Opportunities to Improve Use of Oral Anticoagulants

Christopher St. Clair, PharmD
ORISE Fellow, Division of Health Care Quality
Office of Disease Prevention and Health Promotion
Office of the Assistant Secretary for Health
U.S. Department of Health and Human Services
Disclosures

• The author has no relevant financial or nonfinancial conflicts to disclose.
Learning Objectives

1. Describe the public health significance of anticoagulant adverse drug events (ADEs).
2. Describe the role of anticoagulants in preventing thromboembolic disease.
3. Compare characteristics of warfarin and the direct oral anticoagulants (DOACs).
4. Discuss opportunities to improve use of oral anticoagulants.
Introduction to ODPHP
About ODPHP

• Part of the Office of the Assistant Secretary for Health within the Office of the Secretary at HHS

• Coordinate disease prevention and health promotion work across HHS

• Serve as the HHS lead on the National Action Plan for Adverse Drug Event Prevention

• Other initiatives:
  o National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination
  o Dietary Guidelines for Americans
  o Physical Activity Guidelines for Americans
  o Healthy People
  o healthfinder.gov

Health.gov
@HHSPrevention
Adverse Drug Events (ADEs)
Adverse Drug Events (ADEs)

- An ADE is an “injury resulting from medical intervention related to a drug.”

- Many ADEs are preventable.

- Reducing rates of preventable ADEs is a health care quality issue.

- Institute of Medicine 2000. To err is human: building a safer health system.
Adverse Drug Events (ADEs)

**INSIDE the hospital**
- Affect ~1.9 million hospital stays annually
- Add 1.7 to 4.6 hospital days
- Cost $4.2 billion USD annually

**INSIDE to OUTSIDE the hospital**
- ~ 2/3 of post-discharge complications*
- ~ 1/2 of preventable post-discharge complications

**OUTSIDE the hospital**
- ~3.5 million physician office visits annually
- ~1.3 million ED visits annually
- ~350,000 hospital admissions annually

*Within 3 weeks of discharge

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In 2013-2014, warfarin was the most commonly implicated drug in ED visits for ADEs (15.1%).

In 2013-2014, warfarin ADEs were much more common in older patients (31.9%).

• In 2014, the *National Action Plan for Adverse Drug Event Prevention (the ADE Action Plan)* was released with a focus on 3 high-priority ADEs:

1. Hypoglycemia from diabetes agents
2. Unintentional overdoses from opioids
3. Bleeding from anticoagulants

The ADE Action Plan

• The *ADE Action Plan* identifies the need to improve:
  
  • Surveillance of anticoagulant-related ADEs
  
  • Use of evidence-based management strategies
  
  • Coordination of care
  
  • Anticoagulant use in patients with atrial fibrillation

In June 2017, the U.S. Department of Health and Human Services (HHS) approved targets and measures for the ADE Action Plan:

<table>
<thead>
<tr>
<th>Setting</th>
<th>Measure</th>
<th>Numerator</th>
<th>Denominator</th>
<th>Target Reduction</th>
<th>Measure Alignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient</td>
<td>Rates of adverse drug events from anticoagulants among U.S. inpatient stays</td>
<td># of U.S. hospital discharges with adverse events from anticoagulants</td>
<td># of U.S. hospital discharges in which anticoagulants were administered</td>
<td>10%</td>
<td>Partnership for Patients hospital-acquired condition rate</td>
</tr>
<tr>
<td>Outpatient</td>
<td>Rates of visits to U.S. hospital EDs for adverse events from oral anticoagulants</td>
<td># of visits to U.S. hospital EDs for adverse events from oral anticoagulants</td>
<td># of patients receiving dispensed oral anticoagulants in U.S. retail outpatient settings</td>
<td>10%</td>
<td>HealthyPeople 2020 Medical Product Safety Objective 5.1</td>
</tr>
</tbody>
</table>
Atrial Fibrillation and Stroke
• AFib is the most common chronic arrhythmia in the United States

• AFib affects 3–6 million people, and this number is expected to rise to 12.1 million by 2030.

• AFib increases risk of stroke by 5x, and risk of fatal stroke by 2x.

• 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation.
• **Anticoagulants reduce risk of stroke in AFib patients by up to 67%.**

• Despite this, **anticoagulants are underused in more than half of patients who could benefit.**

• **Underuse of anticoagulants may be driven by fear of bleeding.**

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Oral Anticoagulants
• Anticoagulants reduce risk of stroke in patients with AFib by increasing the time it takes for blood to clot.

• Anticoagulants are indicated for various thromboembolic conditions, such as:
  • Prevention/treatment of deep vein thrombosis (DVT)
  • Prevention/treatment of pulmonary embolism (PE)
  • Prevention/treatment of thromboembolism associated with mechanical heart valves
  • Prevention/treatment of thromboembolism associated with AFib
• Oral anticoagulants FDA-indicated for prevention of thromboembolic complications in AFib include:
  • Warfarin (*Coumadin*)
  • Dabigatran (*Pradaxa*)
  • Rivaroxaban (*Xarelto*)
  • Apixaban (*Eliquis*)
  • Edoxaban (*Savaysa*)
Oral Anticoagulants

Warfarin vs. DOACs (direct oral anticoagulants)

Factor Xa inhibitors
- Rivaroxaban (Xarelto)
- Apixaban (Eliquis)
- Edoxaban (Savaysa)

Direct thrombin inhibitors
- Dabigatran (Pradaxa)
<table>
<thead>
<tr>
<th><strong>Pros</strong></th>
<th><strong>Cons</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low cost</td>
<td>Difficult to dose</td>
</tr>
<tr>
<td>Easily monitored with a lab test (INR)</td>
<td>Requires regular lab monitoring</td>
</tr>
<tr>
<td>Reversal agent is widely available (vitamin K)</td>
<td>Many food interactions (vitamin K)</td>
</tr>
<tr>
<td></td>
<td>Many drug interactions</td>
</tr>
</tbody>
</table>
• In healthy people not taking anticoagulants, INR = 1.

• In patients with AFib, the INR goal = 2–3.

• Conventional INR monitoring – e.g. going to a clinic – can be burdensome to patients and reduce adherence.

• Patient self-testing – at home – is more convenient and is associated with a 58% relative risk of thromboembolic events.


• The appropriate dose of warfarin to achieve the INR goal is different in every patient, and is affected by:

| Genetics       | • CYP 2C9  
|                | • VKORC1  
| Diet           | • Vitamin K₁  
| Other diseases | • Hypo/hyperthyroidism  
|                | • Liver dysfunction  
| Other drugs    | • Acetaminophen  
|                | • Alcohol  
|                | • Amiodarone  
|                | • Antimicrobials (Fluconazole, Metronidazole, SMX-TMP)  
|                | • Herbals (garlic, ginger, gingko, St. John’s Wort)  

Warfarin: Dosing

- Dosing possibilities are endless, with 9 different strengths available...
...but dosing can be complicated even with 1 strength.

**WARFARIN 2.5 MG**

TAKE 2 TABLETS (5 MG) ON MONDAY WEDNESDAY FRIDAY AND SATURDAY. TAKE 1 TABLET (2.5 MG) ON OTHER DAYS

**WARFARIN 2.5 MG**

TAKE 2 TABLETS (5 MG) ON MONDAY WEDNESDAY AND FRIDAY. TAKE 1 TABLET (2.5 MG) ON OTHER DAYS
## Direct Oral Anticoagulants (DOACs)

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy to dose</td>
<td>High cost</td>
</tr>
<tr>
<td>Few food/drug interactions</td>
<td>No standardization for lab monitoring</td>
</tr>
<tr>
<td>Short (~12 hr) half-life</td>
<td>Short (~12 hr) half-life</td>
</tr>
<tr>
<td></td>
<td>Reversal agent only available for dabigatran (idarucizumab - Praxbind)</td>
</tr>
</tbody>
</table>
DOACs: Dosing

- DOAC dosing is more straightforward than for warfarin.

<table>
<thead>
<tr>
<th></th>
<th>Dosage</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRADAXA 150 MG</td>
<td></td>
<td>TAKE 1 TABLET (150 MG) TWICE A DAY</td>
</tr>
<tr>
<td>XARELTO 20 MG</td>
<td></td>
<td>TAKE 1 TABLET (20 MG) ONCE A DAY WITH EVENING MEAL</td>
</tr>
<tr>
<td>ELIQUIS 5 MG</td>
<td></td>
<td>TAKE 1 TABLET (5 MG) TWICE A DAY</td>
</tr>
</tbody>
</table>
Comparative Safety and Effectiveness

- Safety and efficacy profiles vary, **but all DOACs have a lower risk of intracranial bleeding** than warfarin.

<table>
<thead>
<tr>
<th></th>
<th><strong>Stroke</strong> (vs. warfarin)</th>
<th><strong>Any major bleeding</strong> (vs. warfarin)</th>
<th><strong>Intracranial bleeding</strong> (vs. warfarin)</th>
<th><strong>GI bleeding</strong> (vs. warfarin)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apixaban (Eliquis)</strong></td>
<td>Lower risk (HR 0.67; p=0.04)</td>
<td>Lower risk (HR 0.45; p&lt;0.001)</td>
<td>Lower risk (HR 0.24; p&lt;0.001)</td>
<td>Lower risk (HR 0.51; p&lt;0.001)</td>
</tr>
<tr>
<td><strong>Rivaroxaban (Xarelto)</strong></td>
<td>Similar risk (HR 0.93; p=0.56)</td>
<td>Similar risk (HR 1.04; p=0.60)</td>
<td>Lower risk (HR 0.51; p&lt;0.001)</td>
<td>Higher risk (HR 1.21; p=0.03)</td>
</tr>
<tr>
<td><strong>Dabigatran (Pradaxa)</strong></td>
<td>Similar risk (HR 0.98; p=0.98)</td>
<td>Lower risk (HR 0.79; p&lt;0.01)</td>
<td>Lower risk (HR 0.36; p&lt;0.001)</td>
<td>Similar risk (HR 1.03; p=0.78)</td>
</tr>
</tbody>
</table>

Federal Efforts to Improve Anticoagulant Management
Emerging Needs

• In 2016, PCORI held a workshop on AHRQ’s 2013 systematic review for treatment of AFib.

• However, stakeholders agreed that stroke prevention in AFib was in greater need of an update.

• In June 2017, AHRQ published a systematic review update for stroke prevention in AFib.


Emerging Needs

According to the 2017 update:

- “Systemic anticoagulation has been shown to reduce the risk of stroke by two-thirds.”

- “Unfortunately, two critical issues regarding stroke prevention in [AFib] remain:
  (1) despite existing evidence, only a minority of patients who have AF and are at risk for stroke receive optimal treatment for thromboembolic prevention, and
  (2) patients with AF on stroke prophylaxis with warfarin still have higher rates of stroke than non-AF patients, suggesting that gaps still exist in our understanding of risk stratification and treatment.”

Incentives to Improve Use: MIPS

• The CMS Quality Payment Program features incentives for improving oral anticoagulant use.

• 2 quality-based payment programs are available to clinicians:
  o Advanced Alternative Payment Models (APMs)
  o The Merit-based Incentive Payment System (MIPS)

• Under MIPS, a clinician’s performance score is based on:
  o Quality
  o Clinical practice improvement activities
  o Advancing care information
  o Cost
Incentives to Improve Use: MIPS

- For **Quality**, clinicians must report up to 6 measures, including 1 outcome measure.
- 271 outcome measures are available.
- 1 quality measure is specific to anticoagulant use in patients with AFib.

**Incentives to Improve Use: MIPS**

- Quality is judged by proportion of adult patients with AFib, who are at risk of stroke, who are on anticoagulants.

- Risk is determined by CHADS$_2$ score.

## Atrial Fibrillation and Atrial Flutter: Chronic Anticoagulation Therapy

Percentage of patients aged 18 years and older with a diagnosis of nonvalvular atrial fibrillation (AF) or atrial flutter whose assessment of the specified thromboembolic risk factors indicate one or more high-risk factors or more than one moderate risk factor, as determined by CHADS2 risk stratification, who are prescribed warfarin OR another oral anticoagulant drug that is FDA approved for the prevention of thromboembolism.

<table>
<thead>
<tr>
<th>MEASURE NUMBER</th>
<th>NQS DOMAIN</th>
<th>MEASURE TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>eMeasure ID: N/A</td>
<td>Effective Clinical Care</td>
<td>Process</td>
</tr>
<tr>
<td>eMeasure NQF: N/A</td>
<td>NQF: 1525</td>
<td></td>
</tr>
<tr>
<td>Quality ID: 326</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIGH PRIORITY MEASURE</th>
<th>DATA SUBMISSION METHOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Claims, Registry</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PRIMARY MEASURE STEWARD</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Cardiology</td>
</tr>
</tbody>
</table>

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CHADS$_2$ can stratify risk of stroke in patients with AFib.

<table>
<thead>
<tr>
<th>CHADS$_2$ Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>+1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+1</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>+1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>+1</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>+2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHADS$_2$ Score</th>
<th>Adjusted stroke rate (%/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>18.2</td>
</tr>
</tbody>
</table>

2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation.
• For **Clinical Practice Improvement Activities**, clinicians must complete 4 medium-weighted or 2 highly-weighted activities.

• 92 activities are available.

• 2 highly-weighted activities involve anticoagulant management.

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Incentives to Improve Use: MIPS

• In year 1, ≥ 60% of patients on anticoagulants participate in a systematic anticoagulation management program.

**Participation in systematic anticoagulation program**

Participation in a systematic anticoagulation program (coagulation clinic, patient self-reporting program, patient self-management program) for 60 percent of practice patients in year 1 and 75 percent of practice patients in year 2 who receive anti-coagulation medications (warfarin or other coagulation cascade inhibitors).

<table>
<thead>
<tr>
<th>ACTIVITY ID</th>
<th>SUBCATEGORY NAME</th>
<th>ACTIVITY WEIGHTING</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA_PM_1</td>
<td>Population Management</td>
<td>High</td>
</tr>
</tbody>
</table>

• CMS Quality Payment Program. Improvement activities. Available from: [https://qpp.cms.gov/mips/improvement-activities](https://qpp.cms.gov/mips/improvement-activities)
Incentives to Improve Use: MIPS

- In year 1,  60% of patients on warfarin are being managed by a systematic anticoagulation management program for at least 90 days.

- Options for programs include:
  - Clinics
  - Telehealth
  - Patient self-testing/self-management

CDC and Georgia Tech are developing Anticoagulation Manager, a clinical decision support mobile app that guides prescribing, monitoring, switching, and reversing anticoagulation.

Anticoagulation Manager is currently being beta tested in clinical settings and will be released publicly for iOS and other platforms.

Guidance to Improve Use

Guidance to Improve Use

ICD Validation

- ICD-9 “E-codes” may greatly underestimate warfarin-related ADEs.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Positive predictive value</th>
<th>Specificity</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>25.5%</td>
<td>46.6%</td>
<td>98.3%</td>
<td>95.7%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>84%</td>
<td>56.8%</td>
<td>99.1%</td>
<td>99.8%</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>86.7%</td>
<td>59.1%</td>
<td>98.7%</td>
<td>99.7%</td>
</tr>
</tbody>
</table>

- ICD-10 was implemented on October 1, 2015, but validation is needed.


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ODPHP
Office of Disease Prevention and Health Promotion
• CDC is funding studies to identify and validate ICD-10 codes for anticoagulant-related bleeding.

• These codes can help improve:
  o Quality measure development
  o Post-marketing evaluations
  o Public health surveillance

• Centers for Disease Control and Prevention 2016. Advanced and innovative solutions to improve public health – broad agency announcement. Available from: https://www.fbo.gov/index?s=opportunity&mode=form&id=328398ff0414ace726b7af3132abb243&tab=core&_cview=0
Opportunities to Improve Oral Anticoagulant Use
• If patients present with AFib and are not on an evidence-based dose of anticoagulants – *why?*
  o Has their physician ever considered using anticoagulants?
  o Are they on suboptimal antithrombotic therapy?
  o Are they afraid of adverse events?

• If warfarin patients present with uncontrolled INR – *why?*
  o Do they take their warfarin as prescribed?
  o Is their diet consistent/are there food insecurity issues?
  o Are they able to travel to their clinic?
  o Is self-testing an option for this patient?

Anticoagulant Stewardship

• “Anticoagulant stewardship” – using the right anticoagulant, at the right dose, in the right patient, for the right duration – can potentially minimize risks of bleeding, stroke, and readmissions.

• DOAC management is less clearly defined than warfarin management, but many principles are the same:
  o Clinicians need clear guidelines for dosing, monitoring, switching, and reversal
  o Patients need education at a low health literacy level (assume all patients are at risk of not understanding health information) and on a regular basis
  o Patients need direct access to a knowledgeable clinician when questions and concerns arise

Educate and Follow Patients

- Care transitions are an opportunity to assess need for anticoagulation in all patients with AFib, and educate on:
  - Why AFib is significant (especially if they can’t feel symptoms)
  - Difference between rate/rhythm control and stroke prevention
  - Risk of stroke vs. risk of bleeding

- Consider assembling a multidisciplinary team from medicine, pharmacy, nursing, and social work to assess and follow all patients on anticoagulants.
  - All patients on anticoagulants – including DOACs – need direct access to an anticoagulation specialist.
  - Patients will need this clinician to advise them if/when they experience a bleed at home.

Thank you!
Christopher St. Clair, PharmD
christopher.st.clair@hhs.gov
ORISE Fellow, Division of Health Care Quality
Office of Disease Prevention and Health Promotion
Office of the Assistant Secretary for Health
U.S. Department of Health and Human Services

Clydette Powell, MD, MPH, FAAP
clydette.powell@hhs.gov
Director, Division of Health Care Quality
Office of Disease Prevention and Health Promotion
Office of the Assistant Secretary for Health
U.S. Department of Health and Human Services

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