Advanced Anticoagulation Training

TMS Slide Set
2017
Part 2 of 3
Oral Anticoagulants

Anticoagulants are also available for oral dosing (instead of injection). The following is a list of available oral anticoagulants.

- Warfarin (Coumadin)
- Target Specific Oral Anticoagulants (TSOACs)
  - Dabigatran (Pradaxa)
  - Rivaroxaban (Xarelto) and Apixaban (Eliquis)
## Warfarin: Mechanism of Action

<table>
<thead>
<tr>
<th>Inhibits Vitamin K Dependent Clotting Factors</th>
<th>Half-Life in Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>VII</td>
<td>5</td>
</tr>
<tr>
<td>IX</td>
<td>20</td>
</tr>
<tr>
<td>X</td>
<td>30</td>
</tr>
<tr>
<td>II</td>
<td>180</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inhibits Vitamin K Dependent Anticoagulant Proteins</th>
<th>Half-Life in Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein C</td>
<td>T</td>
</tr>
<tr>
<td>Protein S</td>
<td>42.5</td>
</tr>
</tbody>
</table>

* Because the half-life of Protein C is relatively short, heparin or other anticoagulant agents should be overlapped with warfarin for 4-5 days for treatment of acute venous thromboembolism (VTE). Because Protein C inhibition causes a pro-coagulant effect, the patient may be more likely to have a thrombosis for the first few days as the store of vitamin K dependent clotting factors spontaneously degrades.

### Note:

The dose of warfarin required to interfere with the vitamin K clotting factors varies widely between patients.
Warfarin: Initiation

Initiation Guidance

- Establish the goal INR target and planned duration of therapy
- Initiation dose is slightly higher than maintenance dose
- Usual initiation doses are often 2.5mg-5mg, lower doses are common in the elderly
- In healthy young individuals, 10mg initiation doses can be considered
- Inpatient initiation: International Normalized Ratio (INR) is often checked daily. Outpatient initiation: less frequent, every ~3 – 7 days during the first few weeks
- Standard dosing nomograms should be used rather than “empiric” dosing

Situations to consider initiating warfarin at a lower dose include:

- Age (> 65 years of age)
- Genetics (CFP201/VKORC1 polymorphism)
- Significant change in diet* (malnutrition)
- Alcohol and/or tobacco usage
- Interacting medications/herbals/supplements (there are many)
- Disease states (e.g., renal or hepatic disease, CHF, hyperthyroidism, malignancy)
- Non-adherence or miscommunication regarding warfarin dose
- Elevated baseline INR
- Fever/diaphoresis
- Recent major surgery

* It is important for patients to understand that they do not need to avoid foods (including nutritional supplements) containing vitamin K; however, it is important to keep their vitamin K intake consistent from week to week.

NOTE:

Remember: The dose of warfarin is adjusted to maintain the International Normalized Ratio (INR) within target range, typically 2-3 but individualized based on indication (e.g., mechanical valves 2-3.5). Review all potential reasons for changes in the INR with the patient/caregiver before adjusting the warfarin dose.
# Warfarin Monitoring: Factors that Affect INR

During initiation periods, an INR should be checked every 2–4 weeks, (sometimes earlier) due to the long half-life of vitamin K dependent factors plus the concomitant use of other medications and clinical disorders, diet, and multiple factors may impact the stability of INR.

<table>
<thead>
<tr>
<th>Disease States</th>
<th>Increase INR **</th>
<th>Decrease INR ***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Interactions*</td>
<td>Numerous</td>
<td>Numerous</td>
</tr>
<tr>
<td>Disease States</td>
<td>Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Heart failure</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Hepatic congestion</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Liver dysfunction</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Dialyse</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Malnutrition</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Malignancy</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Vitamin K deficiency</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Edema</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Nephrotic Syndrome</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Increased vitamin K intake</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Nonadherence</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Lab error</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Prolonged hot weather</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Quality of therapy management</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Nonadherence</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Lab error</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Quality of therapy management</td>
<td></td>
</tr>
</tbody>
</table>

* Please ensure appropriate staff is notified when any medication changes occur. ** Warfarin dose may need to be decreased. *** Warfarin dose may need to be increased.

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https://www.tms.va.gov/ia_content/2015_06_17_0855_Anticoagulation_Education_Advanced_Module_v4/lesson04/04_005.htm
Warfarin: Adverse Reactions and Reversal Considerations

The main adverse reaction with warfarin is bleeding. Warfarin effect can be easily reversed with vitamin K (oral route preferred) when indicated but this reversal may take 24 hours or more.

- Vitamin K is a group of compounds orally absorbed and produced in the gut that is responsible for making clotting factors.
- When there is over-anticoagulation with warfarin, supplementation with Vitamin K can reverse the associated warfarin effects including bleeding.
- Knowing when to use or not use vitamin K in the management of complications of oral anticoagulation is of great importance.

If urgent reversal of anticoagulation is needed, fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), or recombinant factor VIIa (Villa) should supplement the vitamin K.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR between 4.5 and 10 and no significant bleeding</td>
<td>Hold dose, no oral vitamin K, monitor more frequently as clinically appropriate</td>
</tr>
<tr>
<td>INR &gt; 10, no significant bleeding</td>
<td>Hold warfarin; give oral vitamin K (5 mg), monitor frequently and use additional oral vitamin K if necessary. Resume warfarin at lower dose when INR is therapeutic.</td>
</tr>
<tr>
<td>INR normal or elevated with clinical bleeding</td>
<td>Consult your facility/VIBN approved anticoagulation bleeding policy</td>
</tr>
<tr>
<td>Serious bleeding at any elevated INR</td>
<td></td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td></td>
</tr>
</tbody>
</table>

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: CHEST Evidence-Based Clinical Practice Guidelines

Reviewed/Updated: 06/17/2015 12:04:03
### Oral Anticoagulants Considerations: Pharmacokinetic, Dosing, and Administration

<table>
<thead>
<tr>
<th>Property</th>
<th>TSOACss</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to maximum concentration (Tmax)</td>
<td>1–4 hours (average 2 hours)</td>
<td>4 hours (peak anticoagulant effect delayed 72–96 hours)</td>
</tr>
<tr>
<td>Half-life</td>
<td>~ 5–17 hours</td>
<td>40 hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal; degree varies from agent to agent</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Special dosing consideration</td>
<td>Renal function; High risk features (e.g., age, weight); Drug interactions</td>
<td>Treat to target INR; Varies from patient to patient</td>
</tr>
<tr>
<td>Geriatrics</td>
<td>May be at increased risk for bleeding with some agents</td>
<td>Lower dosing in some</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>Often a consideration in some TSOACs</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Consult current drug information resources</td>
<td>Consult current drug information resources</td>
</tr>
<tr>
<td>Dietary Considerations</td>
<td>Rivaroxaban: Yes, take doses &gt;10 mg with evening meal</td>
<td>Yes, consistency with vitamin K containing foods</td>
</tr>
<tr>
<td></td>
<td>Dabigatran: Take with full glass of water</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abibaxan: Preliminary information suggests none</td>
<td></td>
</tr>
<tr>
<td>Storage Considerations</td>
<td>Dabigatran: Yes, store caps in original bottle to protect against moisture; discard 4 months after opening Rivaroxaban: No Abibaxan: No</td>
<td></td>
</tr>
<tr>
<td>Split, crush, chew</td>
<td>Dabigatran: No, increased exposure Rivaroxaban: OK to crush and mix with water or applesauce immediately prior to use; cannot be administered via feeding tubes placed distal to the stomach due to decreased absorption Abibaxan: Preliminary information suggests OK</td>
<td>OK</td>
</tr>
</tbody>
</table>
Warfarin or TSOACs: Selection Considerations

Appropriate patient selection is required. Patients will need to be involved in the decision making process with the health care team when selecting an appropriate agent. Consider the following factors when choosing between agents:

- Bleeding can occur with all agents; no reversal agent is currently known for TSOACs
- More frequent monitoring with warfarin compared to TSOACs
- Less follow-up contact with TSOACs compared to warfarin
- Will the patient have limited access to INR monitoring?
- Consider the limits of what we know with TSOACs: example, renal failure. Avoid TSOACs in end-stage renal disease
- Shorter half-life with TSOACs compared to warfarin
- Adherence important with all TSOACs agents due to short half-life and lack of monitoring anticoagulation effect
- Long term safety data unclear with TSOACs
- Avoid TSOACs in the presence of prosthetic heart valves
- TSOACs were not studied in patients with moderate/severe hepatic disease and use is not recommended

Check the manufacturer’s full prescribing information, the Pharmacy Benefits Management website, and/or local VA pharmacy for current information and additional updates.
TSOACs: Monitoring

Because of predictable pharmacokinetic properties, routine laboratory monitoring of the anticoagulant effects of the TSOACs is not needed. However, facilities should establish safety protocols requiring periodic lab monitoring such as a complete blood count (CBC) and kidney function for TSOACs.

- Baseline tests: serum creatinine (Scr) to estimate creatinine clearance (CrCl), CBC with platelets
- Follow-up monitoring: Scr (to estimate CrCl) and CBC with platelets as clinically appropriate

It is recommended that these be monitored annually or more frequently in patients with increased bleeding risk or renal impairment (e.g., CrCl < 60 ml/min, or who are 75 years of age or older).

For patients with a history of or suspicion for liver disease, liver function testing may be considered.

For more information about TSOACs monitoring, consult the Guidance for the Oversight and Monitoring of Target Specific Oral Anticoagulants (TSOACs).
TSOACs: Adverse Reactions and Reversal Considerations

TSOACs present some different challenges to consider when compared with warfarin and other anticoagulants. The major risk of TSOACs is bleeding just like warfarin. The risk of bleeding increases with age. However, the TSOACs present some different challenges to consider when compared with warfarin and other anticoagulants.

- TSOACs are associated with a lower risk of intracranial bleeding compared to warfarin.
- A higher risk of GI bleeding with dabigatran and rivaroxaban compared to warfarin has been noted in clinical trials.
  - Apixaban was associated with less risk of bleeding compared to warfarin.
- The frequency and types of other common non bleeding adverse events are generally similar with each of the TSOACs compared to warfarin.
  - Note:
    - Higher rates of dyspepsia and gastritis have been reported with dabigatran in clinical trials.
    - Slightly higher rates of MI are noted in clinical trials with dabigatran.

Important Note:

Unlike warfarin, no complete reversal agents are currently available. Consult your facility's urgent bleeding reversal protocol for updated information.
Question 1

Which of the following statements comparing warfarin and TSOACs is **FALSE**?

- A. Patients taking warfarin or TSOACs need to keep their vitamin K intake consistent from week to week.
- B. A patient taking warfarin may experience more potential drug-drug interactions compared to TSOACs.
- C. Patients need to be counseled to tell their provider(s) when any medication(s) or doses are changed while taking warfarin or TSOACs.
- D. To minimize the risk of developing clots, patients taking oral anticoagulants should be instructed that adherence to their treatment plan is important and not to miss any doses of warfarin or TSOACs.

Yes, that is correct.

Question 2

Select the **FALSE** statement about the pharmacodynamic effects of TSOACs:

- A. Patients starting on a TSOAC usually do not require bridge therapy with an injectable anticoagulant due to the quick onset of anticoagulant effect of the TSOACs (within a few hours).
- B. In addition to supportive care, often times bleeding while on TSOAC therapy can be effectively managed by holding or stopping the drug, since the TSOACs have a relatively short half-life compared to warfarin.
- C. The anticoagulant effect of the TSOACs is delayed for 72–96 hours, similar to warfarin.
- D. Strict adherence to TSOAC therapy and avoidance of missed doses is believed to be particularly important because of the short half-life and duration of action of the TSOACs.

Yes, that is correct.
Typical Clinical Scenarios: Women of Reproductive Age on Anticoagulation

Careful planning is required for pregnancy when women are taking anticoagulants. Some major concerns are:

- Menstrual problems can be exacerbated by anticoagulation therapy.
- Hemorrhagic ovarian cysts estimated to affect 1% of women taking anticoagulants can be life-threatening.
- Pregnancy and the postpartum period increase the risk of thrombosis.
- Warfarin is a known teratogen and can cause birth defects when used by pregnant women. Data on newer anticoagulants (e.g., dabigatran, rivaroxaban, or apixaban) during pregnancy is not yet available. Heparin is preferred during pregnancy.

Additional Patient Education Materials are available.

Remember to keep the following in mind when a female of childbearing age is taking warfarin:

- Assess anticoagulant medication adherence:
  - As a result of not providing alternative strategies to control heavy menses, women may self-decrease warfarin dose to reduce menstrual flow.
  - Patients should be counseled on the importance of adherence to warfarin regimen for the prevention of thromboembolic events and instructed when to seek medical attention for bleeding.
- Assess potential for unintended pregnancy:
  - Urine pregnancy testing is recommended prior to initiation of warfarin.
  - Providers should routinely assess and confirm the use of effective contraception.
Women of Reproductive Age on Anticoagulation: Recommended Management Strategies

For Controlling Heavy Menstrual Flows:

Most effective option: Levonorgestrel-bearing IUD (Mirena), however, all progestin-containing contraceptives can reduce menstrual flow.

- Progestin-only preparations may be preferable over estrogen-containing preparations for use in patients at increased thromboembolic risk.
- The only contraindication to use of progestin-only pills is a history of breast cancer.
- When discussing using progestin-containing contraceptives to reduce heavy menses, the patient may be more accepting of the therapy if it is referred to as "hormonal treatments to control heavy menses" vs. a contraceptive.

Other options to consider for managing heavy menses:

- Etonogestrel subdermal implant (Nexplanon)
- Depot medroxyprogesterone acetate injection (Depo-Provera)
- Progestin-only pills (norethindrone 0.35 mg tab, "Micronor")
Typical Clinical Scenario: Perioperative Management: Concept of Bridging

The management of anticoagulation in patients undergoing surgical procedures is difficult. Interrupting anticoagulation for a procedure may increase the risk of thromboembolism. At the same time, surgery or other invasive procedures may increase the bleeding risk if the anticoagulant is not discontinued. Bridging anticoagulation refers to a balance between reducing the risk of thromboembolism and preventing excessive bleeding by "bridging" with a shorter-acting agent such as LMWH or heparin. The approach is individualized depending on the procedure and what anticoagulant agent is being used.
Typical Clinical Scenario: Perioperative Management: Concept of Anticoagulation Bridging

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Perioperative management is a new science. While recommendations exist, practices may vary from facility to facility and patient to patient. To date, the evidence regarding periprocedural management of patients receiving antithrombotic therapy is evolving.

Please note:
- Recommendations are available from the American College of Chest Physicians/Volume 141/Number 2/February 2012 Supplement on Antithrombotic and Thrombolytic Therapy.
- The use of all LMWHs and fondaparinux for the purpose of bridging is an off labeled use and not an approved indication by the FDA.
- Bridging with injectable anticoagulants may not be required when a patient is taking a TSOAC.
Perioperative Surgical Procedures: Anticoagulation Bridging: Where to Start?

Many studies have been published that provide information about the benefits of using anticoagulants to prevent stroke for non-valvular atrial fibrillation patients. Practitioners are often faced with the decision of whether or not to cover a patient for a planned procedure on anticoagulants and if so, how then to manage the anticoagulant during the transition period.

For any transition, both pre- and post-procedure, the clinician must obtain active patient participation. Improved participation can begin with proper patient education (see Lesson 6: Enhancing Patient Safety with Anticoagulants) on the benefits of anticoagulant use. Participation, combined with objective tools for the provider to make an informed decision on how to proceed with anticoagulation bridging for their individual patients, is helpful.
Perioperative Management: Anticoagulation Bridging Considerations

The following are some things to consider when developing a treatment plan for perioperative anticoagulation:

- What is the risk of thromboembolism off of oral anticoagulants?
  - Evaluation of CHADS2 Score (for risk of thromboembolism in atrial fibrillation)
  - Recent thromboembolism?
  - Type of valve (if present)
  - Presence of thrombophilia?
- What is the risk of bleeding from procedure? Is the patient currently on an anticoagulant prophylactic or treatment dose regimen?
  - Evaluation of Bleeding Risk Score (e.g., HAS-BLED, HEMORR2HAGES, Outpatient Bleeding Risk Index, Shreman, et al.)
  - Type of surgical procedure
- What is the renal status of the patient?
- Which agent(s) is most cost effective for the situation?