Practical aspects of using DOACs (Direct Oral Anticoagulants)

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What’s in a name?

- **DOAC**: Direct oral anticoagulant
- **NOAC**: Non-VKA oral anticoagulant
- **NOAC**: Novel/new oral anticoagulant
- **ODI**: Oral direct inhibitors
- **SODA**: Specific oral direct anticoagulant
- **TSOAC**: Target specific oral anticoagulant

What’s in a name?
That which we call a rose, By any other name...

What’s in a name?

DOAC  **DO....Anti-Coagulate**

NOAC  **NO....Anti-Coagulation**

Outline of today’s talk

Practical aspects of using DOACs in clinical practice

- General overview
- Patient selection – Warfarin vs. DOAC
- Monitoring treatment
- Bridging and peri-procedural management
- Managing serious DOAC-related bleeding
- Reversal agents
General overview

Coagulation Cascade

Intrinsic pathway
Vascular surface changes

Extrinsic pathway
Tissue thromboplastin

Common pathway
Prothrombin (II)
Thrombin

Fibrinogen (I) → Fibrin monomer → Fibrin polymer → Stable fibrin

Am Fam Physician 2001; 64: 419-428
Advantages of DOACs compared to Warfarin

- Rapid onset
- Short half-life (rapid offset)
- Predictable pharmacokinetics
- Fewer drug interactions
- Lack of need for routine monitoring

Disadvantages of DOACs compared to Warfarin

• Difficult to monitor compliance

• No reliable, clinically available blood test to determine drug levels

• Drug accumulates with renal impairment

• No specific antidote to reverse anticoagulant effect


Patient selection

Which patients who require long-term anticoagulation should be treated with a DOAC?
Current FDA-approved indications

<table>
<thead>
<tr>
<th>DOAC</th>
<th>VTE prevention</th>
<th>VTE treatment</th>
<th>ACS</th>
<th>AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>-</td>
<td>X</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Apixaban</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>-</td>
<td>X</td>
<td>-</td>
<td>X</td>
</tr>
</tbody>
</table>


DOAC vs. Warfarin Stroke or Systemic Embolism

![Graph showing comparison of DOAC vs. Warfarin for stroke or systemic embolism events](image)

Figure 1: Stroke or systemic embolic events
Data are n/N, unless otherwise indicated. Heterogeneity: I² = 47%; p = 0.13. NOAC = new oral anticoagulant; RR = risk ratio. *Dabigatran 150 mg twice daily; †Rivaroxaban 20 mg once daily; ‡Apixaban 5 mg once daily; §Edoxaban 60 mg once daily.

Lancet 2014; 383:955-962
DOAC vs. Warfarin
Major Bleeding Events

<table>
<thead>
<tr>
<th></th>
<th>NOAC (events)</th>
<th>Warfarin (events)</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY 2</td>
<td>375/6076</td>
<td>396/6022</td>
<td>0.94 (0.92-1.07)</td>
<td>.34</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>395/7211</td>
<td>386/7235</td>
<td>1.09 (0.96-1.30)</td>
<td>.072</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>327/9196</td>
<td>460/955</td>
<td>0.75 (0.65-0.85)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ENGAGE-AF-TIMI 48</td>
<td>444/7012</td>
<td>557/7032</td>
<td>0.80 (0.71-0.90)</td>
<td>&lt;.0012</td>
</tr>
<tr>
<td>(combined random)</td>
<td>1542/29287</td>
<td>13802/29221</td>
<td>0.86 (0.79-1.01)</td>
<td>.05</td>
</tr>
</tbody>
</table>

Figure 3: Major bleeding
Data are n/N, unless otherwise indicated. Heterogeneity: F=23%; p=0.001. NOAC: new oral anticoagulant. RR: risk ratio. *Dabigatran: 150 mg twice daily. **Rivaroxaban: 20 mg once daily. ***Apixaban: 5 mg twice daily. ****Edoxaban: 60 mg once daily.

Lancet. 2014; 383:955-962

DOAC Trials: Pooled Analysis
Efficacy and Safety

<table>
<thead>
<tr>
<th></th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>0.92 (0.83-1.02)</td>
<td>.10</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.49 (0.38-0.64)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.90 (0.85-0.95)</td>
<td>.003</td>
</tr>
<tr>
<td>ICH</td>
<td>0.48 (0.39-0.59)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Lancet. 2014; 383:955-962
Patients who should **NOT** be treated with a DOAC

- Problems with adherence
- Kidney disease
- Mechanical heart valves

### Dosing and Therapeutic Compliance

Averaged from 76 studies using electronic monitoring

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Took Most Doses</th>
<th>Took Doses on Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 time daily</td>
<td>79%</td>
<td>74%</td>
</tr>
<tr>
<td>2 times daily</td>
<td>69%</td>
<td>58%</td>
</tr>
<tr>
<td>3 times daily</td>
<td>65%</td>
<td>46%</td>
</tr>
<tr>
<td>4 times daily</td>
<td>51%</td>
<td>40%</td>
</tr>
</tbody>
</table>

*Am J Cardiol 2010; 105: 1495-1501*
Using DOACs in patients with chronic kidney disease

- **Creatinine clearance < 30 ml/min**
  - DOACs should generally be avoided.

- **Creatinine clearance between 30-50 ml/min**
  - Preference for factor Xa inhibitors over direct thrombin inhibitors (dabigatran)

- **Creatinine clearance > 95 ml/min**
  - Black box warning cautions against use of edoxaban due to reduced efficacy

*Ann Intern Med* 2015; 163; 382-385

DOACs should NOT be used in pts with mechanical heart valves

*Ischemic or unspecified stroke occurred in 9 patients (5%) in the dabigatran group and no patients in the warfarin group.*

DOACs should NOT be used in pts with mechanical heart valves

All patients with major bleeding had pericardial bleeding


Poorly studied patient groups

- Children
- Very elderly
- Pregnancy
- Cancer patients
Monitoring treatment

Do patients receiving DOACS need to be monitored?
How to monitor patients receiving DOACs
How to monitor patients receiving DOACs

• Adherence with DOAC therapy
  • One or more missed doses in an average week

• Bleeding risk assessment
  • Does not imply that DOAC should be discontinued

• Renal function
  • GFR less than 50 ml/min
  • Use of diuretics or recent dehydrating illness

How to monitor patients receiving DOACs

• Drug interactions
  • Concomitant use of ASA, anti-platelets, NSAIDS

• Physical exam
  • Blood pressure (too high or too low)
  • Gait impairment, assessment of fall risk

• Patient education and counseling
  • Dosing for scheduled procedures/surgeries

Ann Intern Med 2015; 163: 382-385
Laboratory measurement in patients receiving DOACs

Dabigatran

- Normal thrombin time (TT) excludes clinically relevant drug levels.
- Dilute TT and ecarin-based assays can be used for quantification across a broad range of drug levels.
- Normal aPTT excludes excess drug levels.

Factor Xa Inhibitors

- Normal anti-Xa level excludes clinically relevant drug levels.
- Anti-Xa can be used for quantification across a broad range of drug levels.
- Normal PT excludes excess drug levels of rivaroxaban and edoxaban but not apixaban.
Bridging and peri-procedural management

BRIDGE Trial – Study Design

- Randomized, double-blind, placebo-controlled
- 1884 patients with AF scheduled to undergo an elective operation or invasive procedure
- Warfarin stopped 5 days before procedure and resumed 24 hours after procedure
- 30 days post-procedure follow-up for primary outcome of arterial thromboembolism or major bleeding.

BRIDGE Trial- Treatment Group

- Subcutaneous dalteparin 100 IU twice/daily
- LMWH started 3 days before procedure and discontinued 24 hours before procedure
- LMWH resumed 24 hours (low risk procedure) or 48-72 hours (high risk procedure)
- LMWH continued 5-10 days post procedure

BRIDGE Trial- Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Bridging (N=918)</th>
<th>Bridging (N=895)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients</td>
<td>percent</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial thromboembolism</td>
<td>4 (0.4)</td>
<td>3 (0.3)</td>
<td>0.01*, 0.73†</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (0.2)</td>
<td>3 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>2 (0.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>12 (1.3)</td>
<td>29 (3.2)</td>
<td>0.005†</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>5 (0.5)</td>
<td>4 (0.4)</td>
<td>0.88†</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7 (0.8)</td>
<td>14 (1.6)</td>
<td>0.10†</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0.25†</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0.25†</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>110 (12.0)</td>
<td>187 (20.9)</td>
<td>&lt;0.001†</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.01

_N Engl J Med 2015; 373: 823-833_
Example of a pre-operative management strategy for patients receiving Rivaroxaban

Minor surgery/procedure (Low bleeding risk)

• CrCl \( \geq \) 50 ml/min: Hold 1 day before – 1 dose
• CrCl \(< 50\) ml/min: Hold 1-2 days before – 1-2 doses

Major surgery/(High bleeding risk)

• CrCl \( \geq \) 50 ml/min: Hold 1-2 days before – 1-2 doses
• CrCl \(< 50\) ml/min: Hold 2-3 days before – 2-3 doses

*May not be applicable to all patients including those undergoing neuraxial anesthesia*

Example of a post-operative management strategy for patients receiving Rivaroxaban

Minor surgery/procedure (Low bleeding risk)

• Resume 12-24 hours after procedure once adequate hemostasis has been achieved

Major surgery/(High bleeding risk)

• Resume 48-72 hours after procedure once adequate hemostasis has been achieved
Managing serious DOAC-related bleeding

Major bleeding case fatality rates

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>DOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>55/386</td>
<td>14%</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>53/407*</td>
<td>13%</td>
</tr>
<tr>
<td>Apixaban</td>
<td>55/462</td>
<td>12%</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>59/524</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Case Fatality Rates in Patients with Major Bleeding – Warfarin vs. DOAC

Approach to patients with DOAC-related major bleeding

Initial assessment

- Hemodynamic stability
- Source of bleeding
- Time elapsed since last dose
- Renal function
- Baseline coagulation testing

*J Thromb Thrombolysis 2013; 35: 391-398*
Approach to patients with DOAC-related major bleeding

General measures

• Anticoagulant withdrawal
• Mechanical compression of bleeding site
• Monitor hemodynamic status
• Volume replacement
• Definitive interventions
• Oral charcoal if dabigatran ingestion ≤ 2 hrs.

J Thromb Thrombolysis 2013; 35: 391-398

Blood product transfusion

• RBC transfusion for anemia
• Consider platelets if patient receiving an anti-platelet agent
• FFP for coagulopathy (DIC, dilutional coagulopathy)

J Thromb Thrombolysis 2013; 35: 391-398
Approach to patients with DOAC-related major bleeding

Severe/life-threatening bleeding

- Intensive care setting
- Hemodynamic support
- Consider 4-factor PCC (50 U/kg) for Factor Xa inhibitors or activated PCC (80 U/kg) for DTI

Adjunctive therapies

- Hemodialysis for dabigatran removal
- Desmopressin, anti-fibrinolytic agents (?)

Reversal strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-specific</td>
<td></td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>Decontamination</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Accelerated elimination (only for dabigatran)</td>
</tr>
<tr>
<td>PCC</td>
<td>Replacement of factors II, VII, IX, X</td>
</tr>
<tr>
<td>rVIIa, aPCC</td>
<td>Activated coagulation factors</td>
</tr>
<tr>
<td>PER977</td>
<td>Small synthetic molecule</td>
</tr>
<tr>
<td>Specific</td>
<td></td>
</tr>
<tr>
<td>Idarucizumab</td>
<td>Monoclonal antibody against dabigatran</td>
</tr>
<tr>
<td>Andexanet</td>
<td>Recombinant inactive FXa</td>
</tr>
</tbody>
</table>

What’s on the horizon?

Idarucizumab

poke me.

i dare you.
Idarucizumab for Dabigatran Reversal

Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes.

N Engl J Med 2015; 373; 511-520

Resources
Anticoagulation Forum’s Centers of Excellence - Resource Center

- Drug therapy management
- Disease state management
- Transition and coordination of care
- Service operational performance
- Patient and family education
- Comprehensive toolkit
- Apps for practitioner
- Additional resources
Anticoagulation Forum’s Centers of Excellence - Resource Center

excellence.acforum.org