New Treatment Guidelines in Atrial Fibrillation and Updates on NOACs

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Disclosures
I have nothing to disclose
**Session Objectives**

- To review selected recommendations from the 2014 AHA/ACC Guidelines on AF
- Discuss how your management of patients with atrial fibrillation might be impacted
- Review evidence on Novel Oral Anticoagulants (NOACs)

2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

Published in: Circulation. 2014; 129
**Guideline Recommendations**

1. Initial clinical evaluation
2. Preventing thromboembolism
3. Rate control
4. Rhythm control

**Strength of Recommendations: Class and Level of Evidence**

- **Size of Treatment Effect**
  - Class I: you SHOULD do it (benefit >>> risk)
  - Class IIa: it is REASONABLE to do it (benefit >> risk)
  - Class IIb: may CONSIDER doing it (benefit ≥ risk)
  - Class III: no benefit or harm exists (Don’t do it!)

- **Estimates of Certainty of Treatment Effect**
  - Level A: strong evidence, multiple populations
  - Level B: moderate evidence, limited populations
  - Level C: weak evidence, very limited populations
Case

- An 81 yo woman with a history of anti-Western medicine beliefs, HTN and fall risk c/o periodic palpitations. Ambulatory ECG reveals NSR. A 72 hour-Holter demonstrates rare runs of SVT at 140, but no other arrhythmia. She is started on a Beta Blocker, which she only sporadically takes. 12 months later, she presents to ED 3 hours after experiencing aphasia and hemiparesis. She receives TPA and is hospitalized; her neuro sx resolve. Inpatient work-up is -. She receives an outpatient Zio-patch which demonstrates that she is in AF for 10% of the time.

- SHOULD SHE BE ANTI-COAGULATED?

Initial Evaluation of AF
Initial Clinical Evaluation

- Establish the diagnosis of AF using ECG (Class IC)
- Characterize the type of AF
- Define (and treat) associated medical conditions
  - CHF, hypertension
- Assess symptom burden
- Assess thromboembolic risk

AF: Classification

<table>
<thead>
<tr>
<th>Type of AF</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal</td>
<td>AF episodes last &lt; 7 days</td>
</tr>
<tr>
<td>Persistent</td>
<td>Continuous AF &gt; 7 days</td>
</tr>
<tr>
<td>Longstanding persistent</td>
<td>Continuous AF &gt; 12 months</td>
</tr>
<tr>
<td>Permanent</td>
<td>No further efforts to restore sinus rhythm are possible</td>
</tr>
<tr>
<td>Non-valvular</td>
<td>No rheumatic mitral stenosis, prosthetic heart valve, or mitral valve repair</td>
</tr>
</tbody>
</table>
Initial Evaluation

- ECG, telemetry, or event recorders
- Transthoracic echocardiogram to detect underlying cardiac disease, evaluate cardiac function, and measure left atrial size
- Other tests as appropriate
  - Sleep study, thyroid evaluation, pulmonary evaluation

Prevention of Thromboembolism
**Preventing Thromboembolism**

- Individualize decision-making on antithrombotic therapy based on stroke risk, bleeding risk, and patient’s values and preferences (Class IC)
- Periodically re-evaluate need and choice of antithrombotic therapy (Class IC)
- It doesn’t matter if AF is paroxysmal, persistent, or permanent → stroke prevention is the same (Class IB)

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**Case Revisited**

- An 81 yo woman with a history of anti-Western medicine beliefs and HTN and fall risk c/o periodic palpitations. Ambulatory ECG reveals NSR. A 72 hour-Holter demonstrates rare runs of SVT at 140, but no other arrhythmia. She is started on a Beta Blocker, which she only sporadically takes. 12 months later, she presents to the ED 3 hours after experiencing aphasia and hemiparesis. She receives TPA and is hospitalized; her neuro sx resolve. Inpatient work-up is --. She receives an outpatient Zio-patch which demonstrates that she is in AF for 10% of the time.
- SHOULD SHE BE ANTI-COAGULATED?
Estimate Stroke Risk

- Calculate CHA₂DS₂-VASc score (Class IB)
  - Congestive heart failure (1 point)
  - Hypertension (1 point)
  - Age ≥ 75 years (2 points)
  - Diabetes mellitus (1 point)
  - Stroke/TIA (2 points)
  - Vascular disease (1 point)
  - Age 65-74 (1 point)
  - Sex: Female (1 point)


- Her score is 6 = 9.8% annual risk of stroke

Antithrombotic Therapy

<table>
<thead>
<tr>
<th>CHA₂DS₂-VASc Score</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No antithrombotic therapy (Class IIaA)</td>
</tr>
<tr>
<td>1</td>
<td>No antithrombotic therapy vs. Aspirin vs. Oral anticoagulant (Class IIbC)</td>
</tr>
<tr>
<td>2 or higher</td>
<td>Oral anticoagulant (Class IA)</td>
</tr>
</tbody>
</table>
**Calculate Bleeding Risk: HAS-BLED score**

- Derived from a cohort of ~4000 pts with AF
- Assesses 1-year risk for major bleeding (intracranial, hospitalization, hemoglobin decrease > 2 g/L, and/or transfusion)
- **HAS-BLED**: Note that this score does not include fall hx or risk
  - Hypertension
  - Abnormal Liver/Renal Function
  - Stroke History
  - Bleeding Predisposition
  - Labile INRs
  - Elderly (Age > 65)
  - Drugs/Alcohol Usage

- Score can be calculated to an annual bleeding risk: [http://www.qxmd.com/calculate-online/cardiology/has-bled-score-bleeding-in-atrial-fibrillation](http://www.qxmd.com/calculate-online/cardiology/has-bled-score-bleeding-in-atrial-fibrillation)
- Her score is 3 = 3.7% annual risk of major hemorrhage

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**Choice of Anticoagulants**

- In patients with *nonvalvular AF* who need anticoagulation:
  - Warfarin (Class IA)– OR – a novel oral anticoagulant (NOAC, Class IB)

- In patients with a *mechanical heart valve*, use **warfarin** (Class IB)
Novel Oral Anticoagulants

- Direct thrombin inhibitor: **dabigatran**
- Factor Xa inhibitors: **rivaroxaban, apixaban (edoxaban)**
- Consider if unable to maintain therapeutic INRs on warfarin (Class IC)
- Check renal function before initiating and monitor periodically afterwards (Class IB)
- Reduced dosing *might* be considered for patients with moderate to severe renal disease (Class IIbC)
- Not recommended for patients with end stage kidney disease (Class IIIC-no benefit/harm)
- Don’t use in patients with mechanical heart valves (Class IIIB-harm)

AF and Percutaneous Coronary Intervention

- Bare metal stents may be considered in patients with AF undergoing PCI to minimize need for concomitant anticoagulants + dual antiplatelet therapy (Class IIbC)
- In patients with AF and CHA\textsubscript{2}DS\textsubscript{2}VASc ≥ 2 undergoing PCI, it may be reasonable to use clopidogrel concurrently with oral anticoagulants but without aspirin (Class IIbB)
Rate Control for AF

- Control the ventricular rate (Class I)

- Target heart rates
  - < 80 bpm for symptomatic patients (Class IIaB)
  - < 110 if asymptomatic and no heart failure (Class IIbB)
How to Control Rate

- Medications
  - Beta-blocker (Class IB)
  - Non-dihydropyridine calcium channel blocker (Class IB)
  - Amiodarone (if failed other measures, Class IIbC)
- AV nodal ablation + permanent ventricular pacing if pharmacologic therapy is inadequate and rhythm control unachievable (Class IIaB)

Rate Control for Atrial Fibrillation

- No other CV disease
  - Beta blocker
    - Diltiazem
    - Verapamil
- Hypertension or HFpEF
  - Beta blocker
    - Diltiazem
    - Verapamil
- LV dysfunction or HF
  - Beta blocker
    - Digoxin
- Amiodarone
**Don’t Dos**

- Don’t use AV nodal ablation/pacing without an adequate trial of medications (Class IIIC-harm)
- Don’t use non-dihydropyridine CCBs in patients with decompensated HF (Class IIIC-harm)
- Don’t use digoxin, non-dihydropyridine CCBs, or IV amiodarone in patients with pre-excitation and AF (increases risk of VFib) (Class IIIB-harm)
- Don’t use dronedarone as rate control in patients with permanent AF (Class IIIB-harm)

**Rhythm Control for AF**
Rhythm Control

- Treat reversible causes prior to initiating antiarrhythmic drugs (Class IC)
- Antiarrhythmic drugs vs. catheter ablation

Antiarrhythmic Drugs

- Recommended for treating tachycardia-induced cardiomyopathy (Class IIaC)
- Consider if there are infrequent, well-tolerated episodes of AF and treatment reduces symptoms/frequency (Class IIbC)
- Discontinue if AF becomes permanent (Class IIIB-harm)
- Risks of anti-arrhythmic drugs should be considered prior to initiating therapy (Class IC)
**Antiarrhythmic Drugs**

- Amiodarone
  - Should be used only if risks/side effects are considered and other agents are not suitable (Class IC)
- Dofetilide
- Dronedarone
  - Don’t use in heart failure (Class IIIB-harm)
- Flecainide
- Propafenone
- Sotalol
  - Don’t use in heart failure (Class IIIB-harm)

**Catheter Ablation**

- May be useful for symptomatic patients who do not tolerate or have failed antiarrhythmic medications (Class IA)
  - Might be a reasonable initial strategy in some patients
- Need to assess procedural risks and outcomes relevant to your individual patient (Class IC)
- Does not obviate the need for anticoagulation
  - Should not be performed in patients who cannot be treated with anticoagulants peri-procedurally (Class IIIC-harm)
**Catheter Ablation**

- **Symptomatic paroxysmal AF**
  - Consider for patients refractory or intolerant to at least 1 Class I or III antiarrhythmic medication (Class IA)
  - Might be reasonable as an *initial* strategy (Class IIaB)

- **Symptomatic persistent AF**
  - Reasonable for patients refractory or intolerant to at least 1 Class I or III antiarrhythmic medication (Class IIaA)
  - Might be reasonable as an *initial* strategy (Class IIbC)

- **Symptomatic long-standing persistent AF (>12 mo)**: may consider if refractory or intolerant to meds (Class IIbB)

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**Rhythm Control in Symptomatic AF without structural heart disease**

- Dofetilide
- Dronedarone
- Flecaïnide
- Propafenone
- Sotalol
- Catheter ablation
- Amiodarone
Rhythm Control in symptomatic AF with structural heart disease

- CAD
- Heart Failure
- Dofetilide
- Dronedarone
- Sotalol
- Catheter ablation
- Amiodarone
- Dofetilide

AF: Summary of Key Points

- CHA²DS²-VASc should be used to determine stroke risk and need for anticoagulation
- Several choices for oral anticoagulation in AF
- After PCI, if bare stent not used: clopidogrel + anticoagulation (but without aspirin)
- Anti-arrhythmics still have a role in AF patients with symptoms
- Stronger support for catheter ablation in selected symptomatic patients
Implications of Updated Guidelines

- More patients will be considered for catheter ablation
- More patients will be recommended oral anticoagulants (particularly women and younger patients)
- Novel oral anticoagulants (NOACs) are considered viable alternatives to warfarin and their use will probably increase

Case

What would you treat her with?
1. Warfarin (adjusted to goal INR 2-3)
2. Dabigatran 150mg PO BID
3. Rivaroxaban 20mg PO daily
4. Apixaban 5mg PO BID
**NOACs: Objectives**

- Familiarize you with indications for the novel available oral anticoagulants (NOACs)
- Review the evidence supporting their efficacy and safety
- Discuss their advantages and disadvantages

**Vitamin K Antagonists (Warfarin)**

- For the last 60 years, the only oral anticoagulants
- Inexpensive and highly effective, but challenging to manage
  - Requires ongoing monitoring of PT/INR and dose-adjustments
  - Numerous drug-drug interactions
  - Impacted by dietary changes
  - Genetic variability in dosing
- INRs out of range 30-50% of the time
Novel Oral Anticoagulants

- Direct thrombin inhibitors
  - Ximelagatran (discontinued)
  - Dabigatran (Pradaxa®)
- Factor Xa inhibitors
  - Rivaroxaban (Xarelto®)
  - Apixaban (Eliquis®)
- Act further down the clotting cascade and so have more predictable pharmacodynamics

Targets of Novel Oral Anticoagulants
**Advantages**

- Fixed, oral dosing
- Rapid onset of action
- Fewer drug-drug interactions
- Not affected by diet
- No need for routine coagulation monitoring

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**Novel Oral Anticoagulants**

<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>Time to effect</strong></td>
<td>2 hrs</td>
<td>2.5-4 hrs</td>
<td>3 hrs</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>14-17 hrs</td>
<td>9-13 hrs</td>
<td>8-15 hrs</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td><strong>Renal excretion</strong></td>
<td>80%</td>
<td>66%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Drug interactions:</strong></td>
<td>P-gp inhibitors/inducers and CYP3A4 inhibitors/inducers</td>
<td>Verapamil, amiodarone, dronedarone, macrolide antibiotics Rifampin, phenytoin, carbamazepine, phenobarbital, St.John's wort, antifungals (ex/ ketoconazole), protease inhibitors</td>
<td></td>
</tr>
</tbody>
</table>
**Indications for Anticoagulation**

- **Atrial fibrillation**
- **Mechanical heart valves**
- **Venous thromboembolism treatment**
- **Venous thromboembolism prevention**

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**Atrial Fibrillation**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>150mg bid (also tested 110)</td>
<td>20mg daily 15mg if CrCl 30-49</td>
<td>5mg bid 2.5 bid if age ≥80, wt&lt;60kg, Cr≥1.5</td>
</tr>
<tr>
<td><strong>Mean Age</strong></td>
<td>71</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td><strong>Mean CHADS2</strong></td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Prior warfarin</strong></td>
<td>50%</td>
<td>62%</td>
<td>57%</td>
</tr>
<tr>
<td><strong>Excluded</strong></td>
<td>Valvular heart disease, Bleeding risk, CrCl &lt;30</td>
<td>Mitral stenosis Prosthetic valve Bleeding risk CrCl &lt;30</td>
<td>Mitral stenosis Prosthetic valve Bleeding risk CrCl &lt;25</td>
</tr>
</tbody>
</table>
Atrial Fibrillation--Summary

- Newer agents at least as effective as warfarin
  - Reduced risk of stroke/thromboembolism
  - Apixaban had mortality benefit
- Bleeding rates generally similar
  - However, consistently lower risk of intracranial hemorrhage
- Similar rates of discontinuation vs. warfarin
- Studies excluded certain patients:
  - Valvular heart disease
  - Renal insufficiency GFR <30

<table>
<thead>
<tr>
<th>Study</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Discontinued</td>
<td>15.5% vs. 10.2% for warfarin</td>
<td>23.7% vs. 22.2% for warfarin</td>
<td>25.3% vs. 27.5% for warfarin</td>
</tr>
<tr>
<td>Warfarin TTR%</td>
<td>64%</td>
<td>55%</td>
<td>66%</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3.6 vs. 4.1 in warfarin HR=0.88 [0.8-1.0]</td>
<td>1.9 vs. 2.2 in warfarin HR=0.85 [0.7-1.0]</td>
<td>3.5 vs. 3.9 in warfarin HR=0.89 [0.8-0.998]</td>
</tr>
<tr>
<td>(per 100 p-yrs) Stroke/embolism</td>
<td>1.1 vs. 1.7 in warfarin HR=0.66 [0.5-0.8]</td>
<td>1.7 vs. 2.4 in warfarin HR=0.88 [0.75-1.0]</td>
<td>1.3 vs. 1.6 in warfarin HR=0.79 [0.7-0.95]</td>
</tr>
<tr>
<td>Major Bleeds</td>
<td>3.1 vs. 3.4 in warfarin HR=0.93 [0.7-1.1]</td>
<td>3.6 vs. 3.4 in warfarin HR=1.0 [1.0-1.1]</td>
<td>2.1 vs. 3.1 in warfarin HR=0.69 [0.6-0.8]</td>
</tr>
<tr>
<td>(per 100 p-yrs) ICH</td>
<td>0.3 vs. 0.7 in warfarin HR=0.40 [0.3-0.7]</td>
<td>0.5 vs. 0.7 in warfarin HR=0.67 [0.5-0.9]</td>
<td>0.3 vs. 0.8 in warfarin HR=0.42 [0.3-0.6]</td>
</tr>
</tbody>
</table>
Disadvantages

- While there is rapid clearance, anticoagulant effect cannot be acutely reversed
- More difficult to determine whether/when there is residual anticoagulant effect
- Adherence must be strict
- Much more costly than warfarin ($3000 vs. $48 per year), excluding visits

A few more points …

- Dabigatran:
  - higher risk of MI
  - Dyspepsia a common side-effect
  - Increased risk of GI bleeding, particularly in elderly patients or those with renal insufficiency
- Rivaroxaban
  - High rate of stroke noted when transitioning from rivaroxaban to warfarin
  - <50% therapeutic on warfarin within 30 days, highlighting importance of close AC monitoring during transitions
Atrial Fibrillation

- Novel oral anticoagulants are reasonable alternatives to warfarin for atrial fibrillation
- Decision is best individualized
  - Consider adherence, renal function, cost
  - Challenges to warfarin? (diet, drugs, INR monitoring)
- Counsel patients that these agents are not reversible
- Bleeding precautions, Medical Alert bracelets
- Alert other healthcare providers (pre-procedure)

Mechanical Heart Valves

- RE-ALIGN Trial (comparing 150-300mg BID dabigatran to warfarin for prosthetic heart valves)
  - Stopped early due to increased rates of stroke, MI, valve thrombosis (10% vs. 4.5% in warfarin)
  - Higher bleeding with dabigatran (22.5% vs. 13.5%)
- Newer anticoagulants are CONTRAINDICATED in patients with mechanical heart valves
- No data on efficacy or safety in bioprosthetic valves; do not recommend their use at present
**Perioperative Care and Coagulation Testing with NOACs**

- May be important to exclude residual anticoagulant effect prior to invasive procedures
  - Surgery
  - tPA for acute ischemic stroke

- Standard recommendation is to hold for at least 2 to 6 half-lives prior to procedures
  - Affected by renal function

- Standard coagulation testing (PT/PTT) do not accurately or consistently reflect plasma concentration or anticoagulant effects

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**Coagulation Testing is Variable**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTT</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PT/INR</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Thrombin Time</td>
<td>+++</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Anti Xa</td>
<td>No effect</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>
To Determine If a Patient is on Active NOAC

- Dabigatran: obtain PTT or TT
  - Normal PTT indicates little or no effect
  - Normal TT excludes dabigatran effect
  - Prolonged PT indicates presence of med
- Rivaroxaban: obtain PT or anti-Xa assay
  - Prolonged PT indicates presence of med and normal PT suggests low med levels
  - Anti-Xa assay (still needs validation)
- Apixaban: obtain anti-Xa assay
  - Anti-Xa assay (still needs validation)

Perioperative Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Major Surgery</th>
<th>Minor Surgery</th>
<th>Major Surgery</th>
<th>Minor Surgery</th>
<th>Major Surgery</th>
<th>Minor Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Skip 4 doses if CrCl &gt;50</td>
<td>Skip 6-8 doses if CrCl &lt;50</td>
<td>Skip 1-2 doses if CrCl &gt;50</td>
<td>Skip 3-4 doses if CrCl &lt;50</td>
<td>Skip 3-4 doses</td>
<td>Skip 1-2 doses</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Skip 3-4 doses</td>
<td>Skip 1-2 doses</td>
<td>Skip 1-2 doses</td>
<td>Skip 3-4 doses</td>
<td>Skip 1-2 doses</td>
<td>Skip 3-4 doses</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Skip 3-4 doses</td>
<td>Skip 1-2 doses</td>
<td>Skip 3-4 doses</td>
<td>Skip 1-2 doses</td>
<td>Skip 3-4 doses</td>
<td>Skip 1-2 doses</td>
</tr>
</tbody>
</table>
NOAC Summary

- Non-valvular Atrial fibrillation
  - Dabigatran, rivaroxaban, apixaban, or warfarin
- Mechanical heart valves
  - DO NOT USE NOACs!
- NOAC Cautions:
  - Renal insufficiency (GFR < 30), low body weight, older age
  - Poor adherence
  - Potential for severe bleeding and need for acute reversal
  - Challenges with peri-operative management
  - High Cost

NOACs Conclusions

- Warfarin is not obsolete ... yet
- NOACs are as effective as warfarin for certain indications, and may result in fewer serious bleeds
- Carefully individualize anti-coagulation decision for each patient
Venous Thromboembolism

- VTE treatment
- VTE prevention in medical patients
- VTE prevention in orthopedic patients
Venous Thromboembolism Treatment

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>2564 with VTE, initially treated with enox</td>
<td>3449 with acute DVT (62% unprovoked)</td>
<td>4832 with acute PE (65% unprovoked)</td>
</tr>
<tr>
<td>Dose</td>
<td>150mg bid x 6mo</td>
<td>15mg bid x 3 weeks, then 20mg daily</td>
<td>15mg bid x 3 weeks, then 20mg</td>
</tr>
<tr>
<td>Control</td>
<td>Warfarin x 6mo (TTR 60%)</td>
<td>Enox+warfarin (TTR 58%)</td>
<td>Enox+warfarin (TTR 63%)</td>
</tr>
<tr>
<td>VTE</td>
<td>2.4% vs. 2.1% (warf) HR=1.1 [0.6-1.8]</td>
<td>2.1% vs. 3.0% (control) HR=0.68 [0.4-1.0]</td>
<td>2.1% vs. 1.8% (control) HR=1.1 [0.8-1.7]</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.6% vs. 1.9%, HR=0.82 [0.5-1.5]</td>
<td>0.8% vs. 1.2%, HR=0.65 [0.3-1.3]</td>
<td>1.1% vs. 2.2%, HR=0.49 [0.3-0.8]</td>
</tr>
</tbody>
</table>

Venous Thromboembolism Treatment

- Only rivaroxaban is currently FDA-approved for the acute treatment of VTE
  - Seems to be similarly effective as conventional enoxaparin → warfarin therapy
  - Dose is 15mg PO BID for 3 weeks followed by 20mg daily afterwards
- Might be a more attractive alternative to enoxaparin
- Make sure that it is covered by insurance
# Venous Thromboembolism Prevention

<table>
<thead>
<tr>
<th>Study</th>
<th>Rivaroxaban</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td>EINSTEIN</td>
<td>MAGELLAN</td>
<td>AMPLIFY-EXT</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>1197 patients with acute VTE who completed 6-12 mo anticoagulation</td>
<td>8101 hospitalized medicine patients</td>
<td>2482 patients with VTE who had completed 6-12mo anticoagulation</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Placebo</td>
<td>Enoxaparin 40mg for 10d then placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>20mg daily</td>
<td>10mg daily for 35d</td>
<td>2.5mg bid 5mg bid</td>
</tr>
<tr>
<td><strong>VTE</strong></td>
<td>1.3% vs. 7.1% in placebo (HR=0.18 [0.1-0.4])</td>
<td>2.7% in both at 10d 4.4% vs. 5.7% in placebo at 35d (RR=0.77 [0.6-0.96])</td>
<td>1.7% (2.5mg) vs. 1.7% (5mg) vs. 8.8% in placebo</td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td>0.7% vs. 0% in placebo, p=0.1</td>
<td>2.8% vs. 1.2% (enox) at 10d, 4.1% vs. 1.7% (placebo) at 35d</td>
<td>0.2% (2.5mg) vs. 0.1% (5mg) vs. 0.5% in placebo</td>
</tr>
</tbody>
</table>

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# VTE Prevention After Arthroplasty

| Drug          | RE-MODEL | RE-MOBILIZE | RE-NOVATE | RE-NOVATE II | Overall 
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td>0.97 (0.82-1.13)</td>
<td>1.23 (1.03-1.47)</td>
<td>0.90 (0.63-1.29)</td>
<td>0.88 (0.63-1.22)</td>
<td>1.03 (0.93-1.15)*</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>0.30 (0.18-0.51)</td>
<td>0.21 (0.13-0.35)</td>
<td>0.10 (0.03-0.36)</td>
<td>0.09 (0.01-0.92)</td>
<td>0.46 (0.39-0.54)†</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>1.02 (0.78-1.32)</td>
<td>0.62 (0.51-0.74)</td>
<td>0.36 (0.23-0.56)</td>
<td>0.67 (0.58-0.77)‡</td>
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</tr>
</tbody>
</table>
VTE Prevention

- Rivaroxaban and apixaban can lower recurrent VTE rate in patients who have completed 6-12 months initial therapy for VTE
  - Might be more acceptable than warfarin
- Rivaroxaban approved for VTE prevention after orthopedic surgery
  - 10mg po daily after TKA, THA
  - Keep in mind local restrictions on use after neuraxial anesthesia/epidural catheters

Potential Reversal Strategies?

- Hemodynamic support
- Dabigatran
  - A monoclonal antibody currently in development
  - Hemodialysis (if feasible), activated charcoal
- Rivaroxaban and apixaban
  - 4-factor prothrombin complex concentrate reversed PT prolongation in healthy volunteers for rivaroxaban but not dabigatran
  - activated PCC (FEIBA) had in vitro reversal activity for all three agents