Stroke Prevention and Contemporary Management of Non-Valvular Atrial Fibrillation

Craig T. January, MD, PhD, FACC
Division of Cardiovascular Medicine
University of Wisconsin

Illinois & Wisconsin Chapters American College of Cardiology 2017 Annual Meeting & Symposium

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Version May 4, 2017
Outline and Objectives

• **Part 1**: NOACs (Non-vitamin K Oral Anticoagulants) and warfarin
  – Current approved indications for use
  – Stroke prevention in atrial fibrillation (AF)

• **Part 2**: NOACs and changing practice patterns
  – Post-marketing data

• **Part 3**: Device-based interventions
  – Watchman
Indications for Anticoagulation

• Multiple clinical trials and guideline statements support the use of long-term oral anticoagulation for stroke prophylaxis in higher risk patients with AF.

• Long-term oral anticoagulation is also a mainstay in the management of patients with:
  – Mechanical heart valves
  – Deep venous thrombosis (DVT/VTE)
  – Pulmonary (or other) embolism (PE)

• Short-term oral or parenteral anticoagulation is indicated in a large variety of surgical (cardiac and otherwise) and medical settings.
THE “IDEAL” ANTICOAGULANT

- Oral, once daily fixed dose
- Rapid onset and offset of action
- Predictable pharmacokinetics (PK), and pharmacodynamics (PD)
- Low propensity for food and drug interactions
- No side effects or organ toxicities
- Wide therapeutic window
- No need for monitoring
- Rapidly reversible if bleeding
Anticoagulants in the U.S.

• Oral
  – Vitamin K antagonist: Warfarin
  – NOAC - Factor Xa inhibitor: Rivaroxaban, Apixaban, Edoxaban
  – NOAC - Thrombin inhibitor: Dabigatran

• Parenteral
  – Unfractionated heparin
  – LMW Heparin (more selective for factor-Xa): Enoxaparin, Dalteparin, Tinzaparin
  – Xa inhibitor: Fondaparinux
  – Direct thrombin inhibitors: Hirudin, etc
Coagulation Cascade

Indirect Xa inhibitors
"parinax"  
"LMWH"

Direct Xa inhibitors
"xaban"

Direct thrombin inhibitors
"gatran"

Heparin/AT III complex

Tissue factor
History of anticoagulant therapy


**Anticoagulant in spoiled sweet clover**: (K.P. Link, UW-Madison)

**First clinical use of 4-hydroxy coumarin**

**Warfarin synthesized as rodenticide**: (K.P. Link, UW-Madison)

**Warfarin mechanism elucidated**: (J. Suttie)

**Warfarin dosing/INR**

**Warfarin in multiple clinical trials**

**Oral thrombin and Xa inhibitors**

**Heparin discovered by medical student**: (McLean)

**Requirement for plasma cofactor discovered**: (Brinkhous)

**Continuous infusion of heparin; aPTT monitoring**

**LMWH discovered**

**LMWH trials**

**Fondaparinux trials**

**Hirudin first used**

**Wisconsin Alumni Research Foundation + coumarin = WARFARIN**
### Atrial Fibrillation: Definitions 2014

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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</table>
| Paroxysmal AF         | • AF that terminates spontaneously or with intervention within 7 days of onset.  
                        | • Episodes may recur with variable frequency.                                                                                               |
| Persistent AF         | • Continuous AF that is sustained beyond 7 days.                                                                                           |
| Longstanding Persistent AF | • Continuous AF of >12 months duration.                                                                                                     |
| Permanent AF          | • Permanent AF is used when there has been a joint decision by the patient and clinician to cease further attempts to restore and/or maintain sinus rhythm.  
                        | • Acceptance of AF represents a therapeutic attitude on the part of a patient and clinician rather than an inherent pathophysiological attribute of the AF.  
                        | • Acceptance of AF may change as symptoms, the efficacy of therapeutic interventions, and patient and clinician preferences evolve. |
| Chronic AF            | • A Medicare term.                                                                                                                          |

ACC/AHA/HRS AF Guidelines 2014
AF

A common arrhythmia mainly of the elderly
- ~1% of patients with AF are <60 years of age
- By ages 75-84 years, AF incidence is 10-12%

Associated with stroke/thromboembolism risk
- Nonvalvular AF increases stroke risk ~5-fold over NSR
- Valvular AF (mitral stenosis) increases stroke risk ~20-fold over NSR
- Mechanical heart valve thrombosis and thromboembolism risk varies widely (4 to 23 major events per 100 patient years) depending of many factors (valve type, location, etc), and the presence of AF is thought to further increase stroke/thromboembolism risk.
- Thromboembolism occurring with AF is associated with a greater risk of recurrent stroke, more severe disability, and mortality
- Silent AF is also associated with increased ischemic stroke risk
- Thrombus source usually left atrium/left atrial appendage

Common AF co-associated conditions (Medicare data)
- Hypertension 81-83%
- Ischemic heart disease 64%
- Hyperlipidemia 61-62%
- Heart Failure 52-59%
- Anemia, diabetes mellitus, CKD

* Associated structural heart disease
What Is Nonvalvular AF (~70%)

- **NOAC Trials Definitions - Valvular AF Exclusion**
  - **Re-ly (Dabigatran):** *Exclusion Criteria*
    - History of heart valve disorder (ie, prosthetic valve or hemodynamically relevant valve disease)
  - **Rocket-AF (Rivaroxaban):** *Exclusion Criteria*
    - Hemodynamically significant mitral valve stenosis
    - Prosthetic heart valve (permitted annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty)
  - **Aristotle (Apixaban) and Engage AF Timi 48 (Edoxaban):** *Exclusion Criteria*
    - Clinically significant (moderate or severe) mitral stenosis
    - Prosthetic mechanical heart valve
What Is Nonvalvular AF (~70%)

• **Guideline Definitions**

• ACC/AHA AF Guideline 2011 (Fuster et al, 2011):
  – AF in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair.

• ACC/AHA/HRS AF Guideline 2014 (January et al, 2014)
  – AF in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair (Fuster et al, 2011). Also, absence of hemodynamically significant mitral valve stenosis (Patel et al, 2012).

• ESC AF Guideline 2016 (Kirchhof et al, 2016)
  – AF in the absence of mechanical heart valves or moderate or severe mitral stenosis.

• Emerging definition (my opinion)
  – AF in the absence of moderate to severe (rheumatic) mitral stenosis or a prosthetic (mechanical) heart valve.
Valvular Heart Disease (VHD) in NOAC Trials: A Common Finding

NVAF does not mean absence of valvular HD

Antithrombotic Therapy for AF: 2014 ACC/AHA/HRS Guidelines

- CHA\textsubscript{2}DS\textsubscript{2}-VASc score recommended for risk assessment
- AF and CHA\textsubscript{2}DS\textsubscript{2}-VASc score:
  - ≥2 - oral anticoagulation is recommended
  - 1 * - either anticoagulation, no therapy, or aspirin
  - 0 - no antithrombotic therapy
- * Female only risk factor then CHA\textsubscript{2}DS\textsubscript{2} VASC score = 0

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>POINTS</th>
<th>SCORE</th>
<th>STROKE RATE (%/y)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Congestive HF</td>
<td>1</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>2</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
<td>4</td>
<td>4.0</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
<td>5</td>
<td>6.7</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, aortic plaque)</td>
<td>1</td>
<td>6</td>
<td>9.8</td>
</tr>
<tr>
<td>Age 65-74 y</td>
<td>1</td>
<td>7</td>
<td>9.6</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>1</td>
<td>8</td>
<td>6.7</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
<td>9</td>
<td>15.2</td>
</tr>
</tbody>
</table>
Warfarin

- Anticoagulant effects may not be apparent for days.
- The duration of action of a single dose is 2–5 days.
- The therapeutic effect of warfarin exists within a narrow therapeutic window as dictated by the INR.
  - Time in therapeutic INR range for patients typically is 50–70%
- Considerable inter- and intra-individual dose variability
  - Pathophysiologic (liver and thyroid function)
  - Genetic
  - Environmental (diet, other drugs)
- Regular monitoring of INR is required to avoid excessive or insufficient anticoagulation.
Hart et al, 2007

**Conclusions:**

- **Warfarin reduces stroke risk in (non)-valvular AF.**
- **Minimal to no benefit with anti-platelet agents.**
Dabigatran

Pradaxa®

10/19/10: FDA approval for stroke prevention in nonvalvular AF
12/19/12: FDA Drug Safety Communication. Dabigatran should not be used in patients with mechanical prosthetic heart valves
4/7/14: FDA approval for use in patients with DVT and PE
11/23/15: FDA approval for prophylaxis for DVT and PE after hip surgery. Idarucizumab (Praxbind) approved
Dabigatran

- Direct thrombin inhibitor
- Oral bioavailability 6-7%
- Peak blood level 2 hours after dosing
- Half-life 14-17 hours. Metab; 80% renal, 20% biliary
- Dose (AF): 150 mg bid
  - For patients with CrCl 15-30: 75 mg bid
  - Not recommended for CrCl <15 or dialysis dependent
- Dose (VTE prophylaxis, hip and knee): approved
- Dose (acute VTE and PE): initial parenteral anticoag, then dagibatran
- Affects PT/INR and PTT (not useful for monitoring)
- Drug interactions:
  - Potent P-glycoprotein (P-gp) inducers speed clearance (rifampin, quinidine, amiodarone, verapamil)
  - PPIs decrease absorption
Dabigatran vs Warfarin for AF

The RE-LY trial

- Subjects: 18,113 patients with AF & additional risk factor(s) for stroke
  - Excluded pts with severe valvular heart dz, recent stroke, high risk of bleeding, CrCl < 30, liver dz, pregnancy
  - Mean CHADS$_2$ = 2.1
  - About half of patients were warfarin-naive
- Intervention: Dabigatran 110 or 150 mg bid (blinded) vs standard warfarin (unblinded)
- Primary outcome: Stroke or embolism
- Median follow-up 2 yrs
- Funded by drug manufacturer
- “Non-inferiority” trial

NEJM 2009; 361: 1139
## Dabigatran vs Warfarin for AF

*The RE-LY trial*

<table>
<thead>
<tr>
<th>Outcome (rate per year)</th>
<th>Dabigatran 110 mg bid</th>
<th>Dabigatran 150 mg bid</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or embolism</td>
<td>1.53%</td>
<td>1.11%</td>
<td>1.69%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.71%</td>
<td>3.11%</td>
<td>3.36%</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.12%</td>
<td>0.10%</td>
<td>0.38%</td>
</tr>
<tr>
<td>Mortality</td>
<td>3.75%</td>
<td>3.64%</td>
<td>4.13%</td>
</tr>
</tbody>
</table>

### Conclusions:
- Dabigatran 110 mg associated with similar rates of stroke and embolism, less bleeding than warfarin.
- Dabigatran 150 mg associated with lower rates of stroke and embolism, similar bleeding rate to warfarin.
- Non-inferior to warfarin.

*NEJM 2009; 361: 1139*
Dabigatran vs Warfarin for Mechanical Valves

The RE-ALIGN trial

- 252 patients, bi-leaflet mechanical aortic or mitral replacement within 7 days or >3 months earlier
  - Dabigatran 150, 220, or 300 mg twice daily based on kidney function and trough drug plasma level of at least 50 ng/ml.
  - Warfarin dose was adjusted to INR of 2 to 3 or 2.5 to 3.5
- Trial terminated because of excess thromboembolic and bleeding events in patients in the dabigatran group
  - Dose adjustment or discontinuation of dabigatran was required in 52 of 162 patients (32%).
  - Ischemic or unspecified stroke occurred in 9 patients (5%) in the dabigatran group and in no patients in the warfarin group.
  - Major bleeding occurred in 7 patients (4%) on dabigatran and 2 patients (2%) on warfarin. All patients with major bleeding had pericardial bleeding.

NEJM 2013; 369:1206
Dabigatran vs Warfarin for Mechanical Prosthetic Heart Valves

The RE-ALIGN trial

- 12/19/12: FDA Drug Safety Communication: Pradaxa (dabigatran) should not be used in patients with mechanical prosthetic heart valves (NSR or AF).
Rivaroxaban

Xarelto®

7/1/11: FDA approval for DVT prophylaxis after hip or knee surgery
11/4/11: FDA approval for stroke prevention in nonvalvular Afib
11/2/12: FDA approval for recurrent blood clots (DVT and PE)
6/28/13: FDA does not approve use in stent thrombosis in ACS
Rivaroxaban

- Direct factor Xa inhibitor
- Peak blood level 2.5-4 h after dosing
- Half-life 5-9 h (longer in elderly)
- Metabolism: 66% renal, 33% biliary
- Dose (AF): 20 mg hs (15 mg hs for CrCl 15-50ml/min)
- Dose (DVT, PE): 15 mg bid x 21 days, then 20 mg qd
- Dose (risk of recurrent DVT and PE): 20 mg qd
- Dose (post op VTE prophylaxis): 10 mg qd (12-35 days)
  - Use with caution in moderate renal impairment (CrCl 30-50)
  - Avoid use if CrCl <15 (not dialyzable) or severe liver disease
- Monitoring: anti-Xa level (not routinely needed)
- Drug interactions: Potent CYP3A4 and P-glycoprotein (Pgp) inducers and inhibitors affect clearance
  - Azole antibiotics, HIV protease inhibitors, rifampin
Rivaroxaban vs Warfarin for AF

The ROCKET-AF trial

- **Subjects:** 14,264 patients with nonvalvular AF & additional risk factor(s) for stroke
  - Mitral annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty included
  - Mean CHADS$_2$ = 3.5
  - 25-30% of patients warfarin-naive
- **Intervention:** Rivaroxaban 20 mg hs vs standard warfarin
- **Method:** Randomized, double-blind, double-dummy trial
- **“Non-inferiority” trial**
- **Primary outcome:** Stroke or embolism
- **Warfarin patients** spent 58% of time within INR range
- **Funded by drug manufacturer**

*NEJM 2011; 365:883*
Rivaroxaban vs Warfarin for AF
The ROCKET-AF trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Stroke or embolism</th>
<th>Major bleeding</th>
<th>Intracranial hemorrhage</th>
<th>Fatal bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>1.7%/yr</td>
<td>14.9%/yr</td>
<td>0.5%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>2.2%/yr</td>
<td>14.5%/yr</td>
<td>0.7%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

NEJM 2011; 365:883

Conclusion: Rivaroxaban non-inferior to warfarin for prevention of stroke and embolism in nonvalvular AF patients who are at moderate or high risk of stroke.
Apixaban

Eliquis®

12/28/12: FDA approval to reduce stroke risk in nonvalvular Afib
3/18/14: FDA approval to reduce blood clot risk after hip and knee surgery
8/21/14: FDA approval for DVT and PE, and for use in patients with end-stage renal disease (ESRD) or on dialysis
Apixaban

- Direct factor Xa inhibitor
- Oral bioavailability 80%
- Peak blood level 3 h after dosing
- Half-life 8-15 h
- Metabolism: 25% renal, 75% biliary (differs significantly from other NOACs)
- Dose (AF): 5 or 2.5 mg bid, reduce dose if "high risk",
  - 2 of 3: ≥80 yr, ≤60 kg, creatinine >1.5
- Dose (VTE prophylaxis, hip and knee): 2.5 mg bid
- Dose (acute VTE and PE): 10 mg bid x7 d, the 5 mg bid
- Dose (recurrent VTE and PE): 2.5 mg bid
- Monitoring: anti-Xa level (not routinely needed)
- Drug interactions: Potent CYP3A4 and Pgp inducers and inhibitors affect clearance
  - Azole antibiotics, HIV protease inhibitors, rifampin
Apixaban vs Aspirin for AF
The AVERROES trial

- Subjects: 5599 patients with nonvalvular AF & additional risk factor(s) for stroke considered unsuitable for treatment with Vitamin K Antagonists
  - Mean CHADS$_2$ = 2.1
- Intervention: Apixaban (5 mg bid) vs ASA (81-325 mg/d)
- Method: Randomized double-blind trial
- Primary outcome: Stroke or embolism
- Funded by drug manufacturer
Apixaban vs Aspirin for AF

The AVERROES trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Stroke or embolism</th>
<th>Major bleeding</th>
<th>Intracranial hemorrhage</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>1.6%/yr</td>
<td>1.4%/yr</td>
<td>0.2%</td>
<td>3.5%/yr</td>
</tr>
<tr>
<td>Aspirin</td>
<td>3.7%/yr</td>
<td>1.2%/yr</td>
<td>0.3%</td>
<td>4.4%/yr</td>
</tr>
</tbody>
</table>

Conclusion: Study stopped early because of clear benefit of apixaban over aspirin

NEJM 2011; 364:817
Apixaban vs Warfarin for AF
*The ARISTOTLE trial*

- Subjects: 18,201 patients with nonvalvular AF & additional risk factor(s) for stroke
  - Mean CHADS$_2$: 2.1
  - 60% were warfarin-naive
- Intervention: Apixaban (5 mg bid) vs warfarin (target INR 2.0-3.0)
- Method: Randomized double-blind trial
- Primary outcome: Stroke or embolism
- Mean followup 1.8 years
- Funded by drug manufacturer
- Warfarin patients spent 62% of time in therapeutic range

*NEJM 2011; 365:981*
Apixaban vs Warfarin for AF

The ARISTOTLE trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Stroke or embolism</th>
<th>Major bleeding</th>
<th>Intracranial hemorrhage</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>1.3%/yr</td>
<td>2.1%/yr</td>
<td>0.24%/yr</td>
<td>3.5%/yr</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.6%/yr</td>
<td>3.1%/yr</td>
<td>0.47%/yr</td>
<td>3.9%/yr</td>
</tr>
</tbody>
</table>

Conclusion: Apixaban superior to warfarin in preventing stroke or embolism, caused less bleeding, and first of new drugs associated with lower all-cause mortality

NEJM 2011; 365:981
Edoxaban

Savaysa®

1/8/15: FDA approval for use in nonvalvular AF and to treat DVT and PE

Factor Xa inhibitor, once daily dosing
Edoxaban

- Direct factor Xa inhibitor
- Oral bioavailability 62%
- Peak blood level 1-2 h after dosing
- Half-life 5-11 h
- Metabolism: 50% renal
- Dose (AF): 60 mg once daily CrCL > 50 to < 95 (reduced efficacy if CrCl > 95)
  - If CrCl 15-50 use 30 mg QD
- Dose (DVT and PE): Initial parenteral anticoag, dose depends on CrCl, pt wt, other drugs
- Monitoring: anti-Xa level (not routinely needed)
- Drug interactions: Potent CYP3A4 and Pgp inducers and inhibitors affect clearance
  - Azole antibiotics, HIV protease inhibitors, rifampin
Edoxaban vs Warfarin for AF
The Engage AF Timi 48 trial

- Subjects: 21,105 patients with nonvalvular AF
  - CHADS > 2.0
- Intervention: Edoxaban 1:1:1 CHADS 2-3 vs 4-6 (edoxaban dose reduction) vs warfarin
- Method: Randomized double-blind trial
  - Warfarin (INR 2-3) vs Edoxaban 60 mg (high dose) vs Edoxaban 30 mg (low dose)
- Primary outcome: Stroke or embolism
- Non-inferiority trial
- Funded by drug manufacturer

NEJM 2013; 369:2093
Edoxaban vs Warfarin for AF
The Engage AF Timi 48 trial

• Non-inferior to warfarin for stroke/SEE (both high- and low-dose regimens)
  - High-dose associated with ↓ stroke/SEE on Rx
• Both regimens significantly reduced:
  - Major bleeding (20%/53%) - ICH (53%/70%)
  - Hem. stroke (46%/67%) - CV death (14%/15%)

Conclusion: Edoxaban non-inferior to warfarin for prevention of stroke or systemic embolism; high-dose edoxaban tended to be more effective than warfarin. Edoxaban was associated with lower rates of major, intracranial, and life-threatening bleeding. GI bleeding occurred more frequently with high-dose edoxaban but less frequently with low-dose edoxaban.
Part 2:

Observational Post-marketing Studies: Registries and Databases.

Beginning to Compare NOAC’s.

- Safety
- Efficacy
Direct Comparison of NOACs

Graham et al. Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation.


• Medicare database (65 years or older)
  – 52,240 pts Dabigatran 150 mg BID
  – 66,651 pts Rivaroxaban 20 mg QD

• Stroke, intracranial hemorrhage (ICH), major bleeding including GI, mortality

• Rivaroxaban vs Dabigatran:
  – Rivaroxaban associated with a statistically nonsignificant reduction in thromboembolic stroke (p=0.07, 1.8 fewer cases/1000 person-years)
  – Rivaroxaban associated with a statistically significant increase in ICH (p=0.002, 2.3 excess cases/1000 person-years)
  – Rivaroxaban associated with a statistically significant increase in major extracranial bleeding (p<0.001, 13.0 excess cases/1000 person-years), including major gastrointestinal bleeding (p<0.001, 9.4 excess cases/1000 person-years)
  – Rivaroxaban associated with a statistically nonsignificant increase in mortality (p=0.051, 3.1 excess cases/1000 person-years). In patients ≥75 years or with CHADS2 score >2, rivaroxaban use was associated with a significant increased mortality compared with dabigatran use.
Direct Comparison of NOACs


- U.S. Medicare Database (pts ≥65 yrs): Patients with NVAF on apixaban, dabigatran, or rivaroxaban (Oct 1, 2010, to Feb 28, 2015). Minimum of 12 mo anticoagulant use. 3 matched cohorts. Patients with valvular HD, end-stage CKD, kidney transplant, or dialysis at any time were excluded.
  - Rivaroxaban vs Dabigatran (n = 31,574)
  - Apixaban vs Dabigatran (n = 13,084)
  - Apixaban vs Rivaroxaban (n = 13,130)
- The risk of stroke or systemic embolism was similar.
- Apixaban was associated with a lower risk of major bleeding compared with other NOACs.
- Rivaroxaban was associated with an increased risk of major bleeding compared with dabigatran.
- Dabigatran, rivaroxaban, and apixaban appear to have similar effectiveness, although apixaban may be associated with a lower bleeding risk and rivaroxaban may be associated with an elevated bleeding risk.
Direct Comparison of NOACs + Warfarin


- U.S. Insurance Database: Patients with NVAF on apixaban, dabigatran, rivaroxaban, or warfarin (October 1, 2010, to June 30, 2015). Minimum of 12 mo anticoagulant use. 3 matched cohorts. Patients with valvular HD, end-stage CKD, kidney transplant, or dialysis at any time were excluded.
  - Apixaban versus Warfarin (n=15,390),
  - Dabigatran versus Warfarin (n=28,614),
  - Rivaroxaban versus Warfarin (n=32,350).
- Using Cox proportional hazards regression, for stroke or systemic embolism, apixaban was associated with lower risk (hazard ratio [HR] 0.67, 95% CI 0.46–0.98, P=0.04), but dabigatran and rivaroxaban were associated with a similar risk (dabigatran: HR 0.98, 95% CI 0.76–1.26, P=0.98; rivaroxaban: HR 0.93, 95% CI 0.72–1.19, P=0.56) compared with warfarin.
- For major bleeding, apixaban and dabigatran were associated with lower risk (apixaban: HR 0.45, 95% CI 0.34–0.59, P<0.001; dabigatran: HR 0.79, 95% CI 0.67–0.94, P<0.01), and rivaroxaban was associated with a similar risk (HR 1.04, 95% CI 0.90–1.20], P=0.60) compared with warfarin.
- All NOACs were associated with a lower risk of intracranial bleeding vs warfarin.
- Mortality was not assessed.
Direct Comparison of NOACs + Warfarin


- Observational Danish registry nationwide cohort study of the effectiveness and safety of dabigatran, rivaroxaban, and apixaban compared with warfarin in anticoagulant naïve patients with atrial fibrillation (August 2011 to October 2015).
- The study populations: warfarin (n=35,436, 57%), dabigatran 150 mg (n=12,701, 21%), rivaroxaban 20 mg (n=7192, 12%), and apixaban 5 mg (n=6349, 10%).
  - All NOACs seem to be safe and effective alternatives to warfarin in a routine care setting.
  - No significant difference was found between NOACs and warfarin for ischaemic stroke.
  - The risks of death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran compared with rivaroxaban and warfarin.
**Crude failure curves**

- Apixaban
- Warfarin
- Rivaroxaban
- Dabigatran

**Weighted failure curves (population averaging)**

- Ischaemic stroke or systemic embolism

**Any bleeding**

- 5 per yr
- 3 per yr

**All cause death**

- Rivar & Warf
- 7 per yr
- Dabig & Apix
- 5 per yr

Larsen et al, BJM 2017.
Direct Comparison of NOACs: GI Bleeding


- U.S. Insurance Database: Patients with NVAF on apixaban, dabigatran, or rivaroxaban (Oct 1, 2010, to Feb 28, 2015). Minimum of 12 mo anticoagulant use. 3 matched cohorts using 1:1 propensity score matching. Patients with valvular HD, end-stage CKD, kidney transplant, or dialysis at any time were excluded.
  - Rivaroxaban vs Dabigatran (n = 31,574)
  - Apixaban vs Dabigatran (n = 13,084)
  - Apixaban vs Rivaroxaban (n = 13,130)
- Similar CHA2DS2-VASc (3.2 to 4.0) and HAS-BLED (2.2 to 2.4) scores.
- Apixaban had the most favorable GI safety profile and rivaroxaban least favorable.
- For all NOACs, GI bleeding events increased with age; the risk was greatest among persons ≥75 years old.

• Introduction: Warfarin, a vitamin K antagonist, interferes with vitamin K-dependent γ-carboxylation of glutamic acid residues, which inhibits activation of bone matrix proteins and reduces bone mineralization/density. Dabigatran does not do this.

• Question: What is the risk of osteoporotic fracture associated with the use of dabigatran compared with warfarin among patients with NVAF?

• Findings: In this population-based cohort study of 8152 NVAF patients (dabigatran = 3268, warfarin = 4884, mean age 74 yrs), use of dabigatran was associated with a significantly lower risk of osteoporotic fracture compared with warfarin (incidence, 0.7 vs 1.1 per 100 person-years) during a mean follow-up of approximately 500 days.

• Meaning: Among older adults with NVAF receiving anticoagulation, dabigatran compared with warfarin was associated with a lower risk of osteoporotic fracture.

• RE-CIRCUIT Trial. Randomized multicenter trial funded by manufacturer.

• **Dabigatran** 150 mg BID vs daily **warfarin** (INR 2.0 – 3.0).

• Catheter ablation of paroxysmal or persistent AF.

• Uninterrupted anticoagulation for 4 to 8 weeks pre-ablation which was continued during and for 8 weeks after ablation.

• Enrolled 704 patients across 104 sites; 635 patients underwent AF ablation.

• Lower **major bleeding** (pericardial tamponade, pericardial effusion, groin bleed or hematoma, intracranial bleed, pseudoaneurysm, GI bleed, hematoma) risk with dabigatran than with warfarin (5 patients [1.6%] vs. 22 patients [6.9%], respectively; P<0.001).

• In patients undergoing ablation for AF, anticoagulation with uninterrupted dabigatran was associated with fewer bleeding complications than uninterrupted warfarin.
Observational and Randomized Post-Marketing Studies: What to Conclude?

- These are not prospective randomized controlled clinical trials data. Most not prospective. No control groups.
- Incomplete data.
  - Missing drugs (particularly edoxaban).
  - Doses may vary (U.S. vs Europe).
- Safety:
  - NOACs may offer improved safety (bleeding) over warfarin.
  - Apixaban (Eliquis) and possibly dabigatran (Pradaxa) may be emerging as safer NOACs from a bleeding risk perspective.
- Efficacy: NOACs continue to be at least as effective as warfarin at stroke prevention.
- Less clear is favorable mortality impact of NOACs (apixaban, dabigatran).
Measuring NOAC Serum Drug Levels

Commercial assays exist for apixaban, rivaroxaban, edoxaban and dabigatran.

- Reference ranges derived from published literature are “wide” and currently without outcomes (safety) correlation.

Who might benefit?
- Pre-op (urgent surgery) to assess level of drug in patient.
- CKD patients to see if there is accumulation of drug (in renal insufficiency and hemodialysis).
- Potential drug-drug interactions to guide dose adjustment.
- Obese patients (BMI > 35 or Wt > 120 kg) for VTE treatment with concerns for decreased drug absorption.
- Possibly useful in compliance assessment?
Part 3:
Non Pharmacological Therapies for Stroke Prevention:
WATCHMAN Left Atrial Appendage Closure Device
Left Atrial Appendage

• 90% of stroke-causing clots are from the left atrial appendage (LAA) in non-valvular AF.

• Site specific therapy to occlude LAA?

FDA approved
March 13, 2015
High Rates of Discontinuation of Warfarin and NOACs in Trials: Many Untreated Patients

![Discontinuation Rate (%)](chart)

- **RE-LY (dabigatran)**: 21% (NOAC) vs 17% (Warfarin)
- **ROCKET AF (dabigatran)**: 24% (NOAC) vs 22% (Warfarin)
- **ARISTOTLE (apixaban)**: 25% (NOAC) vs 28% (Warfarin)

References:
- Connolly, S. NEJM 2009; 361:1139-1151
- Patel, M. NEJM 2011; 365:883-891
- Granger, C. NEJM 2011; 365:981-992
# WATCHMAN versus Warfarin

## Meta-Analysis: Roughly Co-equal?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>Efficacy</strong></td>
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<tr>
<td>All stroke or SE</td>
<td>1.02</td>
<td>0.94</td>
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<td>Ischemic stroke or SE</td>
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<td>Hemorrhagic stroke</td>
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<td>Ischemic stroke or SE &gt;7 days</td>
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<td>CV/unexplained death</td>
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<td><strong>All-cause death</strong></td>
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<td></td>
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<tr>
<td>Major bleed, all</td>
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<td>0.98</td>
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<tr>
<td>Major bleeding, non procedure-related</td>
<td>0.51</td>
<td>0.002</td>
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</tbody>
</table>

*Favors WATCHMAN*  
*Favors warfarin*  

From PROTECT AF and PREVAIL. Holmes, et al. JACC 2015; 65(24): 2614-2623
Post-Procedural Anticoagulation

LAA closure device(s) not requiring post-implant warfarin are needed.
WATCHMAN FDA Indication

• Watchman Device barely received FDA approval
• Reduces the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:
  • Are at increased risk for stroke and systemic embolism based on CHADS2 (≥2) or CHA2DS2-VASc (≥3) scores and are recommended for anticoagulation therapy
  • Are deemed by their physicians to be suitable for warfarin
  • Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.
Conclusions (1)

• Many AF patients with guideline indications for anticoagulation are not receiving therapy
  – All anticoagulants reduce stroke/TE risk in AF

• NOACs are FDA approved for the treatment of:
  – Stroke/TE prevention/prophylaxis in nonvalvular AF (all 4)
  – DVT/VTE and PE, but FDA guidelines for use are drug-specific
  – DVT prophylaxis after hip or knee surgery (again drug-specific)

• NOACs are not recommended in the treatment of:
  – Anticoagulation of mechanical heart valves (NSR or AF)
  – Patients with moderate to severe mitral valve stenosis
  – Patients with severe CKD/renal dialysis (except Apixaban)
  – There is uncertainty about NOACs and ACS (not FDA approved)

• Considerations
  – Elderly patients
  – GI bleeding
  – Drug interactions (P-gp and strong CYP3A4 inhibitors may ↑drug conc whereas inducers may ↓drug conc)
  – Reversibility II (idarucizumab (Praxbind), 2 vials (5 gms) i.v.)
  – Reversibility Xa (andexanet alfa (AndexXa), FDA review)
Conclusions (2)

• Bleeding
  – NOACs have less bleeding events except possibly for GI
  – Apixaban and possibly dabigatran may be emerging as safer NOACs

• Efficacy
  – NOACs continue to be at least as effective as Coumadin at stroke prevention
  – Anti-platelet agents including ASA provide minimal to no benefit

• Dosing
  – BID: Dabigatran and Apixaban
  – QD: Rivaroxaban (with evening meal), Edoxaban and Warfarin

• Elimination
  – Mostly renal: Dabigatran > rivaroxaban > edoxaban
  – Mostly hepatic: Apixaban (FDA approved in ESRD) along with warfarin

• Watchman
  – Percutaneous LAA occlusion may be considered for stroke prevention in patients with AF at increased risk of stroke, who are eligible for short-term anticoagulation and have contraindications to long-term anticoagulation

• The use of warfarin will decline as we continue to learn more about NOACs.
Thank you