The Role of Oral Anticoagulants in Atrial Fibrillation: What You Need to Know Now

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Richard F. Otten, MD, FACC
Outline

• Atrial Fibrillation Overview
• Overview of New Oral Anticoagulants (OACs)
• Case Presentations
• New Anticoagulants on Horizon
Atrial Fibrillation Burden

- 1.5-2% of the developed population has atrial fibrillation (afib)
- Increased mortality
- 5-fold increase in stroke risk
- 3-fold increase in congestive heart failure
Stroke Risk Stratification

- \( \text{CHADS}^2 \)
- \( \text{CHA}_2\text{DS}_2\)-VASC
# The CHA$_2$DS$_2$VASc Index

**Stroke Risk Score for Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Weight (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure or LVEF ≤ 35%</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/systemic embolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (MI/PAD/Aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65–74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Truly low risk**

Score = 0

---

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

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; score</th>
<th>Patients (n = 1733)</th>
<th>Adjusted stroke rate % / year</th>
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<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>1.9</td>
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<td>1</td>
<td>463</td>
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<td>2</td>
<td>523</td>
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<td>3</td>
<td>337</td>
<td>5.9</td>
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<td>4</td>
<td>220</td>
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<td>12.5</td>
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<td>6</td>
<td>5</td>
<td>18.2</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc score</th>
<th>Patients (n = 7329)</th>
<th>Adjusted stroke rate % / year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
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<td>4</td>
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<td>5</td>
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<td>7</td>
<td>294</td>
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<tr>
<td>8</td>
<td>82</td>
<td>6.7</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>15.2</td>
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</table>
Are We Anticoagulating Enough?

- Registry Data:
  - Rowan et al: < 50% of patients with afib were anticoagulated.
  - Kowey et al: 64% of patients with CHADS$_2$ 2 or greater were anticoagulated with warfarin.
Why Not Anticoagulate?

- Fear of bleeding, esp gastrointestinal or intracranial
- Drug interactions
- Patient preference
- Difficulty regulating drug
- Fear of warfarin
- Lack of physician insight?
Oral Anticoagulants

- Vitamin K antagonists
- Direct Thrombin Inhibitor
- Factor Xa Inhibitors
| Pharmacological Characteristics of Oral Direct Thrombin Inhibitors and Oral Direct Factor Xa Inhibitors in Phase III Clinical Development |
|---|---|---|---|---|
| **Mechanism of action** | Dabigatran Etxilate | Rivaroxaban | Apxaban | Edoxaban |
| Oral bioavailability, % | 6.5 | 80–100 | 50 | 62 |
| Half-life, h | 12–17 | 5–13 | 8–15 | 6–11 |
| Renal elimination, % | 85 | 66 (36 unchanged and 30 inactive metabolites) | 27 | 50§ |
| Time to maximum inhibition, h | 0.5–2 | 1–4 | 1–4 | 1–2 |
| Potential metabolic drug interactions | Inhibitors of P-gp: verapamil, reduce dose; dronedarone: avoid | Potent inhibitors of CYP3A4 and P-gp*: avoid | Potent inhibitors of CYP3A4 and P-gp*: avoid | Potent inhibitors of P-gp*: reduce dose |
| Potential Inducers of P-gp†: avoid | Potential Inducers of CYP3A4‡ and P-gp: use with caution | Potential Inducers of CYP3A4‡ and P-gp: use with caution | Potential Inducers of P-gp†: avoid |

*Potent inhibitors of CYP3A4 include antifungals (e.g., ketoconazole, itraconazole, voriconazole, posaconazole), chloramphenicol, clarithromycin, and protease inhibitors (e.g., ritonavir, atazanavir). P-gp Inhibitors include verapamil, amiodarone, quinidine, and clarithromycin. †P-gp Inducers include rifampicin, St. John’s wort (Hypericum perforatum), carbamazepine, and phenytoin. ‡Potential CYP3A4 Inducers include phenytoin, carbamazepine, phenobarbital, and St. John’s wort. §Of the absorbed drug.

CYP = cytochrome P450 isoenzyme; F = factor; P-gp = P-glycoprotein.
Site of Action

From DeCaterina et al.
Case 1

- 83 yo woman presents to the hospital with coffee ground emesis, dizziness. Recent viral illness
- Hx of Afib, HTN, CKD 3

- Medications: Atenolol 50 mg daily, Dabigatran 150 mg bid, Spironolactone 25 mg daily, Aspirin 81 mg daily, Atorvastatin 20 mg daily
Case 1

- PE: HR 85 bpm, regular BP 92/50 mm Hg
- Appears pale, +orthostatics
- Labs: Hgb 7.1 g/dL, creat 3.1 mg/dl (nl 1.8), INR 2.6
Case 1 Discussion

• Was the use/dose of dabigatran appropriate?

• What does the INR tell us about the level of anticoagulation in this patient?
The NEW ENGLAND JOURNAL of MEDICINE

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*
RE-LY

- Warfarin vs 110 mg bid dabigatran vs 150 mg bid dabigatran
- Primary outcome was stroke or systemic embolism
Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

RE-LY Results

- Dabigatran 150 mg bid superior to warfarin with respect to primary outcome (110 mg dose was noninferior)
- No increase in major bleeding of 150 mg dose (110 mg dose less bleeding)
- Significant decrease in hemorrhagic stroke with both dabigatran doses
- Trend in improved mortality with both doses vs. warfarin
RE-LY Results

- Dabigatran 150 mg bid higher risk of GI bleed and increased risk of myocardial infarction
Dabigatran (Pradaxa®)

- Direct Thrombin Inhibitor
- Pro-drug, best absorbed in an acidic environment
- Renally cleared
- $T_{1/2} = 12$ hrs
- 85% can be dialyzed
- Peak Effect 2-3 h
Dabigatran Dosing

• FDA recommendation based on GFR:
  1. GFR >30 mL/min $\rightarrow$ 150 mg bid
  2. GFR 15-30 mL/min $\rightarrow$ 75 mg bid
  3. GFR < 15 mL/min $\rightarrow$ cannot recommend use
Measuring Effect of Dabigatran

- INR is not accurate and should not be checked!!
- ECT (ecarin clotting time) and TT (thrombin time) can be measured.
- Activated Partial Thromboplastin Time (aPTT) approximation. ~ 2 x control when therapeutic
- Activated clotting time (ACT) is affected, though therapeutic range not studied
Dabigatran

- No antidote available
- Activated Prothrombin Complex Concentrates may be used to some effect
- Fresh Frozen Plasma (FFP) not typically helpful
Case 1

- GFR at baseline ~27mL/min, reduced to 14 mL/min. 75 mg bid dosing more appropriate
- The patient was transfused 2 units pRBCs
- Vitamin K 10 mg
- EGD-gastritis, no active bleeding
- Dabigatran discontinued, warfarin started.
Case 2

- 70 year old man desires atrial fibrillation ablation
- Paroxysmal afib
- HTN
- Remote cardiac stent
• Medications: amiodarone 200 mg daily, aspirin 81 mg daily, carvedilol 6.25 mg bid, rosuvastatin 20 mg qhs, lisinopril 10 mg daily, dabigatran 150 mg bid
• How should his anticoagulation be managed perioperatively?
Multicenter (8) Observational Study
290 pts (half uninterrupted coumadin, half dabigatran)
Dabigatran dose 150 mg bid
Warfarin target INR 2-3.5
• Dabigatran stopped am of procedure and restarted 3 hrs post hemostasis
• Transesophageal echo performed day of procedure on dabigatran pts but not warfarin patients
• Similar baseline characteristics
Results

• Trend toward increased thromboembolic events in dabigatran group
• Higher risk of major bleeding rate, total bleeding rate, and composite of bleeding and thromboembolic complications in the dabigatran group
<table>
<thead>
<tr>
<th>Safety Endpoints</th>
<th>Dabigatran (n = 145)</th>
<th>Warfarin (n = 145)</th>
<th>Total (N = 290)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding complications</td>
<td>9 (6)</td>
<td>1 (1)</td>
<td>10 (3)</td>
<td>0.019</td>
</tr>
<tr>
<td>Periprocedural pericardial tamponade</td>
<td>6 (4)</td>
<td>1 (1)</td>
<td>7 (2)</td>
<td>0.12</td>
</tr>
<tr>
<td>Late pericardial tamponade</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>3 (1)</td>
<td>0.25</td>
</tr>
<tr>
<td>Minor bleeding complications</td>
<td>12 (8)</td>
<td>8 (6)</td>
<td>20 (7)</td>
<td>0.35</td>
</tr>
<tr>
<td>Groin hematoma</td>
<td>6 (4)</td>
<td>5 (3)</td>
<td>11 (4)</td>
<td>0.76</td>
</tr>
<tr>
<td>Pericardial effusion without tamponade</td>
<td>6 (4)</td>
<td>4 (3)</td>
<td>10 (3)</td>
<td>0.75</td>
</tr>
<tr>
<td>Total bleeding complications</td>
<td>20 (14)</td>
<td>9 (6)</td>
<td>29 (10)</td>
<td>0.031</td>
</tr>
<tr>
<td>Embolic complications (CVA/TIA)</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>3 (1)</td>
<td>0.25</td>
</tr>
<tr>
<td>Composite of bleeding and embolic</td>
<td>23 (16)</td>
<td>9 (6)</td>
<td>32 (11)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Values are n (%).
CVA = cerebrovascular accident; TIA = transient ischemic attack.
Concerns

• Dabigatran not held long enough prior to procedure
• Interaction between unfractionated heparin and dabigatran
• FFP given to reverse dabigatran
• Timing of reinitiation of dabigatran
Our Experience

- Holding coumadin
- Hold dabigatran 48 hours prior to procedure.
Case 3

- 75 year old woman with newly diagnosed afib.

- Recent drug-eluting stent to LAD (3 weeks prior), HTN, DM, obese, nl renal function
Case 3

- Medications: carvedilol 12.5 mg bid, aspirin 325 mg daily, clopidogrel 75 mg daily, simvastatin 40 mg qhs, diabetic meds

- Asymptomatic. Ventricular rate between 60-80 bpm at rest
Case 3

• Should this woman receive anticoagulation?

• Which anticoagulant would be best?
Case 3

- $\text{CHADS}_2 = 3$ (5.9% annual stroke risk)
- $\text{CHA}_2\text{DS}_2\text{-VASc} = 6$ (9.8% annual stroke risk)
Case 3

• ACC/AHA/ESC guidelines: “triple” therapy in PCI patients with afib as a IIb recommendation (Level of Evidence C)

Aka “Proceed with Caution”
Case 3

• Which anticoagulant to use?
What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting?

WOEST Trial

- European Study
- Randomized Controlled Trial - 573 pts
- VKA + clopidogrel 75 mg daily + ASA 80 mg daily
- VKA + clopidogrel 75 mg daily
WOEST Trial

- 1 yr followup (35% BMS, 65% DES)
- Primary endpoint all TIMI bleeding
WOEST Trial

• Dual therapy (clopidogrel + VKA) significantly reduced all TIMI bleeding (driven by minimal and minor)

• No difference in intracranial bleeding

• Trend toward reduced death, stroke, MI, instent thrombosis in dual therapy
Case 3

- Which anticoagulant?
- Only data to date involve VKA
Case 4

- 66 y/o Female
- Paroxysmal Atrial Fibrillation
  - Symptomatic
- HTN
- DM
- MV Repair 5 years ago
- No history of GI bleeding
Case 4

- Meds:
  - Glucophage
  - Lisinopril
  - ASA 81
- NKDA
- Hb 13, Cr=1.1
- EF=60%
- LA size 4.5 cm
Case 4

- CHADS-2 = 2
- CHADS-VASc = 4
- HAS-BLED = 2
Case 4

• Choice?
Case 4

• Reminder
AF category due to aging or development of cardiac abnormalities such as enlargement of the left atrium (LA). Then, the risks of thromboembolism and mortality rise accordingly. By convention, the term “nonvalvular AF” is restricted to cases in which the rhythm disturbance occurs in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair.
Case 4

- Reminder

Fuster et al.  e109
ACC/AHA/ESC Practice Guidelines

AF category due to aging or development of cardiac abnormalities such as enlargement of the left atrium (LA). Then, the risks of thromboembolism and mortality rise accordingly. By convention, the term “nonvalvular AF” is restricted to cases in which the rhythm disturbance occurs in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair.
Case 4

• Reminder

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
PRADAXA is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

1 INDICATIONS AND USAGE
1.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation
XARELTO (rivaroxaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
Case 5

50 y/o Female
- Paroxysmal Atrial Fibrillation
- HTN

Involved in a MVA
- Multiple rib fractures
- Hemothorax – chest tube
- Intubated
Case 5

- **Meds:**
  - Dabigatran 150 mg bid
  - Metoprolol 50 mg po bid

- **NKDA**

- **Hb 8 (12), Cr=1.3 (0.9), INR 1.3**

- **EF=60%**

- **LA size 4.0 cm**
Case 5

- HR 110 (afib)
- BP 80/40
- Intubated
- Abdomen is distended
- Continued output from chest tube
Case 5

• Next step?
Case 5

• Next step?
  – FFP
Case 5

• Next step?
  – FFP
  – Hematology Consult
Case 5

• Why are we comfortable with warfarin?
  – INR

• We can reverse it
  – Vitamin K
  – FFP
Case 5

- **Dabigatran**
  - Prolongs PTT and PT/INR
  - No reversal agent
  - Hemodialysis
    - Low protein binding
    - 60% removed in 2-3 hours
      - Limited data
  - Relatively short half life
Case 5

- Rivaroxaban
  - No reversal agent
  - Hemodialysis
    - 95% protein bound
    - No effect
  - Consider
    - Prothrombin complex concentrate
    - Activated prothrombin complex concentrate
    - Recombinant Factor VIIa
    - Limited data
Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate
A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, MD; Pieter W. Kamphuisen, MD; Meertien K. Sijpkens, BSc; Joost C. Meijers, PhD; Harry R. Buller, MD; Marcel Levi, MD
Case 5

• Observations
  • Rivaroxaban
    • PT was significantly prolonged
    • Immediately normalized
  • Dabigatran
    • PTT and ECT was significantly prolonged
    • No effect
Case 5

• Decision
  – Wait
  – Supportive Care
  – 2 U PRBC
  – OR next day
  – Full recovery
Case 6

76 y/o Female
- Persistent Atrial Fibrillation
- HTN

Elective cardioversion
- Dabigatran for 2 months
Case 6

- **Meds:**
  - Dabigatran 150 mg bid
  - Diltiazem 240 mg bid
  - Amiodarone 200 mg daily

- **NKDA**
- **Cr = 1.1**
- **Cr Clearance > 50**
- **EF=60%**
- **LA size 3.7 cm**
Case 6

- Compliant with medication
- Daughter confirms
Case 6

- Compliant with medication
- Daughter confirms
- Successful cardioversion
  - 100J
Case 6

- CVA
  - <24 hours later
  - Hemorrhagic
Dabigatran Versus Warfarin in Patients With Atrial Fibrillation: An Analysis of Patients Undergoing Cardioversion

Rangadham Nagarakanti, Michael D. Ezekowitz, Jonas Oldgren, Sean Yang, Michael Chernick, Timothy H. Aikens, Greg Flaker, Josep Brugada, Gabriel Kamenský, Amit Parekh, Paul A. Reilly, Salim Yusuf and Stuart J. Connolly
Case 6

- **RE-LY Trial**
  - Cardioversion on randomized treatment permitted
    - 1983 cardioversions performed

- **TEE was encouraged but not mandatory**
  - Dabigatran 110 mg 25%
  - Dabigatran 150 mg 24%
  - Warfarin 13%

- **Stroke and systemic embolism rates similar**
  - Between 3 medication groups
  - Between TEE and non-TEE

*Circulation 2011;123:131-136*
XARELTO® (rivaroxaban) tablets

Few patients in ROCKET AF underwent electrical cardioversion for atrial fibrillation. The utility of XARELTO for preventing post-cardioversion stroke and systemic embolism is unknown.
Case 7

70 y/o Female

- Paroxysmal Atrial Fibrillation
- HTN
- DM
- Dronedarone x 1 year
- Dabigatran x 6 months
Case 7

- Previous visit (6 months ago)
- Cr = 1.4
- EF=60%
- LA size 4.2 cm
- Sinus rhythm
Case 7

- Today’s visit
- Reports no episodes of atrial fibrillation
- HR 70, BP 130/60
- Weight: 90 kg
- Cr = 1.6
- Sinus rhythm
Case 7

• Changes?
Case 7

- Creatinine Clearance
- 6 months ago
  - 53 mL/min
- Today’s visit
  - 46.5 mL/min
- Cockcroft-Gault Equation
  - \[ eCrCl = \frac{(140 - \text{age}) \times (\text{wt in kg})}{72 \times \text{Cr (mg/dL)}} \]
    - Multiply by 0.85 if Female
Case 7

- CrCl >30 ml/min  150 mg po bid
- CrCl 15-30 ml/min  75 mg po bid
Case 7

- CrCl >30 ml/min  150 mg po bid
- CrCl 15-30 ml/min  75 mg po bid

- Dronedarone
  - CrCl 30-50 ml/min  75 mg po bid
  - Also applies to ketoconazole
Case 7

- Dronedarone
  - Inhibits p-glycoprotein transport
Dabigatran etexilate as P-glycoprotein substrate

Dabigatran etexilate → P-glycoprotein Efflux transporter → Dabigatran → Bloodstream

Dabigatran absolute bioavailability = ~6.5%

Intestinal lumen → Gut wall → absorption → Dabigatran etexilate
Case 7

- Inhibitors of p-glycoprotein transport
  - Dronedarone
  - Amiodarone
  - Verapamil
  - Ketoconazole
  - Clarithromycin
  - Quinidine

- Inducers of p-glycoprotein transport
  - Rifampin
Case 7

In patients with moderate renal impairment (Cr Cl 30-50 mL/min), consider reducing the dose of PRADAXA to 75 mg twice daily when administered concomitantly with the P-gp inhibitor dronedarone or systemic ketoconazole. The use of P-gp inhibitors (verapamil, amiodarone, quinidine, and clarithromycin) does not require a dose adjustment of PRADAXA. These results should not be extrapolated to other P-gp inhibitors [see Warnings and Precautions (5.3), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)].

- “In patients with moderate renal impairment (Cr Cl 30-50 mL/min) consider reducing the dose of PRADAXA to 75 mg twice daily when administered concomitantly with the P-gp inhibitor dronedarone or systemic ketoconazole”

- “The use of P-gp inhibitors (verapamil, amiodarone, quinidine, and clarithromycin) does not require a dose adjustment of Pradaxa”
Case 7

- Rivaroxaban
  - Metabolized 2/3 liver, 1/3 kidneys
  - Substrate of Cytochrome P450 3A4 and p-glycoprotein
  - Affected by inhibitors and inducers
  - Ketoconazole (inhibits both)
  - Clarithromycin (inhibits both)
  - Ritonovir (inhibits both)
  - Rifampin (induces both)
Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan), which cause significant increases in rivaroxaban exposure that may increase bleeding risk.

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John’s wort).
Apixaban

- Factor Xa inhibitor
- 87% protein bound
- 25% elimination renal
- 55% elimination fecal
- Primarily metabolized Cyp 3A4/5
- Half life 8-15 hours
- BID
Apixaban

- **AVERROES**
  - 5599 patients
  - Apixaban 5 mg bid vs ASA 81-324 mg qd
  - Primary outcome – Stroke/systemic embolism
  - Early termination
    - 51 events Apixaban (1.6%/year)
    - 113 events ASA (3.7%/year)
  - No significant difference in major bleed or ICH

NEJM 2011; 364:806-17
A Stroke or Systemic Embolism

Hazard ratio with apixaban, 0.45 (95% CI, 0.32–0.62)

Cumulative Hazard

P<0.001

No. at Risk

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<tr>
<th></th>
<th>Aspirin</th>
<th>2791</th>
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<tbody>
<tr>
<td></td>
<td>Apixaban</td>
<td>2808</td>
<td>2758</td>
<td>2566</td>
<td>2125</td>
<td>1522</td>
<td>615</td>
</tr>
</tbody>
</table>

NEJM 2011; 364:806-17
Apixaban

- **ARISTOTLE**
  - 18,201 patients
  - Apixaban 5 mg bid vs Warfarin
  - Primary outcome
    - Ischemic or hemorrhagic stroke/systemic embolism
    - Apixaban – 1.27%/year
    - Warfarin – 1.6%/year
  - Major bleed
    - Apixaban – 2.13%/year
    - Warfarin – 3.09%/year

NEJM 2011; 365: 981-92
A Primary Outcome: Stroke or Systemic Embolism

Hazard ratio, 0.79 (95% CI, 0.66–0.95)
P = 0.01

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

NEJM 2011; 365: 981-92
B  Major Bleeding

Hazard ratio, 0.69 (95% CI, 0.60–0.80)
P<0.001

No. at Risk
Apixaban     9088  8103  7564  5365  3048  1515
Warfarin     9052  7910  7335  5196  2956  1491

NEJM 2011; 365: 981-92
Thank you!