Optimal anticoagulation Strategies for Stroke Prevention in Atrial Fibrillation

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Financial Disclosure Information

I have relationships with the following companies with regard Trial design for Dyslipidemia, Type II DM and CAD

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• I want to thank Drs. Robert McBane and Waldemar Wysokinski for assistance with preparation for this presentation

Anticoagulation for non-valvular atrial fibrillation – update 2016

Learning objectives

• Which patients require long term anticoagulation for stroke prevention?

• Describe novel oral anticoagulants called direct oral anticoagulants (DOACs) currently FDA approved and how do they compare to warfarin with respect to efficacy, bleeding risk?

• How do I choose specific anticoagulant for specific patient?
Atrial fibrillation: Magnitude of the Problem

- 2.7-6.1 mln in USA
- 0.1 % < 50
- 10 % ≥ 80 years
- 72% require AC by CHADS2
- 90-95% by CHA2DS2-VASc
### CHADS<sub>2</sub> Annual Risk of Stroke

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; score</th>
<th>stroke rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9 (1.2-3.0)</td>
</tr>
<tr>
<td>1</td>
<td>2.8 (2.0-3.8)</td>
</tr>
<tr>
<td>2</td>
<td>4.0 (3.1-5.1)</td>
</tr>
<tr>
<td>3</td>
<td>5.9 (4.6-7.3)</td>
</tr>
<tr>
<td>4</td>
<td>8.5 (6.3-11.1)</td>
</tr>
<tr>
<td>5</td>
<td>12.5 (8.2-17.5)</td>
</tr>
<tr>
<td>6</td>
<td>18.2 (10.5-27.4)</td>
</tr>
</tbody>
</table>

JAMA. 2001;285:2864–2870

### CHA<sub>2</sub>DS<sub>2</sub>-VASc

2009 Birmingham Schema

- Congestive heart failure/LV dysfunction: 1
- Hypertension: 1
- Age ≥ 75 y: 2
- Diabetes mellitus: 1
- Stroke/TIA/TE: 2
- **Vascular disease (MI, PVD, or AAA)**: 1
- Age 65-74 y: 1
- **Sex category (female gender)**: 1

Lip G YH et al. Chest 2010
Further Risk Stratification of Patients with Low CHADS<sub>2</sub> Scores (0 or 1)

<table>
<thead>
<tr>
<th>CHA2DS2-VASc</th>
<th>Person-years</th>
<th>EVENTS</th>
<th>Stroke rate (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6,919</td>
<td>58</td>
<td>0.84 (0.65-1.08)</td>
</tr>
<tr>
<td>1</td>
<td>8,880</td>
<td>159</td>
<td>1.79 (1.53-2.09)</td>
</tr>
<tr>
<td>2</td>
<td>11,863</td>
<td>435</td>
<td>3.67 (3.34-4.03)</td>
</tr>
<tr>
<td>3</td>
<td>11,473</td>
<td>660</td>
<td>5.75 (5.33-6.21)</td>
</tr>
<tr>
<td>4</td>
<td>1,137</td>
<td>93</td>
<td>8.18 (6.68-10.02)</td>
</tr>
</tbody>
</table>

Thromb Haemost 2012; 107: 1172–1179

ESC Guidelines 2012
CHA2DS2-VASc – Anticoagulation (AC)

- AC recommended for all NVAF patients except: low risk (aged <65 and lone AF, both M&F) or with contraindications (IA)
  - "0" no AC (IB)
  - "1" consider AC therapy (IIa/A)
  - "≥2" recommend AC therapy (IA) with DOACs rather than adjusted-dose VKA (INR 2–3); antiplatelet therapy only if patient refuses AC
2014 AHA/ACC/HRS Guideline
CHA2DS2-VASc - Anticoagulation (AC)

- “0” - reasonable not to AC (IIa)
- “1” - considered AC (IIb)
- ≥ 2 recommended AC (I)
  - warfarin (INR 2.0 to 3.0) (A),
  - dabigatran (B), rivaroxaban (B), apixaban (B)

Use of Novel Anticoagulants
Real World Experience: ORBIT AF

AF patients: New onset
50% started on a DOAC

AF patients: Chronic on warfarin
25% transitioned to a DOAC

Circ Cardiovasc Qual Outc. 2014; 7: A336
Direct Oral Anticoagulants

- **Factor**
  - Dabigatran: IIa
  - Rivaroxaban: Xa
  - Apixaban: Xa
  - Edoxaban: Xa

- **T½ (hrs)**
  - Dabigatran: 12-17
  - Rivaroxaban: 7-11
  - Apixaban: 7-11
  - Edoxaban: 7-11

- **Elimination**
  - Dabigatran: Renal
  - Rivaroxaban: Renal, Hepatic
  - Apixaban: Renal, Hepatic Enteric
  - Edoxaban: Renal, Hepatic

**Diagram:**
- **Apixaban** → **Rivaroxaban** → **Edoxaban** → **Xa** → **VIIIa**
- **Prothrombin** → **Thrombin** → **Dabigatran**
- **Fibrinogen** → **Fibrin**
63 y/o male

New diagnosed atrial fibrillation. He has noted new onset exercise intolerance with uncomfortable palpitations. CHA2DS2-VASc is 2 (HTN, DM). He has normal renal and liver function. In addition to adding a beta blocker for rate control and enoxaparin for stroke prevention, you arrange for elective TEE guided cardioversion.

Transesophageal Echocardiogram

Dense spontaneous echo contrast
The cardioversion is cancelled. Which antithrombotic will be associated with the lowest risk of ischemic stroke?

1. Apixaban
2. Edoxaban
3. Rivaroxaban
4. Enoxaparin transition to warfarin
5. Dabigatran
## EFFICACY: Ischemic Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY (Dabigatran)</td>
<td>Dabigatran 0.9%</td>
<td>Warfarin 1.2%</td>
<td>Superior</td>
</tr>
<tr>
<td></td>
<td>0.76 (0.60 – 0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF (Edoxaban)</td>
<td>Edoxaban</td>
<td>Warfarin</td>
<td>Non-inferior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE (Apixaban)</td>
<td>Apixaban 2.1%</td>
<td>Warfarin 3.1%</td>
<td>Superior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCKET AF (Rivaroxaban)</td>
<td>Edoxaban 2.8%</td>
<td>Warfarin 3.4%</td>
<td>No Difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

## Safety: Major Bleeding

<table>
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<td>ARISTOTLE (Apixaban)</td>
<td>Apixaban 2.1%</td>
<td>Warfarin 3.1%</td>
<td>Superior</td>
</tr>
<tr>
<td>ROCKET AF (Rivaroxaban)</td>
<td></td>
<td></td>
<td>No Difference</td>
</tr>
<tr>
<td>Drug vs VKA</td>
<td>RE-LY</td>
<td>ROCKET AF</td>
<td>ARISTOTLE</td>
</tr>
<tr>
<td>------------</td>
<td>-------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>HR (CI 25 75)</td>
<td>(dabigatran)</td>
<td>(rivaroxaban)</td>
<td>(apixaban)</td>
</tr>
<tr>
<td>110mg</td>
<td>150 mg</td>
<td>20 mg</td>
<td>5mg</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>*1.11 (0.89-1.40)</td>
<td>0.94 (0.75-1.17)</td>
<td>0.92 (0.74-1.13)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>Not reported</td>
<td>0.23 (0.09-0.61)</td>
<td>0.87 (0.44-1.50)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.31 (0.17-0.56)</td>
<td>0.59 (0.37-0.93)</td>
<td>0.51 (0.35-0.79)</td>
</tr>
<tr>
<td>Major bleed</td>
<td>0.80 (0.69-0.93)</td>
<td>1.04 (0.90-1.20)</td>
<td>0.69 (0.60-0.80)</td>
</tr>
<tr>
<td>Intracranial bleed</td>
<td>0.31 (0.20-0.47)</td>
<td>0.67 (0.47-0.93)</td>
<td>0.42 (0.30-0.58)</td>
</tr>
<tr>
<td>Gastrointestinal bleed</td>
<td>1.10 (0.86-1.41)</td>
<td>*2.2 vs 2.2 p&lt;.001</td>
<td>0.89 (0.70-1.15)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.91 (0.80-1.03)</td>
<td>0.85 (0.70-1.02)</td>
<td>0.89 (0.80-0.98)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>0.90 (0.77-1.06)</td>
<td>0.89 (0.73-1.10)</td>
<td>0.89 (0.76-1.04)</td>
</tr>
</tbody>
</table>

*Relative Risk instead Hazard Ratio; ischemic or uncertain stroke instead ischemic stroke, and vascular mortality instead cardiovascular mortality.

The cardioversion is cancelled. Which antithrombotic will be associated with the lowest risk of ischemic stroke?

1. Apixaban
2. Edoxaban
3. Rivaroxaban
4. Enoxaparin transition to warfarin
5. Dabigatran
Bottom Line

• Dabigatran offers an **efficacy** advantage for patients at elevated risk for **ischemic stroke**.
• Absolute differences in efficacy between agents are modest.

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76 y/o male

Permanent **atrial fibrillation** treated with rate control and aspirin. **CHA2DS2-VASc is 3** (age, htn, DM). He has normal renal and liver function. He comes to the ED with a painful left foot.
The patient undergoes successful Fogarty embolectomy. Which antithrombotic will be associated with the lowest risk of recurrent systemic embolism?

1. Apixaban 5 mg
2. Dabigatran 150 mg
3. Rivaroxaban 20 mg
4. Edoxaban 30 mg
5. Edoxaban 60 mg
6. Enoxaparin transition to warfarin
The patient undergoes successful Fogarty embolectomy. Which antithrombotic will be associated with the lowest risk of recurrent systemic embolism?

1. Apixaban 5 mg
2. Dabigatran 150 mg
3. Rivaroxaban 20 mg
4. Edoxaban 30 mg
5. Edoxaban 60 mg
6. Enoxaparin transition to warfarin

Factors Predisposing to Systemic Embolism in AF

• Geographic Distribution of Emboli
  • Ischemic Stroke 90%
  • Systemic Embolism 10%

• Hydrodynamic
• Anatomic
• Physical factors

Anatomy and inertia imposes a linear projection into common carotid arteries

Thromb Haemost 2008; 99: 951–955
Factors Predisposing to Systemic Embolism in AF

- Geographic Distribution of Emboli
  - Ischemic Stroke 90%
  - Systemic Embolism 10%

Larger thrombi sufficient to occlude iliac (1 cm), femoral (0.9 cm) or popliteal (0.8 cm) arteries pass by the carotid orifice merely as a function of size.

Factors Predisposing to Systemic Embolism in AF

- Independent predictors governing Geographic Distribution of emboli in Atrial Fibrillation
  - Age > 75
  - Severe left atrial enlargement
  - High CHADS2 score

Thromb Haemost 2008; 99: 951–955
### EFFICACY: Systemic Embolism

<table>
<thead>
<tr>
<th>Trial</th>
<th>Outcome</th>
<th>Treatment</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET AF</td>
<td>Superior</td>
<td>Rivaroxaban 0.04%</td>
<td>0.19%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Warfarin</td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF</td>
<td>Non-inferior</td>
<td>Edoxaban 60 0.08%</td>
<td>0.12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Warfarin</td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Non-inferior</td>
<td>Apixaban 0.09%</td>
<td>0.10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Warfarin</td>
<td></td>
</tr>
<tr>
<td>RE-LY</td>
<td>Non-inferior</td>
<td>Dabigatran 0.10%</td>
<td>0.12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Warfarin</td>
<td></td>
</tr>
</tbody>
</table>

### Bottom Line

- Rivaroxaban is the only DOAC to offer an **efficacy** advantage for patients at risk for **recurrent systemic embolism**.
76 y/o female

Permanent atrial fibrillation. **CHA2DS2-VASc is 5** (age, sex, htn, and DM). She has normal liver function. Her creatinine is 1.5 mg/dL, weight 80 kg (CrCl 48 mg/min). Her daughter tells you that she has suffered **recent falls** with one episode of forehead laceration. She lives alone. Her neurologic evaluation reveals **early Parkinson's disease**.

What are your recommendations regarding her management?

1. Stop all anticoagulants
2. Continue Warfarin at adjusted INR goal 1.5 - 2.0
3. Aspirin 81 mg daily.
4. Dabigatran 150 mg twice daily
5. Rivaroxaban 20 mg daily
6. Apixaban 5 mg twice daily
What are your recommendations regarding her management?

1. Stop all anticoagulants
2. Continue Warfarin at adjusted INR goal 1.5 - 2.0
3. Aspirin 81 mg daily.
4. Dabigatran 150 mg twice daily
5. Rivaroxaban 20 mg daily
6. Apixaban 5 mg twice daily

SAFETY vs Warfarin: Major Bleeding

**Superior**

Apixaban 5 mg (ARISTOTLE)

HR 0.69 (0.6 – 0.8)

Edoxaban (ENGAGE AF)

30 mg HR 0.47 (0.41 – 0.55)

60 mg HR 0.80 (0.71 – 0.91)
SAFETY vs Warfarin: Intracranial bleeding

Superior All DOACs

Dabigatran 0.3%
Rivaroxaban 0.8%
Apixaban 0.3%
Edoxaban 0.4%
Warfarin 0.8% - 1.2%

Risk of Falls and Major bleeding on anticoagulants in Afib patients

• Most common reason cited for withholding anticoagulants.
• Frequently elderly patients at highest risk for thromboembolism from AFib.
• Patients at high risk of falls are frequently excluded from AC trials.
Major bleeding rates did not differ comparing High vs. Low fall risk patients

- Overall 0.6 “fall related” bleeds per 100 pt yrs
- More fall related bleeds in “Low risk” group
- Most bleeds were GI
- More ICH in “Low risk” group

Incidence of ICH in AFib patients who are prone to fall

- National registry Atrial Fibrillation
  - 23,657 subjects
- High fall risk patients
  - 2 times more likely to fall
  - 2 times more likely to suffer a fracture
  - 3 fold higher ICH rates
- Warfarin therapy did not impact ICH rates
- 7 times more likely to suffer ischemic stroke compared to ICH.
Bottom Line

• Atrial fibrillation patients taking AC would have to fall \textit{295 times a year} before risk of ICH outweighs benefit of stroke prevention.

• Both apixaban and edoxaban offer superior bleeding rates compared to warfarin therapy.

Arch Intern Med 1999;159:677

76 y/o male
PAF for 2 years. Pacemaker placed for SSS. His \textit{CHA2DS2-VASc is 4} (age, HTN, DM). He has normal renal and liver function. He takes warfarin 5 mg daily and has consistent INRs within normal range. He has had no bleeding or thromboembolism. What would you recommend for this patient?

1. Apixaban
2. Dabigatran
3. Rivaroxaban
4. Continue warfarin
5. Edoxaban
### Warfarin: Anticoagulation Quality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Home INR</th>
<th>AC Clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>208</td>
<td>550</td>
</tr>
<tr>
<td>Age (years, MN±SD)</td>
<td>63±15</td>
<td>63±16</td>
</tr>
</tbody>
</table>

| AC Indication (%)               |          |           |
| DVT/PE                          | 33       | 38        |
| Atrial Fibrillation             | 27       | 31        |
| Mechanical heart valve          | 20       | 15        |
| Other                           | 20       | 16        |

| Outcomes (per 100 patient years) |          |           |
| Time in Range                   | 93%      | 89%       |
| Major Bleeding                  | 1.6      | 1.9       |
| Thromboembolism                 | 1.4      | 1.8       |

### Time in Therapeutic Range Warfarin

- **RE-LY**: 64%
- **ROCKET AF**: 55%
- **ARISTOTLE**: 62%
- **ARISTOTLE**: 68%
76 y/o male
PAF for 2 years. Pacemaker placed for SSS. His CHA2DS2-VASc is 4 (age, HTN, DM). He has normal renal and liver function. He takes warfarin 5 mg daily and has consistent INRs within normal range. He has had no bleeding or thromboembolism. What would you recommend for this patient?

1. Apixaban
2. Dabigatran
3. Rivaroxaban
4. **Continue warfarin**
5. Edoxaban

**Patient scenarios**
best served by warfarin
84 y/o male

Paroxysmal atrial fibrillation for 2 years. Permanent pacemaker placed for sick sinus syndrome. His \( \text{CHA}_2\text{DS}_2\text{-VASc} \) is 3 (age, htn). He has normal renal and liver function. He takes warfarin 5 mg daily and has consistent INRs within normal range. He has had no bleeding or thromboembolism. What would you recommend for this patient?

1. Apixaban
2. Dabigatran
3. Rivaroxaban
4. Edoxaban
5. Continue warfarin

Time in Therapeutic Range
Warfarin

- RE-LY 64%
- ROCKET AF 55%
- ARISTOTLE 62%
**Warfarin: Anticoagulation Quality**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Home INR</th>
<th>AC Clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>250</td>
<td>2550</td>
</tr>
<tr>
<td>Age (years, MN±SD)</td>
<td>63±15</td>
<td>63±16</td>
</tr>
</tbody>
</table>

**AC Indication (%)**

- DVT/PE: 33 vs. 38
- Atrial Fibrillation: 27 vs. 31
- Mechanical heart valve: 20 vs. 15
- Other: 20 vs. 16

**Outcomes (per 100 patient years)**

- **Time in Range**: 93% vs. 89%
- **Major Bleeding**: 1.6 vs. 1.9
- **Thromboembolism**: 1.4 vs. 1.8

---

**2014 ACC/AHA Guidelines: NVAF**

*For CHA₂DS₂-VASc ≥ 2:*

- Warfarin (Grade 1A)
- Dabigatran (Grade IB)
- Rivaroxaban (Grade IB)
- Apixaban (Grade IB)
84 y/o male
Paroxysmal atrial fibrillation for 2 years. Permanent pacemaker placed for sick sinus syndrome. His CHA\textsubscript{2}DS\textsubscript{2}-VASc is 3 (age, htn). He has normal renal and liver function. He takes warfarin 5 mg daily and has consistent INRs within normal range. He has had no bleeding or thromboembolism. What would you recommend for this patient?

1. Apixaban
2. Dabigatran
3. Rivaroxaban
4. Edoxaban
5. Continue warfarin

Bottom Line

- Patients on a stable dose of warfarin without complications should continue warfarin.
64 y/o Executive

Permanent atrial fibrillation is evaluated in the ED following a TIA. He has been prescribed warfarin for stroke prophylaxis. INR in the ED is 1.0. Review of the EMR reveals that he hasn’t had an INR assessed for months. His prescription has not been refilled in some time. What would you recommend for this patient?

1. Apixaban 5 mg twice daily
2. Dabigatran 150 mg twice daily
3. Rivaroxaban 20 mg once daily
4. Edoxaban 60 mg once daily
5. Reinitiate warfarin with AC clinic management
Physician Exhaustion from managing warfarin
Patient Exhaustion from taking warfarin

Medication Non-compliance

**Patient-related factors**
- Disease-related knowledge
- Health literacy
- Cognitive function

**Drug-related factors**
- Adverse effects
- Polypharmacy

**Logistical factors**
- Barriers to obtaining medications
- Patient-provider relationship
2 year Discontinuation Rates

- **ROCKET AF**
  - Rivaroxaban 35%
  - Warfarin 34%
- **RELY**
  - Dabigatran 22%
  - Warfarin 17%
- **ARISTOTLE**
  - Apixaban 25%
  - Warfarin 28%
- **ENGAGE AF**
  - Edoxaban 34%
  - Warfarin 34%

Real World Adherence is Poor!!!

- 500 patients
- Self administered survey (Morisky score)
- AC indication
  - VTE 74%
  - AF 18%
  - Warfarin 74% DOAC 26%
- Medication Adherence
  - Warfarin 56.2%
  - DOACs 57.1%

Improving AC Compliance

• Anticoagulation clinic management
  • Improved TTR
  • Lower major bleeding rates
  • Lower thromboembolism rates
  • Fewer ED visits
  • *Improves compliance!!*

• Routine INR monitoring
  • Identifies poor adherence
  • Encourages better adherence

• Multiple daily dosing
  • Warfarin is once daily

Variable Home INR AC Clinic

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<th>AC Clinic</th>
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<td>2550</td>
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<td>Age (years, MN±SD)</td>
<td>63±15</td>
<td>63±16</td>
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</tbody>
</table>

Outcomes (per 100 patient years)

- *Time in Range* 93% 89%
- *Major Bleeding* 1.6 1.9
- *Thromboembolism* 1.4 1.8

*Discontinuation Rate < 1%*
Atrial Fibrillation and DOACs

Practical Guideline

• Regular follow up: carefully specified and communicated
  • 1 month post initiation
  • Every 3 months
  • Outcome events
  • Medication interactions
  • Lab monitoring

• DOAC cards
  • Specify drug and indication

• Adherence check
  • Pill counting

Bottom Line

• Medication compliance is a large problem.
• Anticoagulation clinics may improve compliance.
• Simply changing to DOAC does not solve the problem.
• Careful follow up of patients receiving DOACs is required to improve compliance.
77 y/o female

Permanent atrial fibrillation. \textit{CHA}_2\textit{DS}_2\textit{-VASc is 5} (age, sex, htn, and DM). She has normal liver function. Her creatinine is 1.5 mg/dL, weight 77 kg (CrCl 38 mg/min). While on warfarin, she has suffered a recent recurrent GI bleed with documented duodenal ulceration. She is now treated with omeprazole. Review of her INR record reveals reasonable control. Her admission INR was 2.1 with widely fluctuating values. You are asked to comment on anticoagulants.

Which anticoagulant will reduce stroke risk while providing her \textit{the lowest risk of GI bleeding}?

1. Warfarin INR 2.0 – 2.5
2. Dabigatran 150 mg twice daily
3. Rivaroxaban 20 mg daily
4. Apixaban 5 mg twice daily
5. Edoxaban 60 mg daily
6. Edoxaban 30 mg daily
Which anticoagulant will reduce stroke risk while providing her the lowest risk of GI bleeding?

1. Warfarin INR 2.0 – 2.5
2. Dabigatran 150 mg twice daily
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5. Edoxaban 60 mg daily
6. Edoxaban 30 mg daily

**GI Bleeding Rates Compared to Warfarin**

<table>
<thead>
<tr>
<th>Agent</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1.50 (1.19 – 1.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1.47 (1.20 – 1.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs. warfarin</td>
<td>0.89 (0.70 – 1.15)</td>
<td>NS</td>
</tr>
<tr>
<td>vs. asa</td>
<td>0.86 (0.40 – 1.86)</td>
<td>NS</td>
</tr>
</tbody>
</table>
**Edoxaban 30 mg** associated with very low rate of major hemorrhage

![Graph showing comparison between high-dose edoxaban and warfarin](image)

**Edoxaban vs. Warfarin in AFib**

**Safety Endpoint – Major Bleeding**

<table>
<thead>
<tr>
<th></th>
<th>Edox 60mg</th>
<th>Edox 30mg</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>2.8%*</td>
<td>1.6%*</td>
<td>3.4%</td>
</tr>
<tr>
<td>ICH*</td>
<td>0.39%*</td>
<td>0.26%*</td>
<td>0.85%</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.21%*</td>
<td>0.13%*</td>
<td>0.38%</td>
</tr>
<tr>
<td>GI</td>
<td>1.51%*</td>
<td>0.82%*</td>
<td>1.23%</td>
</tr>
</tbody>
</table>

* p<0.05

Polypectomy

…… or Lower GI Bleeding
Avoid Dabigatran-etiexilate
Activated by colonic esterases

Should I restart oral anticoagulants in my AF patient who has just suffered a GI bleed?
Stroke and recurrent hemorrhage associated with antithrombotic treatment after GI bleeding in AF patients

- Nation-wide Danish Cohort
- 4602 AF patients admitted with GI bleeding
- AC resumption:
  - Increased risk of rebleed HR 1.37 (1.06 – 1.77)
  - Reduced mortality HR 0.39 (0.34 – 0.46)
  - Reduced thromboembolism HR 0.41 (0.31 – 0.54)

BMJ 2015;351:h5876

Risk of Bleeding and DOACs: Bottom Line

- GI bleeding rates are higher for dabigatran, rivaroxaban and edoxaban 60 mg compared to warfarin.
- Edoxaban 30mg has the lowest GI bleeding rates but...
  - a slightly higher stroke rate (1.77%).
  - Yet...lower mortality including CV mortality.
- Even after a major GI bleed, restarting anticoagulants should be strongly considered for stroke prevention and overall survival advantage.
<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>First choice</th>
<th>Second Choice</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>High thromboembolic and low bleeding risk</td>
<td>dabigatran 150</td>
<td>apixaban, edoxaban 60, rivaroxaban</td>
<td>warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>warfarin</td>
<td></td>
</tr>
<tr>
<td>Low thromboembolic and high bleeding risk</td>
<td>edoxaban 30</td>
<td>apixaban</td>
<td>warfarin dabigatran 150 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>edoxaban 60</td>
<td>rivaroxaban</td>
</tr>
<tr>
<td>High-moderate thromboembolic and bleeding risk</td>
<td>apixaban</td>
<td>dabigatran 150</td>
<td>edoxaban 30</td>
</tr>
<tr>
<td></td>
<td>edoxaban 60</td>
<td>rivaroxaban 15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>edoxaban 30</td>
<td></td>
</tr>
<tr>
<td>≥75–80 years or frail</td>
<td>apixaban, rivaroxaban</td>
<td>warfarin</td>
<td>pradaxa 150</td>
</tr>
<tr>
<td></td>
<td>edoxaban 30</td>
<td>warfarin</td>
<td></td>
</tr>
<tr>
<td>Compliance concerns</td>
<td>edoxaban 60</td>
<td>edoxaban 30</td>
<td>apixaban dabigatran</td>
</tr>
<tr>
<td>CrCl 30-50 ml/min</td>
<td>apixaban</td>
<td>rivaroxaban 15</td>
<td>dabigatran 150 edoxaban 60</td>
</tr>
<tr>
<td>CrCl &lt;30 ml/min</td>
<td>warfarin</td>
<td>apixaban</td>
<td>dabigatran edoxaban rivaroxaban</td>
</tr>
<tr>
<td>Nasogastric tube – crushed form</td>
<td>apixaban, rivaroxaban</td>
<td>edoxaban ???</td>
<td>dabigatran</td>
</tr>
</tbody>
</table>

### 76 y/o male

PAF for 4 years. Aortic bioprosthesis placed. **His CHA\textsubscript{2}DS\textsubscript{2}-VASc is 4** (age, HTN, DM). He has normal renal and liver function. He takes warfarin but has a great difficulty to keep INRs within normal range. He had GI bleeding while INR 6.2. What would you recommend for this patient?

1. Edoxaban 60 mg
2. Aspirin
3. Aspirin with clopidogrel
4. Continue warfarin
DOACs: Valvular Heart Disease

- Mechanical Prostheses & more than Mild MS
  Excluded from ALL Trials

- Valve repair
  Permitted: ROCKET, ENGAGE, ARISTOTLE

- Bioprosthetic heart valves
  Permitted: ENGAGE AF

European Definition of NVAF

AF that occurs in the absence of either mechanical prosthetic heart valves or moderate to severe mitral stenosis (typically of rheumatic origin)

Updated EHRA practical guide Europace (2015) 17, 1467
US Definition of NVAF

AF in the absence of rheumatic mitral stenosis, a mechanical heart valve, bioprosthetic heart valve, or mitral valve repair.

2014 AHA/ACC/HRS Guideline Circulation. 2014;130:e199

DOACs Trials: Atrial Fibrillation

- **Other valve diseases** were defined as ‘non-valvular’ and thus were included.
  - Mitral regurgitation
  - Aortic stenosis/regurgitation
  - Tricuspid regurgitation
- Consequently, AF patients with these valve problems can be treated with DOACs!

Updated EHRA practical guide Europace (2015) 17, 1467
**EHRA Suggestions Regarding biological valves or valve repair**

- Since oral anticoagulation is not required in these patients in the absence of AF, they seem to be eligible for DOAC therapy in case of AF.

*Updated EHRA practical guide Europace (2015) 17, 1467*

---

**EHRA Suggestions Regarding PTAV or TAVI**

- Since oral anticoagulation is not required in these patients in the absence of AF, they seem to be eligible for DOAC in case of AF.

- PTAV or TAVI requires mandatory single or dual antiplatelet therapy which increases bleeding risk. No prospective data in such patients under DOAC therapy, nor is the best combination strategy known.

*Updated EHRA practical guide Europace (2015) 17, 1467*
**SUMMARY**
Relative benefit of DOAC compared to VKA in patients with heart valve disease

*DABIGATRAN* – similar benefits regarding stroke and major bleeding

RIVAROXABAN – similar benefit regarding stroke but higher risk of major bleeding

APIXABAN – similar benefits regarding stroke, major bleeding and death

EDOXABAN – NO DATA

*abstract only

---

**European Valve Guidelines: DOACs and Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Eligible</th>
<th>Contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical prosthetic valve</td>
<td>YES</td>
</tr>
<tr>
<td>Moderate-sever mitral stenosis</td>
<td>YES</td>
</tr>
<tr>
<td>Mild-moderate other native valve disease</td>
<td>YES</td>
</tr>
<tr>
<td>Sever aortic stenosis</td>
<td>YES (limited data, will have in future)</td>
</tr>
<tr>
<td>Bioprosthetic valve</td>
<td>YES (except for the first 3 months post-operatively)</td>
</tr>
<tr>
<td>Mitral valve repair</td>
<td>YES (except for the first 3 months post-operatively)</td>
</tr>
<tr>
<td>PTAV and TAVI</td>
<td>YES</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>YES</td>
</tr>
</tbody>
</table>

**US guidelines do not recommend DOAC in patients with biological heart valves or after valve repair**

Updated EHRA practical guide Europace (2015) 17, 1467
76 y/o male from Ulm (Germany)

PAF for 4 years. Aortic bioprosthesis placed. His \textit{CHA}_{2}\textit{DS}_{2}-\textit{VASc} is 4 (age, HTN, DM). He has normal renal and liver function. He takes warfarin but has a great difficulty to keep INRs within normal range. He had GI bleeding while INR 6.2. What would you recommend for this patient?

1. \textit{Edoxaban} 60 mg
2. Aspirin
3. Aspirin with clopidogrel
4. Continue warfarin

76 y/o male from New Ulm (MN)

PAF for 4 years. Aortic bioprosthesis placed. His \textit{CHA}_{2}\textit{DS}_{2}-\textit{VASc} is 4 (age, HTN, DM). He has normal renal and liver function. He takes warfarin but has a great difficulty to keep INRs within normal range. He had GI bleeding while INR 6.2. What would you recommend for this patient?

1. \textit{Edoxaban} 60 mg
2. Aspirin
3. Aspirin with clopidogrel
4. \textit{Continue warfarin}
DOACs for AF and Valve Disease
How I would do it

• I would **not use** DOAC for mechanical valves or more than mild MS but **use** DOAC for other valve disease.

• Following valve repair, *warfarin is my preference*. If “individualized” variables preclude warfarin, *I prefer apixaban* (better safety than rivaroxaban).

• Until *edoxaban data* are available, I prefer warfarin following bioprosthetic valve placement.

DOAC’s vs Warfarin – Better efficacy and safer – but are they cost effective?

• DOAC’s are superior to Warfarin in many instances and have less risk of bleeding

• DOAC’s are significantly more expensive to prescribe than warfarin, right??
Baseline Assumptions

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Hazard ratios (95% confidence interval): apixaban vs. warfarin and other new oral anticoagulants.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apixaban</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.00</td>
</tr>
<tr>
<td>ICH*</td>
<td>1.00</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>1.00</td>
</tr>
<tr>
<td>Other major bleeding</td>
<td>1.00</td>
</tr>
<tr>
<td>CRNMB</td>
<td>1.00</td>
</tr>
<tr>
<td>MI</td>
<td>1.00</td>
</tr>
<tr>
<td>Other CV hospitalizations</td>
<td>1.00</td>
</tr>
</tbody>
</table>

CRNMB: clinically relevant non-major bleeding; CV: cardiovascular; ICH: intracranial hemorrhage; MI: myocardial infarction.
* Intracranial hemorrhage includes hemorrhagic stroke and other types of intracranial hemorrhage. The proportion of hemorrhagic stroke among intracranial hemorrhage was 77%, 64%, 64%, 41% and 57% for apixaban, warfarin, dabigatran 110 mg, dabigatran 150 mg and rivaroxaban, respectively, according to published studies (secondary analyses of the ARISTOTLE, RE-LY and ROCKET AF trials).
* Assumed, given the low rate of systemic embolism events in the trials.
* Assumed to be the same as apixaban.

Source: Li et al. [20]
Warfarin – 36% of resources assigned to monitoring costs

![Image with bar chart]

Figure 3  Breakdown of mean total costs per patient for each therapeutic option over a lifetime horizon.

<table>
<thead>
<tr>
<th>Costs (in €)</th>
<th>Warfarin</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical events</td>
<td>5467.29</td>
<td>4989.03</td>
<td>5244.03</td>
<td>5386.30</td>
</tr>
<tr>
<td>Therapy</td>
<td>214.42</td>
<td>3754.35</td>
<td>3015.69</td>
<td>3463.96</td>
</tr>
<tr>
<td>Monitoring and routine care</td>
<td>3252.29</td>
<td>1254.77</td>
<td>1311.27</td>
<td>1278.31</td>
</tr>
<tr>
<td>Total</td>
<td>8934.16</td>
<td>9998.14</td>
<td>9570.99</td>
<td>10128.56</td>
</tr>
</tbody>
</table>

Table 6  Total mean cost per patient for each therapeutic option over a lifetime horizon.

<table>
<thead>
<tr>
<th>Table 7  Cost-effectiveness analysis of apixaban compared to the other therapeutic options in the base-case scenario.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban compared to</td>
</tr>
<tr>
<td>Warfarin</td>
</tr>
<tr>
<td>Incremental costs</td>
</tr>
<tr>
<td>Life years gained</td>
</tr>
<tr>
<td>Incremental QALYs</td>
</tr>
<tr>
<td>ICER</td>
</tr>
<tr>
<td>Cost per life year gained</td>
</tr>
</tbody>
</table>

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years.
Warfarin – DOAC: Similar Cost / Value Data

Are DOAC’s cost effective?

- Actual costs associated with warfarin and the DOAC’s are similar
- DOAC agents have higher acquisition costs
- Warfarin has substantially higher monitoring and adjustment costs
- All are associated with bleeding – DOAC’s have lower rates than warfarin
Thank you

Questions & Discussion