Towards Better Patient Care – Education and Self Monitoring

Kong Ming Chai
Senior Principal Clinical Pharmacist
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Outline
1. Warfarin Counseling
2. Self Monitoring, Self-Testing
1. Common misconception with patient education on warfarin

1. Patient stopped eating all green vegetables?

2. Patient skip the dose if forget to take in the morning?

3. How come need to do frequent INR testing?

4. What is INR?

5. Warfarin have a lot of interaction, cannot eat this, cannot eat that, cannot do any exercise in case of injury........

6. Patient stopped warfarin on their own, wanted to try and see what would happen?
Objectives

• To review the steps of warfarin counseling and importance of effective patient counseling

• To educate pharmacist to become a more effective counselor
Outlines

- WHO should be counseled?
- WHY should counseling be performed?
- HOW should counseling be performed?
Newly started/already on warfarin for various indication

**Prophylaxis** - effective prevention of serious vascular events for high-risk patients
- Atrial Fibrillation
- Prosthetic heart valves
- Tissue Heart Valves
- Venous Thrombo Embolism (VTE) Prophylaxis

**Treatment of Acute arterial or venous thrombosis**
- Coronary Heart Disease
- Myocardial Infarction
- Deep Vein thrombosis
- Pulmonary embolism

![Diagram of arterial and venous thrombosis](image)
 WHY Counsel?
• To promote safe and effective use of medicine
  – Adherence to medications
  – Cope any potential medication side effects
  – Highlight the potential drug interactions with OTC, herbs and prescription medications
HOW to counsel?

• Be aware of barriers to counseling
  – Disease state : dementia, stroke
  – Primary caregiver : family, maid
  – Language : verify primary language
  – Hearing/vision problems
  – Environmental : noise, lack of privacy
  – Educational level : reading ability
  – Patient motivation
Prior to Counseling

3 basic questions to ask...
## Target INR

<table>
<thead>
<tr>
<th>Indication</th>
<th>INR</th>
<th>Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thromboembolism (including pulmonary embolism)</td>
<td>2.0–3.0</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Thromboembolic complications associated with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.0–3.0</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Bioprosthetic heart valves</td>
<td>2.0–3.0</td>
<td>6-12 weeks</td>
</tr>
<tr>
<td>Mechanical heart valves</td>
<td>2.5–3.5</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Post-myocardial infarction</td>
<td>2.0–3.0</td>
<td>Lifetime</td>
</tr>
</tbody>
</table>

Note: an INR of greater than 4.0 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding.
Effective Communication Skills

• Proper environment
  – Private, quiet
  – Free from distractions, e.g. ask patient to lower volume on TV

• Introduce yourself
  – Greet the patient
  – Explain your purpose
  – Ask the patient’s permission to counsel
Effective Communication Skills

• Know your audience
  – Educational level: tailor talk for understanding

  – Use appropriate language eg English, Bahasa Malay, Mandarin, dialects

  – Religious or ethnic beliefs, e.g. asking Muslim patients about alcohol intake
Effective Communication Skills

• 3 ‘S’
  – Specific
  – Selective
  – Sensitive

• Sensitive/empathetic
  – Listen to the patient
  – Speak distinctly and clearly
  – Return later if patient is not alert, distracted etc.
Specific & selective counseling
Case Study

- Mr TKS, 40 yo Male, Chinese
- Occupation: professional
- Indication for warfarin: Proximal DVT
- Started on warfarin:

<table>
<thead>
<tr>
<th>Date</th>
<th>Warfarin Dose (mg)</th>
<th>INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/02/2010</td>
<td>5mg</td>
<td>-</td>
</tr>
<tr>
<td>07/02/2010</td>
<td>3mg</td>
<td>-</td>
</tr>
<tr>
<td>08/02/2010</td>
<td>3mg</td>
<td>1.7</td>
</tr>
</tbody>
</table>

- What is the target INR?
- What is the duration of treatment?
Case Study

- Mr TKS, 40 yo Male, Chinese
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</tr>
<tr>
<td>08/02/2010</td>
<td>3mg</td>
<td>1.7</td>
</tr>
</tbody>
</table>

- What is the target INR? 2-3
- What is the duration of treatment? 6 months
Mode of action

• Treatment of DVT/PE:
  – Warfarin does NOT dissolve clots that have already formed.
  – Warfarin stabilize the clots so that it will not grow bigger; prevent embolism
  – Our natural process e.g. plasminogen to dissolve the clots and WBC to engulf the clot (3-6 months)

• How does warfarin stabilize the clot?
• How is it metabolized and cleared from the body?
• How long does warfarin takes to work?
Factors, 30% to 50%

Protein C
Protein S
Vitamin K Utilization Reduced

Synthesis of Dysfunctional Coagulation Factors, reduction by 30% to 50%.
**Administration**

- Once daily with water
- Regular timing, e.g. 8am
- With/Without food
- If missed, take within 8hrs of usual timing eg before 4pm
- Do not double dose
- Record missed dose and inform doctors/pharmacist

- *Must warfarin be strictly taken with food?*
- *Does it matter if I take warfarin at night?*
- *What will happen if I missed my medicine?*
Blood tests

• International Normalized Ratio
  – Routine monitoring to establish effectiveness of warfarin anticoagulation therapy
  – Time taken for blood to clot as compared to control

• Target INR: 2-3

• How do you calculate INR?
• I still don’t understand. What does this mean?
• So what if my INR is not within range?
INR = International Normalized Ratio

ISI  = International sensitivity index

PT  = Prothrombin Time

\[ \text{INR} = \frac{\text{Patient’s PT in seconds}}{\text{Mean normal PT in seconds}} \times \text{ISI} \]
Narrow therapeutic range

Intensity of Anticoagulation (INR)

Clinical Events

Thromboembolic

Therapeutic Window

Hemorrhagic
Thromboembolic risk in AF patient

- PTR above 2.0 (INR of 3.7 to 4.3) increases the risk of bleeding
- The estimated odds ratio of subdural hemorrhage increased 7.6 fold as the PTR increased from 2.0 to 2.5

Bleeding risk

- Bleeding of gums/nose
- Blood in urine
- Black sticky foul stools
- Unexplained bruising

- Can I die from the major bleeding?
- Why are you giving me a medication that will cause me to bleed and die?
- When should I seek medical help at the A&E?
- How long does the bruise take to subside?
Dose adjustment

• Dose adjustment is necessary to reach target INR range.
  - Anticipate frequent blood monitoring and f/u

• I have already on warfarin. Why do I still need to take clexane injection?
• How much blood is required for monitoring?
• How often do I have to come back for f/u during the initial stage of dose titration?
Drug-Food interaction

- Diet high in Vitamin K are known to inhibit and decrease the warfarin effect
- Daily requirement of Vit K is 1mcg/kg/day
- Recommended dietary allowance of Vitamin K for adult male is 80mcg and for female is 65mcg.

- Is there Vit K diet available? **NO**
- What are some of the food that are rich in Vit K?
- How should my diet be control?
# Warfarin : Drug-Food interaction

**USDA National Nutrient Database for Standard Reference, Release 17**

Vitamin K (phylloquinone)(µg) Content of Selected Foods per Common Measure, sorted by nutrient content

<table>
<thead>
<tr>
<th>Description</th>
<th>Weight (g)</th>
<th>Common Measure</th>
<th>Content per Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kale, frozen, cooked, boiled, drained, without salt</td>
<td>130</td>
<td>1 cup</td>
<td>1146.6</td>
</tr>
<tr>
<td>Kale, cooked, boiled, drained, without salt</td>
<td>130</td>
<td>1 cup</td>
<td>1062.1</td>
</tr>
<tr>
<td>Collards, frozen, chopped, cooked, boiled, drained, without salt</td>
<td>170</td>
<td>1 cup</td>
<td>1059.4</td>
</tr>
<tr>
<td>Spinach, frozen, chopped or leaf, cooked, boiled, drained, without salt</td>
<td>190</td>
<td>1 cup</td>
<td>1027.3</td>
</tr>
<tr>
<td>Spinach, canned, drained solids</td>
<td>214</td>
<td>1 cup</td>
<td>987.8</td>
</tr>
<tr>
<td>Spinach, cooked, boiled, drained, without salt</td>
<td>180</td>
<td>1 cup</td>
<td>888.5</td>
</tr>
<tr>
<td>Turnip greens, frozen, cooked, boiled, drained, without salt</td>
<td>164</td>
<td>1 cup</td>
<td>851.0</td>
</tr>
<tr>
<td>Collards, cooked, boiled, drained, without salt</td>
<td>190</td>
<td>1 cup</td>
<td>836.0</td>
</tr>
<tr>
<td>Beet greens, cooked, boiled, drained, without salt</td>
<td>144</td>
<td>1 cup</td>
<td>697.0</td>
</tr>
<tr>
<td>Turnip greens, cooked, boiled, drained, without salt</td>
<td>144</td>
<td>1 cup</td>
<td>529.3</td>
</tr>
<tr>
<td>Mustard greens, cooked, boiled, drained, without salt</td>
<td>140</td>
<td>1 cup</td>
<td>419.3</td>
</tr>
<tr>
<td>Brussels sprouts, frozen, cooked, boiled, drained, without salt</td>
<td>155</td>
<td>1 cup</td>
<td>299.9</td>
</tr>
<tr>
<td>Broccoli, cooked, boiled, drained, without salt</td>
<td>156</td>
<td>1 cup</td>
<td>220.1</td>
</tr>
<tr>
<td>Brussels sprouts, cooked, boiled, drained, without salt</td>
<td>156</td>
<td>1 cup</td>
<td>218.9</td>
</tr>
<tr>
<td>Onions, spring or scallions (includes tops and bulb), raw</td>
<td>100</td>
<td>1 cup</td>
<td>207.0</td>
</tr>
<tr>
<td>Dandelion greens, cooked, boiled, drained, without salt</td>
<td>105</td>
<td>1 cup</td>
<td>203.6</td>
</tr>
<tr>
<td>Broccoli, frozen, chopped, cooked, boiled, drained, without salt</td>
<td>184</td>
<td>1 cup</td>
<td>183.1</td>
</tr>
</tbody>
</table>
## Warfarin: Drug-Food Interaction

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<th>Weight (g)</th>
<th>Common Measure</th>
<th>Content per Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lettuce, butterhead (includes boston and bibb types), raw</td>
<td>163</td>
<td>1 head</td>
<td>166.7</td>
</tr>
<tr>
<td>Parsley, raw</td>
<td>10</td>
<td>10 sprigs</td>
<td>164.0</td>
</tr>
<tr>
<td>Noodles, egg, spinach, cooked, enriched</td>
<td>160</td>
<td>1 cup</td>
<td>161.8</td>
</tr>
<tr>
<td>Spinach, raw</td>
<td>30</td>
<td>1 cup</td>
<td>144.9</td>
</tr>
<tr>
<td>Asparagus, frozen, cooked, boiled, drained, without salt</td>
<td>180</td>
<td>1 cup</td>
<td>144.0</td>
</tr>
<tr>
<td>Sauerkraut, canned, solids and liquids</td>
<td>236</td>
<td>1 cup</td>
<td>135.0</td>
</tr>
<tr>
<td>Lettuce, iceberg (includes crisphead types), raw</td>
<td>539</td>
<td>1 head</td>
<td>129.9</td>
</tr>
<tr>
<td>Endive, raw</td>
<td>50</td>
<td>1 cup</td>
<td>115.5</td>
</tr>
<tr>
<td>Lettuce, green leaf, raw</td>
<td>56</td>
<td>1 cup</td>
<td>97.2</td>
</tr>
<tr>
<td>Broccoli, raw</td>
<td>88</td>
<td>1 cup</td>
<td>89.4</td>
</tr>
<tr>
<td>Okra, frozen, cooked, boiled, drained, without salt</td>
<td>184</td>
<td>1 cup</td>
<td>88.0</td>
</tr>
<tr>
<td>Cabbage, cooked, boiled, drained, without salt</td>
<td>150</td>
<td>1 cup</td>
<td>73.4</td>
</tr>
<tr>
<td>Rhubarb, frozen, cooked, with sugar</td>
<td>240</td>
<td>1 cup</td>
<td>71.0</td>
</tr>
<tr>
<td>Plums, dried (prunes), stewed, without added sugar</td>
<td>248</td>
<td>1 cup</td>
<td>64.7</td>
</tr>
<tr>
<td>Okra, cooked, boiled, drained, without salt</td>
<td>160</td>
<td>1 cup</td>
<td>64.0</td>
</tr>
<tr>
<td>Cowpeas (blackeyes), immature seeds, frozen, cooked, boiled, drained, without salt</td>
<td>170</td>
<td>1 cup</td>
<td>62.6</td>
</tr>
<tr>
<td>Pie crust, cookie-type, prepared from recipe, graham cracker, baked</td>
<td>239</td>
<td>1 pie shell</td>
<td>59.0</td>
</tr>
<tr>
<td>Cabbage, chinese (pak-choi), cooked, boiled, drained, without salt</td>
<td>170</td>
<td>1 cup</td>
<td>57.8</td>
</tr>
<tr>
<td>Lettuce, cos or romaine, raw</td>
<td>56</td>
<td>1 cup</td>
<td>57.4</td>
</tr>
<tr>
<td>Celery, cooked, boiled, drained, without salt</td>
<td>150</td>
<td>1 cup</td>
<td>56.7</td>
</tr>
<tr>
<td>Fast foods, coleslaw</td>
<td>99</td>
<td>3/4 cup</td>
<td>56.4</td>
</tr>
<tr>
<td>Bread crumbs, dry, grated, seasoned</td>
<td>120</td>
<td>1 cup</td>
<td>55.2</td>
</tr>
</tbody>
</table>
## Warfarin : Drug-Food interaction – Enteral Feeds

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>Unit</th>
<th>Vit K Content / unit</th>
<th>Vit K Content / 100ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucerna</td>
<td>Specialized nutritional formula for diabetic patients</td>
<td>250ml can</td>
<td>15 mcg</td>
<td>6 mcg</td>
</tr>
<tr>
<td>Resource Diabetic</td>
<td>Complete liquid supplement with fibre to improve glucose control in diabetic patients</td>
<td>237ml can</td>
<td>16 mcg</td>
<td>6.8 mcg</td>
</tr>
<tr>
<td>Ensure</td>
<td>Complete, balance nutrition</td>
<td>250ml can</td>
<td>20 mcg</td>
<td>8 mcg</td>
</tr>
<tr>
<td>Novasource</td>
<td>Calorically-dense, high nitrogen, complete liquid formula for the management of fluid restriction</td>
<td>237ml can</td>
<td>20 mcg</td>
<td>8.4 mcg</td>
</tr>
<tr>
<td>Pulmocare</td>
<td>Nutritional formula for patients with respiratory insufficiency of COPD or ventilator-dependent</td>
<td>237ml can</td>
<td>20 mcg</td>
<td>8.4 mcg</td>
</tr>
<tr>
<td>Resource Standard</td>
<td>Nutritionally balance food supplement</td>
<td>237ml can</td>
<td>20 mcg</td>
<td>8.4 mcg</td>
</tr>
<tr>
<td>Resource Plus</td>
<td>High-calorie formula for nutritionally compromised patients</td>
<td>237ml can</td>
<td>20 mcg</td>
<td>8.4 mcg</td>
</tr>
<tr>
<td>Suplena</td>
<td>Specialized nutrition for low protein, electrolyte and fluid requirements</td>
<td>237ml can</td>
<td>20 mcg</td>
<td>8.4 mcg</td>
</tr>
<tr>
<td>Nephro</td>
<td>A moderate-protein, nutritionally complete formula with a vitamin-mineral profile specifically designed for the dialyzed patient with chronic or acute renal failure</td>
<td>237ml can</td>
<td>20 mcg</td>
<td>8.4 mcg</td>
</tr>
<tr>
<td>Isocal</td>
<td>Nutritional complete formula</td>
<td>237ml can</td>
<td>31 mcg</td>
<td>13 mcg</td>
</tr>
<tr>
<td>Jevity</td>
<td>Complete nutrition with fibre to regulate bowel movement</td>
<td>946ml can</td>
<td>58 mcg</td>
<td>6 mcg</td>
</tr>
</tbody>
</table>
Vegetables

- Vegetables high in vitamin K antagonizes the effect of warfarin.
- Higher concentrations of Vitamin K found in the outer leaves & peels of vegetables.
- **Avoid sudden and drastic changes in vegetable intake.**
Dietary Changes

- Eat in **moderation** vegetables high in Vit K (1-2 portions/week)
- Examples: Soya bean products, green tea, broccoli, cauliflower, spinach, brussel sprouts
- Maintain **consistency** in **weekly** intake especially on high Vit K rich vege.
Drug-Food interaction

• Alcohol
  – Excessive consumption should be avoided.
  – Limit to 5 cans of beer/week or 1 bottle of wine/week

• What happen if I binge drink during a party?
• I have been drinking 2 cans of beer/night for 3 years. Will it affect my INR values?
Drug-Herb/Supplement interaction

- Avoid any form of traditional, herbal remedies and OTC supplements as the effects on warfarin are unpredictable.
  - Gingko
  - Garlic
  - Ginseng

- My friend recommended me some ginseng powder. Can I take? Will it affect my INR values?
- Can I take brand’s essence and bird nest?
1. Efficacy: Pertinent drug interactions for Warfarin

- Genetic polymorphism
  - CYP2C9

- Efficacy
- Pertinent drug interactions for Warfarin

- Metabolism
  - Prothrombin Precursor
  - Prothrombin
  - Reduced Vitamin K
  - Oxidized Vitamin K
  - Vitamin K Oxide Reductase
  - CYP 2C19
  - CYP 2C8
  - CYP 2C18
  - CYP1A2
  - CYP3A4

Ansel et al; Pharmacology and Management of the Vitamin K Antagonists: ACCP Guidelines 8th Ed; Chest 2008;133;160-198
# Drug-Drug Interactions.

Anticoagulation Clinics of North America (ACNA). Drug Interactions with Warfarin - Requiring Preventive Dosage Changes

<table>
<thead>
<tr>
<th>Effect on INR</th>
<th>Drugs</th>
<th>Reaction</th>
<th>ACNA Warfarin Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase INR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-trimoxazole (Bactrim, Septrin)</td>
<td>Generally see INRs in the 8 - 20 range</td>
<td>Decrease dose 20 - 30%</td>
<td></td>
</tr>
<tr>
<td>Fluconazole (more than one dose)</td>
<td>Have seen INRs 15 - 30</td>
<td>Decrease dose 30 - 40%</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Dose and time dependent INRs in the 8 - 20 range</td>
<td>At 2 week intervals, decrease the dose by approximately 5-10% (usually a total of 30-50% is required)</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>INRs usually 6-10</td>
<td>Avoid or stop Aspirin and adjust dose as for any high INR</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Variable - not much change in patient with chronic diarrhea or UC; others INR may increase to 8-20 range</td>
<td>Decrease dose by 10% and reassess within 3-4 days</td>
<td></td>
</tr>
</tbody>
</table>
## Drug-Drug Interactions.
Anticoagulation Clinics of North America (ACNA). Drug Interactions with Warfarin - Requiring Preventive Dosage Changes

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<th>Drugs</th>
<th>Reaction</th>
<th>ACNA Warfarin Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease INR</td>
<td>Phenobarbitone</td>
<td>Dependent on number of doses taken - generally INR 1.0 - 1.4</td>
<td>Increase dose by 20% for continuous use; adjust INR to upper end of range for intermittent use</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
<td>INR = 1.0</td>
<td>Double or Triple dose</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
<td>Dependent on dose and time frame, often INR 1.0 - 1.5</td>
<td>Increase dose by 30%</td>
</tr>
<tr>
<td></td>
<td>Primidone (Mysoline)</td>
<td>Dependent on dose, INR subtherapeutic to 1.0</td>
<td>Increase the dose by 10% to 40% dependent on INR response</td>
</tr>
</tbody>
</table>
Drug-Disease interaction

• Decreased INR
  – Edema
  – Heredity coumarin resistance
  – Hypothyrodism
  – Hyperlipidemia

• Increased INR
  – Cancer
  – CHF
  – Diarrhea
  – Hepatic disorders (infectious hepatitis, jaundice)
  – Hyperthyrodism
  – Poor nutrient state
Lifestyle changes

- Avoid high-risk activities
- Care in the use of sharp objects
- Stress
- Excessive physical activities
- Smoking
Interaction Facts

- Not all food/herbs/drugs/disease/lifestyle interactions are predictable, some are unavoidable
- Concurrent use of interacting drugs is not an absolute contraindication
- Select alternatives if available
- **Increase frequency of monitoring**
- Dosage adjustment
- **Patient Education**
## Side Effects - Bleeding

<table>
<thead>
<tr>
<th>Blood in Urine</th>
<th>Black sticky foul stools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cloudy or dark urine</td>
<td></td>
</tr>
<tr>
<td>Bleeding of gums/nose</td>
<td>Red spots on the skin</td>
</tr>
<tr>
<td></td>
<td>Hair loss</td>
</tr>
<tr>
<td>Heavy menstrual bleeding</td>
<td>Unexplained bruising</td>
</tr>
</tbody>
</table>
14. Side Effects – Hematoma, ie avoid intramuscular (i/m) injection
### Risk Factors for bleeding during Warfarin therapy

<table>
<thead>
<tr>
<th>PATIENT-RELATED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age:</strong> Above 65 years old</td>
</tr>
<tr>
<td><strong>Cardiac:</strong> Recent MI, AF, severe hypertension (diastolic pressure &gt; 100mmHg, systolic pressure &gt; 180mmHg)</td>
</tr>
<tr>
<td><strong>GI:</strong> Active peptic ulcer disease, history of GI bleeding, hepatic insufficiency</td>
</tr>
<tr>
<td><strong>Hematologic/oncologic:</strong> Anaemia, thrombocytopenia, platelet dysfunction, coagulation defect, malignancy</td>
</tr>
<tr>
<td><strong>Neurologic:</strong> History of stroke, dementia, cognitive or psychological impairment</td>
</tr>
<tr>
<td><strong>Medications:</strong> Use of other medications, such as NSAIDS, or “natural remedies” that interfere with hemostasis.</td>
</tr>
<tr>
<td><strong>Others:</strong> Recent trauma or surgery, excessive alcohol intake, intramuscular injection, potential bleeding sites (lumbar puncture, biopsy site, intra-arterial puncture)</td>
</tr>
</tbody>
</table>
Management of Bleeding complication

Bleeding

– The most common adverse effect of warfarin is bleeding with reported rates of major bleeding between 1.1 to 8.1% during each year of long term warfarin treatment.

– Although the risk of bleeding for patients on warfarin increases substantially at INR values greater than 5, bleeding can occur at any INR value.

– The use of warfarin often unmasks bleeding potential e.g. a non bleeding peptic ulcer may bleed if the patient is put on warfarin.
Management of Bleeding complication

• **Bleeding**
  – The risk of bleeding is additive and related to the intensity of anticoagulation, use of concurrent medications and the patient’s clinical condition.

  – The risk of bleeding on oral anticoagulants is closely related to the INR.

  – Especially when INR is > 5, risk of bleeding also increase
The Recommendation for Management if there is **No Significant Bleeding** and Patient has Low Bleeding Risks

<table>
<thead>
<tr>
<th>INR</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0 to 5.0</td>
<td>Reduce dose or omit 1 to 2 doses. Monitor INR more frequently and resume therapy at a lower dose when INR is within therapeutic range.</td>
</tr>
<tr>
<td>5.0 to 9.0</td>
<td>Check for bleeding / headache / anaemia. Admit if any suspicion of bleeding or if patient is unwell. If not for admission, advise patient of risk of bleeding and to go to A &amp; E if there is any suspicion of bleeding or if patient is unwell. Omit 2 to 3 doses. Monitor INR more frequently and resume therapy at a lower dose when INR is within therapeutic range. Alternatively, omit 1 dose and administer 1-3mg of oral vitamin K. Check INR in 24 hours. If INR remains high, administer additional 1-2mg of oral vitamin K. Resume therapy at a lower dose when INR is within therapeutic range.</td>
</tr>
<tr>
<td>Above 9.0</td>
<td>Admit. Check for bleeding / headache / anaemia. Omit warfarin and administer 3-5mg of oral vitamin K. Check INR in 24 hours. Administer additional vitamin K if necessary. Resume therapy at a lower dose when INR is within therapeutic range.</td>
</tr>
</tbody>
</table>
The Recommendation for Management if there is Serious Bleeding and INR is Elevated

Hold warfarin therapy and administer 10mg vitamin K by slow IV infusion, supplemented with fresh plasma or prothrombin complex concentrate 50IU/kg, depending on the urgency of the situation. Vitamin K administration can be repeated every 12 hours.

For life-threatening bleed, hold warfarin therapy and administer prothrombin complex concentrate 50IU/kg, supplemented with 10mg vitamin K by slow IV infusion. Check INR every 6 hours and repeat the procedure if necessary, depending on the INR.

*Oral Vitamin K is given for outpatients. The oral preparation is prepared from KONAKION MM ® preparation. IV Konakion ® has oral bioavailability of 50% (Roche company data).
Considerations for Vitamin K

The dose of vitamin K used to reverse over-anticoagulation depends on the INR. Ideally, vitamin K should be administered in a dose that will quickly lower INR into a safe but not sub-therapeutic range. For most patients, 1 to 3 mg of vitamin K is sufficient in the absence of bleeding. These small doses are obtained by dilutions from a 10 mg vial of injectable vitamin K and this is administered via oral or parental route.

High doses of vitamin K (10mg) are very effective but will lower the INR to sub-therapeutic range and lead to warfarin resistance for up to a week.

Due to near complete absorption, oral vitamin K has shown to be convenient and effective.

Intravenous injection produces a rapid response but anaphylactic reaction is a rare complication. This is reserved for patients who require very rapid reversal of anticoagulation; and can be administered by slow intravenous infusion (10mg over 30 minutes in 50ml dextrose 5%).
Storage

- Cool, dry place, away from children
- Protect from light
- Case report of fluctuating INR when warfarin was stored in the refrigerator.
- Medline search and communicating with manufacturer provided no info regarding storage of warfarin outside room temp

Pharmacotherapy 2002;22(1):102-104
Challenges

- Education for new warfarin patients is quite challenging due to the many important counseling points that the patient must grasp.
- Warfarin VCD available in English, Mandarin and Malay languages, S$8.60/pcs.
- Warfarin PIL available in Intranet PIL website.
Informing healthcare professional

- Doctors
- Pharmacists
- Dentists
- Physiotherapist
- Dieticians

- Can I take IM injections while on warfarin?
- How many days do I have to stop warfarin before getting the IM injections?
14. Side Effects – Hematoma, ie avoid intramuscular (i/m) injection
Assessing patient’s understanding

• “Just to make sure I did not leave anything out, could you tell me...[examples]
  – What is the medication used for?”
  – When are you going to take the medication?”
  – What side effects might you experience?”
  – What will you do if that occurs?”
  – What will you do if you miss a dose?”
Importance of Warfarin Counseling

Importance of patient counseling
Patients who reported receiving medication instructions from either a physician or nurse plus a pharmacist had a 60% reduced rate of subsequently experiencing a serious bleeding event over the next two years (adjusted risk ratio 0.40; 95% CI 0.24-0.68).

Patients reported that receiving these instructions made it clear what to do if a dose of warfarin was missed as well as what drugs to avoid while taking warfarin.

Patient Education vs INR Control (TTR) & Outcomes

- N = 323, mean f/u of 28.8 months
- 68 (21.3%) “satisfactory education”
- 23 (17%) “insufficient education”
- Time in Therapeutic range: 45.1% vs 34.9% (p < 0.01)
- Maj. bleeds: 0.5 vs. 5.2 per 1,000 patient-month. (Odds ratio: 8.83, p< 0.001)

Triple Intervention Study

INR Self-Testing +
Low Dose Vitamin K +
Automated Online Monitoring

Henry I. Bussey, Pharm.D., FCCP, FAHA
bussey@ClotCare.com

Study Co-ordinator: Felicia Ramirez 210-495-4335
The Future of Oral Anticoagulation

• 83% - 100% time in-range will double the efficacy and half the bleeding complications
• How do we achieve the above goal and reduce the time and “hassle” of management?
  – Patient education
  – Low dose vitamin K
  – Self-testing (POC)
  – Automated online monitoring & management

Triple Intervention Study, INR Self-Testing + Low Dose Vitamin K + Automated Online Monitoring
Henry I. Bussey, Pharm.D., FCCP, FAHA, bussey@ClotCare.com,
Study Co-ordinator: Felicia Ramirez 210-495-4335
2. Safety and Quality – Low dose Vit K daily

Daily Low Dose Vitamin K

- Daily low dose vitamin K:
  - Doubled in-range INRs for poorly controlled INRs\(^1\)
  - 59 % → 87\(^2\)
  - 79 % → 90% in-range\(^3\)
  - 43% in range 100 % of time\(^3\)

1. Safety and Quality – Low dose Vit K daily

**Warfarin and Low Dose Daily Vitamin K**

Doubled in-range INRs for poorly controlled INRs

<table>
<thead>
<tr>
<th>Patient</th>
<th>Before</th>
<th>After</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>60</td>
<td>69</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>41</td>
<td>33</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>53</td>
<td>36</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>18</td>
<td>17</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>38</td>
<td>33</td>
<td>46</td>
</tr>
<tr>
<td>6**</td>
<td>37</td>
<td>36</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>30</td>
<td>45</td>
<td>38</td>
</tr>
<tr>
<td><strong>Group</strong></td>
<td><strong>18</strong>*</td>
<td><strong>42</strong>*</td>
<td><strong>32</strong></td>
<td><strong>57</strong>*</td>
</tr>
</tbody>
</table>

*Note: 18% and 42% to 57% are consistent with lowest and 2nd – 4th quartile, respectively in Veeger, et al. J Thromb Haemost 2006; 4:1625-1627. **Lupus anticoag. and hyperfunctioning thyroid nodule

## 2. Safety and Quality – Low dose Vit K daily

### Vit. K vs. Placebo in Unstable** Patients

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>Vit. K 150 mcg. n = 35</th>
<th>Before</th>
<th>Placebo n = 33</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD of INR</td>
<td>0.72</td>
<td>0.47*</td>
<td>0.7</td>
<td>0.59*</td>
</tr>
<tr>
<td>% Time in range</td>
<td>59</td>
<td>87*</td>
<td>63</td>
<td>78*</td>
</tr>
<tr>
<td>Improved/Stable</td>
<td>33/19</td>
<td></td>
<td>24/7</td>
<td></td>
</tr>
<tr>
<td>Inc. in dose</td>
<td>16%</td>
<td></td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>Vit. K conc pg/ml</td>
<td>1502*</td>
<td></td>
<td>619*</td>
<td></td>
</tr>
<tr>
<td># dose chg./6 mo.</td>
<td>5</td>
<td>2*</td>
<td>5</td>
<td>3*</td>
</tr>
</tbody>
</table>

**Unstable: INR SD > 0.5 and ≥ 3 dosage changes in prev. 6 months

#### 2. Safety and Quality – Low dose Vit K daily
Phenprocoumonon + Vit. K or Placebo (x 6 mo)

<table>
<thead>
<tr>
<th></th>
<th>Vit. K 100 mcg.</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before n = 94</td>
<td>After n = 95</td>
</tr>
<tr>
<td>% Time in range</td>
<td>79</td>
<td>89.5</td>
</tr>
<tr>
<td>% Time below range</td>
<td>2.1</td>
<td>3.1</td>
</tr>
<tr>
<td>% Time above range</td>
<td>8.5</td>
<td>11.4</td>
</tr>
<tr>
<td>% in range 100%</td>
<td>43</td>
<td>24</td>
</tr>
<tr>
<td>% dosage change</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

DOI:10.1111/j.1538-7836.2007.02715.x

Slide 18
Consideration for Vit K

- Eat in **moderation** vegetables high in Vit K (1-2 portions/week)

- **Avoid sudden and drastic** changes in vegetable intake.

- Maintain **consistency** in **weekly** intake especially on high Vit. K rich vegetables
## 2. Safety and Quality

### Aspirin vs Warfarin in TIA/CVA with Intracranial Stenosis

<table>
<thead>
<tr>
<th>INR</th>
<th>(pat-yrs)</th>
<th>Maj Bld-%/yr (n)</th>
<th>Isc CVA-%/yr (n)</th>
<th>Maj Card-%/yr (n)</th>
<th>Comb-%/yr (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>(92.5)</td>
<td>1.1 (1)</td>
<td>24.9 (23)</td>
<td>10.8 (10)</td>
<td>36.8 (34)</td>
</tr>
<tr>
<td>2 – 3</td>
<td>(256.9)</td>
<td>3.5 (9)</td>
<td>5.1 (13)</td>
<td>0.4 (1)</td>
<td>9.0 (23)*</td>
</tr>
<tr>
<td>3.1 – 4.4</td>
<td>(52.6)</td>
<td>15.2 (8)</td>
<td>5.7 (3)</td>
<td>5.7 (3)</td>
<td>26.6 (14)</td>
</tr>
<tr>
<td>&gt; 4.5</td>
<td>(4.9)</td>
<td>123.3 (6)</td>
<td>20.6 (1)</td>
<td>0 (0)</td>
<td>143.9 (7)</td>
</tr>
<tr>
<td>All groups (406.9)</td>
<td>5.9 (24)</td>
<td>9.8 (40)</td>
<td>3.4 (14)</td>
<td>19.2(78)*</td>
<td></td>
</tr>
</tbody>
</table>

2. Safety and Quality

RELATIVE EFFICACY OF DIFFERENT MANAGEMENT PROGRAMS

• Meta-analysis of 67 studies involving 50,208 patients followed for a total of 57,155 patient-years.

• The average TTR* 64%, and varied with different setting:-
  □ Self-management — 72 % TTR
  □ Randomized trials — 66 % TTR
  □ Anticoagulation clinics — 66 % TTR
  □ Community physicians — 57 % TTR


* TTR : Time in Therapeutic Range
1. Efficacy: Indications for Anticoagulation – local data

Percentage INR within/Below/Above Target Range over the Study Period

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>46.63</td>
<td>53.71</td>
<td>54.65</td>
<td>53.75</td>
<td>56.55</td>
<td>54.26</td>
<td>60.31</td>
<td>66.30</td>
<td>18.14</td>
</tr>
<tr>
<td>No. of Days Within target range</td>
<td>9.25%</td>
<td>8.1%</td>
<td>8.1%</td>
<td>7.2%</td>
<td>6.4%</td>
<td>6.4%</td>
<td>10.0%</td>
<td>11.0%</td>
<td>11.0%</td>
</tr>
<tr>
<td>No. of Days Below target range</td>
<td>9.25%</td>
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<td>8.1%</td>
<td>7.2%</td>
<td>6.4%</td>
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<td>11.0%</td>
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<td>6.4%</td>
<td>10.0%</td>
<td>11.0%</td>
<td>11.0%</td>
</tr>
</tbody>
</table>

- **Periods**:
  - Year 0: 9/2000 to 9/2001
  - Year 1: 9/2001 to 9/2002
  - Year 4: 9/2004 to 9/2005
  - Year 8: 9/2008 to 9/2009

- **Graphs**:
  - No. of Days Within target range
  - No. of Days Below target range
  - No. of Days Above target range

- **Categories**:
  - Year 0 to Year 8
  - % within target range: 9.25%
  - % below target range: 9.25%
  - % above target range: 9.25%

- **Legend**:
  - Major Bleeding (%)
  - Minor Bleeding (%)
  - Thrombosis (%)
  - Total Patient
2. Safety and Quality -- ITTR

<table>
<thead>
<tr>
<th></th>
<th>Poor &lt; 60% (48%)</th>
<th>Mod. 60 – 75% (69%)</th>
<th>Good &gt; 75% (83%)</th>
<th>Combined (estimated)</th>
<th>Ximelag.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 1190</td>
<td>n = 1207</td>
<td>n = 1190</td>
<td>n = 3587</td>
<td></td>
</tr>
<tr>
<td>Stroke + Systemic Embolic Event</td>
<td>2.1</td>
<td>1.34</td>
<td>1.07</td>
<td>1.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>3.85</td>
<td>1.96</td>
<td>1.58</td>
<td>2.46</td>
<td>“no diff.”</td>
</tr>
<tr>
<td>Mortality</td>
<td>4.2</td>
<td>1.84</td>
<td>1.69</td>
<td>2.58</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1.38</td>
<td>0.89</td>
<td>0.62</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11.53*</td>
<td>6.03</td>
<td>4.96*</td>
<td>7.5</td>
<td></td>
</tr>
</tbody>
</table>

*Number needed to treat for 1 year to prevent 1 event would be 15 patients in “good” vs “poor” control groups.

*NNT to prevent one of the above events = 39.4 for 83% in range group compared to entire warfarin group.

*approx 34% fewer events in 83% gp vs. combined gps. (or ximelag.) and 50% fewer events vs. 48% pg.

**In the 2 studies the stroke + SEE event rates with warfarin were 2.3% and 1.2%, major bleeding was not different with warfarin vs. ximelagatran

2. Safety and Quality -- ITTR

Individual Time in Therapeutic Range (ITTR) [% and (mean TTR)] vs Event Rates (%/yr)

<table>
<thead>
<tr>
<th></th>
<th>Poor &lt; 60% (48%)</th>
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**In the 2 studies the stroke + SEE event rates with warfarin were 2.3% and 1.2%, major bleeding was not different with warfarin vs. ximelagatran.


- Good INR control, with TTR > 75%
- 50% fewer bleeding events
- 50% fewer TE events (stroke, MI, death)
2. Safety and Quality – Automated Online Monitoring

Automated Online Monitoring

• “The feasibility and potential value of automated online anticoagulation monitoring of warfarin-treated patients”¹
  – 52 unselected patients = 194 patient-years of data

<table>
<thead>
<tr>
<th>Number (%) Stable</th>
<th>Pat-yrs (% Time) Stable</th>
<th>Mean Duration of Stability</th>
<th>Stability Duration Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>52 (100%)</td>
<td>149.6 (77%)</td>
<td>5.17 mo.</td>
<td>56 d – 33.7 mo</td>
</tr>
</tbody>
</table>

Conclusion: automated monitoring 77% of the time were stable with evaluation approx. every 5 months may be feasible.

Benefits of home monitoring

More frequent testing will lead to an increased percentage of INR values within the therapeutic range.

Statement and chart based on the results of: D. Horstkotte et al.: Optimal frequency of patient monitoring and intensity of oral anticoagulation therapy on valvular heart disease; (Journal of Thrombosis and Thrombolysis 1998; 5: 19-24)
Two meta-analyses of 14 to 16 randomized trials have concluded that appropriately trained patients who self-adjusted and/or self-monitored their oral anticoagulation had fewer thromboembolic events, no difference in episodes of major bleeding, and a lower mortality compared with those undergoing standard monitoring.


References

1. AHSF Drug Information 2000
2. AHSP 2000: Potential Interaction btw Alternative therapies and Warfarin
6. Patient Information leaflet, SGH
7. Adverse Drug Reaction News Nov 2003 Vol. 5 No. 3
Thank you!

Email: kong.ming.chai@sgh.com.sg