Oral Anticoagulant Therapy in ‘Special’ AF populations
The Anticoagulation Fairytale
Should all AF Patients Receive Anticoagulation

- Dependent on the risk for stroke vs the risk for bleeding
  - Patients with low stroke risk may not require anticoagulation therapy
Without treatment, approximately one in three AF patients would ultimately suffer an ischemic stroke.

- Both major adverse CV events, such as stroke, and major bleeding events are associated with a high risk of morbidity and mortality.
- The aim of treatment is to remain in the optimal zone of anticoagulation.
‘Special’ AF Population

- older age
- significant renal or hepatic disease
- prior stroke
- CAD
- or prior bleeding event
- malignancy

due to their

‘special’ risk profile that includes increased risks of both thromboembolic and bleeding events

High risk of bleeding (HAS-BLED score ≥3)
Clinical Adverse Events and Mortality

30-day mortality (%)

- Ischaemic stroke
- Intracranial bleeding
- Extracranial bleeding

Clinical event
Risk–Benefit Balance

- Weighing all haemorrhagic events equivalently to that of an ischaemic stroke might be an oversimplification of their true effect.
- Substantial heterogeneity in both morbidity and mortality after ischaemic and haemorrhagic events in patients with AF.
VKAs: Net Clinical Benefit in AF pts. Swedish AF cohort study

In almost all patients with AF, the risk of ischaemic stroke without OAC treatment is far higher than the risk of ICH with OAC.

CHA$_2$DS$_2$-VASc score was more sensitive than the CHADS$_2$ score in identifying patients who were ‘truly low risk’ in whom anticoagulation may be associated with a net disadvantage.

Olesen et al. Thromb Haemost. 2011
Hemorrhagic and Thrombotic events according to HAS-BLED

%/year

[Bar chart showing the percentage of hemorrhagic and thrombotic events per year, categorized by the number of bleeding risk factors (0-5).]

Pilar Gallego et al. Circ Arrhythm Electrophysiol. 2012
The net clinical benefit with any OAC was greater among those at higher bleeding risk

Elderly Patients with AF

The Increasing Burden of Atrial Fibrillation
Elderly Patients in RCTs

In real world data ~45% of pts with AF are ≥75 years
Stroke rates of up to 36.2% at age of 80–89 years

Go et al. JAMA 2001 and NOACs Trials

<table>
<thead>
<tr>
<th></th>
<th>RE-LY²</th>
<th>ROCKET³,⁴</th>
<th>ENGAGE⁵,⁶</th>
<th>ARISTOTLE⁷,⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=18113</td>
<td>n=14264</td>
<td>n=21105</td>
<td>n=18201</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>~72*</td>
<td>73</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>16%</td>
<td>56%</td>
<td>26%</td>
<td>30%</td>
</tr>
<tr>
<td>65–74 years</td>
<td>44%</td>
<td>34%</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>≥75 years</td>
<td>40%</td>
<td>44%</td>
<td>40%</td>
<td>31%</td>
</tr>
</tbody>
</table>
Major Outcomes According to Age

NOACs were as effective in elderly AF patients as in the main trials
there was a significant treatment-by-age interaction with dabigatran and rivaroxaban compared with warfarin
  - regarding extracranial and clinically relevant non-major bleeding, respectively
There was **no significant treatment-by-age interaction** for the safety of apixaban.
The benefits of apixaban are consistent in pts with AF regardless of age
Owing to the higher risk at older age, the absolute benefits of apixaban are
greater in the elderly

S. Halvorsen et al. European Heart Journal 2014
AF Patients with Chronic Kidney Disease

The patients know more about their diseases than me. I must get faster modem, higher speed internet access than them.
Antithrombotic Therapy in AF: Renal Impairment

Distribution of patients with AF according to renal function

Leiden Anticoagulation Clinic (n=5,039; 1997–2005)

- eGFR, mL/min/1.73 m² (MDRD formula)
  - >60: 65.8%
  - 30-60: 30.9%
  - 15-30: 2.5%
  - 0-15: 0.8%

AURICULA Registry, Malmö (n=2,603; 2007–2008)

- eGFR, mL/min/1.73 m² (MDRD formula)
  - <60: 40.4%
  - <45: 16.3%
  - <30: 4.3%

Using Different eGFR Cut-off Values

CKD increases the risk of stroke, bleeding, MI and all-cause death in AF patients.

Risk of Events in NVAF Patients with Non-end-stage CKD (n=3,587) or with CKD Requiring Renal Replacement Therapy (n=901) vs. NVAF Patients with No Renal Disease (n=127,884) – Danish Registry (1997–2008)

<table>
<thead>
<tr>
<th>Event</th>
<th>Reference: Patients with no renal disease</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke or Systemic Thromboembolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-end-stage CKD</td>
<td></td>
<td>1.49 (1.38; 1.59)</td>
</tr>
<tr>
<td>CKD requiring renal replacement therapy</td>
<td></td>
<td>1.83 (1.57; 2.14)</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-end-stage CKD</td>
<td></td>
<td>2.24 (2.10; 2.38)</td>
</tr>
<tr>
<td>CKD requiring renal replacement therapy</td>
<td></td>
<td>2.70 (2.38; 3.07)</td>
</tr>
<tr>
<td><strong>Myocardial Infarction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-end-stage CKD</td>
<td></td>
<td>2.00 (1.86; 2.16)</td>
</tr>
<tr>
<td>CKD requiring renal replacement therapy</td>
<td></td>
<td>3.00 (2.58; 3.50)</td>
</tr>
<tr>
<td><strong>Death from Any Cause</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-end-stage CKD</td>
<td></td>
<td>2.37 (2.30; 2.44)</td>
</tr>
<tr>
<td>CKD requiring renal replacement therapy</td>
<td></td>
<td>3.35 (3.13; 3.58)</td>
</tr>
</tbody>
</table>

Stroke/SE and major bleeding event rates for subgroups of patients with stage III CKD

**Stroke/SE**
- Dabigatran 110 mg bid: 0.77 (0.51 – 1.18)
- Dabigatran 150 mg bid: 0.55 (0.40 – 0.81)
- Rivaroxaban 15 mg qd: 0.86 (0.63 – 1.17)
- Apixaban 2.5/5.0 mg bid: 0.79 (0.55 – 1.14)

**Major bleeding**
- Dabigatran 110 mg bid: 0.99 (0.76 – 1.28)
- Dabigatran 150 mg bid: 1.03 (0.80 – 1.34)
- Rivaroxaban 15 mg qd: 0.95 (0.72 – 1.26)
- Apixaban 2.5/5.0 mg bid: 0.50 (0.38 – 0.66)

Phase III trial data suggest NOACs may be preferable to warfarin in patients with moderate renal impairment.

Hart et al. Canadian Journal of Cardiology 2013
The benefits of apixaban vs. warfarin were consistent across different levels of renal function.

<table>
<thead>
<tr>
<th>Stroke/SE</th>
<th>Apixaban %/yr (n)</th>
<th>Warfarin %/yr (n)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft-Gault (eGFR mL/min)</td>
<td></td>
<td></td>
<td></td>
<td>0.705</td>
</tr>
<tr>
<td>&gt;80</td>
<td>0.99 (70)</td>
<td>1.12 (79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50–80</td>
<td>1.24 (87)</td>
<td>1.69 (116)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>2.11 (54)</td>
<td>2.67 (69)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Bleeding</th>
<th>Apixaban %/yr (n)</th>
<th>Warfarin %/yr (n)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft-Gault (eGFR mL/min)</td>
<td></td>
<td></td>
<td></td>
<td>0.030</td>
</tr>
<tr>
<td>&gt;80</td>
<td>1.46 (96)</td>
<td>1.84 (119)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50–80</td>
<td>2.45 (157)</td>
<td>3.21 (199)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>3.21 (73)</td>
<td>6.44 (142)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Patients with calculated creatinine clearance of <25 ml/minute were excluded from ARISTOTLE.
In elderly patients (≥ 75 years) the benefits of apixaban vs. warfarin were consistent across the range of estimated GFR.

<table>
<thead>
<tr>
<th>No. of patients ≥ 75 years</th>
<th>Apixaban %/yr (n)</th>
<th>Warfarin %/yr (n)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke/SE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cockcroft-Gault (eGFR mL/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>597</td>
<td>1.41 (8)</td>
<td>2.16 (11)</td>
<td>0.4954</td>
</tr>
<tr>
<td>&gt;50–80</td>
<td>2922</td>
<td>1.45 (39)</td>
<td>1.70 (45)</td>
<td></td>
</tr>
<tr>
<td>&gt; 30-50</td>
<td>1906</td>
<td>1.74 (28)</td>
<td>2.69 (44)</td>
<td></td>
</tr>
<tr>
<td>≤ 30</td>
<td>222</td>
<td>1.70 (3)</td>
<td>5.57 (9)</td>
<td></td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cockcroft-Gault (eGFR mL/min)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>596</td>
<td>2.10 (11)</td>
<td>3.39 (15)</td>
<td>0.1635</td>
</tr>
<tr>
<td>&gt;50–80</td>
<td>2912</td>
<td>3.53 (85)</td>
<td>4.45 (104)</td>
<td></td>
</tr>
<tr>
<td>&gt; 30-50</td>
<td>1898</td>
<td>3.32 (47)</td>
<td>6.27 (87)</td>
<td></td>
</tr>
<tr>
<td>≤ 30</td>
<td>221</td>
<td>4.64 (7)</td>
<td>13.4 (17)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Patients with calculated creatinine clearance of <25 ml /minute were excluded from ARISTOTLE.

Halvorsen S et al. European Heart February 2014
## Major Bleeding in pts with Renal Dysfunction

<table>
<thead>
<tr>
<th>Cockcroft-Gault (eGFR mL/min)</th>
<th>Apixaban %/yr (n)</th>
<th>Warfarin %/yr (n)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>1.46 (96)</td>
<td>1.84 (119)</td>
<td></td>
<td>0.030</td>
</tr>
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<td></td>
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<td>≤50</td>
<td>3.21 (73)</td>
<td>6.44 (142)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Significant safety interaction** between the effect of apixaban and renal dysfunction
- **No significant safety interactions** relative to renal function with other NOACs

**NOTE:** Patients with calculated creatinine clearance of <25 ml/minute were excluded from ARISTOTLE

**Potpara et al. PROGRESS IN CARDIOVASCULAR DISEASES 2015**

**Hohnloser et al Eur Heart J. 2012**
Major Bleeding by Creatinine

Creatinine (mg/dL) at randomization

5 mg Twice Daily Dose Only

Hohnloser SH et al Eur Heart J. 2012
Major Bleeding by Creatinine Clearance

5 mg Twice Daily Dose Only

CrCl (ml/min) at randomization

Hohnloser SH et al Eur Heart J. 2012
Low-dose Apixaban vs Warfarin

At least 2 of 3...
Age ≥80 yrs, Cr ≥1.5 mg/dL, Wt ≤60 kg

Female, 66 years old, hypertension, stable coronary artery disease (PTCA 1 year ago, MI), Body weight: 75kg, Creatinine: 1.6 mg/dl, PAF, labile INR user, TTR=45% on VKAs, aspirin, clopidogrel
## Stroke and Bleeding Risk Ssessment

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac failure</td>
<td>1</td>
</tr>
<tr>
<td>HTN</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
</tr>
<tr>
<td>Vasc (MI, PAD, aortic ath)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 y</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>1</td>
</tr>
</tbody>
</table>

### Clinical Characteristic Table

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal Liver or Renal Function</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (age &gt; 65)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or Alcohol</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

**Maximum Score**

9
What would be the preferable antithrombotic therapy for this patient?

What is the most important factor when choosing anticoagulation therapy in a patient with high stroke and high bleeding risk?

1. Prevention of thromboembolic events
2. Low bleeding risk
3. Sum of $A+B = \text{net benefit}$
Contemporary treatment of patients with ACS should take into careful consideration hazards of both major bleeding and MI to provide best possible patient management.
NOAC vs Warfarin: Major Bleeding

New antithrombotic therapies compared to warfarin
Major bleeding

- Dabigatran 150 mg b.i.d.
- Dabigatran 110 mg b.i.d.
- Rivaroxaban 20 mg o.d.
- Abxaban 5 mg b.i.d.

New antithrombotic therapies compared to warfarin
Major + clinically relevant bleeding

- Dabigatran 150 mg b.i.d.
- Dabigatran 110 mg b.i.d.
- Rivaroxaban 20 mg o.d.
- Abxaban 5 mg b.i.d.

Not all NOACs display an advantage in terms of major bleeding compared with warfarin.
Apixaban, compared with warfarin, was associated with:

- fewer intracranial hemorrhages,
- less adverse consequences following extracranial hemorrhage,
- 50% reduction in fatal consequences at 30 days in cases of major hemorrhage
The period of triple therapy should be as short as possible
- Acute vs. elective procedures
- Stroke risk
- Bleeding risk

Advantages of NOACs over VKAs likely to be preserved
- NOACs may be safe and effective alternatives to VKAs

No preference given to any of OACs
- Well-controlled adjusted dose VKA (with TTR>70%)
- If NOACs, lower tested dose for stroke prevention in AF
Anticoagulation without additional antiplatelet agents is sufficient for most AF patients with stable CAD
What do the ESC Guidelines Recommend for our Patient (HAS BLED >3)?

In patients with a HAS-BLED score ≥3, caution and regular review are appropriate, as well as efforts to correct the potentially reversible risk factors for bleeding (uncontrolled blood pressure, concomitant use of aspirin/NSAIDs, labile INRs, etc.)

Assessment of the risk of bleeding is recommended when prescribing antithrombotic therapy (whether with VKA, NOAC, aspirin/clopidogrel, or aspirin).

The HAS-BLED score should be considered as a calculation to assess bleeding risk, whereby a score ≥3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or antiplatelet therapy (LoE = A).

Correctable risk factors for bleeding [e.g. uncontrolled blood pressure, labile INRs if the patient was on a VKA, concomitant drugs (aspirin, NSAIDs, etc.), alcohol, etc.] should be addressed (LoE = B).

Use of the HAS-BLED score should be used to identify modifiable bleeding risks that need to be addressed, but should not be used on its own to exclude patients from OAC therapy (LoE = B).

The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and – especially in the elderly – also with aspirin monotherapy) should be considered as being similar to OAC.

Where dabigatran is prescribed, a dose of 150 mg b.i.d. should be considered for most patients in preference to 110 mg b.i.d., with the latter dose recommended in:
- elderly patients, age ≥ 80
- concomitant use of interacting drugs (e.g. verapamil)
- high bleeding risk (HAS-BLED score ≥3)
- moderate renal impairment (CrCl 30–49 mL/min).

Where rivaroxaban is being considered, a dose of 20 mg o.d. should be considered for most patients in preference to 15 mg o.d., with the latter dose recommended in:
- high bleeding risk (HAS-BLED score ≥3)
- moderate renal impairment (CrCl 30–49 mL/min).

Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year.

NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min).

Better Control of Hypertension

- Office blood pressure: 165/90 mmHg
- Amlodipin 5mg od was added
- Ambulatory blood pressure monitoring showed very good control
Concomitant use of Antiplatelets/NSAIDs

- Pts with ACS > 1 year ago and atrial fibrillation
- Anticoagulation (either with VKA or NOACs) “without additional antiplatelet agent is considered sufficient for most AF patients with stable CAD”
- ASA and Clopidogrel were discontinued
VKA - Time in Therapeutic Range

- Last INR value 3.6
- Closer look on INR values: about 50% of values out of target with some being too low and several being too high
- As we did not expect to reach a desirable time in therapeutic range of 70% the patient was switched to a NOAC

De Caterina R et al. J Am Coll Cardiol 2012
Balancing Stroke and Bleeding Risk

- During a routine screening occult blood in stool was detected
  - Haemoglobin was 10.2 g/dl
- A colonoscopy showed a polyp which was successfully removed but no other source of GI bleeding
- The patient was referred to our out-patient office with a prophylactic dose of LMWH
Resuming Anticoagulation after GI Hemorrhage

Qureshi et al. Am J Cardiol 2014
What Should We do now with Anticoagulation?

1. Antiplatelet therapy only
2. Vitamin K antagonist
3. NOAC with standard dose
4. NOAC with reduced dose
GI Bleeding and Aspirin

- Aspirin used long-term for prevention of CV events in patients with CVD or multiple risk factors
- Aspirin is associated with increased risk of major GI bleeding\(^a\)
- Meta-analysis found an approximately two-fold higher risk of GI bleeding among individuals regularly using aspirin vs placebo\(^b\)
AVERROES: Stroke or Systemic Embolic Event

RR=0.45
95% CI, 0.32-0.62
P<.001

AVERROES Primary Safety Outcome: Major Bleeding

Cumulative Hazard

Months

Apixaban

ASA

HR 1.13 (95% CI: 0.74-1.75); p=0.57

Antithrombotic Therapy in AF: GI Bleeding

New antithrombotic therapies compared to warfarin
Gastrointestinal bleeding

- Dabigatran 150 mg b.i.d.
- Dabigatran 110 mg b.i.d.
- Rivaroxaban 20 mg o.d.
- Apixaban 5 mg b.i.d.

% of patients/year experiencing GI Bleed

* Statistically significant increased rate of gastrointestinal bleeding compared to warfarin

Clinical trial results demonstrate a lower risk for GI bleeding for Apixaban compared with warfarin

What Happened with our Patient?

- A NOAC (with low lower Gl-bleeding risk) was given
  - Apixaban
Selection of OAC in ‘special’ AF Populations

Prior bleeding event?

NO
Age > 75y?

YES

RELATED CKD?

Apix 5mg * bid
Riva 20mg od
Edox 60mg $ od
Dabi 110mg bid
VKA

NO
(CrCl ≥ 50ml/min)

CrCl 30-49ml/min
Apix 5mg * bid
Riva 15mg od
Dabi 110mg bid
Edox 30mg od

CrCl 15-29ml/min
Apix 2.5mg bid
Dabi 110mg bid
Edox 30mg od
VKA

YES
GI
Secure haemostasis and verify the lesion healing

Apix 5mg * bid
Edox 30mg $ od

YES

ICH

Localization?
(consult a neurologist)

SUBDURAL
Resume a NOAC after ‘acute’ phase

DEEP INTRACEREBRAL
Consider resuming a NOAC

LOBAR (SUB)CORTICAL
The highest risk of recurrent ICH, consider LAA occlusion

Individual patient risk assessment
Conclusions

- Any oral anticoagulant therapy is better than no therapy or aspirin in almost all AF patient
  - regardless of the bleeding risk level
- People at high risk of bleeding should not be precluded from anticoagulation
  - regular clinical review is recommended
  - treat correctable risk factors for bleeding
- Choose the proper anticoagulant in consultation with the patient
  - discuss the potential benefits and harms of treatment options
Conclusions

Apixaban has demonstrated a lower risk of major bleeding vs warfarin (ARISTOTLE) and comparable risk vs ASA (AVERROES) in patients with NVAF.

Apixaban has been extensively studied in the ARISTOTLE and shown to be superior to warfarin, with consistent results across multiple sub-groups.

- Lower risk of major bleeding especially in higher-risk sub-groups.
- Lower-dose apixaban (2.5 mg BID) is indicated for vulnerable patient sub-groups and appears to have a superior efficacy and safety profile compared with warfarin.