Managing Anticoagulation for Atrial Fibrillation 2015

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Atrial Fibrillation

- Background and Guidelines
- Decisions to anticoagulate
- Treatment options
- Bleeding management
- Special populations
- Bridging therapy
Atrial Fibrillation
Background

- Most common cardiac arrhythmia
  - overall prevalence of ~1%
- Increased risk of mortality, heart failure and thromboembolic events.
- Hospitalization rates increased by 23% from 2000 to 2010;
- In-hospital mortality 1% and as high as 1.9% for patients >80y/o;
  Concomitantly heart failure up to 8.2%
Prevalence of atrial fibrillation increases with age.

Prevalence is higher in men than women in all age groups.
The estimated US prevalence of atrial fibrillation (AF) in the year 2050 ranges from 5.6 million to as high as 15.9 million individuals.
Lifetime risk for developing atrial fibrillation (AF) from the Framingham Heart Study.
Types of atrial fibrillation:

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
</table>
| Paroxysmal AF               | • AF that terminates spontaneously or with intervention within 7 d of onset.  
                                • Episodes may recur with variable frequency.                                                                                                 |
| Persistent AF               | • Continuous AF that is sustained >7 d.                                                                                                                                                                   |
| Long-standing persistent AF | • Continuous AF >12 mo in duration.                                                                                                                                                                       |
| Permanent AF                | • The term “permanent AF” is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm.  
                                • Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF.  
                                • Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve.                               |
| Nonvalvular AF              | • AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.                                                                                       |

AF indicates atrial fibrillation.
Risk of embolism is equivalent

CONCLUSIONS
In this large cohort of AF patients given aspirin, those with intermittent AF had stroke rates similar to patients with sustained AF and similar stroke risk factors. Many elderly patients with recurrent intermittent AF have substantial rates of stroke and likely benefit from anticoagulation. High-risk patients with intermittent AF can be identified using the same clinical criteria that apply to patients with sustained AF. (J Am Coll Cardiol 2000;35:183–7) © 1999 by the American College of Cardiology
2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary

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
Decision to anticoagulate comes down to risk of embolism versus bleeding.

Guideline recommendation:

3. In patients with nonvalvular AF, the CHA₂DS₂-VASc* score is recommended for assessment of stroke risk (68–70). (Level of Evidence: B)
**TABLE 1** The 2009 Birmingham Schema Expressed as a Point-Based Scoring System, With the Acronym CHA₂DS₂-VASc

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure or left ventricular dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 yrs</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke, transient ischemic attack, or thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65–74 yrs</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (i.e., female)</td>
<td>1</td>
</tr>
<tr>
<td>Maximum total points</td>
<td>9</td>
</tr>
</tbody>
</table>
• CHADS2VASC increases the number of patients who meet criteria for anticoagulation therapy and more accurately identifies truly low risk patients

• More people who were considered low risk before (ie females, age 65-74, vascular dx) are moved to the higher risk categories to better reflect risk of embolization.
• Risk of bleeding should be assessed prior to initiating anticoagulation

• Several calculators available, however one of the most validated one is the HAS-BLED score
<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal Liver or Renal Function</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 INR</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (age &gt; 65)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or Alcohol</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

**Maximum Score** 9
HAS-BLED Score:
Score of 3 or more indicates increase risk of major bleeding

- Major bleeding defined:
  - Intracranial
  - Hospitalization
  - Hemoglobin decrease >2g/L
  - Transfusion
5. For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA₂DS₂-VASc score of 2 or greater, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0) (68-70) (Level of Evidence: A), dabigatran (74) (Level of Evidence: B), rivaroxaban (75) (Level of Evidence: B), or apixaban (76). (Level of Evidence: B)
Treatment options:

Vitamin K Antagonist
  - Warfarin

Non-Vitamin K Antagonist
  - NOAC—> Novel Oral Anticoagulants
  - NOAC—> Non-Vitamin K Oral Anticoagulants
  - DOAC—> Direct-acting Oral AntiCoagulants
Direct-acting oral anticoagulants (DOAC)

Two classes available:

- Direct thrombin inhibitors
  - Dabigatran

- Factor Xa inhibitors
  - Rivaroxaban
  - Apixaban
  - Edoxaban
Dabigatran: RE-LY trial

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*
Dabigatran

- Half-life 12-17 hours
- Uses P-gp transporter with bowel absorption
- Clearance:
  - 80% Renal Excretion
- Oral, twice daily dosing without need for coagulation monitoring

Dabigatran

Risk of stroke

- 1.69%/year in warfarin group
- 1.53%/year in dabigatran 110mg (non-inferior)
- 1.11%/year in dabigatran 150mg (superior)

Dabigatran

Risk of major bleeding

- 3.36%/year in warfarin
- 2.71%/year in dabigatran 110mg
- 3.11%/year in dabigatran 150mg
Dabigatran

Rate of hemorrhagic stroke

- 0.38%/year in warfarin
- 0.12%/year in dabigatran 110mg
- 0.10%/year in dabigatran 150mg
CONCLUSIONS

In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. (ClinicalTrials.gov number, NCT00262600.)
Rivaroxaban: ROCKET-AF trail

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*
Anticoagulant Mechanisms of Action

Initiation

TF/VIIa → VII

Propagation

Warfarin

Xa → IXa

Fondaparinux Heparin LWMH

Fibrin formation

Fibrinogen → Fibrin

Rivaroxaban Apixaban

Dabigatran

Rivaroxaban

• Direct, competitive factor Xa inhibitor
• Half-life 5-13 hours
• Clearance:
  • 1/3 direct renal excretion
  • 2/3 metabolism via CYP 450 enzymes

Oral, once daily dosing with largest meal without need for coagulation monitoring
Rivaroxaban

- Non-inferior in stroke reduction when compared to warfarin

**CONCLUSIONS**
In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. (Funded by Johnson & Johnson and Bayer; ROCKET AF ClinicalTrials.gov number, NCT00403767.)
Rivaroxaban

- No significant difference in major bleeding risk
- Slightly lower risk of fatal and intracranial bleeding

<table>
<thead>
<tr>
<th>Table 3. Rates of Bleeding Events.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Principal safety end point: major and nonmajor clinically relevant bleeding§</td>
</tr>
<tr>
<td>Major bleeding</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>Decrease in hemoglobin ≥2 g/dl</td>
</tr>
<tr>
<td>Transfusion</td>
</tr>
<tr>
<td>Critical bleeding¶</td>
</tr>
<tr>
<td>Fatal bleeding</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td>Nonmajor clinically relevant bleeding</td>
</tr>
</tbody>
</table>

Apixaban: ARISTOTLE trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812  SEPTEMBER 15, 2011  VOL. 365  NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

Eliquis® apixaban
Apixaban

• Direct, competitive factor Xa inhibitor
• Half-life 12 hours
• Clearance:
  • 27% direct renal excretion
  • Biliary and direct intestinal excretion
  • P-gp transport
• Oral, twice daily dosing
  • 5mg BID
  • 2.5mg BID if 2 of the following (ABC):
    • Age > 80 years
    • Body weight < 60kg
    • Creatinine > 1.5

CONCLUSIONS

In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. (Funded by Bristol-Myers Squibb and Pfizer; ARISTOTLE ClinicalTrials.gov number, NCT00412984.)
Edoxiban: *ENGAGE AF trial*

**ORIGINAL ARTICLE**

Edoxaban versus Warfarin in Patients with Atrial Fibrillation


*Savaysa (edoxaban) tablets*
Edoxiban

- Direct, competitive factor Xa inhibitor
- Half-life 10-14 hours
- Clearance:
  - 50% Renal
- Oral, once daily dosing
  - 60 mg daily (GFR 50-95)
  - 30mg daily (GFR 15-30)

Edoxaban

- Caution with GFR >95

**FULL PRESCRIBING INFORMATION**

**WARNING** (A) REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CREATININE CLEARANCE (CRCL) > 95 ML/MIN (B) PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS (C) SPINAL/EPIDURAL HEMATOMA

**A. REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CRCL > 95 ML/MIN**

SAVAYSA should not be used in patients with CrCL > 95 mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used [see Dosage and Administration (2.1), Warnings and Precautions (5.1), and Clinical Studies (14.1)].
Edoxaban

CONCLUSIONS
Both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes. (Funded by Daiichi Sankyo Pharma Development; ENGAGE AF-TIMI 48 ClinicalTrials.gov number, NCT00781391.)
Direct-acting oral anticoagulants (DOAC)

Clinical trials:

- Patients benefit of stroke prevention depends on Time to Therapeutic range (TTR)
- Time to therapeutic range (TTR) with warfarin in all trials was <69%
- Unsure if DOAC are better if TTR >75%
- Patients with TTR <58% despite adequate warfarin dosing adjustments may benefit the most from DOAC
- Clinical trials have also shown lower risk of ICH with DOACs when compared with warfarin.
### TABLE 2  Summary of Selected DOACs Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>RE-LY (33) (N = 18,113) (3 arms)*</th>
<th>ROCKET-AF (34) (N = 14,264)</th>
<th>ARISTOTLE (35) (N = 18,201)</th>
<th>ENGAGE AF-TIMI 48 (36) (N = 21,105) (3 arms)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug, dose</strong></td>
<td>Dabigatran, 150 mg bid</td>
<td>Rivaroxaban, 20 mg daily</td>
<td>Apixaban, 5 mg bid</td>
<td>Edoxaban, 60/30 mg daily</td>
</tr>
<tr>
<td><strong>Adjusted dose?</strong></td>
<td>No</td>
<td>Yes, at randomization only: 15 mg daily if CrCl 30-49 ml/min</td>
<td>Yes, at randomization only: 2.5 mg bid if 2 of: age ≥80 yrs, weight &lt;60 kg, Scr ≥1.5 mg/dl</td>
<td>Yes, at randomization and during study: both doses halved if any 1 of the following: CrCl 30-50 ml/min, weight ≤60 kg, use of verapamil, quinidine, or dronedarone</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Randomized open-label</td>
<td>Randomized double-blind, double-dummy</td>
<td>Randomized double-blind, double-dummy</td>
<td>Randomized double-blind, double-dummy</td>
</tr>
<tr>
<td><strong>Mean age, yrs</strong></td>
<td>71.5</td>
<td>73</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td><strong>Prior stroke/ transient ischemic attack/systemic embolism</strong></td>
<td>20%</td>
<td>55%</td>
<td>19%</td>
<td>28%</td>
</tr>
<tr>
<td><strong>Mean CHADS2</strong></td>
<td>2.2</td>
<td>3.5</td>
<td>1.9</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Warfarin-naive</strong></td>
<td>50.4%</td>
<td>37.6%</td>
<td>43%</td>
<td>41%</td>
</tr>
<tr>
<td><strong>Comparator warfarin INR 2-3</strong></td>
<td>67% TTR (median)</td>
<td>58% TTR (median)</td>
<td>66% TTR (median)</td>
<td>68% (median)</td>
</tr>
<tr>
<td><strong>Comparator Warfarin INR 2-3</strong></td>
<td>64% TTR (mean)</td>
<td>55% TTR (mean)</td>
<td>62% TTR (mean)</td>
<td>65% (mean)</td>
</tr>
<tr>
<td><strong>Outcome, RR (95% CI)</strong></td>
<td><strong>Stroke/systemic embolism</strong></td>
<td>0.66 (0.53-0.82)</td>
<td>0.88 (0.75-1.03)</td>
<td>0.79 (0.66-0.95)</td>
</tr>
<tr>
<td></td>
<td><strong>Ischemic stroke</strong></td>
<td>0.76 (0.60-0.98)</td>
<td>0.94 (0.75-1.17)</td>
<td>0.92 (0.74-1.13)</td>
</tr>
<tr>
<td></td>
<td><strong>Hemorrhagic stroke</strong></td>
<td>0.26 (0.14-0.49)</td>
<td>0.59 (0.37-0.93)</td>
<td>0.51 (0.35-0.75)</td>
</tr>
<tr>
<td></td>
<td><strong>Major bleeding</strong></td>
<td>0.93 (0.81-1.07)</td>
<td>1.04 (0.90-1.20)</td>
<td>0.69 (0.60-0.80)</td>
</tr>
<tr>
<td></td>
<td><strong>Intracranial hemorrhage</strong></td>
<td>0.40 (0.27-0.60)</td>
<td>0.67 (0.47-0.93)</td>
<td>0.42 (0.30-0.58)</td>
</tr>
<tr>
<td></td>
<td><strong>Gastrointestinal bleeding</strong></td>
<td>1.50 (1.19-1.89)</td>
<td>1.39 (1.19-1.61)</td>
<td>0.89 (0.70-1.15)</td>
</tr>
<tr>
<td></td>
<td><strong>Cardiovascular mortality</strong></td>
<td>0.85 (0.72-0.99)</td>
<td>0.89 (0.73-1.10)</td>
<td>0.89 (0.76-1.04)</td>
</tr>
<tr>
<td></td>
<td><strong>All-cause mortality</strong></td>
<td>0.88 (0.77-1.00)</td>
<td>0.85 (0.70-1.02)</td>
<td>0.89 (0.80-0.998)</td>
</tr>
</tbody>
</table>

*Estimate creatinine clearance (CrCl) using Cockcroft-Gault formula: ([140 - age] × weight [in kg] × 0.85 if female)/(72 × creatinine [in mg/dl]). *Results are shown for dabigatran 150 mg bid. †Results are shown for edoxaban 60 mg daily.

CHADS2 = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke or transient ischemic attack; CI = confidence interval; CrCl = creatinine clearance; DOAC = direct-acting oral anticoagulant; INR = international normalized ratio; RR = risk ratio; Scr = serum creatinine; TTR = time in therapeutic range.
Severe renal impairment were excluded from phase III trials. Warfarin remains treatment of choice. However, FDA has approved apixaban in patients with end-stage renal disease on hemodialysis on the basis of pharmacokinetic modeling data.

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>FDA-Approved Direct Acting Oral Anticoagulants for Nonvalvular Atrial Fibrillation*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran (Pradaxa) (107)</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Direct thrombin inhibitor</td>
</tr>
<tr>
<td>Dosing for nonvalvular AF†</td>
<td>150 mg twice daily</td>
</tr>
<tr>
<td>Dosing considerations for nonvalvular AF with renal adjustments</td>
<td>If CrCl is 15-50 ml/min: 75 mg twice daily; if CrCl is &lt;15 ml/min: avoid use</td>
</tr>
<tr>
<td>Dosing considerations for nonvalvular AF with hepatic adjustments</td>
<td>Administration in patients with moderate hepatic impairment (Child-Pugh B) showed no evidence of change in exposure or pharmacodynamics</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Avoid concomitant use with P-gp inducers (e.g., rifampin). P-gp inhibitors and impaired renal function can lead to increased exposure to dabigatran; avoid concomitant use with severe renal impairment (&lt;30 ml/min); for moderate renal impairment reduce dose to 75 mg twice daily when used concomitantly with dronedarone or systemic ketoconazole</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto) (108)</td>
<td></td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Factor Xa inhibitor</td>
</tr>
<tr>
<td>Dosing for nonvalvular AF†</td>
<td>20 mg daily with evening meal</td>
</tr>
<tr>
<td>Dosing considerations for nonvalvular AF with renal adjustments</td>
<td>If CrCl is 15-50 ml/min: 15 mg daily with evening meal</td>
</tr>
<tr>
<td>Dosing considerations for nonvalvular AF with hepatic adjustments</td>
<td>Avoid use in patients with Child-Pugh B and C hepatic impairment or with any degree of hepatic impairment associated with coagulopathy</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Avoid concomitant use with strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, ritonavir, erythromycin) or reduce apixaban dose</td>
</tr>
<tr>
<td>Apixaban (Eliquis) (109)</td>
<td></td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Factor Xa inhibitor</td>
</tr>
<tr>
<td>Dosing for nonvalvular AF†</td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td>Dosing considerations for nonvalvular AF with renal adjustments</td>
<td>If the patient has at least 2 of the following: Age ≥80 years old; Weight ≥60 kg; 5Cr ≥1.5 mg/dl; 2.5 mg twice daily</td>
</tr>
<tr>
<td>Dosing considerations for nonvalvular AF with hepatic adjustments</td>
<td>Mild hepatic impairment: no dose adjustment needed</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Avoid concomitant use with strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, ritonavir, erythromycin) or reduce apixaban dose</td>
</tr>
<tr>
<td>Edoxaban (Savaysa) (24)</td>
<td></td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Factor Xa inhibitor</td>
</tr>
<tr>
<td>Dosing for nonvalvular AF†</td>
<td>If CrCl &gt;50 ml/min to =95 ml/min: 60 mg daily</td>
</tr>
<tr>
<td>Dosing considerations for nonvalvular AF with renal adjustments</td>
<td>If CrCl &gt;95 ml/min: do not use; may have an increased risk of ischemic stroke as compared with warfarin</td>
</tr>
<tr>
<td>Dosing considerations for nonvalvular AF with hepatic adjustments</td>
<td>Avoid use in patients with Child-Pugh B and C hepatic impairment</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Avoid concomitant use with P-gp inducers (e.g., rifampin)</td>
</tr>
</tbody>
</table>

J AM Coll Cardiol. 2015; 65 (13): 1340-1360
## Drug interactions:

<table>
<thead>
<tr>
<th>Mechanism of Drug Interaction</th>
<th>Dabigatran (Pradaxa) (107)</th>
<th>Rivaroxaban (Xarelto) (108)</th>
<th>Apixaban (Eliquis) (109)</th>
<th>Edoxaban (Savaysa) (24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Avoid use</td>
<td>Avoid use</td>
<td>Avoid use</td>
<td>No specific recommendations</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>No adjustment needed</td>
<td>No adjustment needed</td>
<td>Reduce dose from 5 mg twice daily to 2.5 mg twice daily if on 2.5 mg twice daily, discontinue apixaban</td>
<td>No specific recommendations</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>With CrCl 30-50 ml/min, reduce dose to 75 mg twice daily</td>
<td>No specific recommendations</td>
<td>No specific recommendations</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>No adjustment needed</td>
<td>Avoid use</td>
<td>Reduce dose from 5 mg twice daily to 2.5 mg twice daily if on 2.5 mg twice daily, discontinue apixaban</td>
<td>No specific recommendations</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>With CrCl 30-50 ml/min, reduce dose to 75 mg twice daily</td>
<td>Avoid use</td>
<td>Reduce dose from 5 mg twice daily to 2.5 mg twice daily if on 2.5 mg twice daily, discontinue apixaban</td>
<td>No specific recommendations</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Avoid use</td>
<td>Avoid use</td>
<td>Avoid use</td>
<td>No specific recommendations</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Avoid use</td>
<td>Avoid use</td>
<td>Avoid use</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>No adjustment needed</td>
<td>Avoid use</td>
<td>Reduce dose from 5 mg twice daily to 2.5 mg twice daily if on 2.5 mg twice daily, discontinue apixaban</td>
<td>No specific recommendations</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Avoid use</td>
<td>Avoid use</td>
<td>Avoid use</td>
<td>No specific recommendations</td>
</tr>
</tbody>
</table>

*This is not a comprehensive list of all drug interactions. Please refer to individual medication manufacturer prescribing information for complete information. Estimate creatinine clearance (CrCl) using Cockcroft-Gault formula: ([140 - age] × weight [in kg] × 0.85 if female) / (72 × creatinine [in mg/dl]).

Abbreviations as in Table 3.
<table>
<thead>
<tr>
<th>Transitioning Between Anticoagulants and Interruption of Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conversion</strong></td>
</tr>
<tr>
<td>From warfarin to DOAC</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>From DOAC to warfarin†</td>
</tr>
<tr>
<td>From parenteral anticoagulant to DOAC</td>
</tr>
<tr>
<td>From DOAC to DOAC</td>
</tr>
<tr>
<td>Temporary interruption of DOAC for surgery and other invasive procedures</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Bleeding:

- Annual rate of major bleeding range between 2.1% to 3.6%
- Fatal bleeding occurs in up to 0.5%
- Major bleeding is associated with higher mortality
  - *30-day mortality after major bleeding episode 13% with warfarin and 9% with dabigatran*
Bleeding definitions

**Major Bleeding**
- Involves major organ including central nervous system bleeding (intracranial or epidural), pericardial, intraocular, retroperitoneal, intra-articular, intramuscular with compartment syndrome
- Clinically overt bleeding with a drop in hemoglobin of at least 2 g/dl
- Requires transfusion of at least 2 units
- Requires surgical correction
- Requires intravenous vasoactive agents

**Clinically Relevant Non-Major Bleeding**
Clinically overt bleeding that does not satisfy criteria for major bleeding but requires:
- hospitalization or increased level of care, or
- prompt physician guided medical or surgical treatment, or
- a change in antithrombotic therapy

**Minor Bleeding**
- Self-terminating
- Does not require an office visit
- No hospitalization or treatment by a health care professional
Bleeding management:

Agents to reverse anticoagulation

- More complicated as DOAC reversal is limited *(until recently)*
- Develop institutional plan
- Consult hematology
Bleeding management: Warfarin

- Vitamin K
  - Vit K 5-10mg slow IV infusion
    - IV Vitamin K does not begin to reduce INR for 6hrs (usually longer than 24hrs)
    - IV vitamin K allergic reaction if given as bolus
  - Subcutaneous and IM Vitamin K not recommended
  - PO Vitamin K used in minor bleeding
  - Does not work for DOAC

- Fresh frozen plasma
  - Along with blood transfusion provide volume
  - >1500 ml of FFP
  - Does not work for DOAC
Bleeding management: DOAC

- Prothrombin complex concentrate (PCC)
  - 10-30min infusion improves INR within minutes and last 24-48hrs
    - Use Vitamin K along with this
  - Limited reversal of dabagatran and rivaroxiban in 2hrs in healthy volunteers
  - Small concern about myocardial infarction and arterial thromboembolism
  - Some have heparin therefore cautious use in patients with heparin-induced thrombocytopenia

Bleeding management: DOAC

- Gastric lavage (recent ingestion)
- Activated charcoal if ingesting occurred 2-6 hours
- PCC or aPCC
- Dialysis can be considered with dabigatran because 35% plasma bound

♠ Rivaroxaban, apixaban and edoxaban are highly protein-bound and therefore hemodialysis is likely to be ineffective
Post-bleeding management

- Restart VKA if source of bleeding is addressed
- DOAC cannot lower dose because there would be under anticoagulation and therefore higher risk of stroke.
- If minor GI bleeding occurs with dabigatran or rivaroxaban, switch to apixaban or edoxaban since they have lower GI risk.
- Switch from DOAC to Vit K.
Bleeding management, reversal: *Dabigatran*

- antibody fragment developed to reverse the anticoagulation effects of dabigatran
Bleeding management, reversal: *Factor Xa inhibitors*

- Andexanet
  - Recombinant factor Xa with minor amino acid deletions; Therefore lacks pro or anticoagulation affects on its own
  - Active binding site of Andexanet functions as a decoy and binds to factor Xa inhibitors with high affinity
  - Overall factor Xa inhibitors concentration is reduced
  - Phase 3 ANNEXA trial (data presentation in March 2016)
Bleeding management, reversal: *Factor Xa inhibitors*

- Aripazine
  - synthetic small molecule with broad activity against heparin, LMWH, and DOAC
  - IV dosing
  - reversal seen in 10 minutes in the phase I study
Anticoagulation in special populations

- Coronary artery disease
- Stenting
- Acute CVA
- Mechanical valves
- Cardioversion
Anticoagulation in CAD patients

- AF occurs in 5-10% patients with MI
  -Associated with higher mortality

- Combining antiplatelet agents with OAC increases bleeding risk
  -RE-LY trial risk of major bleeding increased:
    -2.8% to 4.8%/year when antiplatelet agents were added to warfarin.
    -2.6% to 4.4%/year with dabigatran and antiplatelet therapy
  -ARISTOLE
    -Increase risk with use of aspirin and warfarin or apixaban
      -Although absolute bleeding risk lower with ASA + apixaban
Anticoagulation in CAD patients

WOEST Trail

(What is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting)

- In patients receiving oral anticoagulants and undergoing PCI use of clopidogrel without aspirin was associated with significant reduction in bleeding and complications
- No increase in rate of thrombotic events
Anticoagulation in CAD patients

- **Elective stenting**
  - Concomitant glycoprotein IIb/IIIa inhibitors should generally be avoided
  - Radial access and bare-metal stents should be considered
  - If triple therapy is used, low dose ASA plus clopidogrel recommended
  - Ticagrelor and prasugrel not recommended due to increase risk
  - Lower INR range (2-2.5) can be considered
Anticoagulation in CAD patients

- Medically managed CAD and Afib
  - Data is murky
  - Lower risk of MI with warfarin and ASA compared to warfarin alone
    - WARIS II (Warfarin-Aspirin Reinfarction II) trial. NEJM 2002; 347: 969-974
  - Warfarin better than ASA plus Clopidogrel
Anticoagulation in CAD patients

- Patient who develop AFib AFTER stent placement
  - ♦ BMS (< 1month) or DES (< 6months)
    - □ CHADS2 Vasc 0 or 1 → DAPT alone
    - □ CHADS2VASC >2 → VKA and Clopidogrel
  - ♦ BMS (> 1month) or DES (> 6months)
    - □ VKA or DOAC alone

J AM Coll Cardiol. 2015; 65 (13): 1340-1360
If acute CVA/TIA is presumed cardioembolic origin, anticoagulation is recommended

- DOAC is preferable to warfarin because of reduced risk of ICH
Anticoagulation in Mechanical Valves

RE-ALIGN study

- Randomized, phase II study to evaluate safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement

- Tested high dose dabigatran as alternative to warfarin

- Stopped early due to excessive bleeding and higher thromboembolic events in patients treated with dabigatran

- FDA info says to avoid DOAC in all prosthetic valves

4. For patients with AF who have mechanical heart valves, warfarin is recommended, and the target international normalized ratio (INR) intensity (2.0 to 3.0 or 2.5 to 3.5) should be based on the type and location of the prosthesis (71-73). (Level of Evidence: B)
Anticoagulation with cardioversion

- If attempting cardioversion without transesophogeal echocardiogram evaluation for thrombus, Afib/atrial flutter of unknown duration or >48hrs,
  - ♠ DOACs is required for >3weeks prior to cardioversion
  - ♠ Continued for >4week post-cardioversion
Bridging therapy

- Estimate risk of embolism
- Estimate risk of bleeding
- Determine whether bridging is necessary
- Determine timing of anticoagulation interruption
Bridging therapy

• Estimate embolism risk

  • High
    • CHADS VASC 5-6

  • Low
    • CHADS VASC <2 and no previous embolism or intracardiac thrombus

Estimate bleeding risk

Moderate to High
  * Two-day risk of major bleeding 2-4%
    * CABG, Renal Biopsy, procedure lasting >45min, etc

Low
  * Two-day risk of major bleeding 0-2%
    * Cholecystectomy, carpal tunnel repair, pacemaker, etc

Table 1. Procedures That May Be Safely Performed Without Warfarin Interruption

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental extraction</td>
</tr>
<tr>
<td>Bone marrow biopsy</td>
</tr>
<tr>
<td>Endoscopy (± mucosal biopsy)</td>
</tr>
<tr>
<td>Cataract surgery</td>
</tr>
<tr>
<td>Pacemaker placement</td>
</tr>
<tr>
<td>Venography</td>
</tr>
<tr>
<td>Dermatologic surgery</td>
</tr>
<tr>
<td>Joint aspiration</td>
</tr>
</tbody>
</table>
Bridging therapy

• Determine whether to use bridging anticoagulation

• Risk of bleeding versus embolism

• Moderate to High (CHADSVASc 5-6) —> Bridging
  • Bridge with LMWH as outpatient pre-operative once INR falls below 2
  • Restart Coumadin as soon as possible (12-24hrs)
  • Therapeutic heparin given 48hrs after surgery and continued for 5days or INR is therapeutic

• DOAC bridging is not necessary due to rapid offset
Bridging therapy

• Determine timing of anticoagulation interruption

• Coumadin —> 4-5 days before surgery; Restart post-op day 0

• Dabigatran
  • 2-3 days before surgery in normal or mildly impaired renal function (GFR >50ml/min)
  • 3-4 days before surgery in patient with GFR 30-50mL/min
Bridging therapy

• Determine timing of anticoagulation interruption

• Rivaroxaban
  • average 2-3 days before surgery (depending on high versus low risk)
  • restart after surgery on post-op day 0
  • if epidural or spinal anesthesia used, usually wait 6hrs
    • unless traumatic puncture in which case start 24hrs after

• Apixaban
  • average 2-3 days (longer if high risk surgery)
  • restart one day post op in low risk surgery; two days post op in high risk surgery
Bridging therapy *update*:

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

for the BRIDGE Investigators*
1884 patients enrolled taking warfarin therapy

950 patients received no bridging therapy

934 patients received bridging therapy

Valvular and non-valvular atrial fibrillation and flutter patients enrolled

DOAC patients not included

Primary end-point was rate of arterial thromboembolism (CVA/TIA/systemic embolism)

Primary safety outcome was major bleeding

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of the Patients.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Age — yr</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
</tr>
<tr>
<td>Race — no. (%)†</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Nonwhite</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Weight — kg</td>
</tr>
<tr>
<td>CHADS² score.§</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Distribution — no. (%)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>
Rates of thromboembolism were similar between the two groups.

Rates of major bleeding was lower in the non-bridging group.

CONCLUSIONS
In patients with atrial fibrillation who had warfarin treatment interrupted for an elective operation or other elective invasive procedure, forgoing bridging anticoagulation was noninferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism and decreased the risk of major bleeding. (Funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health; BRIDGE ClinicalTrials.gov number, NCT00786474.)
Anticoagulation Bridge Calendar

Date: ___________________ Patient: ___________________

This is to eliminate confusion regarding bridge details and to ensure that the patient, surgeon, hospital/facility and prescribing physician are on the same page.

<table>
<thead>
<tr>
<th>Day</th>
<th>Medication Instructions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5</td>
<td>Take last dose of Coumadin</td>
<td></td>
</tr>
<tr>
<td>-4</td>
<td>Lovenox ______mg subcutaneous  twice a day or daily (circle one)</td>
<td>NO Coumadin</td>
</tr>
<tr>
<td>-3</td>
<td>Lovenox ______mg subcutaneous  twice a day or daily (circle one)</td>
<td>NO Coumadin</td>
</tr>
<tr>
<td>-2</td>
<td>Lovenox ______mg subcutaneous  twice a day or daily (circle one)</td>
<td>NO Coumadin</td>
</tr>
<tr>
<td>-1</td>
<td>Lovenox ______mg subcutaneous  twice a day or daily (circle one)</td>
<td>NO Coumadin</td>
</tr>
<tr>
<td></td>
<td>Day of Surgery</td>
<td>Notes</td>
</tr>
<tr>
<td></td>
<td>NO Lovenox</td>
<td>No Coumadin</td>
</tr>
<tr>
<td>+1</td>
<td>No Morning Lovenox</td>
<td>Take Coumadin (if ok with surgeon)</td>
</tr>
<tr>
<td></td>
<td>Lovenox ______mg subcutaneous  at  ____ PM</td>
<td></td>
</tr>
<tr>
<td>+2</td>
<td>Lovenox ______mg subcutaneous  twice a day or daily (circle one)</td>
<td>Take Coumadin</td>
</tr>
<tr>
<td>+3</td>
<td>Lovenox ______mg subcutaneous  twice a day or daily (circle one)</td>
<td>Take Coumadin</td>
</tr>
<tr>
<td>+4</td>
<td></td>
<td>Take Coumadin</td>
</tr>
<tr>
<td>+5</td>
<td></td>
<td>Take Coumadin</td>
</tr>
</tbody>
</table>
Conclusion:

- Decision to anticoagulate should be guideline driven but individualized to the patient.
- Use objective assessment tools for bleeding and embolic risk calculation.
- Direct oral anticoagulants (DOAC) provide good anticoagulation options to warfarin.
- Bridging therapy in high risk patients remains controversial but new evidence suggests bridging might not necessary. However, additional trials are needed to validate this.