Management of Oral Anticoagulant Therapy

About this Presentation
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The entire presentation is available from the American Heart Association.

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**Warfarin Dosing Guidelines**

**Warfarin Dosing Information**

- Individualize dose according to patient response (as indicated by INR)
- Use of large loading dose not recommended*
- May increase hemorrhagic complications
- Does not offer more rapid protection
- Low initiation doses are recommended for elderly/frail/liver-diseased/malnourished patients

**Notes:**
Three recommendations designed to increase the safety of warfarin use are listed on this slide.

Large loading doses (>10 mg) are no longer recommended for the initiation of therapy. As demonstrated in slide 17c, large loading doses cause an abrupt and dramatic fall in Factor VII levels (close to 0%), but do not speed up the reduction of Factors IX, X, or II compared to lower doses. It still takes 4–5 days to get all of the Vitamin K dependent coagulation factors down to a therapeutic range, at which time, therapy needs to overlap with heparin therapy in patients with venous thrombotic disease. Because Factor VII levels can fall so low with large loading doses, there is a risk of hemorrhage during the first few days of therapy. Furthermore, large loading doses cause a precipitous fall in Protein C (a Vitamin K dependent coagulation inhibitor that also has a short half life of about six hours), and if this protein falls significantly during early therapy before all of the Vitamin K dependent factors are decreased, one could potentially develop a hypercoagulable state before a hypocoagulable state develops. Consequently, initiation of therapy today is recommended to start with 5 mg of warfarin (in some cases 10 mg may be used initially). Thereafter, subsequent doses are based on the INR response. For patients who may already have impaired coagulation (liver disease), who may have low levels of Vitamin K (malnourishment), or may be at a greater risk of bleeding, it is recommended to start with even lower initial doses such as 2.5 mg of warfarin.

Warfarin: Dosing & Monitoring

Start low

- Initiate 5 mg daily*
- Educate patient

Stabilize

- Titrate to appropriate INR
- Monitor INR frequently (daily then weekly)

Adjust as necessary

- Monitor INR regularly (every 1–4 weeks) and adjust

*Elderly, frail, liver disease, malnourished: 2 mg/day

Notes:
This slide provides guidelines for safe and effective warfarin use. The dose of warfarin should be monitored daily until the INR is in the therapeutic range and then less frequently when a stable dose-response relationship is achieved. Regardless of the degree of stability in warfarin dosing and INR value in the hospital, it is important to monitor the INR frequently post hospital discharge (i.e., at least 1–3 days after discharge) and to spread out the interval of monitoring thereafter depending on INR response. Monitoring is necessary in all patients, but can be reduced to four weekly intervals in the low risk (for bleeding) patient who shows a stable dose-response.
Notes:
This shows the comparative effects on the Vitamin K dependent coagulation factors of initiating warfarin with a loading or a maintenance dose.
Dosage Adjustment Algorithm

<table>
<thead>
<tr>
<th>INR</th>
<th>Warfarin Dose Adjustment*</th>
<th>Adjusted Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0-2.0</td>
<td>Increase x 2 days</td>
<td>5.0  7.5  10.0  12.5 15.0</td>
</tr>
<tr>
<td>2.0-3.0</td>
<td>No change</td>
<td>-       -       -       -       -</td>
</tr>
<tr>
<td>3.0-6.0</td>
<td>Decrease x 2 days</td>
<td>1.25  2.5  5.0  7.5  10.0</td>
</tr>
<tr>
<td>6.0-10.0¹</td>
<td>Decrease x 2 days</td>
<td>0      1.25  2.5  5.0  7.5</td>
</tr>
<tr>
<td>10.0-18.0²</td>
<td>Decrease x 2 days</td>
<td>0      0      0      0      2.5</td>
</tr>
<tr>
<td>&gt;18.0²</td>
<td>Discontinue warfarin and consider hospitalization / reversal of anticoagulation</td>
<td></td>
</tr>
</tbody>
</table>

¹ Consider oral vitamin K 2.5-5 mg
² Oral vitamin K 2.5-5 mg0
* Allow two days after dosage change for clotting factor equilibration. Repeat prothrombin time two days after increasing or decreasing warfarin dosage and use new guide to management (INR = International Normalized Ratio). After increase or decrease or dose for two days, go to new higher (or lower) dosage level (e.g., if 5.0 qd, alternate 5.0/7.5; if alternate 2.5/5.0, increase to 5.0 qd.

Notes:
This shows a dosage adjustment algorithm which has been used successfully in an anticoagulation clinic.

Special Considerations in the Elderly - Bleeding

- Increased age associated with increased sensitivity at usual doses
- Comorbidity
- Increased drug interactions
- ? Increased bleeding risk independent of the above

Notes:
The elderly are at special risk for bleeding because:

- Increased age is associated with an increased sensitivity to warfarin, therefore the elderly often require lower doses of warfarin to maintain their INR in the therapeutic range
- They often have concomitant disorders that either influence their response to warfarin or expose them to the risk of bleeding
• These disorders may require therapy with drugs that either interfere with the pharmacodynamics of warfarin or increase the risk of bleeding.
• Increased age itself (due to increased vascular fragility) might be an independent risk factor for warfarin-associated bleeding.

Because of an increased sensitivity to warfarin, comorbidity and increased drug interactions, the elderly require even more careful management of dose adjustment. In the case of intracranial hemorrhage, there may be a slight, but real increased risk in the very elderly regardless of the quality of management.

## Warfarin Dosing in Elderly Patients

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>&lt;50</th>
<th>50-59</th>
<th>60-69</th>
<th>70-79</th>
<th>&gt;80</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gurwitz, et al, 1992</strong> (n=530 patients total study)</td>
<td>6.4</td>
<td>5.1</td>
<td>4.2</td>
<td>3.6</td>
<td>ND</td>
</tr>
<tr>
<td><strong>James, et al, 1992</strong> (n=2305 patients total study)</td>
<td>6.1</td>
<td>5.3</td>
<td>4.3</td>
<td>3.9</td>
<td>3.5</td>
</tr>
</tbody>
</table>

(Increasing age has been associated with an increased response to the effects of warfarin.)

### Notes:
This slide summarizes the results of two studies demonstrating the inverse relationship between mean warfarin dosage requirements and increasing age.

The elderly require a lower dose of warfarin to achieve the same level of therapeutic effectiveness.

### References:
Conversion of Heparin to Warfarin

- May begin concomitantly with heparin therapy
- Heparin should be continued for a minimum of four days
- Time to peak antithrombotic effect of warfarin is delayed 96 hours (despite INR)
- When INR reaches desired therapeutic range, discontinue heparin (after a minimum of four days)

Notes:
When short-term heparin followed by long-term warfarin are used, both anticoagulants can be started simultaneously. Heparin should be continued for a minimum of four days because the peak antithrombotic effect of warfarin is delayed for about 96 hours, independently of the INR, until Factor II (prothrombin is reduced). Heparin can be discontinued after a minimum of four days when the INR reaches the therapeutic range.
Managing Warfarin Overdosage

Signs of Warfarin Overdosage

Any unusual bleeding

- Blood in stools or urine
- Excessive menstrual bleeding
- Bruising
- Excessive nose bleeds/bleeding gums
- Persistent oozing from superficial injuries
- Bleeding from tumor, ulcer, or other lesion

Notes:
Hemorrhagic complications from warfarin therapy are more likely to occur with excessive degrees of anticoagulation, but even with an INR in the therapeutic range, bleeding can occur. Because of the likelihood of finding an underlying lesion in an individual who has gastrointestinal bleeding or significant genito-urinary bleeding in the face of therapeutic levels of anticoagulation, one is advised to consider and evaluate for underlying abnormalities predisposing to the bleeding. The return on such evaluations in the face of an excessive degree of anticoagulation diminishes, and one must use judgement whether or not to pursue an evaluation.

Managing Patients with High INR Values - Minor or No Bleeding

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Guidelines</th>
</tr>
</thead>
</table>
| INR > therapeutic range but <5.0, no clinically significant bleeding, rapid reversal not indicated for reasons of surgical intervention | • Lower the dose or omit the next dose; resume warfarin therapy at a lower dose when the INR approaches desired range  
• If the INR is only minimally above therapeutic range, dose reduction may not be necessary |

| INR > 5.0 but < 9.0, no clinically significant bleeding | Patients with no additional risk factors for bleeding; omit the next dose or two of warfarin, monitor INR more frequently, and resume warfarin therapy at a lower dose when the INR is in therapeutic range  
• Patients at increased risk of bleeding: omit the next dose of warfarin, and give vitamin K (1.0 to 2.5 mg orally)  
• Patients requiring more rapid reversal before urgent surgery or dental extraction: vitamin K (2–4 mg orally); if the INR remains high at 24 h, an additional dose of 1–2 mg |
Notes:
An approach to the management of patients who are excessively over anticoagulated and either have minor bleeding or no obvious bleeding is outlined on this slide.

In all cases, warfarin treatment should be interrupted the INR checked and warfarin restarted at a lower dose when the INR returns to the therapeutic range.

If the INR is above 5 but below 9, oral Vitamin K, should be considered if the patient is at excessive risk of bleeding.

Managing Patients with High INR Values - Serious Bleeding

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Guidelines</th>
</tr>
</thead>
</table>
| INR >9.0, no clinically significant bleeding | • Vitamin K (3–5 mg orally); closely monitor the INR; if the INR is not substantially reduced by 24–24 h, the vitamin K dose can be repeated  
• Serious bleeding, or major warfarin overdose (e.g., INR >20.0) requiring very rapid reversal of anticoagulant effect: Vitamin K (10 mg by slow IV infusion), with fresh plasma transfusion or prothrombin complex concentrate, depending upon urgency; vitamin K injections may be needed q12h.  

Life-threatening bleeding or serious warfarin overdose | • Prothrombin complex concentrate, with vitamin K (10 mg by slow IV infusion); repeat if necessary, depending upon the INR |

Continuing warfarin therapy indicated after high doses of vitamin K | • Heparin, until the effects of vitamin K have been reversed, and patient is responsive to warfarin |

Notes:
If the INR is between 9 and 20; oral Vitamin K should be administered in a dose of 2.5 mg.

If the INR is >20 more aggressive measures should be used. Vitamin K should be administered by slow intravenous infusion over 10 minutes in a dose of at least 5 mg, an infusion of fresh frozen plasma and hospitalization should be considered, and the hematocrit checked for hidden bleeding.

If the INR is excessively out of range and dose not make sense with the recent trend in INR results in individual patients, the clinician is advised to consider the possibility of laboratory error before a dose adjustment is made. In this case, it is optimal to repeat the INR before a dose change is made to verify the results.

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If there is serious bleeding, the patient should be hospitalized. Vitamin K should be administered by slow intravenous infusion over 10 minutes in a dose of 5–10 mg, an infusion of fresh frozen plasma should be given Prothrombin concentrate should be considered if bleeding is life-threatening.
**Warfarin Drug Interactions**

**Drug Interactions with Warfarin - Potentiation**

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Potentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Alcohol (if concomitant liver disease), amiodarone (anabolic steroids, cimetidine, *clofibrate, cotrimoxazole, erythromycin, fluconazole, isoniazid [600 mg daily] metronidazole), miconazole, omeprazole, phenylbutazone, piroxicam, propafenone, sulfinpyrazone (biphasic with later inhibition).</td>
</tr>
<tr>
<td>II</td>
<td>Acetaminophen, chloral hydrate, ciprofloxacin, dextropropoxyphene, disulfiram, itraconazole, quinidine, phenytoin (biphasic with later inhibition), tamoxifen, tetracycline, flu vaccine.</td>
</tr>
<tr>
<td>III</td>
<td>Acetylsalicylic acid, disopyramide, fluorouracil, ifosfamide, ketoprofen, lovastatin, metozalone, moricizine, nalidixic acid, norfloxacin, ofloxacin, propoxyphene, sulindac, tolmetin, topical salicylates.</td>
</tr>
<tr>
<td>IV</td>
<td>Cefamandole, cefazolin, gemfibrozil, heparin, indomethacin, sulfisoxazole.</td>
</tr>
</tbody>
</table>

*In a small number of volunteer subjects, an inhibitory drug interaction occurred.*

**Notes:**
This slide lists the various drugs that have been reported to interact with and potentiate warfarin. The strength of the evidence is shown in the left hand column with level I being strongest and level IV the weakest based on the study design of the report.

**Drug Interactions with Warfarin - Inhibition**

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Barbiturates, carbamazepine, chlordiazepoxide, cholestyramine, griseofulvin, nafcillin, rifampin, sulfasalazine</td>
</tr>
<tr>
<td>II</td>
<td>Dicloxacillin</td>
</tr>
<tr>
<td>III</td>
<td>Azathioprine, cyclosporine, etretinate, trazodone</td>
</tr>
<tr>
<td>IV</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
This slide lists the various drugs and foods that have been reported to have no effect on warfarin. The strength of the evidence is shown in the left hand column. With excessive consumption, alcohol potentiates the effect, but when limited to two glasses of wine/day, it has been reported not to influence the ant/coagulant effect of warfarin.
Drug Interactions with Warfarin - No Effect

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>No Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Alcohol, antacids, atenolol, bumetadine, enoxacin, famotidine, fluoxetine, ketorolac metoprolol, naproxen, nizatidine, psyllium, ranitidine‡</td>
</tr>
<tr>
<td>II</td>
<td>Ibuprofen, ketoconazole</td>
</tr>
<tr>
<td>III</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Diltiazem, tobacco, vancomycin</td>
</tr>
</tbody>
</table>

Notes:
This slide lists the venous drugs and foods that have been reported to have no effect on warfarin. The strength of the evidence is shown in the left hand column. With excessive consumption, alcohol potentiates the effect, but when limited to two glasses of wine /day, it has been reported not to influence the anticoagulant effect of warfarin.