Controversies in Anticoagulation

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Patient Case: DS

- DS 67 y/o CC: Chest Pain & “Heart racing”
- PMH: aortic valve replacement (porcine), HTN, & GERD
- Afib with RVR – metoprolol & warfarin

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>warfarin</td>
<td>5mg</td>
<td>5mg</td>
<td>Held</td>
<td>Held</td>
</tr>
<tr>
<td>INR</td>
<td>1.2</td>
<td>1.5</td>
<td>3.9</td>
<td>4.0*</td>
</tr>
<tr>
<td>Hct</td>
<td>31.2</td>
<td>30</td>
<td>27.5</td>
<td>26</td>
</tr>
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</table>

- Would you have considered doing warfarin genetic testing on this patient prior to warfarin initiation?
- Would you do genetic testing after his GI bleed?

Warfarin Sensitivity Genotyping

- CYP2C9
  - Responsible for metabolizing warfarin S-isomer
  - Gene mutations – CYP2C9*2, CYP2C9*3
  - Both mutations are associated with reduced warfarin dosing requirements to achieve therapeutic INR

- VKORC1
  - Gene that determines the activity of vitamin K epoxide reductase (VKOR)
  - Gene mutations – A/A, G/A, G/G – increased sensitivity to warfarin

- These 2 gene variations account for more than 1/3 of the variance associated with stable therapeutic warfarin dosing
Pharmacogenetic Algorithm = Better Dose Prediction

P value < 0.001 for both comparisons

Pharmacogenetic algorithm available at www.warfarindosing.com

IWPC, N Eng J Med 2009;360:753-64
National, prospective, comparative effectiveness study comparing the 6 month incidence of hospitalization in patients receiving warfarin genotyping (896) vs historical control group (2688).

- A secondary analysis to rule out temporal trends with 2 external control groups

Results: Compared to historical controls:

Patients in the genotyped group had 31% fewer hospitalizations overall, 28% fewer hospitalizations for bleeding or thromboembolism.

Limitations – historical control group

Where do we go from here?

- 8/07 – FDA added info to warfarin package insert regarding lowering warfarin doses in patients with CYP 2C9 and VKORC1 SNP
- 08/09 – CMS will not reimburse for warfarin pharmacogenomic testing unless it is part of a clinical trial
- Cost – Effectiveness?
  - If restricted to patients at high risk for hemorrhage
  - Meet criteria: prevent > 32% of bleeding events, be available within 24 hours, and cost less than $200
- More Studies – COAG, GIFT
Patient Case: DM

- DM is a 45 female admitted for treatment of LE cellulitis
- PMH: HTN, Asthma, DM Type II
- Admitted to medicine – home meds continued, started on vancomycin and unnasyn, **dalteparin 5000 iu daily**
- HD #4 – new painful swelling in R LE, US shows new DVT
- Did this patient receive adequate DVT Proph?

Antifactor Xa activity & Body Weight

- N = 17 patients and 2 volunteers
- Anti-Xa levels hourly x 10 hours
- Enoxaparin 40 mg SC x1 dose
- AUC for Hour 10

PREVENT Trial

- Fixed dose dalteparin was effective in reducing VTE by 45% in medicine pts > 45 y/o.
- Subgroup Analysis
  - Obesity defined as BMI > 30 for males, > 28.6 for females
  - Primary endpoint – Obese 2.8% vs 4.3%, Non-obese 2.8% vs 5.2%
- RRR of 36% across BMI subgroups EXCEPT pt with BMI > 40

Enoxaparin 30 mg BID vs 40 mg BID in Bariatric Surgery

- 481 pts undergoing either primary or revisional bariatric surgery (BMI = 51)
- Patients receiving lovenox 40 mg bid had fewer VTE events compared with 30 mg bid (2 DVT vs 1 DVT/4 PE, p < 0.01)
- 1 bleeding complication in each group


Enoxaparin for VTE Prophylaxis in Orthopedic Surgery

Dose: 40 units qd
Obese: BMI > 32 kg/m²
N = 807

Incidence (%)


Where do we go from here?

- Recommendations – Increasing VTE prophylactic doses of LMWH's MAY be appropriate in morbidly obese patients (BMI > 40 kg/m²)
- How much do we increase VTE prophylactic doses?
  - Enoxaparin 40 mg sq BID
  - Dalteparin & UFH – 6500 Units? 7500 Units?
Patient Case: JJ

JJ is a 59 y/o male with CC SOB, increasing dyspnea on exertion & LEE
- BP 150/87, HR 85, Cr 1.6, BNP 2400
- PMH: HTN (has not seen a Dr in 10 years)
- ECHO – LVEF severely reduced with global hypokinesis
- Hospital Course: Diuresis and medication optimization
  - R2 asks on rounds “Shouldn’t we anticoagulate him for low EF?”

Guideline & Consensus Recommendations for Anticoagulation in HF

<table>
<thead>
<tr>
<th>Organization</th>
<th>Guideline or Recommendation</th>
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<tr>
<td>American College of Chest Physicians</td>
<td>In pts with CHF due to nonischemic etiology, we recommend against routine use of aspirin or oral vitamin K antagonists (Grade 1B)</td>
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<tr>
<td>Heart Failure Society of America</td>
<td>In the absence of a/fib, a recent large anterior MI, or LV thrombus, warfarin anticoagulation may be considered in pts with dilated cardiomyopathy and LVEF &lt; 35%. Careful assessment of potential risks and benefits should be undertaken. (Strength of Evidence = C)</td>
</tr>
<tr>
<td>American College of Cardiology – AHA</td>
<td>The usefulness of anticoagulation is not well established in pts with heart failure who do not have a/fib or previous thromboembolic event. (Class IIb, level of evidence B)</td>
</tr>
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Thromboembolism Rates in HF

- 2 Prospective observational studies:
  - 406 pts, EF – 23%, A/fib 16%, TE rate – 2.7% 8
  - 264 pts, EF – 27%, 24 months. Cerebral TE 1.7 events per 100 pt years 9
- Post Hoc Analysis:
  - SAVE – LVEF independently ass. with stroke risk (p = 0.01), risk of TE ↑ by 18% for every 5 % ↓ in EF 11
  - SOLVD – 6378 pt over 40 months, Overall TE events 2.4% in woman and 1.6% in men.
  - Annual risk of stroke: mild/mod EF – 1.5%, Severe EF – 4% vs 0.5% in general population 12
- In more recent trials annual incidence of thromboembolic events in HF ranged from 1-3%.
Data Supporting Anticoagulation in HF

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<tr>
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<th>Design</th>
<th>Findings</th>
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<tr>
<td>SAVE Post Hoc 11</td>
<td>Warfarin vs no Warfarin</td>
<td>Warfarin ass. with an 81% RRR in stroke*</td>
</tr>
<tr>
<td>Oral Milrinone Multicenter trial in 1088 pts</td>
<td>Warfarin sig reduced the risk of stroke in pts with EF &lt; 20% (0.6% risk vs 3.3%)</td>
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<tr>
<td>SOLVD Post Hoc Cohort 12</td>
<td>Warfarin pt (n=861) vs No Warfarin (n=5652)</td>
<td>After adjustments Warfarin ass. with reduced all cause &amp; CV mortality (p = 0.006 &amp; p = 0.002)</td>
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Data Refuting Anticoagulation in HF

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<td>HELAS 14</td>
<td>Designed to recruit 6000 pts, only 197 enrolled</td>
<td>No difference in stroke, embolism, MI or re-infarction, HF exac, or death</td>
</tr>
<tr>
<td>WASH 15</td>
<td>279 pts followed 26-28 months (6.1% had afib)</td>
<td>No difference in primary outcome (composite of death, MI &amp; stroke)</td>
</tr>
<tr>
<td>WATCH 16</td>
<td>Designed for 4500 pts followed 3.5 years, only 1587 pts followed for 23 month</td>
<td>No difference in primary outcome (composite of all cause mortality, MI &amp; stroke)</td>
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Where do we go from here?

- More Studies – WARCEF:
  - Warfarin vs ASA 325 daily in 3-5 year event-free survival for composite endpoint of death and stroke with EF < 35% (no afib/ mechanical valves)

- Anticoagulate?
  - **YES** - LVEF < 35% PLUS AFib, Recent MI & mural thrombus, Intracardiac thrombus, Mechanical Valve
  - **Evaluate case by case** - LVEF < 35% and no additional risk factors

- Who would anticoagulate patient JJ?
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