapy of VTE
- Duration of anticoagulation
- Thrombophilia work-ups