Antithrombotic Therapy in Atrial Fibrillation, Venous Thromboembolism and Cerebral Vascular Accident

Presented by:
Nibal R. Chamoun, PharmD, BCPS
Objectives

- Review the mechanism of action, indications and contraindications of vitamin K antagonists versus new oral anticoagulation
- Identify patients who may benefit from specific antithrombotic therapy
- Discuss pertinent monitoring
- Review important counseling tips
Abbreviations

- AC: Anticoagulation
- NOACS: Novel oral anticoagulants
- SPAF: Stroke prevention in Atrial Fibrillation
- VTE: Venous thromboembolism
- DVT: Deep venous thrombosis
- PE: Pulmonary embolus
- Hb/Hct: hemoglobin/hematocrit
- PK and PD: pharmacokinetic and pharmacodynamic
Mechanism of Action: VKA versus NOACS

## VKAs versus NOACS

<table>
<thead>
<tr>
<th>VKAs (acenocoumarol, hydroxycoumarol)</th>
<th>NOACS (rivaroxaban, dabigatran, apixaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variability in dosing</td>
<td>Fixed dosing</td>
</tr>
<tr>
<td>More monitoring</td>
<td>Less monitoring</td>
</tr>
<tr>
<td>Long half life</td>
<td>Shorter half lives ➔</td>
</tr>
<tr>
<td>Numerous drug/food interactions</td>
<td>Less drug food interactions</td>
</tr>
<tr>
<td></td>
<td>Dosage adjustment required for renal impairment</td>
</tr>
</tbody>
</table>
Vitamin K antagonists (VKAs)

- **Mode of Action (MOA):**
  - Inhibits the formation of vitamin K dependent clotting factors. Factors IX, VII, X, II & protein C & S

- **Onset of action is slow due to:**
  - Half life of the medication to reach steady state
    - Hydroxycoumarol: 20-60 hours
    - Acenocoumarol: 8 to 11 hours

- **Full therapeutic effect of VKA antagonist:**
  - Hydroxycoumarol: 5-7 days
  - Acenocoumarol: 5 days
Vitamin K antagonists (VKAs)

- Because the full therapeutic effect of VKA antagonist takes 5 days (even if the INR will change fast with sintrom), this doesn’t mean full therapeutic effect has been achieved.

- Overlap parenteral and VKAs for a minimum of 4-5 days and until we reach therapeutic INR goal and discontinue parenteral AC upon having 2 consecutive therapeutic INR readings.
<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>6</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Bid</td>
<td>Bid or daily</td>
<td>bid</td>
</tr>
<tr>
<td><strong>T- max (h)</strong></td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Half life (h)</strong></td>
<td>12-17</td>
<td>7-11</td>
<td>9-14</td>
</tr>
<tr>
<td><strong>Protein binding(%)</strong></td>
<td>35</td>
<td>95</td>
<td>87</td>
</tr>
<tr>
<td><strong>CYP metabolism (%)</strong></td>
<td>None</td>
<td>32</td>
<td>15</td>
</tr>
<tr>
<td><strong>P-gp transport</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Renal excretion (%)</strong></td>
<td>80</td>
<td>66</td>
<td>25</td>
</tr>
<tr>
<td><strong>Non renal excretion(%)</strong></td>
<td>20</td>
<td>34</td>
<td>75</td>
</tr>
<tr>
<td><strong>Available in Lebanon</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*CHEST 2012; 141(2)(Suppl):e120S–e151S*
<table>
<thead>
<tr>
<th>Oral Anticoagulant</th>
<th>Routine laboratory test</th>
<th>Other monitoring parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKA Antagonists</td>
<td>PT/ INR</td>
<td>LFTs</td>
</tr>
<tr>
<td>Oral DTI (Dabigatran)</td>
<td>No routine test</td>
<td>SrCr</td>
</tr>
<tr>
<td>Direct Xa inhibitor (Rivaroxaban)</td>
<td>No routine test</td>
<td>SrCr</td>
</tr>
<tr>
<td>Direct Xa inhibitor (Apixaban)</td>
<td>No routine test</td>
<td>SrCr</td>
</tr>
</tbody>
</table>
Indications for Antithrombotic Therapy

- Stroke prevention in Atrial Fibrillation (SPAF)
- Treatment of VTE (PE and DVT)
- Antithrombotic therapy for CVA
Indications for Antithrombotic Therapy

- Stroke prevention in Atrial Fibrillation (SPAF)
- Treatment of VTE (PE and DVT)
- Antithrombotic therapy for CVA
## Risk Assessment Scores: Stroke Assessment Scores

<table>
<thead>
<tr>
<th>Risk</th>
<th>Point Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke or TIA</td>
<td>2 points</td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td>1 point</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 point</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 point</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1 point</td>
</tr>
<tr>
<td>No risk factors</td>
<td>0 points</td>
</tr>
</tbody>
</table>

### Use of $\text{CHA}_2\text{DS}_2$-$\text{VASc}$ for Stroke Risk Stratification

- ESC AF guideline recommendations
  - $\text{CHADS}_2$ should be used as the initial method for stroke risk stratification in patients with AF
  - $\text{CHADS}_2$ score $\geq 2 \rightarrow$ Warfarin (target INR 2-3)
  - $\text{CHADS}_2$ score of 0-1 $\rightarrow$ Perform $\text{CHA}_2\text{DS}_2$-$\text{VASc}$


Am J Cardiol 2010; 105: 502-10
### Table 9  Approach to thromboprophylaxis in patients with AF

<table>
<thead>
<tr>
<th>Risk category</th>
<th>CHA2DS2-VASc score</th>
<th>Recommended antithrombotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>One ‘major’ risk factor or ( \geq 2 ) ‘clinically relevant non-major’ risk factors</td>
<td>( \geq 2 )</td>
<td>OAC&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>One ‘clinically relevant non-major’ risk factor</td>
<td>1</td>
<td>Either OAC&lt;sup&gt;a&lt;/sup&gt; or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin.</td>
</tr>
<tr>
<td>No risk factors</td>
<td>0</td>
<td>Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; CHA2DS2-VASc = cardiac failure, hypertension, age \( \geq 75 \) (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female); INR = international normalized ratio; OAC = oral anticoagulation, such as a vitamin K antagonist (VKA) adjusted to an intensity range of INR 2.0–3.0 (target 2.5).
# HASBLED Score: Bleeding Risk Score

## Table 10 Clinical characteristics comprising the HAS-BLED bleeding risk score

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical characteristic</th>
<th>Points awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (e.g. age &gt;65 years)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

Maximum 9 points
Case 1

- MM is a 67 year old woman who underwent a mechanical mitral valve replacement 7 months ago. She presents to clinic with atrial fibrillation and during work up expresses interest in being started on rivaroxaban instead on acenocoumarol. Creatinine Clearance ~ 90ml/min.

- At home is on:
  - acenocoumarol regimen: MWFSS 2mg & TTH 3mg
  - INR goal 2.5-3.5
  - Last INR (1 week ago, 2.7)

- **Which of the following is the best treatment plan for this patient?**
  - A. Switch to rivaroxaban 20mg po daily
  - B. Switch to rivaroxaban 15 mg po daily
  - C. Switch to dabigatran 150mg po bid
  - D. Keep on acenocoumarol
NOACS: Stroke Prevention in Atrial Fibrillation

- Data randomized controlled trials (~70,000 patients)
  - Majority are non-inferiority trials in terms of decrease in stroke (Ischemic & hemorrhagic) in comparison to VKA
  - Less incidence of intracranial hemorrhage

- NOACs are associated with an increase in GI bleeds as compared to warfarin
Non-valvular atrial fibrillation
+
Indication for Anticoagulation

*Dose adjustments of NOACS are necessary for renal impairment* in Stroke Prevention in Atrial Fibrillation (SPAF)
## NOACS in SPAF Trials

<table>
<thead>
<tr>
<th></th>
<th>RE-LY&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ROCKET-AF&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ARISTOTLE&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ENGAGE AF&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td><strong># Randomized</strong></td>
<td>18,113</td>
<td>14,266</td>
<td>18,201</td>
<td>21,105</td>
</tr>
<tr>
<td><strong>Dose, mg</strong></td>
<td>150, 110</td>
<td>20</td>
<td>5</td>
<td>60, 30</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Twice Daily</td>
<td>Once Daily</td>
<td>Twice Daily</td>
<td>Once Daily</td>
</tr>
<tr>
<td><strong>Dose adjustment</strong></td>
<td>No</td>
<td>20 $\rightarrow$ 15</td>
<td>5 $\rightarrow$ 2.5</td>
<td>60 $\rightarrow$ 30</td>
</tr>
<tr>
<td>• At baseline</td>
<td>0</td>
<td>21</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>• After randomization</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>&gt; 9%</td>
</tr>
<tr>
<td><strong>Target INR (warfarin)</strong></td>
<td>2.0-3.0</td>
<td>2.0-3.0</td>
<td>2.0-3.0</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>PROBE&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2x blind</td>
<td>2x blind</td>
<td>2x blind</td>
</tr>
</tbody>
</table>

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Dose Reduction TSOACs in SPAF Trials

<table>
<thead>
<tr>
<th>RE-LY&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ROCKET-AF&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ARISTOTLE&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ENGAGE-AF&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| Not studied in CrCl < 30ml/min! | • 20 → 15 mg QD for:  
  - Creatinine clearance < 30-49 mL/min | • 5 → 2.5 mg BID for ANY TWO of:  
  - Age ≥ 80 years  
  - body weight ≤ 60 kg  
  - Serum creatinine ≥ 1.5 mg/dL |
| 2 doses studied:  
  150mg PO BID  
  110mg PO BID | | | • 60 → 30 mg QD or 30 → 15 mg QD for:  
  - Creatinine clearance 30-50 mL/min  
  - body weight ≤ 60 kg  
  - Use of quinidine, verapamil, or dronedarone |
| Approved on the market is also 75mg po BID | | | |

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WHY NOT NOACS IN VAVULAR ATRIAL FIBRILLATION
N= 256 patients

Terminated early:

The use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk.
WHAT IS THE EXACT DEFINITION OF VAVLUAR AFIB?
Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Valvular Indications and Contraindications to NOACs in Afib

- **Contraindicated for NOACS**
  - Mechanical prosthetic heart valves
  - Mitral stenosis (moderate to severe)

- **Eligible for NOACS**
  - Other native valve diseases (mild to moderate)
  - Severe aortic stenosis
  - Bioprosthetic heart valves (except in the first 3 months)
  - Mitral valve repair (except in the first 3-6 months)
Recognizing Drug Interactions: Community or Hospital Setting

**Figure 3** Absorption and metabolism of the different new anticoagulant drugs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolization and excretion. See also Table 5 for the size of the interactions based on these schemes.

Europace doi:10.1093/europace/euv309
Recognizing Drug Interactions: Community or Hospital Setting

- **Mechanism of interaction:** cytochrome P450 3A4 and P-glycoprotein (P-gp)

- **Concern:** minimal guidance for dose adjustments & monitoring is not possible

- **Interacting medications:**
  - Antimicrobials (antifungals, antibiotics, antiretrovirals)
  - Antiepileptics
  - Immunosuppressant
  - Verapamil
Interpreting medication interactions with NOACs based on the EHRA

- **Red**: contra-indicated/not recommended.

- **Orange**: reduce dose (from 150 to 110 mg BID for dabigatran; from 20 to 15 mg OD for rivaroxaban; from 5 to 2.5 mg BID for apixaban).

- **Hatching**: no clinical or PK data available.

- **Brown**: contraindication for interactions that lead to reduced NOAC plasma levels.

- **Yellow**: consider dose reduction if 2 or more ‘yellow’ factors are present.
Table 6 Continued

<table>
<thead>
<tr>
<th></th>
<th>via</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fungostatics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Moderate CYP3A4 inhibition</td>
<td>No data yet</td>
<td>No data yet</td>
<td>No data yet</td>
<td>+42% (if systemically administered)²⁴²</td>
</tr>
<tr>
<td>Itraconazole, Ketoconazole, Posaconazole, Voriconazole</td>
<td>potent P-gp and BCRP competition; CYP3A4 inhibition</td>
<td>+140-150% (US: 2 x 75 mg if CrCl 30-50 ml/min)</td>
<td>+100%⁶⁰⁰</td>
<td>+87-95%⁴⁴ (reduce NOAC dose by 50%)</td>
<td>Up to +160%²⁴⁷</td>
</tr>
<tr>
<td><strong>Immunosuppressive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporin, Tacrolimus</td>
<td>P-gp competition</td>
<td>No data yet</td>
<td>+73%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiphlogistics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>P-gp competition</td>
<td>No data yet</td>
<td>+55%¹⁴⁴</td>
<td>No effect (but pharmacodynamics increased bleeding time)</td>
<td>No data yet</td>
</tr>
<tr>
<td>Carbamazepine***, Phenobarbital***, Phenytoin***, St John's wort***</td>
<td>P-gp/BCRP and CYP3A4/CYP2J2 inducers</td>
<td>minus 66%²⁵³</td>
<td>minus 54%⁵ᵐᵖᶜ</td>
<td>minus 35%</td>
<td>Up to minus 50%</td>
</tr>
<tr>
<td>Other factors:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 80 years</td>
<td>Increased plasma level</td>
<td>#</td>
<td></td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>Increased plasma level</td>
<td>#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight ≤ 60 kg</td>
<td>Increased plasma level</td>
<td>#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal function</td>
<td>Increased plasma level</td>
<td>See Table 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other increased bleeding risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history of GI bleeding; recent surgery on critical organ (brain, eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3</td>
<td>#</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Take Home Message:

Anticoagulation in Stroke Prevention in Atrial Fibrillation

- **VKA**
  - Approved for both valvular and non-valvular atrial fibrillation
  - **VKA and bridging with parenteral anticoagulation is recommended**

- **NOACS:**
  - Approved for **non-valvular atrial fibrillation**
  - Imperative to **dose adjust in renal dysfunction**
  - **Less intracranial hemorrhage** but **more gastrointestinal bleeding** (except apixaban)
  - Necessitate that pharmacists **screen for drug interactions**
Case 1

- MM is a 67 year old woman who underwent a **mechanical mitral valve replacement** 7 months ago. She presents to clinic with atrial fibrillation and during work up expresses interest in being started on rivaroxaban instead on acenocoumarol. Creatinine Clearance ~ 90ml/min.

- At home is on:
  - acenocoumarol regimen: MWFSS 2mg & TTH 3mg
  - INR goal 2.5-3.5
  - Last INR (1 week ago, 2.7)

- **Which of the following is the best treatment plan for this patient?**
  - A. Switch to rivaroxaban 20mg po daily
  - B. Switch to rivaroxaban 15 mg po daily
  - C. Switch to dabigatran 150mg po bid
  - D. **Keep on acenocoumarol**
Indications for Antithrombotic Therapy

- Stroke prevention in Atrial Fibrillation (SPAF)
- Treatment of VTE (PE and DVT)
- Antithrombotic therapy for CVA
2016 ACCP Guidelines (Jan 2016)

- NOACs (dabigatran, apixaban, edoxaban or rivaroxaban) are first line options
- Conventional treatment (VKA (sintrom or warfarin) + parenteral anticoagulation) is second line option
Clinical Practice Guideline Recommendations: Treatment of Venous Thromboembolism (DVT & PE)

1. **Bridging: (Conventional Therapy)**
   - Parenteral anticoagulant + bridge to oral therapy VKA (we start oral VKA and the parenteral at the same time, we keep the patient on the parenteral AC, for at least 4-5 days and until we are sure that the VKA is therapeutic, then we stop the parenteral and keep the patient on oral VKA)

2. **Directly oral treatment: (using target specific oral anticoagulants (TSAACS))**
   - Rivaroxaban 15mg PO BID for 21 days, followed by 20mg PO daily
   - Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily

3. **Switching: (using target specific oral anticoagulants (TSAACS))**
   - Start parenteral anticoagulant for 2 weeks, then switch to Dabigatran 150mg PO BID
   - Start parenteral anticoagulant, then switch to Edoxaban 60mg po daily or if impaired renal function (CrCl 30-50ml/min, weight<60kg or taking potent pgp inhibitors) 30mg PO daily
NOACS: Treatment of Venous Thromboembolism (DVT & PE)

- Randomized controlled trials (~ 25,000 patients)
  - Non-inferior to conventional treatment for VTE recurrence (margins of non-inferiority between 1.5-2.75)
  - Less bleeding (notably more GI bleeding, except apixaban)
  - Superior to placebo for the prevention of recurrent VTE and are associated with lower bleeding rates.

Case 2

A 70 yo woman (wt=80kg, ht=173cm) is diagnosed with a DVT. No significant PMH. Pertinent history is that she’s not very active and had recent travel. Her CrCl is estimated at 25ml/min. **Which of the following treatment choices is most suitable for this patient?**

A. Enoxaparin that is bridged to acenocoumarol 2mg po daily
B. Rivaroxaban 15mg po BID for 21 days followed by 20mg po daily
C. Enoxaparin for 7 days followed by Dabigatran 150mg po BID
D. Dabigatran 150mg po BID
NOACS: Treatment of Venous Thromboembolism (DVT & PE)

DVT or PE

+ Good renal function defined as CrCl(≥ 30 ml/min)

**NO DOSE ADJUSTMENTS EXIST**

for CrCL < 30ml/min for Apixaban, Dabigatran or Rivaroxaban in the treatment of VTE
Patients who should NOT receive NOACS in VTE

- Severe renal impairment defined as: CrCl<30 mL/min for rivaroxaban, dabigatran and edoxaban; and <25 mL/min for apixaban
- VTE in the setting of Cancer
- VTE in the setting of thrombophilic conditions
- When compliance is a concern
- History of GI bleeds
- Nursing mothers
- Pregnancy
- Extreme body weight

Blood 2014;124(7):1020-1028
Appropriate candidates for NOACS in VTE

- On VKA antagonists with erratic INRs
- Those who find INR testing burdensome
- Reliable and compliant patients

Blood 2014;124(7):1020-1028
NOACs in VTE: Which agent is the best for your patient?

<table>
<thead>
<tr>
<th>Patient specific criteria</th>
<th>NOAC selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefers to avoid injections</td>
<td>Apixaban or Rivaroxaban</td>
</tr>
<tr>
<td>CrCl between 30-50 ml/min</td>
<td>Apixaban, rivaroxaban, edoxaban (not dabigatran)</td>
</tr>
<tr>
<td>Dyspepsia or GERD</td>
<td>Rivaroxaban, apixaban, edoxaban</td>
</tr>
<tr>
<td>Recent GI bleed</td>
<td>Apixaban</td>
</tr>
<tr>
<td>Poor compliance with twice daily dosing</td>
<td>Rivaroxaban or edoxaban</td>
</tr>
<tr>
<td>Recent myocardial infarction</td>
<td>Rivaroxaban, apixaban, edoxaban</td>
</tr>
</tbody>
</table>

Blood 2014;124(7):1020-1028
Take Home Message: Anticoagulation in VTE Treatment

- **Verify** appropriate renal function \(\text{CrCl}> 30\text{ml/min}\)
- Screen for interactions & caution providers
- **Remember the strategies:**
  - Start **directly oral** therapy with Rivaroxaban or Apixaban
  - If *dabigatran* or *edoxaban* are selected, *the first week* should be **parenteral** treatment, then **SWITCH** to NOACS
- Emphasize on **compliance**, especially the switch in doses

  - **VKA** and bridging with parenteral anticoagulation is recommended if:
    - \(\text{CrCl}< 30\text{ml/min} \ & \text{in} \) special populations: cancer, pregnancy, thrombophilic conditions, extreme body weight
Case 2

A 70 yo woman (wt=80kg, ht=173cm) is diagnosed with a DVT. No significant PMH. Pertinent history is that she’s not very active and had recent travel. Her CrCl is estimated at 25ml/min. Which of the following treatment choices is most suitable for this patient?

A. Enoxaparin that is bridged to acenocoumarol 2mg po daily
B. Rivaroxaban 15mg po BID for 21 days followed by 20mg po daily
C. Enoxaparin for 7 days followed by Dabigatran 150mg po BID
D. Dabigatran 150mg po BID
Indications for Antithrombotic Therapy

- Stroke prevention in Atrial Fibrillation (SPAF)
- Treatment of VTE (PE and DVT)
- Antithrombotic therapy for Cerebral Vascular Accident (CVA)
Classification of CVA

**Figure 22-1.** A classification of stroke by mechanism with estimates of the frequency of various categories of abnormalities. Approximately 30% of ischemic strokes are cryptogenic.
Antithrombotics for Secondary Stroke Prevention

- Pharmacologic categories used in secondary stroke prevention
  - Antiplatelets
  - Anticoagulants
Selection of the appropriate antithrombotic agent: Cardioembolic Vs Non-cardioembolic

Non-cardioembolic Stroke or TIA

- Antiplatelet
  - ASA
  - Plavix
  - Extended Release Dipyridamole+ ASA

Cardioembolic Stroke or TIA (Presence of Afib or Valvular disease)

- Afib:
  - Anticoagulation (CHADS2 score automatically ≥2)
    - NOACs or VKA anticoagulant based on the presence of valvular or non-valvular AFIB
  - Non-tolerant → give antiplatelets

- Valvular heart disease (ex. Mechanical valve)
  - Antithrombotic therapy depending on:
    - Valve type
    - Location (mitral or aortic)
    - when the valve was placed (> or < 3 mo ago)
Case

- G.R is a 55 year old man with a PMH of a non-cardioembolic stroke, CAD, dyslipidemia and peptic ulcers. What would be the best option for secondary stroke prevention?
  a) Aspirin 81mg po daily
  b) Acenocoumarol 2mg po daily
  c) Clopidogrel 75mg daily
  d) Rivaroxaban 20mg po daily
Non-cardioembolic strokes: Antiplatelet options for Secondary Stroke Prevention

- Antiplatelet options (all acceptable options for initial therapy):
  - Aspirin (50 mg/d to 325 mg/d) monotherapy
  - The combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily
  - Clopidogrel 75 mg monotherapy

- Combination aspirin/extended release dipyridamole or clopidogrel is preferred over aspirin alone (Guyatt, 2012).

- The combination of ASA +clopidogrel might be considered in minor non-cardioembolic stroke/TIA and continued for 90 days
The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, and other clinical characteristics.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Aspirin</th>
<th>Clopidogrel</th>
<th>ASA+ERDP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GI upset</td>
<td>Less GI bleed</td>
<td>GI upset</td>
</tr>
<tr>
<td></td>
<td>GI bleed</td>
<td>Less diarrhea</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rash</td>
<td>(usually self limiting)</td>
</tr>
<tr>
<td>Monitor</td>
<td>Periodic assessment of : Hemoglobin, Hct, platelets and signs of bleeding</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case

- G.R is a 55 year old man with a PMH of a non-cardioembolic stroke, CAD, dyslipidemia and peptic ulcers. What would be the best option for secondary stroke prevention?
  a) Aspirin 81mg po daily
  b) Acenocoumarol 2mg po daily
  c) Clopidogrel 75mg daily
  d) Rivaroxaban 20mg po daily
Cardioembolic Stroke make up 20% of IS

50% Afib

25% Valve related

33% Left Ventricle Thrombus (usually post MI)

Stroke.2006;37:577-617
Case

- G.R is a 55 year old man with a PMH of a cardioembolic stroke, with a history of atrial fibrillation, CAD, dyslipidemia. The patient lives very far from access to a laboratory for monitoring of therapy. **What would be the best option for secondary stroke prevention?**
  a) Aspirin 81mg po daily
  b) Acenocoumarol 2mg po daily, INR goal 2-3
  c) Clopidogrel 75mg daily
  d) Rivaroxaban 20mg po daily
## Cardioembolic Source Risk

<table>
<thead>
<tr>
<th>Major Risk</th>
<th>Minor or Uncertain Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>Mitral annular calcification</td>
</tr>
<tr>
<td>Prosthetic mechanical valves</td>
<td>PFO</td>
</tr>
<tr>
<td>Recent myocardial infarction</td>
<td>Atrial septal aneurysm</td>
</tr>
<tr>
<td>Left ventricular thrombus</td>
<td>Calcific aortic stenosis</td>
</tr>
<tr>
<td>Atrial myxoma</td>
<td></td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathies</td>
<td></td>
</tr>
<tr>
<td>Marantic endocarditis</td>
<td></td>
</tr>
</tbody>
</table>

*Table 4—Cardioembolic Sources (Section 4.4)*

Chest 2008;630S-669S
Secondary Stroke Prevention in patients who experienced Cardioembolic stroke due to Atrial Fibrillation

- **Anticoagulation (CHADS2 score automatically ≥2)**
  - NOACs or VKA anticoagulant based on the presence of valvular or non-valvular AFIB

- **How soon after having a cardioembolic stroke can anticoagulation be started?**
  - Within 14 days after the onset of neurological symptoms
  - Delay initiation beyond 14 days if the patient is diagnosed with a high risk for hemorrhagic conversion
    - High risk of hemorrhagic conversion: large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension
Secondary Stroke Prevention in patients who experienced Cardioembolic stroke due to Atrial Fibrillation

- For ischemic stroke or TIA with **valvular AFib**, anticoagulation with a VKA (target INR 2.0 to 3.0)

- For ischemic stroke or TIA with **NON-VALVULAR AFIB**:
  - VKA therapy
  - Apixaban
  - Dabigatran
  - Rivaroxaban

  The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including renal function and time in INR therapeutic range
Secondary Stroke Prevention in patients who experienced Cardioembolic stroke due to Atrial Fibrillation

- For patients who are unable to take oral anticoagulants:
  - Aspirin alone is recommended (Class I; Level of Evidence A).
  - Aspirin + clopidogrel (Class IIb; Level of Evidence B).

- The combination of Oral Anticoagulation (VKA or NOAC) + antiplatelet therapy
  - not recommended for all patients after ischemic stroke or TIA
  - reasonable after acute coronary syndrome or stent placement
Case

- G.R is a 55 year old man with a PMH of a cardioembolic stroke, with a history of atrial fibrillation, CAD, dyslipidemia. The patient lives very far from access to a laboratory for monitoring of therapy. **What would be the best option for secondary stroke prevention?**

  a) Aspirin 81mg po daily
  b) Acenocoumarol 2mg po daily, INR goal 2-3
  c) Clopidogrel 75mg daily
  d) Rivaroxaban 20mg po daily
Cardioembolic Stroke make up 20% of IS

- 50% Afib
- 25% Valve related
- 33% Left Ventricle Thrombus (usually post MI)

Stroke.2006;37:577-617
Secondary Stroke Prevention in patients who experienced Cardioembolic stroke in the presence of prosthetic heart valves

- Patients with a history of ischemic stroke/ TIA who have a mechanical valve replacement:
  - mechanical mitral heart valves, VKA goal INR 2.5 to 3.5
  - mechanical aortic heart valves, VKA goal INR 2 to 3

- Patients with mechanical prosthetic heart valves who have an ischemic stroke despite therapeutic INR:
  - Consider adding aspirin 75 mg/d to 100 mg/d to VKA and maintain INR at a target.
Secondary Stroke Prevention in patients who experienced Cardioembolic stroke in the presence of prosthetic heart valves

- Patients with a history of ischemic stroke/ TIA who have a BIOprosthetic valve replacement:
  - **Bioprosthetic aortic or mitral valve**, give 3 to 6 months of anticoagulation *(INR 2-3)* from the time of valve placement.
  - After 3-6 months of AC, stop anticoagulation and continue on long-term aspirin 75 to 100 mg/d


Antithrombotic Therapy for CVA

- Antithrombotic therapy for secondary prevention of CVA depends on the type of stroke:
  - If atherosclerotic stroke, give antiplatelet

- If cardio-embolic stroke (stroke associated with atrial fibrillation or valvular heart disease), give anticoagulant
  - Select anticoagulation (NOACs versus VKA) depending on factors such:
    - as renal impairment
    - presence of a valve replacement
Anticoagulation Counseling
Anticoagulation Counseling Tips

- Involve your patient
- Compliance – frequency of medication
- NOACS: Importance of follow up even if no INR checks
- VKA: Importance of checking INR
- Inform the doctor about new medications
- Missed doses
- How to take the medication
- How to store the medication
- In case of bleeding, share with physician time of last dose and renal function
Anticoagulation Counseling Tips

- **Dabigatran**
  - Do not crush or chew tablets
  - Do not open or sprinkle the capsule
  - Avoid in patients with GERD, history of GI bleed, MI

- **Rivaroxaban**
  - Take with food
  - You can crush tablets
  - Avoid in history of GI bleed

- **Apixaban**
  - You can crush tablets
Consider Counseling Initiatives

Anticoagulants

What are anticoagulants?

Anticoagulants are medicines that prevent the blood from clotting as quickly or as effectively as normal.

- It is used to thin the blood so that clots will not form.
- It is used to treat blood clots.

What are some things I need to know or do while I take this drug?

- Tell dentists, surgeons, and other doctors that you use this drug.
- Keep a list of all your drugs (prescription, natural products, vitamins, Over The Counter) with you.
- Talk with the doctor before starting or stopping any drug, including prescription or OTC, natural products, or vitamins.
- Talk with your doctor if you have recently had or will be having a spinal or epidural procedure.
Consider Counseling Initiatives

When do I have to call my doctor or get medical help about right away?

- Allergic reaction, you may feel:
  - rash; itching
  - tightness in the chest or throat
  - swelling of the mouth, face, lips, tongue, or throat

- Signs of bleeding:
  - throwing up or coughing blood that looks red or like coffee grounds (or dark brown)
  - blood in the urine that looks either pink or brown
  - black, red, or tarry stools
  - bruises without a reason or that get bigger
  - any bleeding that is very bad or that you cannot stop like bleeding from the nose, gums or vaginal or menstrual bleeding

- A fall or when you hit your head even if you feel fine
- Stomach pain
- Change in thinking clearly, trouble speaking, change in balance, blurred eyesight.
- Very bad headache, numbness, muscle weakness or paralysis, loss of bladder or bowel control
Helpful Links:
Provider & Patient Education

- http://www.doacresources.org/resources
- http://www.anticoagulationtoolkit.org/
- http://excellence.acforum.org/
Conclusion

- NOACS have provided a significant advancement in oral anticoagulation
  - Appropriate patient selection is mandatory
  - Good renal function is important
  - Screen for unrecognized drug interactions

- SPAF:
  - CHADS2 score < 2, antiplatelet is reasonable
  - CHADS 2 Score ≥2: give anticoagulation
    - NOACS if non-valvular atrial fibrillation and dose adjust for renal impairment
    - VKA if valvular atrial fibrillation

- VTE:
  - NOACs are first link but contraindicated in renal impairment, no dose adjustments are available for VTE treatment
  - Conventional bridge therapy with (VKA + parenteral anticoagulant) is second line, unless patient cannot get NOACs

- CVA:
  - If atherosclerotic stroke, give antiplatelet
  - If cardio-embolic stroke, give anticoagulant
    - For anticoagulation: select between NOACs and VKA depending on factors such as renal impairment
Thanks!