Perspectives based on Korean AF and Clinical data with Apixaban

KHRS 2018 ELIUQIS luncheon

양필성
차의대 분당차병원 심장내과
A large proportion of strokes could be prevented

Strokes are the cause of ~140 million deaths worldwide every year\(^1\)

15–20% are AF-related\(^2\)

~28 million are due to AF

RRR of 64% with warfarin vs no treatment\(^3\)

250,000 are preventable with warfarin therapy

62% of eligible patients are treated with OAC\(^4\)

~95,000 strokes could potentially have been prevented

\(\text{RRR: relative risk reduction.}\)
Prevalence, incidence, and projected number of AF

Annual prevalence of AF between 2006 and 2015 stratified according to sex (A) and age (B)

*P value for increasing trends <0.001. †P value for decreasing trends <0.001. AF, atrial fibrillation.

DH, Kim et al. S0002-8703(18)30140-6
Prevalence, incidence, and projected number of AF

Annual incidence of AF between 2006 and 2015 stratified according to sex (A) and age (B)

*P value for increasing trends <0.001. †P value for decreasing trends <0.001. AF, atrial fibrillation.
Prevalence, incidence, and projected number of AF

Projected prevalence rate (A) and number (B) of AF

AF, atrial fibrillation.

DH, Kim et al. S0002-8703(18)30140-6
Trends of the CHA2DS2-VASc and HAS-BLED scores

Temporal trends of the distribution of the patients with newly diagnosed AF according to the CHA2DS2-VASc and HAS-BLED scores between 2006 and 2015

AF, atrial fibrillation.

DH, Kim et al. S0002-8703(18)30140-6
Trends of the adverse outcomes among the patients with AF

Temporal trends of the 1-year adverse event rates of the (A) patients with prevalent AF and (B) non-AF Korean population in each year

*P value for trends <0.001. The 1-year adverse event rates (%/year) were calculated by dividing the number of the first lifetime event that occurred in each year by the total number of patients at the start of the year who had not experienced that event before. AF, atrial fibrillation; HF, heart failure.

DH, Kim et al. S0002-8703(18)30140-6
Trends of the adverse outcomes among the patients with AF

Temporal trends of the adjusted HRs of the adverse outcomes in the 2-year follow-up after AF diagnosis

The HR was adjusted for age, sex, economic status, and comorbidities. AF, atrial fibrillation; HF, heart failure; HR, hazard ratio
Trends of AF hospitalisations

Temporal trends of AF hospitalisation per 100 patients with AF

*P value for increase trends <0.001. †P value for decrease trends <0.001. AF, atrial fibrillation; MI, myocardial infarction; PM, pacemaker; RFCA, radiofrequency catheter ablation; SSS, sick sinus syndrome.

Trends of AF hospitalisation costs

Temporal trends of medical cost between 2006 and 2015

(A) Korean NHIS total expenditure (million €), (B) total AF hospitalisation cost (million €) and (C) the proportion of total AF hospitalisation cost to Korean NHIS total expenditure (%). *P value for trends <0.001. AF, atrial fibrillation; NHIS, National Health Insurance Service.

Increasing trends in hospital care burden of atrial fibrillation in Korea, 2006 through 2015

What is already known on this subject?

- The healthcare burden of atrial fibrillation (AF) is growing considerably, and is mainly related to hospitalisations. However, the impact of AF on hospitalisations and mortality, and the economic burden of AF is less understood in Asian populations.

What might this study add?

- AF hospitalisations have increased exponentially among Korean adults from 2006 to 2015, in association with an increase in comorbid chronic diseases. Mortality associated with AF hospitalisations decreased during the last decade, but hospitalisation costs have markedly increased.

How might this impact on clinical practice?

- Prevention of AF hospitalisations and streamlined integrated AF management should be pursued in a holistic manner to lessen the healthcare burden of AF.

Unpredictable anticoagulant effect
Slow onset and offset of action
Narrow therapeutic window
Established efficacy/safety profile
Food and drug interactions
Difficult perioperative management
Routine visits to clinic/hospital to monitor INR
Diet and drug restrictions

VKA superior to ASA for stroke prevention in AF
VKA reduces stroke in AF by two-thirds versus placebo

ASA: acetylsalicylic acid; INR: international normalised ratio; VKA: vitamin K antagonist.

Anticoagulation in NVAF: NOACs in the current era

NOAC properties\(^1\)

- Good efficacy and safety profile vs VKA\(^2\)–\(^6\)
- Fixed dose
- No need for monitoring
- Few drug and food interactions
- Few drug and diet restrictions
- Fast onset and offset of action
- Simpler perioperative management

VKA superior to ASA for stroke prevention in AF\(^2\)

- VKA reduces stroke in AF by two-thirds versus placebo\(^2\)
- Dabigatran Phase III NVAF trial published\(^3\)
- Apixaban Phase III NVAF trial published\(^5\)
- Edoxaban Phase III NVAF trial published\(^6\)
- Meta-analyses and healthcare databases: favourable risk–benefit profile of NOACs vs VKA for stroke prevention\(^7\)


2016 ESC Guidelines: Most patients with NVAF should be managed with NOACs as first-line anticoagulant

Mechanical heart valves or moderate or severe mitral stenosis

No

Estimate stroke risk based on number of CHA\textsubscript{2}DS\textsubscript{2}-VASc risk factors

0\textsuperscript{a}

No antiplatelet or anticoagulant treatment (IIIB)

1

OAC should be considered (IIaB)

≥2\textsuperscript{b}

Oral anticoagulation indicated
Assess for contraindications
Correct reversible bleeding risk factors

LAA occluding devices may be considered in patients with clear contraindications for OAC (IIbC)

NOAC (IA)\textsuperscript{c}

VKA (IA)\textsuperscript{c}

Patients with moderate–severe mitral stenosis or mechanical heart valves should be treated with VKA (IB)

ASA and other antiplatelets have no role in stroke prevention (IIIA)

NOACs recommended as first-line anticoagulant (IA)

*Solid arrow indicates preference; a. Includes women without other stroke risk factors; b. IIaB for women with only one additional stroke risk factor; c. IB for patients with mechanical heart valves or mitral stenosis. LAA: left atrial appendage; OAC: oral anticoagulant.

OAC prescription increased from 34.7% to 50.6% between 2008 and 2015 (p for trend < 0.001)

Aspirin prescription consistently decreased from 48.2% to 31.5%,

NOAC prescription increased with wider approval of NOACs in 2015 (25.4% of total patients with CHA2DS2-VASc score 2 and 50.2% of OAC prescriptions).

Temporal trends of antithrombotic therapy prescription. A. Temporal trends of antithrombotic therapy prescription in patients with CHA2DS2-VASc score 2. Abbreviation: ASA, aspirin; NOAC, non-vitamin K oral anticoagulants; VKA, vitamin K antagonists.
Distribution of NOACs in Korea

- The use of Apixaban is getting more and more.
- Among patients on NOACs, 43.3% received rivaroxaban, 34.2% received dabigatran and 22.5% received apixaban in 2015.

Temporal trends of antithrombotic therapy prescription. Distribution of three NOACs use since 2013 in patients with CHA2DS2-VASc score ≥ 2. Abbreviation: ASA, aspirin; NOAC, non-vitamin K oral anticoagulants; VKA, vitamin K antagonists.

Warfarin has a long onset of action and long half-life compared with NOACs

<table>
<thead>
<tr>
<th></th>
<th>Warfarin&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>Dabigatran&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Rivaroxaban&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Apixaban&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Edoxaban&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Inhibitor of vitamin K-dependent factors</td>
<td>Direct thrombin inhibitor</td>
<td>Direct FXa inhibitor</td>
<td>Direct FXa inhibitor</td>
<td>Direct FXa inhibitor</td>
</tr>
<tr>
<td><strong>Oral bioavailability</strong></td>
<td>&gt;95%</td>
<td>~6.5%</td>
<td>80–100%</td>
<td>~50%</td>
<td>~62%</td>
</tr>
<tr>
<td><strong>Pro-drug</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Food effect</strong></td>
<td>Yes (foods high in vitamin K)</td>
<td>No*</td>
<td>Yes (20 mg and 15 mg doses need to be taken with food)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt;</strong></td>
<td>Within 4 hours&lt;sup&gt;†&lt;/sup&gt;</td>
<td>0.5–2 hours</td>
<td>2–4 hours</td>
<td>3–4 hours</td>
<td>1–2 hours</td>
</tr>
<tr>
<td><strong>Renal clearance</strong></td>
<td>8%</td>
<td>85%</td>
<td>~33%&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>~27%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Mean half-life (&lt;i&gt;t&lt;/i&gt;&lt;sub&gt;1/2&lt;/sub&gt;)</strong></td>
<td>40 hours</td>
<td>12–14 hours&lt;sup&gt;§&lt;/sup&gt;</td>
<td>5–9 hours (young)</td>
<td>11–13 hours (elderly)</td>
<td>12 hours</td>
</tr>
</tbody>
</table>

The information in this table is based on the SmPCs for apixaban, rivaroxaban, dabigatran and edoxaban. Please refer to the SmPCs for further information.<sup>3–6</sup>

*Food does not affect the bioavailability of dabigatran etexilate, but delays the time to peak plasma concentrations by 2 hours; <sup>†</sup>Time to peak effect is up to 3–5 days; <sup>‡</sup>Direct renal excretion as unchanged active substance; <sup>§</sup>Prolonged in patients with impaired renal function.

FXa: factor Xa; SmPC: summary of product characteristics; <i>T</i><sub>max</sub>: time to reach peak plasma concentration; <i>t</i><sub>1/2</sub>: half-life.

## NOACs in NVAF: Study design of randomised trials

|                | RE-LY (dabigatran)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>18,113</td>
</tr>
<tr>
<td>Design</td>
<td>Blinded (dabigatran)</td>
</tr>
<tr>
<td></td>
<td>Open-label (warfarin)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Dabigatran 150 mg BID</td>
</tr>
<tr>
<td></td>
<td>Dabigatran 110 mg BID*</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban 20 mg OD†</td>
</tr>
<tr>
<td></td>
<td>Apixaban 5 mg BID‡</td>
</tr>
<tr>
<td>Objective</td>
<td>Non-inferiority</td>
</tr>
</tbody>
</table>

|                | ROCKET AF (rivaroxaban)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>14,264</td>
</tr>
<tr>
<td>Design</td>
<td>Double-blind, double-dummy</td>
</tr>
<tr>
<td>Treatment</td>
<td>Rivaroxaban 20 mg OD†</td>
</tr>
<tr>
<td>Objective</td>
<td>Non-inferiority</td>
</tr>
</tbody>
</table>

|                | ARISTOTLE (apixaban)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>18,201</td>
</tr>
<tr>
<td>Design</td>
<td>Double-blind, double-dummy</td>
</tr>
<tr>
<td>Treatment</td>
<td>Apixaban 5 mg BID‡</td>
</tr>
<tr>
<td>Objective</td>
<td>Non-inferiority</td>
</tr>
</tbody>
</table>

|                | AVERROES (apixaban)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>5,599</td>
</tr>
<tr>
<td>Design</td>
<td>Double-blind, double-dummy</td>
</tr>
<tr>
<td>Treatment</td>
<td>Apixaban 5 mg BID‡</td>
</tr>
<tr>
<td>Objective</td>
<td>Non-inferiority</td>
</tr>
</tbody>
</table>

|                | ENGAGE AF-TIMI 48 (edoxaban)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>21,105</td>
</tr>
<tr>
<td>Design</td>
<td>Double-blind, double-dummy</td>
</tr>
<tr>
<td>Treatment</td>
<td>Edoxaban 60 mg OD</td>
</tr>
<tr>
<td>Objective</td>
<td>Non-inferiority</td>
</tr>
</tbody>
</table>

*Per the dabigatran SmPC, the recommended dose is 150 mg BID. A dose of 110 mg BID is recommended in selected patients. Please refer to the SmPC for further details.1

15 mg OD in selected patients; Patients with CrCl between 30–49 mL/min;7 2.5 mg BID in selected patients; Patients with more than two of the following criteria: age ≥80 years, body weight ≤60 kg, or a serum creatinine level ≥1.5 mg/dL (133 μmol/L). Per the apixaban SmPC, patients with NVAF and the exclusive criterion of severe renal impairment (CrCl 15–29 mL/min) should also receive the lower dose of apixaban 2.5 mg BID. This criterion differs from the trial conduct;8 Patients with any of the following: CrCl 30–50 mL/min, body weight ≤60 kg or concomitant use of specific P-gp inhibitors. Per the edoxaban SmPC, the recommended dose is 60 mg OD.9

A dose of 30 mg OD is recommended in selected patients. Please refer to the SmPC for further details.9

ASA: acetylsalicylic acid; INR: international normalised ratio.

## NOAC Phase III trials in NVAF: Study characteristics

<table>
<thead>
<tr>
<th></th>
<th>RE-LY (dabigatran)&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>ROCKET AF (rivaroxaban)&lt;sup&gt;3&lt;/sup&gt;</th>
<th>ARISTOTLE (apixaban)&lt;sup&gt;4&lt;/sup&gt;</th>
<th>AVERROES (apixaban)&lt;sup&gt;5&lt;/sup&gt;</th>
<th>ENGAGE AF-TIMI 48 (edoxaban)&lt;sup&gt;6,7&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean)</strong></td>
<td>72</td>
<td>73&lt;sup&gt;†&lt;/sup&gt;</td>
<td>70&lt;sup&gt;†&lt;/sup&gt;</td>
<td>70</td>
<td>72&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Gender (men)</strong></td>
<td>64%</td>
<td>60%</td>
<td>65%</td>
<td>59%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Type of AF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent/permanent</td>
<td>67.2%</td>
<td>81.1%</td>
<td>84.7%</td>
<td>73%</td>
<td>74.6%</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>32.8%</td>
<td>17.6%</td>
<td>15.3%</td>
<td>27%</td>
<td>25.4%</td>
</tr>
<tr>
<td>Newly diagnosed</td>
<td>–</td>
<td>1.4%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>CHADS&lt;sub&gt;2&lt;/sub&gt; score, mean</strong></td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
<td>2.0</td>
<td>2.8</td>
</tr>
<tr>
<td>0 or 1</td>
<td>31.9%</td>
<td>0%</td>
<td>34.0%</td>
<td>36.5%</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>36%</td>
<td>13.0%</td>
<td>35.8%</td>
<td>35.5%</td>
<td>77.4%&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>3–6</td>
<td>32.5%</td>
<td>86.9%</td>
<td>30.2%</td>
<td>28.0%</td>
<td>22.6%&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>TTR in the warfarin group (mean % of the study period)</strong></td>
<td>64.4%</td>
<td>55.0%</td>
<td>62.2%</td>
<td>N/A</td>
<td>68.4%</td>
</tr>
</tbody>
</table>

*Data calculated for the entire study group; †Median age; ‡77.4% for CHADS<sub>2</sub> score of ≤3 of 77.4%; 4–6 of 22.6%.

AF: atrial fibrillation; N/A: not applicable; TTR: time in therapeutic range.

Meta-analysis of NOAC randomised clinical trials

**Objective:** To assess the relative benefit of NOACs in the prevention of stroke in patients with NVAF

**Method:**

- Prespecified meta-analysis of all 71,683 participants included in the following Phase III trials:
  - RE-LY, ROCKET AF, ARISTOTLE and ENGAGE AF-TIMI 48
- RRs and 95% CIs were calculated for each of the main efficacy and safety outcomes of each study
- Outcomes were pooled and compared with a random effects model and tested for heterogeneity

*CI: confidence interval; RR: relative risk.*

Meta-analysis: Efficacy of NOACs versus warfarin for stroke prevention in patients with NVAF

<table>
<thead>
<tr>
<th>Study</th>
<th>NOAC (events)</th>
<th>Warfarin (events)</th>
<th>RR (95% CI)</th>
<th>RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY (dabigatran)*</td>
<td>134/6,076</td>
<td>199/6,022</td>
<td></td>
<td>0.66 (0.53–0.82)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ROCKET AF (rivaroxaban)†</td>
<td>269/7,081</td>
<td>306/7,090</td>
<td></td>
<td>0.88 (0.75–1.03)</td>
<td>0.12</td>
</tr>
<tr>
<td>ARISTOTLE (apixaban)‡</td>
<td>212/9,120</td>
<td>265/9,081</td>
<td></td>
<td>0.80 (0.67–0.95)</td>
<td>0.012</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 (edoxaban)§</td>
<td>296/7,035</td>
<td>337/7,036</td>
<td></td>
<td>0.88 (0.75–1.02)</td>
<td>0.10</td>
</tr>
<tr>
<td>Combined (random)</td>
<td>911/29,312</td>
<td>1,107/29,229</td>
<td></td>
<td>0.81 (0.73–0.91)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are n, unless otherwise indicated
Heterogeneity: $I^2=47\%$, $P=0.13$

*150 mg BID; †20 mg OD; ‡5 mg BID; §60 mg OD.
SE: systemic embolism.

There are no head-to-head randomised clinical trials comparing the NOACs. Comparisons cannot be made between individual NOACs based on these data

## Meta-analysis: Safety of NOACs versus warfarin for stroke prevention in patients with NVAF

### Major bleeding

<table>
<thead>
<tr>
<th>Study</th>
<th>NOAC (events)</th>
<th>Warfarin (events)</th>
<th>RR (95% CI)</th>
<th>RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY (dabigatran)*</td>
<td>375/6,076</td>
<td>397/6,022</td>
<td>0.94 (0.82–1.07)</td>
<td>0.94 (0.82–1.07)</td>
<td>0.34</td>
</tr>
<tr>
<td>ROCKET AF (rivaroxaban)†</td>
<td>395/7,111</td>
<td>386/7,125</td>
<td>1.03 (0.90–1.18)</td>
<td>1.03 (0.90–1.18)</td>
<td>0.72</td>
</tr>
<tr>
<td>ARISTOTLE (apixaban)‡</td>
<td>327/9,088</td>
<td>462/9,052</td>
<td>0.71 (0.61–0.81)</td>
<td>0.71 (0.61–0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 (edoxaban)§</td>
<td>444/7,012</td>
<td>557/7,012</td>
<td>0.80 (0.71–0.90)</td>
<td>0.80 (0.71–0.90)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Combined (random)</td>
<td>1,541/29,287</td>
<td>1,802/29,211</td>
<td>0.86 (0.73–1.00)</td>
<td>0.86 (0.73–1.00)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Data are n, unless otherwise indicated. Heterogeneity: $I^2=47\%$, $P=0.13$

*150 mg BID; †20 mg OD; ‡5 mg BID; §60 mg OD. SE: systemic embolism.

There are no head-to-head randomised clinical trials comparing the NOACs. Comparisons cannot be made between individual NOACs based on these data.

The apixaban trial programme for NVAF covers a broad patient population

Documented NVAF and at least one risk factor(s) for stroke

Suitability for VKA

Yes

ARISTOTLE Trial\(^1\)
(n=18,201)

No

AVERROES Trial\(^2\)
(n=5,599)

*Some reasons for VKA unsuitability: INR could not be maintained in therapeutic range or patient preference against VKA. The non-suitability was not because of a high bleeding risk, since such patients were excluded.

VKA: vitamin K antagonist.

**ARISTOTLE**: Apixaban was superior to warfarin in preventing stroke or SE\(^1\)

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**Graph**

- **Patients with event (%)**
  - **Months**: 0, 6, 12, 18, 24, 30
  - **Y-axis**: 0, 20, 40, 60, 80, 100
  - **X-axis**: 0, 6, 12, 18, 24, 30

**Lines**
- **Apixaban**
- **Warfarin**

**Key Points**
- **RRR**: 21%
- **ARR**: 0.33%
- **HR**: 0.79 (95% CI: 0.66–0.95)
- **P**<0.001 for non-inferiority
- **P**=0.01 for superiority

**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at risk</td>
<td>9,120</td>
<td>9,081</td>
</tr>
<tr>
<td>6 months</td>
<td>8,726</td>
<td>8,620</td>
</tr>
<tr>
<td>12 months</td>
<td>8,440</td>
<td>8,301</td>
</tr>
<tr>
<td>18 months</td>
<td>6,051</td>
<td>5,972</td>
</tr>
<tr>
<td>24 months</td>
<td>3,464</td>
<td>3,405</td>
</tr>
<tr>
<td>30 months</td>
<td>1,754</td>
<td>1,768</td>
</tr>
</tbody>
</table>

**ARR**: absolute relative risk; **HR**: hazard ratio; **RRR**: relative risk reduction.

**Reproduced from Granger et al. 2011\(^1\)**

ARISTOTLE: Apixaban significantly reduced the risk of major bleeding versus warfarin

Major bleeding defined by ISTH criteria.

ISTH: International Society for Thrombosis and Haemostasis.

Reproduced from Granger et al. 2011

ARISTOTLE: Statistically significant reduction for apixaban compared with warfarin in all-cause death\(^1\)

Key secondary efficacy endpoint: all-cause mortality

HR=0.89
(95% CI: 0.80–0.99; \(P=0.047\))
RRR 11%, ARR 0.42%

Event rate (%/year)

- Warfarin: 3.94%
- Apixaban: 3.52%

Created from Granger et al. 2011\(^1\)

The apixaban trial programme for NVAF covers a broad patient population

Documented NVAF and at least one risk factor(s) for stroke

Suitability for VKA

Yes

ARISTOTLE Trial¹
(n=18,201)

No

AVERROES Trial*²
(n=5,599)

*Some reasons for VKA unsuitability: INR could not be maintained in therapeutic range or patient preference against VKA. The non-suitability was not because of a high bleeding risk, since such patients were excluded.
VKA: vitamin K antagonist.

**AVERROES:** Apixaban versus ASA – significant reduction in stroke or SE\(^1\)

![Cumulative hazard rate graph](image)

**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>Months</th>
<th>ASA</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>2,791</td>
<td>2,808</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2,716</td>
<td>2,758</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2,530</td>
<td>2,566</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>2,112</td>
<td>2,125</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>1,543</td>
<td>1,522</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>628</td>
<td>615</td>
</tr>
</tbody>
</table>

**ARR 2.1%**

HR=0.45 (95% CI: 0.32–0.62)

\(P<0.001\) for superiority

Due to clear benefit in favour of apixaban the study was terminated early.\(^1\)

ASA: acetylsalicylic acid.


Reproduced from Connolly et al. 2011\(^1\)
**AVERROES**: Apixaban versus ASA – comparable rates of major bleeding\(^1,2\)

### Proportion of subjects with major bleeding

<table>
<thead>
<tr>
<th>Days since first dose</th>
<th>ASA</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2,780</td>
<td>2,798</td>
</tr>
<tr>
<td>90</td>
<td>2,569</td>
<td>2,618</td>
</tr>
<tr>
<td>180</td>
<td>2,446</td>
<td>2,496</td>
</tr>
<tr>
<td>270</td>
<td>2,116</td>
<td>2,154</td>
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<tr>
<td>360</td>
<td>1,722</td>
<td>1,715</td>
</tr>
<tr>
<td>450</td>
<td>1,215</td>
<td>1,207</td>
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<tr>
<td>540</td>
<td>773</td>
<td>763</td>
</tr>
<tr>
<td>630</td>
<td>452</td>
<td>453</td>
</tr>
<tr>
<td>720</td>
<td>205</td>
<td>237</td>
</tr>
<tr>
<td>810</td>
<td>71</td>
<td>66</td>
</tr>
</tbody>
</table>

**Safety population patients who had been randomised to treatment and received at least one dose of study drug.**

**NS**: not significant.

**Reproduced from Connolly et al. 2011\(^1\)**

There were significantly higher rates of bleeding for apixaban versus ASA for the secondary safety endpoints of major/CRNM bleeding* (HR=1.38, 95% CI: 1.07–1.78; P=0.0144) and all bleeding (HR=1.30, 95% CI: 1.10–1.53; P=0.0017)\(^1\)

\[\text{Created from Apixaban SmPC and Connolly et al. 2011}^{1,2}\]

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**Major bleeding**\(^*\)^1

<table>
<thead>
<tr>
<th>Event rate (%)/year</th>
<th>Apixaban</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.41</td>
<td>0.92</td>
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</table>

**Intracranial**

<table>
<thead>
<tr>
<th>Event rate (%)/year</th>
<th>Apixaban</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**Extracranial**

<table>
<thead>
<tr>
<th>Event rate (%)/year</th>
<th>Apixaban</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**Major GI bleeding**\(^2\)

<table>
<thead>
<tr>
<th>Event rate (%)/year</th>
<th>Apixaban</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

\(^1\) HR shown with 95% CI.

\(^*\) Major bleeding analysis based on safety population.

\(^2\) Extracranial bleeding also included unclassified bleeding.

CRNM: clinically relevant non-major.
Proven efficacy and safety of Apixaban

- NOACs are preferred over VKA for stroke prevention in NVAF according to the ESC guidelines\(^1\)

- All NOACs have benefits over warfarin, but differ in pharmacological characteristics and efficacy and safety profiles versus warfarin\(^2\)
  - Apixaban demonstrated superior efficacy versus warfarin, with a significant reduction in the risk of major bleeding in patients with NVAF\(^3\)

- Apixaban is the only NOAC that has been studied versus ASA for stroke prevention in NVAF patients not suitable for warfarin\(^4\)

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