Updates in Anticoagulation: New Recommendations, Expanding Options, and Pharmacogenetic Considerations

James Lee, PharmD, BCACP and Shubha Bhat, PharmD, BCACP

ICHCP Champion Webinar
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The speakers do not have any conflicts of interest to disclose

Objectives

1. Describe factors that influence the use of direct oral anticoagulants (DOAC)
2. Discuss the utilization of pharmacogenomics in anticoagulation therapy

2016 CHEST VTE Guidelines: Select Key Changes

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade &amp; Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE (no cancer): DOACs recommended over VKA</td>
<td>2B</td>
</tr>
<tr>
<td>VTE (no cancer): VKA recommended over LMWH</td>
<td>2C</td>
</tr>
<tr>
<td>VTE (cancer): LMWHs recommended over VKAs and DOACs</td>
<td>2C</td>
</tr>
</tbody>
</table>

3 months of anticoagulation treatment recommended for:
- VTE provoked by surgery
- VTE provoked by nonsurgical transient risk factor
- First unprovoked VTE (then reevaluate risk-benefit ratio of extended therapy)

Extended treatment beyond 3 months recommended for:
- Second unprovoked VTE with low bleeding risk
- Second unprovoked VTE with moderate or high bleeding risk
- VTE and active cancer with low bleeding risk
- VTE and active cancer with high bleeding risk

VTE = venous thromboembolism
DOAC = direct oral anticoagulant
VKA = vitamin K antagonist
LMWH = low molecular weight heparin

Outpatient Anticoagulation Options

- Vitamin K Antagonists (VKA)
  - Warfarin [Coumadin®]
- Low Molecular Weight Heparins (LMWH)
  - Enoxaparin [Lovenox®]
  - Dalteparin [Fragmin®]
- Factor Xa Inhibitors (Parenteral only)
  - Fondaparinux [Arixtra®]
- Direct Oral Anticoagulants (DOAC)
  - Dabigatran [Pradaxa®]
  - Rivaroxaban [Xarelto®]
  - Apixaban [Eliquis®]
  - Edoxaban [Savaysa®]

Considerations for DOAC Use

- Indication
- Dosing
- Diet
- Pharmacokinetics / Pharmacodynamics
- Drug interactions
- Monitoring parameters and frequency
- Reversibility
- Insurance coverage

DOAC FDA-Approved Indications & Dosing
Pharmacokinetics/Pharmacodynamics

<table>
<thead>
<tr>
<th>Prodrug?</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P-gp substrate?</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>No relevant CYP involvement</th>
<th>CYP 3A4</th>
<th>CYP 2J2</th>
<th>No relevant CYP involvement</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>T½ (hours)</th>
<th>12-17</th>
<th>6-9</th>
<th>8-15</th>
<th>10-14</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Elimination</th>
<th>80% renal</th>
<th>49% renal (65% as unchanged drug)</th>
<th>21% renal as unchanged drug</th>
<th>50% renal</th>
</tr>
</thead>
</table>

Reversal Agents

<table>
<thead>
<tr>
<th>Target</th>
<th>Idarucizumab</th>
<th>Andexanet Alfa</th>
<th>Ciraparantag</th>
</tr>
</thead>
</table>

| Mechanism of Action | Humanized monoclonal antibody fragment: higher binding affinity to dabigatran than to thrombin | Acts as decoy receptor: higher binding affinity to FXa inhibitor | Binds to drug, neutralizes anticoagulant activity |

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>REVERSE-AD</th>
<th>ANNEXA-A, ANNEXA-R</th>
<th>ASSIST-1, ASSIST-2</th>
</tr>
</thead>
</table>

Case Study

JK is a 40-year-old Caucasian female newly diagnosed with VTE, likely caused by immobility during a long flight (10 hours). Past medical history includes hypertension, for which she is taking metoprolol tartrate BID. Her labs are WNL. She is willing to start a DOAC, but is afraid of needles and admits forgetting to take the evening dose of metoprolol.

Which of the following anticoagulation medications and durations would be the best DOAC to recommend for JK?

A. Dabigatran 150 mg BID for 3 months
B. Rivaroxaban 15 mg BID x 21 days, then 20 mg daily for 3 months
C. Apixaban 10 mg BID x 7 days, then 5 mg BID for 6 months
D. Edoxaban 60 mg daily for 6 months

DOAC Resources

ASHP DOACs: Resources for Managing and Reversing Therapy
www.doacresources.org

Anticoagulation Forum VTE guidelines (2016)
http://acforum.org/landing/index.html

Michigan Anticoagulation Quality Improvement Initiative (MAQ2)
www.anticoagulationtoolkit.org

Anticoagulation Pharmacogenetics
Pharmacist’s Role in Pharmacogenetic Testing

- **ASHP**
  - Leadership role in ordering, design and workflow processes, reporting results, interpreting results, research endeavors
  - All pharmacists should have basic understanding of pharmacogenetics (PGT/PGx)
- Support from other healthcare disciplines for significant pharmacist role

Anticoagulation Guideline Stance

**American College of Chest Physicians**

- Vitamin K antagonists
  - Do not recommend routine use when initiating VKA (Grade 1B)
- DOACs
  - No recommendation provided

Last updated 4 years ago
Warfarin Pharmacogenetics

- **CYP 2C9**
  - Major determinant: 9% dose variability
  - Variants lead to decreased warfarin metabolism
  - Reported as CYP 2C9 *1/*1, *1/*2, *2/*2, etc.

- **VKORC1**
  - Major determinant: 25% dose variability
  - Variants lead to decreased VKORC1 expression
  - G vs A, C vs T
  - Reported as VKORC1 GG, GA, AA, etc.

- **CYP 4F2**
  - Minor determinant: 1-2% dose variability
  - Variants lead to decreased vitamin K metabolism
  - rs12777823 (CYP2C cluster)
  - GG, CALU

Others

- CYP 4F2
  - Minor determinant: 1-2% dose variability
  - Variants lead to decreased vitamin K metabolism
  - rs12777823 (CYP2C cluster)
  - GG, CALU

Warfarin Pharmacogenomics

**How has the evidence changed?**

- Major trials published in 2013
  - COAG (−): USA (27% African American)
  - EU-PACT (+): European (UK, Sweden)

- Major limitation relates to SNP relevance in the study population
  - COAG/EU-PACT: CYP 2C9 *2, *3 only
  - *5, *6, *8, *11 more commonly found with African American ancestry

Pharmacogenetic Guidelines

- Peer-reviewed
- Expert consensus based on clinical evidence and available literature
- Assist with HOW available genetic test results should be applied
- Warfarin guideline first published 2011
  - Update pending
  - Addresses appropriateness of applying genetic results based on SNPs tested, ancestry

Pharmacogenetic Recommendations for Warfarin

**Dosing algorithms**

- Genetic factors included > clinical-factors-only algorithms and fixed-dose approaches
- Electronic algorithms > table-based algorithms
  - Gage algorithm: warfarindosing.org
  - IWPC (International Warfarin Pharmacogenetics Consortium)

- Limitations
  - Mostly focused on INR goal range 2-3
  - Different clinical factors incorporated
  - SNP incorporation
  - Adults, not children
  - Low accuracy in dose range extremes
  - Does not replace clinical judgment, need for INR monitoring

Fixed-Dose Algorithm

- Introduced into FDA package 2007, 2011

Fixed-Dose Algorithm Table

<table>
<thead>
<tr>
<th>VKORC1 Genotype</th>
<th>CYP2C9 *1/*1</th>
<th>CYP2C9 *1/*2</th>
<th>CYP2C9 *1/*3</th>
<th>CYP2C9 *2/*2</th>
<th>CYP2C9 *2/*3</th>
<th>CYP2C9 *3/*3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>5-7 mg</td>
<td>5-7 mg</td>
<td>3-4 mg</td>
<td>3-4 mg</td>
<td>0.5-2 mg</td>
<td>0.5-2 mg</td>
</tr>
<tr>
<td>GA</td>
<td>5-7 mg</td>
<td>5-7 mg</td>
<td>3-4 mg</td>
<td>3-4 mg</td>
<td>0.5-2 mg</td>
<td>0.5-2 mg</td>
</tr>
<tr>
<td>AA</td>
<td>3-4 mg</td>
<td>3-4 mg</td>
<td>0.5-2 mg</td>
<td>0.5-2 mg</td>
<td>0.5-2 mg</td>
<td>0.5-2 mg</td>
</tr>
</tbody>
</table>
Pharmacogenetic Testing for DOACs

- Evidence gathering ongoing
- Targets of interest
  - Dabigatran
    - ABCB1, CES1
  - Rivaroxaban
    - CYP 2J2, CYP 3A4, CYP 3AS, ABCB1
  - Apixaban
    - SULT1A1, SULT1A2
  - Edoxaban
    - ABCB1

Reimbursement for Pharmacogenetic Testing

- Remains a challenge due to inconsistent/lack of clinical outcomes
- CMS currently does not reimburse, although this continues to evolve and is region-specific
  - Commercial vs public payor
  - Will likely require individual prior authorization based on drug and treatment indication
  - Once in a lifetime

Case Study

JK is a 40-year-old Caucasian female newly diagnosed with VTE, likely caused by immobility during a long flight (10 hours). The DOACs have a high copay, thus JK is started on warfarin. The medical team would like to pursue pharmacogenetic testing and asks for pharmacist guidance. Which of the following is TRUE?

A. CPIC guidelines provide guidance for when pharmacogenetic testing should be ordered
B. CPIC guidelines for warfarin provide guidance for interpreting CYP2C9 and VKORC1 genotypes
C. Dosing algorithms to assist with genotype-guided warfarin dosing are currently available as subscription services
D. Recent evidence strongly supports genotype-guided dosing in all individuals initiating warfarin therapy

Questions?
Self-Assessment Question

Which of the following statement is TRUE regarding the use of direct oral anticoagulants (DOAC)?

A. Every DOAC has an FDA-approved indication for VTE treatment and prophylaxis.
B. Every DOAC is eliminated by the kidneys and may warrant dose adjustment.
C. Every DOAC is administered orally once a day and must be taken with food.
D. Every DOAC can be reversed by the only DOAC antidote currently available.

Self-Assessment Question

Which of the following statements is TRUE regarding pharmacogenetic testing in anticoagulation therapy?

A. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are designed to inform clinicians when pharmacogenetic testing should be ordered.
B. Currently available pharmacogenetic guidelines for warfarin provide guidance on interpreting CYP 3A4 and VKORC1 genotypes.
C. Dosing algorithms for warfarin utilizing genetic factors perform similarly to dosing algorithms utilizing clinical factors only.
D. Genes of interest for the direct oral anticoagulants are being explored and include ABCB1, CYP 2J2, CYP 3A4/5, and SULT1A1.