Disclosures

• Educational and clinical research grants
  • Astra Zeneca
  • Biosense Webster
  • Medtronic
  • Boston Scientific
  • Abbott
  • Pfizer
Clinical Considerations

• Type and combinations of Anticoagulant/antiplatelet therapy
• Coronary Stent Patient
• Atrial Fibrillation
• Biomechanical vs. Biologic Prosthetic Valves
• Genetic Hypercoaguable Patients
• Procedural Plan
• Bleeding management/Prevention in emergent cases
• Bridging therapy
Anticoagulant Mechanisms of Action

Initiation

TF/VIIa → VII

Propagation

VIIIa → IXa

Xa → Va

Xa → X

Fondaparinux
Heparin LWMH

Rivaroxaban
Apixaban

Fibrin formation

Fibrinogen → Fibrin

Dabigatran

Warfarin

### Baseline Patient Demographics: Comparison of ROCKET AF With Previous VKA-controlled Trials

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; score (%)</th>
<th>ROCKET AF&lt;sup&gt;a&lt;/sup&gt;</th>
<th>RE-LY&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ACTIVE&lt;sup&gt;c&lt;/sup&gt;</th>
<th>AMADEUS&lt;sup&gt;d&lt;/sup&gt;</th>
<th>SPORTIF V&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>&lt;1</td>
<td>32</td>
<td>N/A</td>
<td>41</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>36</td>
<td>N/A</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>≥ 3</td>
<td>86</td>
<td>32</td>
<td>N/A</td>
<td>27</td>
<td>44</td>
</tr>
<tr>
<td>Median CHADS&lt;sub&gt;2&lt;/sub&gt; score</td>
<td>≥ 3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

### Baseline Patient Demographics (cont)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>ROCKET AF&lt;sup&gt;a&lt;/sup&gt;</th>
<th>RE-LY&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ACTIVE&lt;sup&gt;c&lt;/sup&gt;</th>
<th>AMADEUS&lt;sup&gt;d&lt;/sup&gt;</th>
<th>SPORTIF V&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF or LVEF ≤ 35%</td>
<td>63</td>
<td>32</td>
<td>30</td>
<td>23</td>
<td>39</td>
</tr>
<tr>
<td>Hypertension</td>
<td>90</td>
<td>79</td>
<td>82</td>
<td>77</td>
<td>81</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>44</td>
<td>–</td>
<td>–</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td>Diabetes</td>
<td>40</td>
<td>23</td>
<td>21</td>
<td>10*</td>
<td>19†</td>
</tr>
<tr>
<td>Prior stroke, TIA, or non-CNS SE</td>
<td>55</td>
<td>20</td>
<td>15</td>
<td>24</td>
<td>18</td>
</tr>
</tbody>
</table>

<sup>a</sup> Diabetes and age 65-75 years

<sup>b</sup> Diabetes and age ≥ 65 years

Warfarin Narrow Therapy Safety

Warfarin: Narrow therapeutic window

Odds ratio

International normalized ratio

Ischemic stroke

Intracranial bleeding

# NOAC Trial summaries

## 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>Rivaroxaban, 20 mg daily</td>
<td>Apixaban, 5 mg bid</td>
<td>Edoxaban, 60/30 mg daily</td>
<td></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 yr 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 ≤50 kg, use of verapamil, quinidine, or dexamethasone</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>2.1</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>56% TTR (median)</td>
<td>68% TTR (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 (median)</td>
<td>65% (median)</td>
</tr>
</tbody>
</table>

**Outcome, RR (95% CI):**
- **Stroke/systemic embolism**: 0.65 (0.53–0.82) 0.88 (0.75–1.03) 0.79 (0.66–0.95) 0.88 (0.75–1.03)
- **Ischemic stroke**: 0.76 (0.60–0.98) 0.94 (0.75–1.17) 0.92 (0.74–1.13) 1.00 (0.83–1.19)
- **Hemorrhagic stroke**: 0.26 (0.14–0.49) 0.59 (0.37–0.93) 0.51 (0.35–0.75) 0.54 (0.38–0.77)
- **Major bleeding**: 0.93 (0.81–1.07) 1.04 (0.90–1.20) 0.69 (0.60–0.80) 0.80 (0.71–0.91)
- ** Intracranial hemorrhage**: 0.40 (0.27–0.63) 0.67 (0.47–0.93) 0.42 (0.30–0.58) 0.47 (0.34–0.63)
- **Gastrointestinal bleeding**: 1.50 (1.19–1.89) 1.39 (1.19–1.61) 0.89 (0.70–1.15) 1.23 (1.02–1.50)
- **Cardiovascular mortality**: 0.85 (0.72–0.99) 0.89 (0.73–1.10) 0.89 (0.76–1.04) 0.86 (0.77–0.97)
- **All-cause mortality**: 0.88 (0.77–1.00) 0.89 (0.70–1.02) 0.89 (0.80–0.998) 0.92 (0.83–1.01)

*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.
Dual Antiplatelet Therapy and Heparin “Bridging” Significantly Increase the Risk of Bleeding Complications After Pacemaker or Implantable Cardioverter-Defibrillator Device Implantation

Median Time of Late Stent Thrombosis

Months

DES/BMS  SES/BMS  PES/BMS

p = 0.0003  p = 0.0052  p = 0.04

Bavry, Kumbhani, Helton, Borek, Mood, Bhatt. AJM 2006
Predictors of stent thrombosis
period 0-6 months

- No thieno* (0-6) HR=11.47; 95%CI, 3.57-36.84; p<0.0001
- LVEF* < 30% HR=4.18; 95%CI, 1.38-12.62; p=0.01
- Prior Brachytherapy HR=3.53; 95%CI, 1.10-11.30; p=0.03
- RVD* HR=0.12; 95%CI, 0.01-0.92; p=0.04
- ATM* HR=0.53; 95%CI, 0.21-1.34; p=0.18
- Stent Lenght HR=3.19; 95%CI, 1.81-5.59; p<0.0001

* Abbreviations: thieno=thienopyridine; LVEF=left ventricle ejection fraction; RVD=reference vessel ejection fraction; ATM= final stent atm inflation.
NOACS post ACS

European Heart J 2013
Perioperative Stent Patient Dose Management

• Emergent

• Elective
  • Aspirin hold 7-10 days but not a great idea
  • Thienpyridines hold 5-7 days pre operatively
  • Dual Therapy
  • Dipyridamole? At least 2 days
  • Aggrenox hold 7-10 days
### Table 2—Suggested Patient Risk Stratification for Perioperative Arterial or Venous Thromboembolism

<table>
<thead>
<tr>
<th>Risk Stratum</th>
<th>Mechanical Heart Valve</th>
<th>Atrial Fibrillation</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Any mitral valve prosthesis</td>
<td>CHADS₂ score of 5 or 6</td>
<td>Recent (within 3 mo) VTE</td>
</tr>
<tr>
<td></td>
<td>Older (caged-ball or tilting disc) aortic valve prosthesis</td>
<td>Recent (within 3 mo) stroke or transient ischemic attack, rheumatic valvular heart disease</td>
<td>Severe thrombophilia (e.g., deficiency of protein C, protein S or antithrombin, antiphospholipid antibodies, or multiple abnormalities)</td>
</tr>
<tr>
<td></td>
<td>Recent (within 6 mo) stroke or transient ischemic attack</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Bicaval aortic valve prosthesis and one of the following: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age &gt; 75 yr</td>
<td>CHADS₂ score of 3 or 4</td>
<td>VTE within the past 3 to 12 mo</td>
</tr>
<tr>
<td></td>
<td>Nonsevere thrombophilic conditions (e.g., heterozygous factor V Leiden mutation, heterozygous factor II mutation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrent VTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Active cancer (treated within 6 mo or palliative)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Bicaval aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke</td>
<td>CHADS₂ score of 0 to 2 (and no prior stroke or transient ischemic attack)</td>
<td>Single VTE occurred &gt; 12 mo ago and no other risk factors</td>
</tr>
</tbody>
</table>

*CHADS₂ = Congestive heart failure-Hypertension-Age-Diabetes-Stroke.*

Douketis JD et al. Chest 2012; 141(2) suppl. e3265-505
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;
  Concomitant 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.

Therapy for AF

- Prevent Thromboembolism
- Control ventricular response
- Restore/Maintain sinus rhythm
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
# Types of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal AF</td>
<td>• AF that terminates spontaneously or with intervention within 7 d of onset. • Episodes may recur with variable frequency.</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>• Continuous AF that is sustained &gt;7 d.</td>
</tr>
<tr>
<td>Long-standing persistent AF</td>
<td>• Continuous AF &gt;12 mo in duration.</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>• The term &quot;permanent AF&quot; 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.</td>
</tr>
<tr>
<td>Nonvalvular AF</td>
<td>• AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation.
Prevention of Thromboembolism

Decision to anti-coagulate comes down to risk of embolism versus bleeding.

Guideline recommendation:

3. In patients with nonvalvular AF, the CHA$_2$DS$_2$-VASc* score is recommended for assessment of stroke risk (68-70). *(Level of Evidence: B)*
CHADS2-Vasc Score

- 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 (i.e., females, age 65-74, vascular dx) are moved to the higher risk categories to better reflect risk of embolization.

### Table 6

Comparison of the CHADS2 and CHA2DS2-VASc Risk Stratification Scores for Subjects With Nonvalvular AF

<table>
<thead>
<tr>
<th>Definition and Scores for CHADS2 and CHA2DS2-VASc</th>
<th>Stroke Risk Stratification With the CHADS2 and CHA2DS2-VASc Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>Adjusted Stroke Rate (% per y)</td>
</tr>
<tr>
<td>CHADS2</td>
<td></td>
</tr>
<tr>
<td>Congestive HF</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age $\geq$75 y</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td>Maximum score</td>
<td>6</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td></td>
</tr>
<tr>
<td>Congestive HF</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age $\geq$75 y</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 y</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (i.e., female sex)</td>
<td>1</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol. 2014; 64 (21): 2246-2280
Guideline recommendation for anticoagulation in AF

- Anticoagulation recommended

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)
Managing Perioperative Anticoagulation

• Biomechanical Valves
  • Risk of thrombo-embolic event peri-operatively
    • Aortic ~2%
    • Mitral ~4%
    • Aortic/Mitral ~6%

Douketis JD et al. Chest 2012; 141(2) suppl. e3265-505
**Is bridging anticoagulation needed during warfarin interruption?**

- **No**
  - Patient is at low risk for thromboembolism
    - Day -5: stop warfarin (last dose Day -6)
    - Day -1: INR testing (if INR >1.5, administer vitamin K₁, 1.0 to 2.0 mg orally)
    - Day 0: resume warfarin on evening after surgery if patient drinking fluids
    - Day +1 to +3: resume warfarin when patient drinking fluids

- **Yes**
  - Patient is at high/moderate risk for thromboembolism
    - Day -5: stop warfarin (last dose on Day -6)
    - Day -3: start therapeutic-dose heparin bridging
    - Day -1: INR testing (if INR >1.5, give vitamin K₁, 1.0-2.0 mg orally); stop LMWH on morning before surgery (omit evening dose with twice-daily dosing; reduce total daily dose by 50% with once-daily dosing)
    - Day 0: assess postoperative surgical site hemostasis; resume warfarin on evening after surgery if patient taking fluids
    - Day +1 to +3: resume heparin bridging when hemostasis secured and not within 24 hours after surgery; resume warfarin when patient taking fluids
    - Day +5 to +6: stop LMWH when INR therapeutic
Procedural back up

• In house catheterization lab capable of direct intervention

• Cardiac Surgical capabilities

• Advanced support options
Bleeding Risk

- 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

J AM Coll Cardiol. 2015; 65 (13): 1340-1360
<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>
<tr>
<td></td>
<td><strong>Maximum Score</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>
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, 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
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
Thromboembolism Prevention Conclusions

• Decision to anti-coagulate 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.