New Aspects in the Diagnosis and Treatment of Atrial Fibrillation: Antithrombotic Therapy

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- BMS
Stroke Prevention in Atrial Fibrillation

- Vitamin-K antagonists
- Combination of warfarin plus aspirin
- Antiplatelet combination therapy
- New antithrombotic drugs
Stroke Prevention in Atrial Fibrillation

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Warfarin is more effective than aspirin for primary stroke prevention in AF

39% RRR of stroke with adjusted-dose warfarin compared to antiplatelets (meta-analysis of 12 RCTs in AF; n=12,963)


RRR: relative risk reduction
Combination of oral anticoagulation and aspirin in patients with atrial fibrillation (AF)

Akins et al, SPORTIF Pooled Analysis, Stroke 2007
Need for intense monitoring with OAC

Narrow therapeutic index:
- INR < 2.0 = higher risk of stroke
- INR > 3.0 = higher risk of bleeding

Unpredictable INR (food/drug interactions, low specificity)

Stroke Prevention in Atrial Fibrillation

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ACTIVE W: preventive superiority of OACs

Stopped early after median follow-up 1.28 years

ACTIVE Writing Group of the ACTIVE Investigators
Lancet 2006;367:1903-12

-30%  
\( p=0.0003 \)

-41%  
\( p=0.001 \)

-77%  
\( p=0.005 \)

-28%  
\( p<0.0001 \)
Figure 2: Cumulative risk of primary outcome

RR = 1.44 (1.18–1.76), p = 0.0003

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Clopidogrel + aspirin</th>
<th>Oral anticoagulation therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3335</td>
<td>3371</td>
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<tr>
<td></td>
<td>3152</td>
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<td>2458</td>
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<tr>
<td></td>
<td>927</td>
<td>924</td>
</tr>
</tbody>
</table>
ACTIVE A: benefit in stroke reduction when adding clopidogrel to aspirin

Significant reduction by clopidogrel + aspirin versus aspirin alone is primarily due to reduction in stroke (no or only weak differential treatment effects for subgroups) after median follow-up of 3.6 years

Panel B shows the cumulative incidence of stroke. The relative risk for aspirin plus clopidogrel, as compared with aspirin alone, was 0.72 (95% CI, 0.62 to 0.83; P<0.001)
Conclusions 1

• Patients with TIA or stroke and cardiac source of embolism who are not willing to take oral anticoagulation have only a small benefit from aspirin.

• The combination of aspirin and clopidogrel is inferior to warfarin and carries a similar bleeding risk.

• The combination of aspirin plus clopidogrel is superior to aspirin mono-therapy but carries a higher bleeding risk.

• The combination of warfarin plus aspirin carries a higher bleeding risk and offers no additional benefit.
Stroke Prevention in Atrial Fibrillation

• Vitamin-K antagonists
• Combination of warfarin plus aspirin
• Antiplatelet combination therapy
• New antithrombotic drugs
Targets for novel antithrombotic agents in the coagulation cascade


AT = antithrombin; Ph = Phase

Vitamin K antagonist: Tecarfarin (Ph II completed)

Indirect factor Xa inhibitors:
Idraparinux (Ph III terminated)
SSR 126517 (withdrawn 2009)

Direct thrombin inhibitors:
Dabigatran etexilate (Ph III completed)
Ximelagatran (withdrawn 2006)
AZD0837 (Ph II completed)

Direct factor Xa inhibitors:
Apixaban (Ph III ongoing)
Rivaroxaban (Ph III ongoing)
Edoxaban (Ph III ongoing)
Betrixaban (Ph II ongoing)
Potential advantages of new anticoagulants

- High specificity
- Good efficacy-safety balance
- No monitoring / dose adjustment requirement (fixed dose)
- Quick onset of action
- Less drug interactions
- No food interaction
Study design of SPORTIF III and V trials

**Stroke Prevention using an ORal direct Thrombin Inhibitor in atrial Fibrillation**

Patients with non-valvular AF and risk factors for stroke
N=7329

Adjusted-dose warfarin (target INR 2–3)

Fixed-dose ximelagatran (36 mg BID)

SPORTIF III:¹ 23 nations Open-label (n=3407)

SPORTIF V:² US, Canada Double-blind (n=3922)

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BID = twice daily; INR = international normalized ratio
Non-inferiority of ximelagatran compared with warfarin in patients with AF

Stroke and systemic embolism

- Ximelagatran better
- Warfarin better

SPORTIF III\(^1\) P=0.10

SPORTIF V\(^2\) P=0.13

Pooled\(^3\) P=0.94

Non-inferiority

Difference in absolute event rates (ximelagatran – warfarin)

\[ -4 \quad -3 \quad -2 \quad -1 \quad 0 \quad 1 \quad 2 \quad 3 \quad 4 \]

\[ -0.66 \quad +0.45 \quad -0.03 \]

## Clinical trials for stroke prevention in AF (2)

<table>
<thead>
<tr>
<th>Drug class</th>
<th>OAC</th>
<th>Phase II</th>
<th>Phase III (comparison with warfarin unless*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKAs</td>
<td>tecarfarin (ATI-5923)</td>
<td>1 completed</td>
<td><strong>EmbraceAC</strong> almost finished <strong>ROCKET-AF</strong> in follow-up <strong>ARISTOTLE and AVERROES</strong> (<em>comparison to aspirin in AVERROES</em>)</td>
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<tr>
<td>FXa inhibitors</td>
<td>rivaroxaban</td>
<td>1 completed (Japanese)</td>
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<td>YM150</td>
<td></td>
<td>1 completed</td>
<td></td>
</tr>
<tr>
<td>DU-176b</td>
<td></td>
<td>1 completed</td>
<td><strong>EngageAFTIMI48</strong> recruiting</td>
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<tr>
<td>apixaban</td>
<td></td>
<td>1 (effect on bleeding) recruiting</td>
<td><strong>RE-LY</strong> completed <strong>RELY-ABLE</strong> recruiting</td>
</tr>
<tr>
<td>betrixaban</td>
<td></td>
<td>EXPLORE-Xa recruiting</td>
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</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td>dabigatran</td>
<td>PETRO completed, PETRO-Ex terminated</td>
<td></td>
</tr>
</tbody>
</table>

Phase 3 AVERROES clinical trial of apixaban for atrial fibrillation closes early due to clear evidence of efficacy
11. June 2010 01:09
RE-ly® – study design

Atrial fibrillation with $\geq 1$ risk factor
Absence of contraindications

Primary objective: To establish the non-inferiority of dabigatran etexilate to warfarin

Minimum 1 year follow-up, maximum of 3 years and mean of 2 years of follow-up

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

DOI 10.1056/NEJMoa0905561

Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation.
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Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation.
OAC is more effective than aspirin for secondary stroke prevention in AF

- EAFT: European, multi-centre RCT
- 1,007 patients with non-rheumatic AF and recent TIA or minor ischaemic stroke (mean follow-up 2.3 years)

EAFT Study Group. Lancet 1993;342:1255-62

Stroke risk reduction versus placebo (%)

- OAC (INR 2.5-4.0)
- Aspirin (300 mg/day)

66

p<0.001

14

p=0.31
Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation.

Haemorrhagic stroke: all patients

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)

D110 mg bid  
6015  
RRR 69%

D150 mg bid  
6076  
RRR 74%

Warfarin  
6022  
45
Intra-cranial bleeding rates in patients with prior stroke or TIA

Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation.
Strengths of RE-LY

- Large study with two doses of dabigatran
- Rigorous adjudication of events
- Subgroup of patients with prior TIA or ischemic stroke
- ~ 50% of patients VKS naive
Conclusions

- Dabigatran etexilate has shown to concurrently reduce both thrombotic and hemorrhagic events.

- Both doses of dabigatran provide different and complimentary advantages over warfarin.
  - 150 mg BID has superior efficacy with similar bleeding.
  - 110 mg BID has significantly less bleedings with similar efficacy.
  - Similar net clinical benefit was seen between the two dabigatran doses.

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Stroke Prevention in Atrial Fibrillation

- Vitamin-K antagonists: Difficult to handle, poor compliance
- Combination of warfarin plus aspirin: Not recommended (exception: stent)
- Antiplatelet combination therapy: Not superior to warfarin, bleeding
- New antithrombotic drugs: Superior or equivalent to warfarin or aspirin
Thank you for your attention