ATRIAL FIBRILLATION (AF)

Anticoagulant therapy, coumadines or direct antithrombins

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1% of the general population is estimated to have AF
In 2012 the world population = 7 000 000 000
1% of 7 billion → 70 000 000 with AF worldwide

15 000 000 strokes per year worldwide
Up to ~1/5 of strokes are AF-related
1/5 of 15 000 000 → 3 000 000 AF-related strokes per yr

The average annual stroke rate in untreated nonvalvular (NV)AF is ~ 5%
5% of 70 million → 3 500 000 AF-related strokes per yr

Camm et al. EHJ 2010;31:2369-429 - en.wikipedia.org/wiki/World_population
WHO world health report 2002 - 2011 Canadian AF Guidelines
AF-related strokes are serious

Ischemic strokes are more severe with, than without, AF
Hemorrhagic strokes are the most dreaded

Relative risk of death post-event in ACTIVE A

<table>
<thead>
<tr>
<th>Event</th>
<th>Ischemic Stroke</th>
<th>Hemorrhagic Stroke</th>
<th>Subdural Hemorrhage</th>
<th>Extracranial Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighting</td>
<td>1.00</td>
<td>3.00</td>
<td>0.64</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Antithrombotic therapy in NVAF

% Relative risk reduction (RRR) of Stroke or MACE* in NVAF

- War v Pla: 64%
- War v A+C: 44%
- Asa v Pla: ~20%
- A+C v Asa: 11%

* major adverse CV event

P ≤ 0.01

ACTIVE A. NEJM 2009;360:2067-78
Risk of major bleeds with warfarin therapy

Annual risk of major bleed on warfarin ~2 - 3% per annum

<table>
<thead>
<tr>
<th>Study</th>
<th>Year published</th>
<th>Population (n)</th>
<th>Major haemorrhage, % per year</th>
<th>ICH % per year</th>
<th>New to warfarin, %</th>
<th>Age, mean</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomised trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AF</td>
<td>1994</td>
<td>AF (n = 3691)</td>
<td>1.3</td>
<td>0.3</td>
<td>100</td>
<td>69</td>
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<tr>
<td>SPAF II (2 age strata)</td>
<td>1994</td>
<td>AF (n = 715)</td>
<td>1.7</td>
<td>0.5</td>
<td>100</td>
<td>NR</td>
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<tr>
<td>AFFIRM</td>
<td>2002</td>
<td>AF (n = 4060)</td>
<td>2.0</td>
<td>0.6</td>
<td>NR</td>
<td>70</td>
</tr>
<tr>
<td>SPORTIF II</td>
<td>2003</td>
<td>AF (n = 3407)</td>
<td>2.2</td>
<td>0.4</td>
<td>27</td>
<td>70</td>
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<tr>
<td>SPORTIF V</td>
<td>2005</td>
<td>AF (n = 2422)</td>
<td>3.4</td>
<td>0.1</td>
<td>15</td>
<td>72</td>
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<tr>
<td>ACTIVE W</td>
<td>2006</td>
<td>AF (n = 6706)</td>
<td>2.2</td>
<td>NR</td>
<td>23</td>
<td>71</td>
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<tr>
<td>RE-LY</td>
<td>2009</td>
<td>AF (n = 18006)</td>
<td>3.4</td>
<td>0.74</td>
<td>51</td>
<td>72</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>Presented 2010</td>
<td>AF (n = 14364)</td>
<td>3.5</td>
<td>0.7</td>
<td>37</td>
<td>73</td>
</tr>
<tr>
<td><strong>Inception cohorts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Langedal and Goldman</td>
<td>1989</td>
<td>All (n = 565)</td>
<td>7.4</td>
<td>1.3</td>
<td>100</td>
<td>61</td>
</tr>
<tr>
<td>Steffensen et al</td>
<td>1997</td>
<td>All (n = 682)</td>
<td>6.0</td>
<td>1.3</td>
<td>100</td>
<td>59f/66M</td>
</tr>
<tr>
<td>Beyth et al</td>
<td>1998</td>
<td>All (n = 264)</td>
<td>5.0</td>
<td>0.9</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>Pengo et al</td>
<td>2001</td>
<td>AF (n = 433)</td>
<td>Age ≥ 75: 5.1</td>
<td>NA</td>
<td>100</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age &lt; 75: 1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hylek et al</td>
<td>2007</td>
<td>AF (n = 472)</td>
<td>7.2</td>
<td>2.5</td>
<td>100</td>
<td>77</td>
</tr>
<tr>
<td><strong>Non-inception cohort (prevalent warfarin use)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van der Meer et al</td>
<td>1993</td>
<td>All (n = 6814)</td>
<td>2.7</td>
<td>1.3</td>
<td>NR</td>
<td>66</td>
</tr>
<tr>
<td>Fihn et al</td>
<td>1996</td>
<td>All (n = 928)</td>
<td>4.0</td>
<td>1.3</td>
<td>NR</td>
<td>58</td>
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<tr>
<td>ATRIA</td>
<td>2003</td>
<td>AF (n = 6320)</td>
<td>1.52</td>
<td>0.46</td>
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<td>71</td>
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<tr>
<td>Poli et al</td>
<td>2009</td>
<td>AF (n = 783)</td>
<td>1.4</td>
<td>2.5</td>
<td>NR</td>
<td>75</td>
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<tr>
<td>Rose et al</td>
<td>2009</td>
<td>AF (n = 3396)</td>
<td>1.9</td>
<td>NA</td>
<td>5</td>
<td>74</td>
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</tbody>
</table>

## Bleeding risk by HASBLED in AF patients

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical characteristic</th>
<th>Points awarded</th>
<th>Score</th>
<th>Major bleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
<td>0</td>
<td>~ 1 % / yr</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
<td>1 or 2</td>
<td>~ 2 % / yr</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
<td>2</td>
<td>~ 2 % / yr</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
<td>2</td>
<td>~ 2 % / yr</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs</td>
<td>1</td>
<td>2</td>
<td>~ 2 % / yr</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (e.g. age &gt;65 years)</td>
<td>1</td>
<td>2 or 3</td>
<td>~ 5 % / yr</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or alcohol (1 point each)</td>
<td>1 or 2</td>
<td>3 or 4</td>
<td>~ 5 % / yr</td>
</tr>
</tbody>
</table>

Maximum 9 points

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Pisters et al. Chest 2010;138: 1093-100
Limitations of coumadines

1. Individual variability – Food & drug interactions
2. Dose adjustments - Slow onset/offset
3. Mandatory monitoring – Logistic difficulties
Warfarin use in eligible patients with AF

Piccini et al. Curr Opin Cardiol 2010;25:312-20
Optimal warfarin therapy in the setting of a RCT*

* randomized controlled trial

Mean time in therapeutic range (%)

Wallentin et al. Lancet 2010;376:975-83
Real life anticoagulation with warfarin

Warfarin eligible patients with NVAF

- No Warfarin 64%
- Supratherapeutic INR 9%
- Therapeutic INR 12%
- Subtherapeutic INR 15%

## Multiple warfarin drug interactions

<table>
<thead>
<tr>
<th>Specific Drugs Reported</th>
<th>Increase INR</th>
<th>Decrease INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cinacalcet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etodolac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibandronate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Increase INR**:
  - Acenocoumarol
  - Aminocoumarin
  - Apixaban
  - Aspirin
  - Atorvastatin
  - Azithromycin
  - Bevacizumab
  - Captopril
  - Eflornithine
  - Efavirenz
  - Etoracacetron
  - Ergotamine
  - Enoxaparin
  - Etoracacetron
  - Etoracacetron

- **Decrease INR**:
  - Amlodipine
  - Atenolol
  - Atorvastatin
  - Azithromycin
  - Bevacizumab
  - Captopril
  - Eflornithine
  - Efavirenz
  - Etoracacetron
  - Etoracacetron
  - Etoracacetron

[www.nhssb.n-i.nhs.uk](http://www.nhssb.n-i.nhs.uk)
New anticoagulants

Adapted from Weitz & Bates, J Thromb Haemost 2005
Main features of new anticoagulants

- against free and bound targets
- powerful

- rapid on/offset
- few interactions
- no routine monitoring
- fixed dosing

- specific antidote?
- longterm safety?

Clinical pharmacology of edoxaban, apixaban, rivaroxaban and dabigatran

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Edoxaban</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct factor Xa inhibitor</td>
<td>~60%</td>
<td>~50%</td>
<td>80–100%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Availability</td>
<td>CYP 3A4 effect</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>P-GP effect</td>
<td>Pro-drug</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Food effect</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Mean $t_{1/2}$</td>
<td>6-11 h</td>
<td>~12 h</td>
<td>7–11 h</td>
</tr>
<tr>
<td>Tmax</td>
<td>1-2 h</td>
<td>3-4 h</td>
<td>2-4 h</td>
<td>0.5-2 h</td>
</tr>
<tr>
<td>Laboratory assay</td>
<td>Anti-FXa</td>
<td>Anti-FXa</td>
<td>Anti-FXa</td>
<td>Thrombin time</td>
</tr>
</tbody>
</table>

Renal clearance of new anticoagulants

Clearance of active compound

% 80 70 60 50 40 30 20 10 0

Betri- Api- Otami- Rivaro- Edo- Dabigatran

XABANS

Programs for the most advanced new oral anticoagulants (NOACs)

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran Pradaxa®</th>
<th>Rivaroxaban Xarelto®</th>
<th>Apixaban Eliquis®</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE p Ortho</td>
<td>RE-MODEL</td>
<td>RECORD 1</td>
<td>ADVANCE I</td>
<td>STARS E3</td>
</tr>
<tr>
<td></td>
<td>RE-NOVATE</td>
<td>RECORD 2</td>
<td>ADVANCE 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RE-MOBILIZE</td>
<td>RECORD 3</td>
<td>ADVANCE 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RECORD 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE p M Ill</td>
<td>RE-SOLVE</td>
<td>MAGELLAN</td>
<td>ADOPT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE tx</td>
<td>RE-COVER</td>
<td>EINSTEIN-DVT</td>
<td>AMPLIFY</td>
<td>HOKUSAI</td>
</tr>
<tr>
<td></td>
<td>RE-MEDY</td>
<td>EINSTEIN-PE</td>
<td>AMPLIFY-EXT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RE-SONATE</td>
<td>EINSTEIN-EXT</td>
<td></td>
<td></td>
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<tr>
<td>SPAF</td>
<td>RE-LY</td>
<td>ROCKET-AF</td>
<td>ARISTOTLE</td>
<td>ENGAGE-TIMI48</td>
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<tr>
<td></td>
<td></td>
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<td>AVERROES</td>
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</tr>
<tr>
<td>ACS</td>
<td></td>
<td>ATLAS 2</td>
<td>APPRAISE 2</td>
<td>XANADU-ACS</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
RE-LY®: study design

Atrial fibrillation with ≥1 risk factor
Absence of contraindications

Randomized Evaluation of Long-term anticoagulation therapy

- Warfarin
  1 mg, 3 mg, 5 mg (INR 2.0–3.0)
  N=6000
- Dabigatran etexilate
  110 mg BID
  N=6000
- Dabigatran etexilate
  150 mg BID
  N=6000

Primary endpoint: stroke or systemic embolism
2 year follow-up

Efficacy, Safety and Mortality Outcomes

Stroke or Systemic Embolism in W v D110 v D150: 1.7 v 1.5 v 1.1* %/yr

Study Major Bleeds: 3.4 v 2.7* v 3.1 %/y; HS: 0.4 v 0.1*. v 0.1* %/y
GI bleed: 1.0 v 1.1 v 1.5* %/y; MI: 0.5 v 0.7 v 0.7* %/y
CV death: 2.7 v 2.4 v 2.3* %/y; any death: 4.1 v 3.8 v 3.6 %/y

Connolly et al. NEJM 2009;361:1139-51
RE-LY stroke or systemic embolism

Dabigatran 110 mg vs. warfarin

- Noninferiority p-value: <0.001
- Superiority p-value: 0.34
- Margin = 1.46
- 9% RRR

Dabigatran 150 mg vs. warfarin

- Noninferiority p-value: <0.001
- Superiority p-value: <0.001
- 34% RRR

Connolly et al. NEJM 2009;361:1139-51
**RE-LY hemorrhagic stroke**

- **RR 0.31** (95% CI: 0.17–0.56)  
  p<0.001 (sup)

- **RR 0.26** (95% CI: 0.14–0.49)  
  p<0.001 (sup)

Number of events:
- **D110 mg BID**  
  14 (0.12%)
  (6,015 patients)

- **D150 mg BID**  
  12 (0.10%)
  (6,076 patients)

- **Warfarin**  
  45 (0.38%)
  (6,022 patients)

Connolly et al. NEJM 2009;361:1139-51
NOAC perform BETTER than WAR regardless of INR quality

Compared with warf, benefits of dabig 150 in reducing stroke, of dabig 110 in reducing bleeds, and of both regimens in reducing ICH were found regardless of INR quality

Wallentin L et al. Lancet 2010;376:975-83
ROCKET design

NV Atrial Fibrillation

Rivaroxaban
- 20 mg daily
- 15 mg for Cr Cl 30-49 ml/min
- Randomize Double Blind / Double Dummy (n ~ 14,000)

Warfarin
- INR target - 2.5 (2.0-3.0 inclusive)

Monthly Monitoring
Adherence to standard of care guidelines

Primary endpoint: stroke or systemic embolism

2 or 3 Risk Factors*
- CHF
- Hypertension
- Age ≥ 75
- Diabetes OR
- Stroke, TIA or Systemic embolus

* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%

Patel et al. NEJM 2011;365:883-91
ROCKET stroke and systemic embolism

Patel et al. NEJM 2011;365:883-91

- **Rivaroxaban**: Event Rate %/y 1.71, ICH, %/y 0.5, p=0.02
- **Warfarin**: Event Rate %/y 2.16, ICH, %/y 0.7

HR (95% CI): 0.79 (0.66, 0.96)
P-value nonInferiority: <0.001
Per Protocol on Treatment Population

No. at risk:
- Rivaroxaban: 6958, 6211, 5786, 5468, 4406, 3407, 2472, 1496, 634
- Warfarin: 7004, 6327, 5911, 5542, 4461, 3478, 2539, 1538, 655
Events after Discontinuation in ITT population

**Stroke or Systemic Embolism**

**Before end of study**

**At end of study**

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate %/y</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2.1</td>
<td>2.4</td>
</tr>
</tbody>
</table>

HR (95% CI): 0.88 (0.74, 1.03)

P-value nonInferiority: <0.001

Intention to treat (ITT) analysis

Patel et al. NEJM 2011;365:883-91
ARISTOTLE design

Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize double blind, double dummy (n = 18,201)

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Major exclusion criteria
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Warfarin (target INR 2-3)

Primary outcome: stroke or systemic embolism

Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

Granger et al. NEJM 2011;365:981-92
ARISTOTLE stroke (ischemic or hemorrhagic) or systemic embolism

P (non-inferiority)<0.001

Apixaban 212 patients, 1.27% per year
Warfarin 265 patients, 1.60% per year
HR 0.79 (95% CI, 0.66–0.95); P (superiority)=0.011

Granger et al. NEJM 2011;365:981-92
**Efficacy, Safety and Net Clinical Outcomes**

### Stroke or Systemic Embolism

- **Warfarin**: 1.60%/yr
- **Apixaban**: 1.27%/yr

### ISTH Major Bleeding

- **Warfarin**: 3.09%/yr
- **HS**: 0.47%/yr
- **Apixaban**: 2.13%/yr
- **HS**: 0.24%/yr

Granger et al. NEJM 2011;365:981-92

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**Any death (3.52 v 3.94%/yr), stroke, systemic embolism or major bleeding:**

- **Apixaban**: 6.13% per year
- **Warfarin**: 7.20% per year

HR 0.85 (95% CI, 0.78–0.9); P (superiority)<0.001

Granger et al. NEJM 2011;365:981-92
ARISTOTLE

Efficacy Outcomes

- Stroke / Systemic Embolism
- Stroke
- Ischemic Stroke
- Hemorrhagic Stroke
- Myocardial Infarction
- All Cause Mortality

Safety Outcomes

- ICH
- Major Bleeding
- Major GI Bleeding
- Any Bleeding

Granger et al. NEJM 2011;365:981-92
ENGAGE AF TIMI 48 design

Largest Study in AF
N = 20,500

AF on Electrical Recording ≤ 12 mo
Intended oral A/C - CHADS² ≥ 2

Only Factor Xa inhibitor with two doses in phase III

Low Exposure Strategy
Edoxaban 30 mg QD

High Exposure Strategy
Edoxaban 60 mg QD

Active Control Warfarin (INR 2.0 – 3.0)

Double blind
Once daily

Median duration of follow up 24-months

Primary Objective: Edoxaban Non inferior to Warfarin (HR boundary 1.38)

1º EP = Stroke or systemic embolic event - 2º EP = Stroke or SEE or All-Cause Death
Safety EPs = modified ISTH Major Bleeding, Hepatic Function

Ruff et al. AHJ 2010;160:635-41
<table>
<thead>
<tr>
<th>Effect on outcome event</th>
<th>D150</th>
<th>D110</th>
<th>Riva</th>
<th>Apix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninferiority stroke/syst embol</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Superiority stroke or syst embol</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>↓ Hemorrhagic stroke</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>↓ Ischemic stroke</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ Mortality</td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>↓ Major bleeding</td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>↑ GI bleeding</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>↑ MI</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fewer discontinuations</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Validation in 2nd RCT</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

Antithrombotic therapy in NVAF update

% Relative risk reduction of Stroke or MACE* in NVAF

* major adverse CV event

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>% Relative Risk Reduction (RRR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>War v Pla</td>
<td>64%</td>
</tr>
<tr>
<td>War v A+C</td>
<td>44%</td>
</tr>
<tr>
<td>NOAC v War</td>
<td>22%</td>
</tr>
<tr>
<td>Asa v Pla</td>
<td>~20%</td>
</tr>
<tr>
<td>A+C v Asa</td>
<td>11%</td>
</tr>
</tbody>
</table>

* P ≤ 0.01

ACTIVE A. NEJM 2009;360:2067-78 – Miller et al. AJC 2012;Apr 24
NOACs vs coumadin, in patients with nonvalvular atrial fibrillation, can prolong life and improve its quality through stroke prevention, are generally safer and more convenient, and are projected to be cost-effective.
Conclusions

A new era of anticoagulation for patients with NVAF

- All 3 new OACs are non inferior to warfarin in reducing the risk of stroke and systemic embolization
- All three agents reduce the risk of life-threatening bleeding and intracranial hemorrhage

Differences and Future Challenges:
- Dabigatran has a 2-dose approach to the treatment of patients with AF; at a dose of 150 mg it was associated with a reduction in ischemic stroke.
- Rivaroxaban is a once a day drug associated with a lower rate of fatal bleeding
- Apixaban was associated with a reduction in all-cause mortality
Other established thromboembolic risk factors

On TEE, the presence of

- LA thrombus (RR 2.5; P=0.04),
- complex aortic plaques (RR 2.1; P<0.001),
- spontaneous echo-contrast (RR 3.7; P<0.001), and
- low LAA velocities (≤20 cm/s; RR 1.7; P<0.01)

are independent predictors of stroke and thromboembolism

### Stroke risk by CHADS2 or CHADS-VASc

**2010 ESC AF Guidelines**

#### Table IV: Stroke risk according to CHADS2 score (1).

<table>
<thead>
<tr>
<th>Score</th>
<th>CHADS2 risk criteria</th>
<th>Score</th>
<th>Annual risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>1 CHADS2 risk criteria score</td>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Congestive heart failure</td>
<td>1</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>1</td>
<td>5.9</td>
</tr>
<tr>
<td>3</td>
<td>Age &gt;75 years</td>
<td>1</td>
<td>8.5</td>
</tr>
<tr>
<td>4</td>
<td>Diabetes mellitus</td>
<td>1</td>
<td>12.5</td>
</tr>
<tr>
<td>5 (Prior) stroke or TIA</td>
<td>18.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHADS2-VASc score</th>
<th>Patients (n=7329)</th>
<th>Adjusted stroke rate (%/year)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>422</td>
<td>1.3%</td>
</tr>
<tr>
<td>2</td>
<td>1230</td>
<td>2.2%</td>
</tr>
<tr>
<td>3</td>
<td>1730</td>
<td>3.2%</td>
</tr>
<tr>
<td>4</td>
<td>1718</td>
<td>4.0%</td>
</tr>
<tr>
<td>5</td>
<td>1159</td>
<td>6.7%</td>
</tr>
<tr>
<td>6</td>
<td>679</td>
<td>9.8%</td>
</tr>
<tr>
<td>7</td>
<td>294</td>
<td>9.6%</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>6.7%</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>15.2%</td>
</tr>
</tbody>
</table>
AF and ≥1 risk factor, and demonstrated or expected unsuitable for VKA

**APRINAPS design**

**Apixaban 5 mg BID**
2.5 mg BID in selected patients

**5600 patients: median 1 yr FU**

**Double-Blind**

**ASA (81-324 mg/d)**

**Primary outcome: stroke or systemic embolism**

AVERROES stroke/systemic embolism

RR = 0.45
95% CI = 0.32-0.62
P < 0.001

**AVERROES major bleeding**

Cumulative Risk

**RR = 1.13**
**95 % CI = 0.74-1.75**
**P = 0.57**

ICH: 0.4%/yr in both groups

Warfarin vs aspirin for stroke prevention in an elderly (≥75y) community with AF (the Birmingham AF Treatment of the Aged study, BAFTA): a randomised controlled trial


Mean follow-up: 2.7 yrs
### BAFTA: stroke, ICH, arterial embolism

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>Warfarin (n=488)</th>
<th>Aspirin (n=485)</th>
<th>Warfarin vs aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Risk per year</td>
<td>n</td>
</tr>
<tr>
<td>Stroke</td>
<td>21</td>
<td>1.6%</td>
<td>44</td>
</tr>
<tr>
<td><strong>By severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>13</td>
<td>1.0%</td>
<td>21</td>
</tr>
<tr>
<td>Disabling non-fatal</td>
<td>8</td>
<td>0.6%</td>
<td>23</td>
</tr>
<tr>
<td><strong>Type of stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic</td>
<td>10</td>
<td>0.8%</td>
<td>32</td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>6</td>
<td>0.5%</td>
<td>5</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td>0.4%</td>
<td>7</td>
</tr>
<tr>
<td>Other intracranial haemorrhage†</td>
<td>2</td>
<td>0.2%</td>
<td>1</td>
</tr>
<tr>
<td>Systemic embolism‡</td>
<td>1</td>
<td>0.1%</td>
<td>3</td>
</tr>
<tr>
<td>Total number of events</td>
<td>24</td>
<td>1.8%</td>
<td>48</td>
</tr>
</tbody>
</table>

# Drug Interactions of NOAC

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxa</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
</table>

- **Verapamil** - reduce dose
- **Dronedarone** - avoid

**Potential metabolic drug interactions**

- Potent inhibitors of CYP3A4 and Potent inhibitors of CYP3A4 and
- Potent inhibitors of CYP3A4** - avoid

Potential inducers of CYP3A4** - avoid
- and P-gp - use with caution

**Potent 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, or phenytoin.

*** Potent CYP3A4 inducers include phenytoin, carbamazepine, phenobarbital or St. John’s Wort.

De Caterina R et al. JACC 2012

> AUC

< AUC
Fewer ICH with NOACs vs warfarin

RE-LY | ROCKET AF | ARISTOTLE

Major bleed (%/yr)

Intracranial hemorrhage (ICH, %/yr)

Patients (%/year)

*P<0.05 vs warfarin