Anticoagulation in ‘Special’ populations

Ng Heng Joo
Department of Haematology
Singapore General Hospital
Special Populations

Anticoagulation Symposium & Workshop 2015
Objectives

Safer anticoagulation for

• The elderly
• Chronic kidney disease
• Obese patients
• Pregnancy
• Cancer patients
• Some unique situations

↓ Thrombosis
↓ Bleeding
The ‘elderly’ paradox

Table 1  Stroke Risk Stratification with the CHADS$_2$ and CHA\textsubscript{DS}-VASc Scores

<table>
<thead>
<tr>
<th>CHADS$_2$ Acronym</th>
<th>Score</th>
<th>CHADS$_2$ Score</th>
<th>Adjusted Stroke Rate (%/Year) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>0</td>
<td>1.9%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
<td>2.8%</td>
</tr>
<tr>
<td>Aged $\geq$75 years</td>
<td>1</td>
<td>2</td>
<td>4.0%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>3</td>
<td>5.3%</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
<td>4</td>
<td>8.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>12.5%</td>
</tr>
<tr>
<td>Maximum score</td>
<td>6</td>
<td>6</td>
<td>18.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHA\textsubscript{DS}-VASc Acronym</th>
<th>Score</th>
<th>CHA\textsubscript{DS}-VASc Score</th>
<th>Adjusted Stroke Rate (%/Year) †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Aged $\geq$75 years</td>
<td>2</td>
<td>2</td>
<td>1.9%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>3</td>
<td>4.7%</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
<td>4</td>
<td>2.3%</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
<td>1</td>
<td>5</td>
<td>3.9%</td>
</tr>
<tr>
<td>Aged 65-74 years</td>
<td>1</td>
<td>6</td>
<td>4.5%</td>
</tr>
<tr>
<td>Sex category (M, female sex)</td>
<td>1</td>
<td>7</td>
<td>10.1%</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
<td>8</td>
<td>14.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 3  Clinical Characteristics Comprising the HAS-BLED Bleeding Risk Score

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical Characteristic*</th>
<th>Score</th>
<th>HAS-BLED Score</th>
<th>Bleeds per 100 Patient-years ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs</td>
<td>1</td>
<td>4</td>
<td>8.70</td>
</tr>
<tr>
<td>E</td>
<td>Elderly</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Drugs or alcohol (1 point each)</td>
<td>1 or 2</td>
<td>Maximum 9 points</td>
<td></td>
</tr>
</tbody>
</table>

Lip GY. Am J Med 2011
Dear Anticoagulation Specialist...

Thank you for seeing this pleasant 78 year old eligible bachelor with the following problems:

1. Chronic atrial fibrillation with recent TIA. No significant neurological deficit
2. Diabetes mellitus
3. Hypertension
4. IHD with previous CABG
5. Congestive cardiac failure (EF – 45%)
6. Stable chronic renal failure (creatinine 154 umol/L)
7. Osteoarthritis of both knees

CHA2DS2-VASc - 8
He lives alone and is currently taking the following:

1. Frusemide
2. Aspirin
3. Glicazide
4. Amlodipine,
5. Enalapril,
6. Occasional TCM medicines,
7. Sometimes NSAIDs from GP
We are convinced he will benefit from anticoagulation therapy and trust you will do the best for him and assume full responsibility for his anticoagulation management.

Thank you and Good Luck!
What comes with age?

• Age is an independent risk factor for bleeding and thrombosis

• Higher chance of sub- or supra- therapeutic anticoagulation
  – Lower initiating and maintenance dose
  – Multiple concomitant medical conditions
  – Polypharmacy and concomitant anti-platelet agents
  – Poorer compliance (social or physical incapacities)
Safety of oral anticoagulants in the elderly

<table>
<thead>
<tr>
<th>Indication</th>
<th>Therapeutic range (INR)</th>
<th>Mean duration of OAC</th>
<th>No. (age) of pts receiving OAC</th>
<th>Pts with major bleeding (%)</th>
<th>Incidence per treatment-year (%)</th>
<th>Ratio of incidence rates</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>2.0-4.5</td>
<td>2.0 vs 3.1y</td>
<td>197 (&gt;75) vs 358 (&lt;75)</td>
<td>8.1 vs 5.0</td>
<td>4.2 vs 1.7</td>
<td>2.5</td>
<td>16^a</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>2.0-4.5</td>
<td>1.1 vs 1.3y</td>
<td>50 (&gt;75) vs 198 (&lt;75)</td>
<td>10.0 vs 6.1</td>
<td>9.5 vs 4.8</td>
<td>2.0</td>
<td>17</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>2.0-4.5</td>
<td>0.8 vs 0.7y</td>
<td>966 (&gt;70) vs 1779 (&lt;70)</td>
<td>2.2 vs 0.4</td>
<td>2.9 vs 0.5</td>
<td>5.8</td>
<td>18</td>
</tr>
<tr>
<td>Mechanical heart valve prosthesis</td>
<td>3.0-4.5</td>
<td>3.6 vs 5.5y</td>
<td>67 (&gt;60) vs 204 (&lt;60)</td>
<td>13.4 vs 14.7</td>
<td>3.7 vs 2.7</td>
<td>1.4</td>
<td>19</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1.8-3.6^b</td>
<td>1.4 vs 1.7y</td>
<td>1244 (&gt;60) vs 1132 (&lt;60)</td>
<td>2.0 vs 1.1</td>
<td>1.4 vs 0.6</td>
<td>2.3</td>
<td>20</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>2.5-3.5</td>
<td>1.1 vs 1.0y</td>
<td>479 (&gt;60) vs 203 (&lt;60)</td>
<td>7.5 vs 3.0</td>
<td>6.8 vs 2.9</td>
<td>2.3</td>
<td>21</td>
</tr>
<tr>
<td>DVT, PE</td>
<td>2.0-3.0</td>
<td>2.6 vs 2.6mo</td>
<td>588 (&gt;60) vs 433 (&lt;60)</td>
<td>1.2 vs 0.7</td>
<td>1.4 vs 0.8^c</td>
<td>1.8</td>
<td>22^a</td>
</tr>
<tr>
<td>DVT</td>
<td>2.0-3.0</td>
<td>2.7 vs 2.7mo</td>
<td>227 (&gt;60) vs 173 (&lt;60)</td>
<td>0.0 vs 1.2</td>
<td>0.0 vs 1.3^c</td>
<td>0.0</td>
<td>23^a</td>
</tr>
</tbody>
</table>

Hutten BA et al Drugs & Aging 1999 Apr; 14 (4)
Risk of oral anticoagulant therapy with increasing age

Table 3. Hazard Ratios for Major Bleeding and Thromboembolic Events According to Age

<table>
<thead>
<tr>
<th>Event/Age, y</th>
<th>Events, No.</th>
<th>Patient-Years</th>
<th>Crude HR (95% CI)</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>24</td>
<td>1574</td>
<td>1.0 (Reference)</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>60-70</td>
<td>49</td>
<td>2358</td>
<td>1.3 (0.8-2.0)</td>
<td>1.3 (0.8-2.1)</td>
</tr>
<tr>
<td>71-80</td>
<td>68</td>
<td>2742</td>
<td>1.5 (1.0-2.4)</td>
<td>1.7 (1.0-2.5)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>47</td>
<td>1114</td>
<td>2.7 (1.7-4.4)</td>
<td>2.9 (1.7-4.8)</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>16</td>
<td>1574</td>
<td>1.0 (Reference)</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>60-70</td>
<td>32</td>
<td>2358</td>
<td>1.3 (0.7-2.4)</td>
<td>1.3 (0.7-2.5)</td>
</tr>
<tr>
<td>71-80</td>
<td>43</td>
<td>2742</td>
<td>1.6 (0.9-2.8)</td>
<td>1.7 (1.0-3.1)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>27</td>
<td>1114</td>
<td>2.2 (1.2-4.2)</td>
<td>2.7 (1.4-5.2)</td>
</tr>
</tbody>
</table>
Warfarin sensitivity and age

Wynne HA. Age and Ageing 1996:25:429-431
Warfarin sensitivity and age

Table 3 Relationship between clinic INR, dose of warfarin in maintenance phase and age (years)

<table>
<thead>
<tr>
<th></th>
<th>Age &lt;65</th>
<th>Age 65–74</th>
<th>Age 75 and above</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>320</td>
<td>241</td>
<td>178</td>
</tr>
<tr>
<td>Mean clinic INR (SD)</td>
<td>2.98 (1.1)</td>
<td>3.20 (1.2)</td>
<td>3.29 (1.6)</td>
</tr>
<tr>
<td>Number (%) with INR&gt;4.0</td>
<td>34 (11%)</td>
<td>32 (13%)</td>
<td>29 (16%)</td>
</tr>
<tr>
<td>Number (%) with INR&gt;6.0*</td>
<td>5 (2%)</td>
<td>8 (3%)</td>
<td>11 (6%)</td>
</tr>
<tr>
<td>Mean weekly dose (SD) (mg)</td>
<td>33.5 (14)</td>
<td>28.4 (14)</td>
<td>23.9 (11)</td>
</tr>
<tr>
<td>Median duration (IQR)</td>
<td>9 (3–46)</td>
<td>20 (4–64)</td>
<td>8 (3–58)</td>
</tr>
</tbody>
</table>

* Significant difference between age groups, Chi-square, p<0.05; IQR = inter-quartile range.
Warfarin sensitivity, age and pharmacogenetics


**A**

Warfarin daily dose (mg)

Age (years)

CYP2C9*1 and CYP2C9*2 genotypes combined

**B**

Warfarin daily dose (mg)

Age (years)

CYP2C9*1/*3 genotype
Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease


<table>
<thead>
<tr>
<th>Source or Subcategory</th>
<th>OAC+ Aspirin, n/N</th>
<th>OAC, n/N</th>
<th>OR, Fixed (95% CI)</th>
<th>Weight, %</th>
<th>OR, Fixed (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afran et al. 1976</td>
<td>7/57</td>
<td>7/65</td>
<td></td>
<td>10.83</td>
<td>1.16 (0.38-3.53)</td>
</tr>
<tr>
<td>Dale et al. 1980</td>
<td>7/75</td>
<td>5/73</td>
<td></td>
<td>8.68</td>
<td>1.40 (0.42-4.63)</td>
</tr>
<tr>
<td>Cohen et al. 1990</td>
<td>0/37</td>
<td>0/24</td>
<td></td>
<td></td>
<td>Not Estimable</td>
</tr>
<tr>
<td>Meade et al. 1992</td>
<td>12/127</td>
<td>9/1268</td>
<td></td>
<td>16.89</td>
<td>1.33 (0.56-3.16)</td>
</tr>
<tr>
<td>Turpie et al. 1993</td>
<td>24/186</td>
<td>19/184</td>
<td></td>
<td>31.42</td>
<td>1.29 (0.64-2.44)</td>
</tr>
<tr>
<td>Guliev et al. 1999</td>
<td>1/171</td>
<td>3/167</td>
<td></td>
<td>5.70</td>
<td>0.32 (0.03-3.12)</td>
</tr>
<tr>
<td>Laffort et al. 2000</td>
<td>21/109</td>
<td>10/120</td>
<td></td>
<td>14.51</td>
<td>2.63 (1.18-5.66)</td>
</tr>
<tr>
<td>Huyhn et al. 2001</td>
<td>2/44</td>
<td>1/45</td>
<td></td>
<td>1.73</td>
<td>2.10 (0.18-23.98)</td>
</tr>
<tr>
<td>Lechat et al. 2001</td>
<td>3/76</td>
<td>1/81</td>
<td></td>
<td>1.76</td>
<td>3.29 (0.33-32.31)</td>
</tr>
<tr>
<td>Casais et al. 2002</td>
<td>3/57</td>
<td>3/64</td>
<td></td>
<td>0.43</td>
<td>0.66 (0.15-2.67)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2389</td>
<td>2091</td>
<td></td>
<td>100.00</td>
<td>1.43 (1.06-2.02)</td>
</tr>
</tbody>
</table>

Total Events: 80 (OAC + Aspirin); 60 (OAC)
Test for Heterogeneity $\chi^2 = 5.79 (P = .07); I^2 = 0$
Test for Overall Effect: $Z = 1.98 (P = .05)$

Figure 4. Risk for major bleeding in patients receiving aspirin-oral anticoagulant (OAC) therapy or OAC therapy alone. CI indicates confidence interval; n/N, number of patients at risk/total number of patients in treatment group; and OR, odds ratio.
How should we treat our elderly patients on anticoagulants?

- Conservative warfarin dose at initiation (Role for pharmacogenetic testing)
- Appropriate monitoring intervals (without micromanaging INR) – value for bleeding risk assessment
- Narrower INR target ranges
- Omitting aspirins, NSAIDs and Chinese medicines
- Advise compliance. Be nice to him.
- Be ready to stop if the balance on the scale becomes unfavorable
- Consider alternative oral anticoagulants in some cases
## INITIATION OF WARFARIN
Target INR: 2.0-3.0

<table>
<thead>
<tr>
<th>Day</th>
<th>INR</th>
<th>Warfarin Dose (mg) For &lt; 70 Years</th>
<th>Warfarin Dose (mg) For &gt; 70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;1.4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>&lt;1.8</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1.8</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>&gt;1.8</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>&lt;1.2</td>
<td>6 to 8</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>1.2-1.5</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1.5-2.0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2.0-3.0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;3.0</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>4</td>
<td>&lt;1.3</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>1.3-1.5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>1.5-1.7</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1.7-2.0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2.0-2.5</td>
<td>2.5</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>2.5-3.0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3.0-3.5</td>
<td>1.5</td>
<td>Omit 1 day then 1mg</td>
</tr>
<tr>
<td></td>
<td>3.5-4.0</td>
<td>Omit 2 days then 0.5mg</td>
<td>Omit 1 day then 1mg</td>
</tr>
<tr>
<td></td>
<td>&gt;4.0</td>
<td>Omit 2 days then 0.5mg</td>
<td>Omit 2 days then 0.5mg</td>
</tr>
</tbody>
</table>

Warfarin initiation guide. SGH/NHC

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How should we treat our elderly patients on anticoagulants?

• Conservative warfarin dose at initiation (? Role for pharmacogenetic testing)

• Appropriate monitoring intervals (without micromanaging INR) – value for bleeding risk assessment

• Narrower INR target ranges

• Omitting aspirins, NSAIDs and Chinese medicines

• Advise compliance. Be nice to him.

• Be ready to stop if the balance on the scale becomes unfavorable

• Consider alternative oral anticoagulants in some cases
Predicting the risk of bleeding

<table>
<thead>
<tr>
<th>HAS-BLED SCORE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension &gt;160mmHg</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal/liver disease (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding tendency/predisposition</td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs (if on warfarin)</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (&gt;65)</td>
<td>1</td>
</tr>
<tr>
<td>Drug or Alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>
Where and which is your patient?

INR

Time

Anticoagulation Symposium & Workshop 2015
How should we treat our elderly patients on anticoagulants?

• Conservative warfarin dose at initiation (? Role for pharmacogenetic testing)
• Appropriate monitoring intervals (without micromanaging INR) – value for bleeding risk assessment
• Narrower INR target ranges
• Omitting aspirins, NSAIDs and Chinese medicines
• Advise compliance. Be nice to him.
• Be ready to stop if the balance on the scale becomes unfavorable
• Consider alternative oral anticoagulants in some cases
INR ranges and complications

Table 5. Incidence Rates of Ischemic Stroke and Intracranial Hemorrhage among Patients with Nonvalvular Atrial Fibrillation Who Were Taking Warfarin, According to the International Normalized Ratio (INR) at the Time of the Stroke.*

<table>
<thead>
<tr>
<th>INR</th>
<th>Person-yr</th>
<th>Stroke (95% CI) (N=152)</th>
<th>Intracranial Hemorrhage (95% CI) (N=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.5</td>
<td>556</td>
<td>7.7 (5.7–10.4)</td>
<td>0.5 (0.2–1.7)</td>
</tr>
<tr>
<td>1.5–1.9</td>
<td>2847</td>
<td>1.9 (1.4–2.4)</td>
<td>0.3 (0.1–0.6)</td>
</tr>
<tr>
<td><strong>2.0–2.5</strong></td>
<td>5357</td>
<td><strong>0.4 (0.3–0.7)</strong></td>
<td><strong>0.3 (0.2–0.4)</strong></td>
</tr>
<tr>
<td>2.6–3.0</td>
<td>2388</td>
<td>0.9 (0.6–1.4)</td>
<td>0.5 (0.3–0.9)</td>
</tr>
<tr>
<td>3.1–3.5</td>
<td>834</td>
<td>0.7 (0.3–1.6)</td>
<td>0.6 (0.3–1.4)</td>
</tr>
<tr>
<td>3.6–3.9</td>
<td>243</td>
<td>0.4 (0.1–2.9)</td>
<td>0.4 (0.1–2.9)</td>
</tr>
<tr>
<td>4.0–4.5</td>
<td>144</td>
<td>1.4 (0.4–5.5)</td>
<td>2.7 (1.0–7.3)</td>
</tr>
<tr>
<td>&gt;4.5</td>
<td>115</td>
<td>2.6 (0.8–8.1)</td>
<td>9.4 (5.2–16.9)</td>
</tr>
</tbody>
</table>

Real-World Impact of Setting a Narrow International Normalized Ratio Target Range in the Management of Older Adult Patients on Warfarin

Peter Y. S. Ong, BSc¹, Narendran Koomanan, BSc¹, McVin H. H. Cheen, BSc¹,², Yi Feng Lai, BSc¹, Seng Han Lim, BSc¹,², Ming Chai Kong, BSc¹, and Heng Joo Ng, MBBS, MMed³

Table 5. Percentage Time Below INR 2.0, Above INR 2.5, and 3.0.

<table>
<thead>
<tr>
<th></th>
<th>INR 2.0-2.5 Group (n = 150)</th>
<th>INR 2.0-3.0 Group (n = 164)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time below INR 2.0</td>
<td>36.82 (25.38)</td>
<td>35.73 (28.17)</td>
<td>.72</td>
</tr>
<tr>
<td>Time above INR 2.5</td>
<td>17.56 (15.60)</td>
<td>27.65 (25.23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time above INR 3.0</td>
<td>4.53 (8.40)</td>
<td>6.85 (10.54)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: INR, international normalized ratio; SD, standard deviation.

Table 6. Number of Hospitalization Events per 100 Patient-Years.

<table>
<thead>
<tr>
<th>Clinical Events</th>
<th>INR 2.0-2.5 Group (n = 150)</th>
<th>INR 2.0-3.0 Group (n = 164)</th>
<th>Adjusted Incidence Rate Ratio (IRR)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Hospitalizations per 100 patient-years</td>
<td>All bleeding 4.22</td>
<td>7.87</td>
<td>0.34&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(0.12-0.95)</td>
</tr>
<tr>
<td></td>
<td>Minor bleeding 2.92</td>
<td>4.63</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Major bleeding 1.30</td>
<td>3.24</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Thromboembolic 2.27</td>
<td>3.24</td>
<td>0.51&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(0.13-1.97)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; INR, international normalized ratio.

<sup>a</sup>IRR was adjusted for age, gender, ethnicity, indications for warfarin, study treatment duration and HAS-BLED scores.

<sup>b</sup>IRR was adjusted for age, gender, ethnicity, indications for warfarin, study treatment duration, history of trauma and immobility.
How should we treat our elderly patients on anticoagulants?

• Conservative warfarin dose at initiation (? Role for pharmacogenetic testing)

• Appropriate monitoring intervals (without micromanaging INR) – value for bleeding risk assessment

• Narrower INR target ranges

• Omitting aspirins, NSAIDs and Chinese medicines

• Advise compliance... be nice to him

• Be ready to stop if the balance on the scale becomes unfavorable

• Consider alternative oral anticoagulants in some cases
NOACs for the elderly?

• No contraindication by age
• Be aware of manufacturer recommendations on dosage adjustments
• Take into account co-morbidities e.g. renal function
• Certain situations where NOACs may be superior to warfarin
  – Difficult titration
  – Difficulties with coming for monitoring
  – Concerns about intracranial bleeds
Chronic Kidney Disease
• CKD associated with increased risk of strokes or systemic embolism and bleeding in AF patients
• Warfarin reduces strokes or systemic embolism
• Warfarin and aspirin increases risk of bleeding in CKD patients

Warfarin dosing in CKD

Warfarin and the CKD patient

• Inherent increase in bleeding and thrombotic risk
  – Uremia and associated platelet dysfunction
  – Thrombocytopenia
  – Instrumentations and indwelling catheters
  – Loss of natural anticoagulants e.g nephrotic syndrome

• Reduced metabolism of warfarin

• Closer monitoring and less aggressive initiation and titration
**LMWH and the CKD patient**

Meta analysis: low molecular weight heparin and bleeding in patients with severe renal insufficiency

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Patients with Renal Insufficiency, n/n</th>
<th>Patients with No Renal Insufficiency, n/n</th>
<th>Peto OR (95% CI)</th>
<th>Weight, %</th>
<th>Peto OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collet et al., 2001 (39)</td>
<td>0/28</td>
<td>1/83</td>
<td>2.14</td>
<td></td>
<td>0.26 (0.00–23.94)</td>
</tr>
<tr>
<td>Chow et al., 2003 (30)</td>
<td>0/5</td>
<td>0/13</td>
<td>5.08</td>
<td>100</td>
<td>0.28 (0.01–5.16)</td>
</tr>
<tr>
<td>Khazan et al. (adjusted), 2003 (28)</td>
<td>0/10</td>
<td>3/42</td>
<td>15.71</td>
<td></td>
<td>1.33 (0.25–7.05)</td>
</tr>
<tr>
<td>Khazan et al. (prophylactic), 2003 (28)</td>
<td>3/36</td>
<td>3/47</td>
<td>9.17</td>
<td></td>
<td>3.09 (0.35–27.31)</td>
</tr>
<tr>
<td>Khazan et al. (therapeutic), 2003 (28)</td>
<td>2/17</td>
<td>3/61</td>
<td>16.95</td>
<td></td>
<td>10.05 (2.02–49.98)</td>
</tr>
<tr>
<td>Spiller et al., 2003 (29)</td>
<td>5/69</td>
<td>74/3432</td>
<td>2.83</td>
<td></td>
<td>8.26 (0.16–418.42)</td>
</tr>
<tr>
<td>Green et al., 2005 (18)</td>
<td>1/18</td>
<td>0/20</td>
<td>2.36</td>
<td></td>
<td>0.24 (0.00–17.90)</td>
</tr>
<tr>
<td>Kruse and Lee, 2004 (19)</td>
<td>0/50</td>
<td>1/120</td>
<td>2.85</td>
<td></td>
<td>9.77 (19.61–48752.07)</td>
</tr>
<tr>
<td>Macie et al., 2004 (24)</td>
<td>2/7</td>
<td>6/201</td>
<td>37.84</td>
<td></td>
<td>1.85 (0.63–5.40)</td>
</tr>
<tr>
<td>Peng et al., 2004 (26)</td>
<td>0/7</td>
<td>0/43</td>
<td>5.06</td>
<td></td>
<td>2.74 (0.15–51.73)</td>
</tr>
<tr>
<td>Thorevska et al., 2004 (27)</td>
<td>7/65</td>
<td>11/171</td>
<td>100</td>
<td>100</td>
<td>2.59 (1.34–5.01)</td>
</tr>
</tbody>
</table>

Therapeutic dose

<table>
<thead>
<tr>
<th>Study</th>
<th>Adjusted dose</th>
<th>Favors Reduction in Bleeding</th>
<th>Favors Increase in Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chow et al., 2003 (30)</td>
<td>0/5</td>
<td>0/13</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Khazan et al. (therapeutic), 2003 (28)</td>
<td>2/17</td>
<td>3/61</td>
<td>12.77</td>
</tr>
<tr>
<td>Spinler et al., 2003 (29)</td>
<td>5/69</td>
<td>74/3432</td>
<td>23.58</td>
</tr>
<tr>
<td>Macie et al., 2004 (24)</td>
<td>2/7</td>
<td>6/201</td>
<td>3.97</td>
</tr>
<tr>
<td>Peng et al., 2004 (26)</td>
<td>0/7</td>
<td>0/43</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Thorevska et al., 2004 (27)</td>
<td>7/65</td>
<td>11/171</td>
<td>52.65</td>
</tr>
<tr>
<td>Bazinet et al., 2005 (17)</td>
<td>1/36</td>
<td>2/160</td>
<td>7.03</td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 206 4081

Total events: 17 (renal insufficiency), 96 (no renal insufficiency)

Test for heterogeneity: Chi-square = 10.97 (P = 0.03), I² = 63.5%

Test for overall effect: Z = 3.41 (P = 0.0007)

Adjusted dose

<table>
<thead>
<tr>
<th>Study</th>
<th>Adjusted dose</th>
<th>Favors Reduction in Bleeding</th>
<th>Favors Increase in Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collet et al., 2001 (39)</td>
<td>0/28</td>
<td>1/83</td>
<td>17.25</td>
</tr>
<tr>
<td>Khazan et al. (adjusted), 2003 (28)</td>
<td>0/10</td>
<td>3/42</td>
<td>40.95</td>
</tr>
<tr>
<td>Green et al., 2005 (18)</td>
<td>1/18</td>
<td>0/20</td>
<td>22.80</td>
</tr>
<tr>
<td>Kruse and Lee, 2004 (19)</td>
<td>0/50</td>
<td>1/120</td>
<td>18.99</td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 106 265

Total events: 1 (renal insufficiency), 5 (no renal insufficiency)

Test for heterogeneity: Chi-square = 2.28 (P = 0.52), I² = 0%

Test for overall effect: Z = 3.41 (P = 0.0007)
### Tinzaparin and CKD – the IRIS study

<table>
<thead>
<tr>
<th></th>
<th>Anti-FXa activity (IU mL⁻¹) on day 2/3</th>
<th>Anti-FXa activity (IU mL⁻¹) on day 5/VS</th>
<th>Anti-FXa accumulation ratio Mean ± SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with severe reninal impairment (CrCl ≤ 30 mL min⁻¹; n = 21)</td>
<td>0.97 ± 0.47 (0.32–2.08)</td>
<td>0.96 ± 0.36 (0.38–1.69)</td>
<td>1.05 ± 0.25 (0.64–1.49)</td>
</tr>
<tr>
<td>Patients with moderate renal impairment (30 &lt; CrCl ≤ 60 mL min⁻¹; n = 66)</td>
<td>0.82 ± 0.28 (0.39–1.89)</td>
<td>0.84 ± 0.29 (0.32–1.81)</td>
<td>1.07 ± 0.31 (0.37–1.73)</td>
</tr>
<tr>
<td>Total (n = 87)</td>
<td>0.86 ± 0.34 (0.32–2.08)</td>
<td>0.87 ± 0.31 (0.32–1.81)</td>
<td>1.06 ± 0.30 (0.37–1.73)</td>
</tr>
</tbody>
</table>

CrCl, creatinine clearance; SD, standard deviation; VS, visit S.

Renal impairment

- Moderate renal impairment (CCT >30 ml/mi) - 2.5 mg (prophylaxis) appears safe
- VTE treatment – use with caution – no definitive recommendations
- CCT<30 ml/min or on dialysis - contraindicated
CKD and the heparins

• ? Consider unfractionated heparin
• Adjusted dose low molecular weight heparins
• Monitoring anti-Xa levels for LMWH (where available)
• Limit duration of use where possible
CKD and NOACs

For all NOACs
• Creatinine clearance >50 ml/min – OK
• Creatinine clearance 30-50ml/min – use with caution

Creatinine < 30 ml/min – why do you want to look for trouble?
Anticoagulating the obese
Warfarin dosing and body weight

Comparison of initial dosing – obese vs non-obese

<table>
<thead>
<tr>
<th>BMI category</th>
<th>Discharge dose (mg) ±SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (n = 10)</td>
<td>4.3 ± 0.8</td>
<td>0.9146</td>
</tr>
<tr>
<td>Normal (n = 45)</td>
<td>4.4 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Overweight (n = 48)</td>
<td>5.3 ± 0.5</td>
<td>0.1979</td>
</tr>
<tr>
<td>Obese (n = 71)</td>
<td>6.7 ± 0.5</td>
<td>0.007</td>
</tr>
<tr>
<td>Morbidly obese (n = 37)</td>
<td>6.7 ± 0.7</td>
<td>0.0062</td>
</tr>
</tbody>
</table>

LMWH in the obese

• VTE Prophylaxis
  – Weight adjusted doses may be more appropriate in obese patients e.g 0.5 mg/kg/day of enoxaparin instead of 40 mg om
LMWH in the obese

• VTE treatment
  – Dose capping may not be necessary in patients with normal renal function
    Hainer JW et al. Thromb Haemostat 2002;87(5) 817-23
  – Consider anti-Xa monitoring if available for extremes of weight (e.g >160 kg)

NOACs

• No weight adjustment recommendations
Anticoagulating the pregnant
Warfarin in pregnancy

• Crosses placenta

• Exposure in first trimester
  – Embryopathy
    • nasal hypoplasia and/or stippled epiphyses
    • limb hypoplasia

• Exposure in any period
  • CNS abnormalities (including ventral midline dysplasia, dorsal midline dysplasia)
  • Spontaneous abortion
  • Fetal hemorrhage
  • Fetal death
Practical recommendations

• Patients on long term warfarin
  – Stop and see doctor the moment they miss period and confirm pregnancy

• VTE treatment
  – Weight adjusted low molecular weight heparin/(UFH)
  – Monitoring of anti-Xa usually not necessary

• VTE/pregnancy loss(APS) prophylaxis
  – LMWH/(UFH)
• Mechanical cardiac valves
  – Weight adjusted LMWH/(UFH) throughout pregnancy
  – Consider anti-Xa monitoring
  – LMWH in the first 12\textsuperscript{th} weeks followed by warfarin
Cancer and Thrombosis
Cancer and Thrombosis

- Cancer patients have a six-fold increase risk of VTE
- Risk highest with
  - Malignant brain tumour
  - Adenocarcinoma of the lung, ovary, pancreas, colon, stomach, prostate and kidney
  - Haematologic malignancies
- Chemotherapy and hormonal manipulation as well as IV catheters further increase risk
Risk assessment for inpatient VTE prophylaxis

### Table 2—Risk Factors for VTE in Hospitalized Medical Patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3</td>
</tr>
<tr>
<td>Previous VTE (with the exclusion of superficial vein thrombosis)</td>
<td>3</td>
</tr>
<tr>
<td>Reduced mobility&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3</td>
</tr>
<tr>
<td>Already known thrombophilic condition&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3</td>
</tr>
<tr>
<td>Recent (≤ 1 mo) trauma and/or surgery</td>
<td>2</td>
</tr>
<tr>
<td>Elderly age (≥ 70 y)</td>
<td>1</td>
</tr>
<tr>
<td>Heart and/or respiratory failure</td>
<td>1</td>
</tr>
<tr>
<td>Acute myocardial infarction or ischemic stroke</td>
<td>1</td>
</tr>
<tr>
<td>Acute infection and/or rheumatologic disorder</td>
<td>1</td>
</tr>
<tr>
<td>Obesity (BMI ≥ 30)</td>
<td>1</td>
</tr>
<tr>
<td>Ongoing hormonal treatment</td>
<td>1</td>
</tr>
</tbody>
</table>
Cancer and VTE prevention

4.2.1. In outpatients with cancer who have no additional risk factors for VTE, we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) and recommend against the prophylactic use of VKAs (Grade 1B).

4.2.2. In outpatients with solid tumors who have additional risk factors for VTE and who are at low risk of bleeding, we suggest prophylactic-dose LMWH or LDUH over no prophylaxis (Grade 2B).
Cancer patients and chemotherapy

The problems with oral anticoagulation in cancer patients

- Difficult to maintain INR within therapeutic range – anorexia, vomiting, drug interactions
- Frequent interruptions by disease or chemotherapy induced thrombocytopenia or invasive procedures
• Frequent monitoring may be required – logistically difficult for sick patients to come for monitoring visits, difficult venous access

What is the case for low molecular weight heparin beyond initial therapy for VTE?
LMWH vs coumarin for the prevention of recurrent venous thromboembolism in patients with cancer (CLOT Study)

• Dalteparin vs warfarin for 6 months
• VTE – 8.8% vs 17.4%. Hazard ratio 0.48, p = 0.0017
• Major bleeding – 5.6% vs 3.6% (NS)
• Any bleeding – 13.6% vs 18.5% (p=0.09)
Why LMWH instead of warfarin in cancer patients?

• Reduces rate of recurrent VTE
• No significantly increased risk of bleeding
• Avoids need for laboratory monitoring and frequent hospital visits
• Can be easily disrupted for thrombocytopenia and invasive procedures
### NOACs and Cancer Patients

#### Efficacy with NOAC in patients with cancer

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>EINSTEIN 2010</td>
<td>4 118</td>
<td>5 89</td>
<td>20.2%</td>
<td>0.59 [0.15–2.26]</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN PE 2012</td>
<td>2 114</td>
<td>3 109</td>
<td>13.0%</td>
<td>0.63 [0.10–3.85]</td>
<td></td>
</tr>
<tr>
<td>LEVINE et al 2012</td>
<td>0 93</td>
<td>3 29</td>
<td>5.4%</td>
<td>0.04 [0.00–0.81]</td>
<td></td>
</tr>
<tr>
<td>MAGELLAN, 2013</td>
<td>20 202</td>
<td>15 203</td>
<td>40.7%</td>
<td>1.38 [0.68–2.77]</td>
<td></td>
</tr>
<tr>
<td>RE-COVER 2009</td>
<td>2 64</td>
<td>3 57</td>
<td>12.8%</td>
<td>0.58 [0.09–3.61]</td>
<td></td>
</tr>
<tr>
<td>RE-MEDY 2013</td>
<td>2 60</td>
<td>1 59</td>
<td>7.9%</td>
<td>2.00 [0.18–22.67]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 651 546 100.0%

Total events: 30 30

Heterogeneity: $\chi^2 = 21$; df = 5 ($P = 0.24$); $I^2 = 26$

Test for overall effect: $Z = 0.61$ ($P = 0.54$)

#### Clinically relevant bleeding with NOAC in patients with cancer

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>EINSTEIN 2010</td>
<td>17 118</td>
<td>14 88</td>
<td>36.3%</td>
<td>0.89 [0.41–1.92]</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN PE 2012</td>
<td>14 114</td>
<td>10 108</td>
<td>31.6%</td>
<td>1.37 [0.58–3.24]</td>
<td></td>
</tr>
<tr>
<td>LEVINE et al 2012</td>
<td>6 93</td>
<td>1 29</td>
<td>7.1%</td>
<td>1.93 [0.22–16.73]</td>
<td></td>
</tr>
<tr>
<td>MAGELLAN, 2013</td>
<td>16 294</td>
<td>5 290</td>
<td>25.0%</td>
<td>3.28 [1.19–9.08]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 619 515 100.0%

Total events: 53 30

Heterogeneity: $\chi^2 = 1.01$; df = 3 ($P = 0.25$); $I^2 = 27$

Test for overall effect: $Z = 1.32$ ($P = 0.19$)

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Anticoagulation Symposium & Workshop 2015
The effects of fasting in Muslim patients taking warfarin

Y. F. LAI,* M. H. H. CHEEN,* S. H. LIM,* F. H. I. YEO,* S. C. NAH,* M. C. KONG,* D. MYA,† L. H. LEE† and H. J. NG†
*Department of Pharmacy, Singapore General Hospital; and †Department of Haematology, Singapore General Hospital, Singapore

Fig. 2. Fluctuations in quality of anticoagulation across study periods.
Thank you