Stroke prevention in NVAF patients: where are we now?

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Prevalence and incidence of AF in Europe

**Prevalence**
- Estimated prevalence of 2% in Europe in 2014, double that reported a decade earlier

**Variation with gender**
- 1.2 : 1 male:female ratio

**Prevalence by age**
- <49 years: 0.12 - 0.16%
- 60–70 years: 3.7 - 4.2%
- >80 years: 10 - 17%

**Incidence**
- 0.21 - 0.41 per 1,000 person/y

**Predicted burden**
- Predicted 14 - 17 million cases in Europe by 2030
- 120 - 215,000 new cases/y

AF: atrial fibrillation; y: year.

NVAF is associated with significant long-term risk of stroke and death

**Morbidity\(^1\)**

Incidence of stroke according to presence of NVAF (Framingham Heart Study)

<table>
<thead>
<tr>
<th>Risk ratio</th>
<th>Absence of CV condition</th>
<th>Presence of CV condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN* 3.4</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>CHD* 2.4</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>CHF* 4.3</td>
<td>8</td>
<td>44</td>
</tr>
<tr>
<td>NVAF* 4.8</td>
<td>9</td>
<td>47</td>
</tr>
</tbody>
</table>

*P<0.001.

**Mortality\(^2\)**

Rate of death after ischaemic stroke

- 30-day mortality
  - Without AF (n=2,661): 16.2%
  - With NVAF (n=674): 34.7%
- 1-year mortality
  - Without AF (n=2,661): 27.1%
  - With NVAF (n=674): 52.4%

CHD: coronary heart disease; CHF: cardiac failure; CV: cardiovascular; HTN: hypertension; NVAF: non-valvular atrial fibrillation.

Anticoagulation in NVAF: The VKA era

VKA properties

- Established efficacy/safety profile
- Unpredictable anticoagulant effect
- Narrow therapeutic window
- Food and drug interactions
- Slow onset and offset of action

Routine visits to clinic/hospital to monitor INR
Diet and drug restrictions
Difficult perioperative management

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

1995 2000

INR: international normalised ratio.

Anticoagulation in NVAF: NOACs in the current era

NOAC properties

- Good efficacy and safety profile vs VKA
- Fixed dose
- Few drug and food interactions
- Fast onset and offset of action

- No need for monitoring
- Few drug and diet restrictions
- Simpler perioperative management

Dabigatran Phase III NVAF trial published
Rivaroxaban Phase III NVAF trial published
Edoxaban Phase III NVAF trial published

ARISTOTLE: Apixaban was superior vs. warfarin in following three outcomes

Superiority Stroke/SE

- **21% RRR**
- **P = 0.01**

Superiority Major bleeding

- **31% RRR**
- **P < 0.001**

Superiority All-cause mortality

- **11% RRR**
- **P = 0.047**

**Event rate (%/ year)**

- **Stoke/SE**
  - Apixaban: 1.27 (212/9120)
  - Warfarin: 1.60 (265/9081)

- **Major bleeding**
  - Apixaban: 2.13 (327/9088)
  - Warfarin: 3.09 (462/9052)

- **All-cause mortality**
  - Apixaban: 3.52 (603/9120)
  - Warfarin: 3.94 (669/9081)

Created from Connolly et al. N Engl J Med 2011;364:806-17

Exploring real-world evidence for OAC

- RCTs have consistently demonstrated that NOACs have a favourable benefit-risk profile compared with VKAs for stroke prevention in NVAF\(^1\)

- In real-world clinical settings, a diversity of patients with NVAF are treated, many with common comorbidities, and use of NOACs may differ from the regulated requirements in RCTs\(^2\)

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NOAC: non-VKA oral anticoagulant; NVAF: non-valvular atrial fibrillation; OAC: oral anticoagulant; RCT: randomised controlled trial; SPAF: stroke prevention in atrial fibrillation; VKA: vitamin K antagonist

Risk of major bleeding with NOACs versus warfarin: A systematic review of real-world observational studies

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-industry</strong></td>
<td></td>
</tr>
<tr>
<td>Adeboyeje 2016*</td>
<td>0.52 (0.41–0.67)</td>
</tr>
<tr>
<td>Larsen 2016</td>
<td>0.63 (0.52–0.76)</td>
</tr>
<tr>
<td>Yao 2016*</td>
<td>0.45 (0.34–0.59)</td>
</tr>
<tr>
<td><strong>Industry</strong></td>
<td></td>
</tr>
<tr>
<td>Amin 2015*</td>
<td>0.71 (0.61–0.83)</td>
</tr>
<tr>
<td>Deitelzweig 2015*</td>
<td>0.58 (0.44–0.75)</td>
</tr>
<tr>
<td>Kamble 2015*</td>
<td>0.53 (0.29–0.97)</td>
</tr>
<tr>
<td>Lin 2015*</td>
<td>0.75 (0.63–0.89)</td>
</tr>
<tr>
<td>Lip 2016*</td>
<td>0.53 (0.39–0.71)</td>
</tr>
</tbody>
</table>

*US-based study.
CI: confidence interval; HR: hazard ratio


Effectiveness and safety of apixaban versus warfarin in NVAF patients in ‘real-world’ clinical practice

Propensity score matched analysis of 76,940 patients

<table>
<thead>
<tr>
<th>Effectiveness endpoints</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SE</td>
<td>0.67 (0.59–0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>0.67 (0.58–0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>0.70 (0.50–0.99)</td>
<td>0.041</td>
</tr>
<tr>
<td>SE</td>
<td>0.46 (0.26–0.82)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Safety endpoints</th>
<th></th>
<th></th>
</tr>
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<tr>
<td>Major bleeding</td>
<td>0.60 (0.54–0.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICH</td>
<td>0.64 (0.50–0.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>0.62 (0.55–0.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other bleeding</td>
<td>0.57 (0.50–0.65)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI: confidence interval; GI: gastrointestinal; ICH: intracranial haemorrhage; HR: hazard ratio; NVAF: non-valvular atrial fibrillation; SE: systemic embolism

Reproduced from Li XS, et al. 2017†
2016 ESC Guidelines: NOACs preferred over VKA

- Mechanical heart valves or moderate or severe mitral stenosis
- Estimate stroke risk based on number of CHA$_2$DS$_2$-VASc risk factors
  - 0$^a$
    - No antiplatelet or anticoagulant treatment (IIIB)
  - 1
    - OAC should be considered (IIaB)
  - ≥2$^b$
    - 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)$^c$
    - VKA (IA)$^c$

*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. CHA$_2$DS$_2$-VASc: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years; ESC: European Society of Cardiology; LAA: left atrial appendage; OAC: oral anticoagulant.

Current guidelines do NOT recommend ASA for stroke prevention in AF patients

2016 ESC Guidelines

<table>
<thead>
<tr>
<th>Recommendations for stroke prevention in patients with AF</th>
<th>Class*</th>
<th>Level†</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP monotherapy is not recommended for stroke prevention in AF patients regardless of stroke risk</td>
<td>III (Harm)</td>
<td>A</td>
</tr>
</tbody>
</table>

NICE 2014 Guidelines on the management of AF

“Do not offer ASA monotherapy solely for stroke prevention to people with AF”

*Class of recommendation; †Level of evidence.
AP: antiplatelet; NICE: National Institute for Health and Care Excellence.

AF is highly prevalent and is a major cause of stroke¹

In line with ESC 2016 recommendations, for AF patients without contra-indication for NOAC, a NOAC is recommended in preference to a VKA

Apixaban was associated with a significantly lower risk of stroke and major bleeding in ARISTOTLE trial

Apixaban data from clinical practice (RWD) are consistent with randomized clinical studies results!

What evidence is there for NOACs in AF + ACS?


*Target enrolment. ACC: American College of Cardiology; AHA: American Heart Association.

- **2016**: PIONEER AF-PCI¹
  - Rivaroxaban
  - N=2,124

- **2017**: RE-DUAL PCI²
  - Dabigatran
  - N=2,725

- **2018**: AUGUSTUS ACS/PCI³
  - Apixaban
  - N=4,600*

- **2019**: ENTRUST AF-PCI⁴
  - Edoxaban
  - N=1,500*

- **2020**

  - **AHA2016**: Parallel assignment
  - **ESC 2017**: Parallel assignment
  - **ACC 2019**: 2x2 factorial
  - **ESC 2019**: Parallel assignment

  - **COMPLETE**
  - **COMPLETE**
  - **COMPLETE**
  - **COMPLETE**

  - **ONGOING**
    - Data expected
    - ESC 2019

*Target enrolment. ACC: American College of Cardiology; AHA: American Heart Association.
Background

- OAC indicated for prevention of stroke and SE in pts with AF
  - not indicated for prevention of stent thrombosis

- Dual antiplatelet therapy indicated for prevention of recurrent ischemic events and stent thrombosis
  - not indicated for stroke and SE prevention in AF
Coronary stenting in patients with AF and high risk of stroke

The problem:
You cannot simultaneously prevent all three!? 

- Stent thrombosis
- Stroke
- Major bleeding

DAPT → Major bleeding
OAC → Major bleeding
Background

- 5-8% of pts undergoing PCI have AF
- 25% of pts with AF will undergo PCI
- Combined therapy (OAC+aspirin+P2Y12) significantly increases the risk of bleeding
- Studies with other NOACs have shown reduced risk of bleeding in combination therapy when compared to warfarin
Background

- RE-DUAL PCI - compared two tested doses of dabigatran+P2Y12 inhibitor vs warfarin+dual antiplatelet therapy

- PIONEER AF - compared two doses of rivaroxaban (15 mg OD and 2.5 mg BID)+P2Y12 inhibitor vs warfarin. Doses of NOAC were not doses tested in landmark RCT for SPAF
Learnings from PIONEER and RE-DUAL

- Only patients undergoing PCI included

- NOAC + P2Y<sub>12</sub> inhibitor appears to be associated with reduced bleeding versus triple therapy with VKA
  - PIONEER assessed doses of rivaroxaban not tested for stroke prevention
  - Due to the design of RE-DUAL, it is unclear whether the reductions in bleeding are due to use of dabigatran or the avoidance of aspirin

- Neither trial powered for efficacy outcomes
  - In PIONEER, both doses of rivaroxaban were associated with numerical increases in CV death, stroke and stent thrombosis
  - In RE-DUAL, the lower dose of dabigatran (110 mg BID) was associated with a numerical increase in death, MI, stroke and stent thrombosis
AUGUSTUS trial design

- prospective, multicenter, two-by-two factorial, RCT
- patients with AF who had a recent ACS or underwent PCI (or both)

**N=4614 patients**

- **Apixaban 5 mg BID**
  - Apixaban 2.5 mg BID in selected patients
  - Open Label
  - Aspirin for all on the day of ACS or PCI
  - Aspirin versus placebo after randomization

- **VKA (INR 2 – 3)**
  - Double Blind
  - Aspirin
  - Aspirin versus placebo after randomization

**Primary outcome:** ISTH major/CRNM bleeding

**Secondary outcome(s):** death/hospitalization, death/ischemic events

Use of apixaban with antithrombotic drugs increases the risk of bleeding. In Europe and the Republic of Croatia, the use of apixaban with thienopyridines is not recommended. Before prescribing, please review the most recent Eliquis's Summary of Product Characteristic.
Results

- 4614 pts from 492 centers (33 countries)
- No difference in baseline characteristics
- 10% (229/2290 pts) received lower dose apixaban
- 59% median TTR
- Ticagrelor 6.2%, prasugrel 1.1%
- Median CHA$_2$DS$_2$-VASc 4 (IQR 3-5)
- Median HASBLED 3 (IQR 2-4)

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AUGUSTUS - summary

ISTH Major/Clinically Relevant Nonmajor Bleeding

- 31% lower with apixaban than VKA
- 89% higher with aspirin than placebo

Death/Hospitalisation

- 17% lower with apixaban than VKA
- Similar between aspirin and placebo

Death/Ischemic Events

- Similar rate between apixaban and VKA
- Similar rate between aspirin and placebo

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Conclusions

 ✓ In patients with atrial fibrillation and a recent acute coronary syndrome or PCI treated with a P2Y$_{12}$ inhibitor, an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in ischemic events than regimens that included a vitamin K antagonist, aspirin, or both.

 ✓ The risk of bleeding was significantly higher with aspirin in combination with either anticoagulants in combination with P2Y$_{12}$ inhibitor compared to P2Y$_{12}$ inhibitor plus anticoagulant without aspirin

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