The Management of Anticoagulation in High-risk patients with AF

Eleftherios M. Kallergis MD, PhD, FESC
Cardiology Department
Heraklion University Hospital
❖ τιμητική αμοιβή από την Pfizer Hellas

❖ Οι απόψεις που εκφράζονται σε αυτή την παρουσίαση ανήκουν στον ομιλητή και δεν εκφράζουν απαραίτητα τις απόψεις της εταιρείας. Για όλα τα φαρμακευτικά προϊόντα που αναφέρονται παρακαλείσθε να συμβουλεύσεσθε τις εγκεκριμένες Περιλήψεις Χαρακτηριστικών των Προϊόντων”
"Ωφελέσαι ή μη βλάπτειν"
– Ιπποκράτης
For Both of us, Efficacy and Safety Profiles Matter
Anticoagulation: The Art of Balance

Both **efficacy** and **safety** are important. Imbalance in efficacy and safety may result in patient harm.
‘Special’ AF Population

Increased risks of both thromboembolic and bleeding events
Between Scylla and Charybdis...
Obtaining the Right Balance with OAC
Choosing the Right Drug…
... to Fit the Patient with AF
Antithrombotic Therapy in AF

A 76 year-old female patient with permanent non-valvular atrial fibrillation is treated with VKA

NSAIDs for osteoarthritis
Antithrombotic Therapy in AF

A 76 year-old female patient

Patient characteristics and history
❖ Permanent non-valvular atrial fibrillation
❖ Diabete mellitus
❖ Body weight: 72 kg
❖ Creatinine: 1.4 mg/dl, eGFR = 39 ml/min
❖ Blood pressure: 165/90 mmHg
❖ CAD with stent 2014

Therapy
❖ Metoprolol 25 mg twice daily
❖ insulin
❖ Lisinopril 20mg once daily
❖ VKA, last INR value 3.6
A Dangerous Triangle

AF

Elderly

Kidney Disease

Devil's Triangle
Prothrombotic and Prohaemorrhagic State

Potpara et al. Nature Reviews Nephrology 2018
Age is a Risk Factor for Efficacy and Safety Outcomes in AF

ICH: Intracranial haemorrhage; SE: systemic embolism  
## Efficacy and Safety Outcomes According to Age

### A. Primary Efficacy Outcome: Stroke and Systemic Embolism

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of patients</th>
<th>Apixaban</th>
<th>Warfarin</th>
<th>Hazard Ratio (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>18,201</td>
<td>212 (1.27)</td>
<td>265 (1.60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 yr</td>
<td>5,471</td>
<td>51 (1.00)</td>
<td>44 (0.86)</td>
<td></td>
<td>0.11*</td>
</tr>
<tr>
<td>65 to &lt; 75 yr</td>
<td>7,052</td>
<td>82 (1.25)</td>
<td>112 (1.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 75 yr</td>
<td>5,678</td>
<td>79 (1.56)</td>
<td>109 (2.19)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### B. Major Bleeding

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of patients</th>
<th>Apixaban</th>
<th>Warfarin</th>
<th>Hazard Ratio (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>18,140</td>
<td>327 (2.13)</td>
<td>462 (3.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 yr</td>
<td>5,455</td>
<td>56 (1.17)</td>
<td>72 (1.51)</td>
<td></td>
<td>0.63*</td>
</tr>
<tr>
<td>65 to &lt; 75 yr</td>
<td>7,030</td>
<td>120 (1.99)</td>
<td>166 (2.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 75 yr</td>
<td>5,655</td>
<td>151 (3.33)</td>
<td>224 (5.19)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Interaction p-values based on continuous age

Adapted from Halvorsen et al. Eur Hear J 2014;Feb 20 [epub ahead of print].
Apixaban vs. Warfarin in pts ≥ 80 years

The benefits of apixaban are consistent in pts with AF regardless of age

2,436 (13%) patients were ≥80 years of age in ARISTOTLE

S. Halvorsen et al. European Heart Journal 2014
The Benefits of Apixaban vs. Warfarin were Consistent Across Different Levels of Renal Function

<table>
<thead>
<tr>
<th></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>0.99 (70)</td>
<td>1.12 (79)</td>
<td></td>
<td>0.705</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>
<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>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>1.46 (96)</td>
<td>1.84 (119)</td>
<td></td>
<td>0.030</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 pts (≥ 75 years) the Benefits of Apixaban vs. Warfarin were Consistent Across the Range of Estimated GFR

<table>
<thead>
<tr>
<th>Stroke/SE</th>
<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>Cockcroft-Gault (eGFR mL/min)</td>
<td></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></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>
<td></td>
</tr>
<tr>
<td>&gt; 30-50</td>
<td>1906</td>
<td>1.74 (28)</td>
<td>2.69 (44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 30</td>
<td>222</td>
<td>1.70 (3)</td>
<td>5.57 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cockcroft-Gault (eGFR mL/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.1635</td>
</tr>
<tr>
<td>&gt;80</td>
<td>596</td>
<td>2.10 (11)</td>
<td>3.39 (15)</td>
<td></td>
<td>0.0625</td>
</tr>
<tr>
<td>&gt;50–80</td>
<td>2912</td>
<td>3.53 (85)</td>
<td>4.45 (104)</td>
<td></td>
<td>0.125</td>
</tr>
<tr>
<td>&gt; 30-50</td>
<td>1898</td>
<td>3.32 (47)</td>
<td>6.27 (87)</td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>≤ 30</td>
<td>221</td>
<td>4.64 (7)</td>
<td>13.4 (17)</td>
<td></td>
<td>0.5</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>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></td>
</tr>
<tr>
<td>&gt;80</td>
<td>1.46 (96)</td>
<td>1.84 (119)</td>
<td></td>
<td>0.030</td>
</tr>
<tr>
<td>&gt;50–80</td>
<td>2.45 (157)</td>
<td>3.21 (199)</td>
<td></td>
<td>0.130</td>
</tr>
<tr>
<td>≤50</td>
<td>3.21 (73)</td>
<td>6.44 (142)</td>
<td></td>
<td>0.720</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
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
Apixaban vs., Warfarin in Relation to Renal Function Over Time

Hijazi Z et al. JAMA Cardiol. 2016
Pharmacokinetics of NOACs

A. Efavargan
- Biliary elimination: 89% active metabolites
- Renal elimination: 3% active metabolites

B. Rivaroxaban
- Biliary elimination: 55% active metabolites
- Renal elimination: 40% active metabolites

C. Dabigatran
- Biliary elimination: 90% active metabolites
- Renal elimination: 7% active metabolites

D. Apixaban
- Biliary elimination: 75% active metabolites
- Renal elimination: 50% active metabolites

Liver metabolism
Direct intestinal excretion

Biliary elimination
Renal elimination (27%)
OACs in Chronic Kidney Disease pts with AF

**Chronic Kidney Disease**

- **eGFR 30 – 49 ml/min**
  - **FIRST CHOICE**
    - Apixaban 5 mg twice daily (or 2.5 mg twice daily in presence of one or more additional criteria: age ≥ 80 years, body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dl)
    - Rivaroxaban 15 mg once daily
    - Edoxaban 30 mg once daily
  - **SECOND CHOICE**
    - Dabigatran 110 mg twice daily
  - **NOT RECOMMENDED**
    - Dabigatran 150 mg twice daily
    - Rivaroxaban 20 mg once daily
    - Edoxaban 60 mg once daily

- **eGFR < 15 ml/min and Dialysis**
  - **FIRST CHOICE**
    - No anticoagulation or vitamin K anticoagulants (VKA) therapy is appropriate
    - NOT RECOMMENDED
    - All NOACs are not recommended, although FDA has approved Apixaban in hemodialysis patients

**Advanced Chronic Kidney Disease**

- *(n = 102,504)*

**Dialysis**

- *(n = 140,918)*

**Prevalence of Anticoagulant (%)**

- **Jan 10**
  - Apixaban
  - Rivaroxaban
  - Dabigatran
  - Edoxaban

**Chan et al J Am Coll Cardiol 2016**
NSAIDs for Osteoarthritis
Aspirin Instead of Warfarin?
Aspirin no Longer Plays a Role in Stroke Prevention in AF

Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.
# Antithrombotic Therapy for AF

**BAFTA: Bleeding Complications with Warfarin vs Aspirin in AF Patients > 75 Years**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major extracranial hemorrhage</td>
<td>1.4</td>
<td>1.6</td>
<td>0.87 (0.43 – 1.73)</td>
</tr>
<tr>
<td>All major hemorrhages</td>
<td>1.9</td>
<td>2.0</td>
<td>0.96 (0.53 – 1.75)</td>
</tr>
</tbody>
</table>

Mant et al. Lancet 2007
AVERROES
Stroke or Systemic Embolic Event

Cumulative Risk

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

ASA
Apixaban

No. at Risk

Months

ASA
2791
2720
2541
2124
1541

Apix
2809
2761
2567
2127
1523

AVERROES
Main Efficacy Outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>Apixaban</th>
<th>ASA</th>
<th>Event</th>
<th>Apixaban</th>
<th>ASA</th>
<th>Event</th>
<th>Apixaban</th>
<th>ASA</th>
<th>Event</th>
<th>Apixaban</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or SE (primary efficacy)</td>
<td>1.6%</td>
<td>3.7%</td>
<td>Stroke</td>
<td>1.6%</td>
<td>3.4%</td>
<td>SE</td>
<td>0.1%</td>
<td>0.4%</td>
<td>Myocardial infarction</td>
<td>0.8%</td>
<td>0.9%</td>
</tr>
<tr>
<td>HR: 0.45</td>
<td>95% CI: 0.32; 0.62</td>
<td>p&lt;0.001</td>
<td>HR: 0.46</td>
<td>95% CI: 0.33; 0.65</td>
<td>p&lt;0.001</td>
<td>HR: 0.15</td>
<td>95% CI: 0.03; 0.68</td>
<td>p=0.01</td>
<td>HR: 0.86</td>
<td>95% CI: 0.50; 1.48</td>
<td>p=0.59</td>
</tr>
</tbody>
</table>
AVEROES
Primary Safety Outcome: Major Bleeding

Cumulative Hazard

0.020
0.015
0.010
0.005
0.000

0 3 6 9 12 18
Months

Apixaban
ASA

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

AVERROES
Increased Efficacy of Apixaban in the Elderly

Age <75 years
HR with apixaban, 0.68
(95% CI, 0.42–1.08)

Age ≥75 years
HR with apixaban, 0.33
(95% CI, 0.19–0.54)

Stroke by Treatment and Age <75 or ≥75 Years

K. H. Ng et al. Age and Ageing 2015
AVERROES
Increased Safety of Apixaban in the Elderly

Age <75 years
HR with apixaban, 1.14
(95% CI, 0.58–2.30)

Age ≥75 years
HR with apixaban, 1.21
(95% CI, 0.69–2.12)

Major Bleeding by Treatment and Age <75 or ≥75 Years
The NNT to treat per year to prevent a stroke was 26 in subjects aged ≥75 years.

Switching 26 patients, aged ≥75 years, from Aspirin to Apixaban avoided one stroke per year.
Even the very Elderly, Derive Benefit from Apixaban

<table>
<thead>
<tr>
<th></th>
<th>Apixaban number of events (%/year)*</th>
<th>Aspirin number of events (%/year)*</th>
<th>HR (95% CI)</th>
<th>$P$ value (treatment effect)</th>
<th>$P_{interaction}$ for age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or SE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥85 years</td>
<td>2 (1.0)</td>
<td>15 (7.5)</td>
<td>0.14 (0.02–0.48)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>&lt;85 years</td>
<td>49 (1.7)</td>
<td>98 (3.4)</td>
<td>0.50 (0.35–0.69)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥85 years</td>
<td>9 (4.7)</td>
<td>35 (1.2)</td>
<td>0.96 (0.38–2.39)</td>
<td>0.93</td>
<td>0.65</td>
</tr>
<tr>
<td>&lt;85 years</td>
<td>10 (4.9)</td>
<td>29 (1.0)</td>
<td>1.21 (0.74–1.99)</td>
<td>1.21</td>
<td>0.45</td>
</tr>
<tr>
<td>ICH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥85 years</td>
<td>1 (0.5)</td>
<td>6 (2.9)</td>
<td>0.17 (0.01–1.02)</td>
<td>0.17</td>
<td>0.04</td>
</tr>
<tr>
<td>&lt;85 years</td>
<td>10 (0.3)</td>
<td>7 (0.2)</td>
<td>1.43 (0.55–3.93)</td>
<td>1.43</td>
<td>0.47</td>
</tr>
</tbody>
</table>

...it is difficult to justify the use of aspirin in elderly patients with AF, if apixaban is available...

The absolute reduction in stroke or SE with apixaban was much larger in subjects ≥85 years than in subjects <85 years (6.5% vs 1.7%/year, respectively)
The Benefits of Apixaban vs. ASA were Maintained in Stage III CKD pts

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>ASA</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%/yr (No. of events / No. of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke / SE</strong></td>
<td></td>
<td></td>
<td>Interaction: 0.10</td>
<td></td>
</tr>
<tr>
<td>eGFR ≥60 mL/min/1.73 m²</td>
<td>1.7% (34/1917)</td>
<td>2.8% (60/1911)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>eGFR 30-59 mL/min/1.73 m²*</td>
<td>1.8% (17/857)</td>
<td>5.6% (51/840)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td></td>
<td></td>
<td>Interaction: 0.82</td>
<td></td>
</tr>
<tr>
<td>eGFR ≥60 mL/min/1.73 m²</td>
<td>0.9% (19/1917)</td>
<td>0.8% (18/1911)</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>eGFR 30-59 mL/min/1.73 m²*</td>
<td>2.5% (24/857)</td>
<td>2.2% (20/840)</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td></td>
<td></td>
<td>Interaction: 0.39</td>
<td></td>
</tr>
<tr>
<td>eGFR ≥60 mL/min/1.73 m²</td>
<td>2.3% (49/1917)</td>
<td>3.3% (71/1911)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>eGFR 30-59 mL/min/1.73 m²*</td>
<td>6.2% (59/857)</td>
<td>7.1% (66/840)</td>
<td>0.42</td>
<td></td>
</tr>
</tbody>
</table>

*eGFR 30-59 mL/min/1.73 m²: stage III CKD patients

Apixaban better  ASA better

Eikelboom et al. J Stroke Cerebrovasc Dis 2012
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure control in anticoagulated patients with hypertension should be considered to reduce the risk of bleeding.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>When dabigatran is used, a reduced dose (110 mg twice daily) may be considered in patients &gt;75 years to reduce the risk of bleeding.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>In patients at high-risk of gastrointestinal bleeding, a VKA or another NOAC preparation should be preferred over dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Advice and treatment to avoid alcohol excess should be considered in all AF patients considered for OAC.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Genetic testing before the initiation of VKA therapy is not recommended.</td>
<td>III (no benefit)</td>
<td>B</td>
</tr>
<tr>
<td>Reinitiation of OAC after a bleeding event should be considered in all eligible patients by a multidisciplinary AF team, considering different anticoagulants and stroke prevention interventions, improved management of factors that contributed to bleeding, and stroke risk.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>In AF patients with severe active bleeding events, it is recommended to interrupt OAC therapy until the cause of bleeding is resolved.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
...2016 ESC Guidelines...
What Should We do now with Anticoagulation?

Apixaban 2.5 mg
Efficacy and Safety Profiles Matter

ARISTOTLE: A Phase III, Randomized, Double-blind Trial
Always on our Mind…

Superior stroke / systemic embolism prevention: 21% RRR p=0.01

Superior profile in reducing major bleeding: 31% RRR p<0.001

Superior reduction in all-cause mortality: 11% RRR p=0.047

Event rate (%/year)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Warfarin (Target INR 2.0–3.0)</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Efficacy Endpoint</td>
<td>1.60% 265/9,081</td>
<td>1.27% 2129,120</td>
</tr>
<tr>
<td>Primary Safety Endpoint</td>
<td>3.09% 462/9,052</td>
<td>2.13% 3279,088</td>
</tr>
<tr>
<td>Key Secondary Endpoint</td>
<td>3.94% 669/9,081</td>
<td>3.52% 603/9,120</td>
</tr>
</tbody>
</table>

Median duration of follow-up 1.8 years

eGFR: estimated glomerular filtration rate; MORD: modification of diet in renal disease; RRR: relative risk reduction; INR: international normalised ratio

Switching 1000 patients from Warfarin to Apixaban over a median treatment period of 1.8 years.
What Should We do now with Anticoagulation?
Acute Coronary Syndrome

- Pressure in the chest
- Spreading pain
- Lightheadedness, sweating or nausea
And Now What?

- Shall we change anticoagulant?
- What is the optimal antithrombotic therapy?
- For what duration?
2018 EHRA Practical Guide on NOACs in AF

AF patient on NOAC

**Elective PCI**
- Stop NOAC: last dose ≥24h before intervention
- Consider alternatives (as in all with need for chronic OAC):
  - Bypass surgery
  - Sole balloon angioplasty

**Periprocedural anticoagulation per local practice:**
- UFH (per ACT/aPTT)
- Bivalirudin
- Avoid GPIb/IIIa inhibitors

**Stent type:**
- Prefer contemporary DES
  (BMS and 1st gen DES to be avoided)

**Acute Coronary Syndrome**
- **STEMI**
  - Fibrinolysis
    - Only if below reference range (Tab. 9)
    - No UFH or enoxaparin until NOAC levels below reference range (Tab. 9)
- Primary PCI (preferred)
  - Radial access
  - Prefer new-generation DES
  - Additional UFH, LMWH, bivalirudin (regardless of last NOAC)
  - Avoid GPIb/IIIa inhibitors unless bail-out
  - Avoid fondaparinux

On admission:
- Stop NOAC
- Load with ASA (150-300 mg) +/- P2Y12 inhibitor as per standard protocol

**Non-STEMI**
- **Urgent**
  - Approach as per primary PCI
- **Non-urgent**
  - Delay PCI
  - Start fondaparinux (preferred) or LMWH ≤12h after last NOAC
  - Avoid upstream bivalirudin, UFH, or GPIb/IIIa inhibitors

After discontinuation of parenteral anticoagulation: restart (same) NOAC according to SmPC, in combination with single or dual antiplatelets (see Figure 11)

PPI should be considered
- Discharge with prespecified step-down plan (Figure 11)
Optimal Treatment Strategy...

Table 9: High-risk features for ischaemic events

- Prior stent thrombosis on adequate antiplatelet therapy
- Stenting of the last remaining patent coronary artery
- Diffuse multivessel disease, especially in diabetic patients
- Chronic kidney disease (i.e. creatinine clearance <60 mL/min)
- At least three stents implanted
- At least three lesions treated
- Bifurcation with two stents implanted
- Total stented length >60 mm
- Treatment of a chronic total occlusion
- History of STEMI

2018 ESC/EACTS Guidelines on myocardial revascularization
What is the Optimal Triple Antithrombotic Therapy?
What is the Optimal Dual Antithrombotic Therapy?
AUGUSTUS Trial

Inclusion
- AF (prior, persistent, or > 6 h duration)
- Physician decision that OAC is indicated
- ACS and/or PCI with planned P2Y_{12} inhibitor for 6 months

N = 4600

Apixaban 5 mg twice daily
- Aspirin
- Placebo

Warfarin
- Aspirin
- Placebo

Primary outcome: major/clinically relevant bleeding (through 6 months)
Secondary objective: death, MI, stroke, stent thrombosis

P2Y_{12} inhibitor for all patients x 6 months
Aspirin for all on the day of ACS or PCI
Aspirin vs placebo after randomization
No Direct Head-to-Head Comparisons…

O Pelé δήλωσε μια μέρα στους δημοσιογράφους: «Με έστειλε ο Θεός να δείξω στον Κόσμο το ποδόσφαιρο!»

Την άλλη μέρα, ρώτησαν τον Μαραντόνα τι έχει να σχολιάσει. Κι αυτός τούς απάντησε: «Εγώ δεν έστειλα κανέναν!»
Real-World Evidence Complements Clinical Trials Data
All is not as it seems
All is not as it seems
Efficacy and Safety of Apixaban in the Treatment of NVAF

A total of 23,799 patients were randomised in the clinical program, including 11,927 randomised to apixaban¹

<table>
<thead>
<tr>
<th>ARISTOTLE²</th>
<th>AVERROES³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised, double-blind, double-dummy, active control, multinational trial</td>
<td>Randomised, double-blind, double-dummy, active control, multinational trial</td>
</tr>
<tr>
<td>In more than 18,000 patients with NVAF</td>
<td>In more than 5500 patients with NVAF</td>
</tr>
<tr>
<td>Who were suitable for VKA therapy</td>
<td>Who were unsuitable for VKA therapy</td>
</tr>
<tr>
<td>Receive either apixaban 5.0 mg BD (or 2.5 mg BD in selected patients*) or warfarin (INR, target: 2.0-3.0)</td>
<td>Receive either apixaban 5.0 mg BD (or 2.5 mg BD in selected patients*) or ASA 81-324 mg</td>
</tr>
</tbody>
</table>

¹Patients with ≥2 of the following: age ≥80 years, body weight ≤60 kg, or a serum creatinine level ≥1.5 mg/dL (133 µmol/L)
An optimal oral anticoagulant for...