Anticoagulation to Reduce Stroke and Systemic Embolism in Patients with Atrial Fibrillation

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Epidemiology of Atrial Fibrillation

- AF affects approximately 2.7 Million Americans
- The Prevalence of AF in the general population is approximately 1-2%
- The Prevalence of AF increases with age:
  - 7.2% in patients > 65 yrs of age.
  - 10.3% in patients > 75 yrs of age.
- Affects men more than women HR 1.5
- Ethnic groups are affected differently
  - Whites: 8% prevalence
  - Blacks (3.8%); Hispanics (3.6%); Asians (3.9%).
- The lifetime Risk of Developing AF
  - 26% for Men
  - 23% for Women
Epidemiology of Stroke

• Stroke is the second leading cause of death worldwide and the 5th leading cause of death in the US.

• Annual Incidence in the US: 795,000
  • 610,000 First strokes
  • 185,000 Prior hx of strokes

• Age adjusted prevalence 2.6% (2010)

• Incidence increases with Age.

• Affects African Americans twice as often as White Americans.

• 87% of strokes are classified as ischemic.

Mozaffarian D et al. Heart Disease and stroke statistics 2015 Update Circulation 2015;e29
Atrial Fibrillation and Stroke

- AF is present in 25-30% of patients who present with ischemic stroke/TIA.
  - 19.7% Prior hx of AF
  - 3.8% New AF in ER
  - 5.2% AF Diagnosed within 3 months
  - 30% AF Documented by ILR @ 36 months

- Cardioembolic
  - Account for 15-20% of all ischemic strokes.
  - Cardioembolic strokes caused by AF are associated with the highest mortality (50% at 1 year) and morbidity.
  - Associated with high rates of recurrent strokes
  - Larger and more debilitating.
    - ¼ of pts require nursing home placement.

Left Atrial Appendage Thrombus

• >90% in LAA when present in pts with non-valvular AF.
• The LAA is located between the LUPV and the left ventricle.
• Lined with endothelium and trabeculated pectinate muscle.
• Anatomy varies as does thrombotic risk:
  • 1 lobe (20%)
  • 2 lobes (54%)
  • 3 lobes (23%)
Trans-Esophageal Echocardiography

- TEE features associated with thrombo-embolism in AF:
  - LA/LAA thrombus
  - LA/LAA SEC
  - Reduced LAA flow velocity (normal 20-40 cm/sec)

- TEE Visualization of Thrombus:
  - Sensitivity (92-100%)
  - Specificity (98-100%)
  - Negative Predictive value (98-100%)

- Thrombus seen in 13.8% of Pts referred for DCCV when AF >48 hrs

- Cardioversion for AF<48hrs without anticoagulation is NOT Safe!
  - 1.06% 6 Neurologic events in 567 cardioversions (484 pts) w/o AC @30 days
  - 0.22% 2 Neurologic events in 898 cardioversions (709)pts on AC @ 30 days
  - No Neurologic events in patients with CHA2DS2Vasc < 2

Klein AL. et al   ACUTE Trial   NEJM 2001;344:1411
Vitamin K Antagonists

- **Warfarin**
  - 68% Reduction in risk of CVA
    - 83% (On treatment Analysis)
  - Narrow Therapeutic Window:
    - Time in Therapeutic Range:
      - 55% (ROCKET AF)
      - Lower in Clinical Practice!
  - Drug Interactions:
    - Amiodarone
    - Verapamil
  - Dietary Interactions (Vit K)

Arch Intern Med 1994;154:1449–57
Cardiac Electrophysiology Clinics, Volume 6, Issue 1, 2014, 61–78
Dabigatran (Pradaxa)

- Direct Thrombin (Factor 2A or X) Inhibitor
- Major Trial: RE-LY
  - 18,113 pts with Non-Valvular AF + 1 Risk Factor
    - Mean CHADS Score: 2.1
  - Randomized to Dabigatran Vs Warfarin
- Findings:
  - Stroke & Embolism
    - Superior to Warfarin (150 mg)
  - Major Bleeding
    - Non-Inferior to Warfarin (150 mg)
    - Less Intracranial Hemorrhage
    - More GI Bleeding
- Dose: 150 mg 2xDay
- Renal Excretion: 80%
  - Dose Adjustment: 75 mg 2xD for CrCl <30 ml/min
- Reversal Agent: Idarucizumab

Rivaroxaban (Xarelto)

• Direct Factor Xa Inhibitor

• Major Trial: ROCKET-AF
  • 14,264 pts with Non-Valvular AF + 2 Risk Factor
    • Mean CHADS: 3.5
  • Findings:
    • Stroke & Embolism
      • Non-Inferior to Warfarin
    • Major Bleeding
      • Non-Inferior to Warfarin (150 mg)
      • Less Intracranial Hemorrhage
      • More GI Bleeding

• Dose: 20 mg Daily (Single Dose)

• Renal Excretion: 33%
  • Dose Adjustment: 15mg/day CrCl 30-49 ml/min

Apixaban (Eliquis)

- Direct Factor Xa Inhibitor
- Major Trial: ARISTOTLE
  - 18,206 pts with Non-Valvular AF +1 Risk Factor
    - Mean CHADS: 2.1
- Findings:
  - Stroke & Embolism
    - Superior to Warfarin
  - Major Bleeding
    - Superior to Warfarin (150 mg)
    - Less Intracranial Hemorrhage/hemorrhagic stroke
    - Mortality Benefit
- Dose: 5 mg 2xD
- Renal Excretion: 27%
  - Dose Adjustment: 2.5mg 2x day (2/3)
    - Age ≥ 80
    - Weight < 60 kg
    - Creatinine ≥ 1.5 mg/dl

Edoxaban (Savaysa)

- Direct Factor Xa Inhibitor
- Major Trial: ENGAGE-AF
  - 21,105 pts with Non-valvular AF +1 Risk Factor
    - Mean CHADS2: 2.8
- Findings:
  - Stroke & Embolism
    - Non Inferior to Warfarin
  - Major Bleeding
    - Superior to Warfarin
  - Mortality Benefit
- Dose: 60 mg/d
- Renal Excretion: 50%
  - Dose Adjustment: 2.5mg 2x day (2/3)
    - Weight ≤ 60 kg
    - Creat Clearance 30-50
    - Creat Clearance > 100 (DO NOT USE)

Safety & Efficacy of NOACs

Meta-Analysis of Randomized Trials

Secondary Safety Outcomes:

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Pooled NOAC (events)</th>
<th>Pooled warfarin (events)</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic stroke</td>
<td>665/29252</td>
<td>724/29221</td>
<td>0.92 (0.83-1.02)</td>
<td>0.10</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>130/29252</td>
<td>263/29221</td>
<td>0.49 (0.38-0.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>413/29252</td>
<td>432/29221</td>
<td>0.97 (0.78-1.20)</td>
<td>0.77</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2022/29292</td>
<td>2245/29221</td>
<td>0.90 (0.85-0.95)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Safety

| Intracranial haemorrhage          | 204/29287             | 425/29211                | 0.48 (0.39-0.59) | <0.0001 |
| Gastrointestinal bleeding         | 751/29287             | 591/29211                | 1.25 (1.01-1.55) | 0.043  |

Major Bleeding:

<table>
<thead>
<tr>
<th>NOAC (events)</th>
<th>Warfarin (events)</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY5*</td>
<td>375/6076</td>
<td>397/6022</td>
<td>0.94 (0.82-1.07)</td>
</tr>
<tr>
<td>ROCKET AF‡</td>
<td>395/7111</td>
<td>386/7125</td>
<td>1.03 (0.96-1.18)</td>
</tr>
<tr>
<td>ARISTOTLE‡</td>
<td>327/9088</td>
<td>462/9052</td>
<td>0.71 (0.61-0.81)</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48§</td>
<td>444/7012</td>
<td>557/7012</td>
<td>0.80 (0.71-0.90)</td>
</tr>
<tr>
<td>Combined (random)</td>
<td>1541/29287</td>
<td>1802/29211</td>
<td>0.86 (0.73-1.00)</td>
</tr>
</tbody>
</table>
Idarucizumab (Praxbind)

- Monoclonal antibody fragment.
  - Binds free and thrombin-bound dabigatran.
- Major Trial: REVERSE AD
  - Prospective cohort study in 300 patients:
    - Serious bleeding (Group A)
    - Required urgent surgery or intervention (Group B).
  - The primary end point was the maximum percentage reversal of the anticoagulant effect of dabigatran
  - Findings:
    - Idarucizumab rapidly and completely reversed the effect of dabigatran in 88 to 98% of the patients who had had elevated clotting times at baseline.
- Dose: 2.5 mg bolus infusions < 15 min apart.

Managing Bleeding on Oral Anticoagulation

Patient with active bleeding
- Compress bleeding sites mechanically
- Assess haemodynamic status, blood pressure, basic coagulation parameters, blood count, and kidney function
- Obtain anticoagulation history (last NOAC / VKA dose)

VKA
- Delay VKA until INR < 2
- Add symptomatic treatment: Fluid replacement, Blood transfusion, Treat bleeding cause (e.g., gastroscopy)
- Consider to add Vitamin K (1-10 mg) i.v.
- Consider PCC and FFP
- Consider replacement of platelets where appropriate

NOAC
- Delay NOAC for 1 dose or 1 day
- Add symptomatic treatment: Fluid replacement, Blood transfusion, Treat bleeding cause (e.g., gastroscopy)
- Consider to add oral charcoal if recently ingested NOAC
- Consider specific antidote, or PCC if no antidote available
- Consider replacement of platelets where appropriate
# Discontinuing NOAC’s Prior to Procedures

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th></th>
<th>Rivaroxaban-Apixaban-Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Risk</td>
<td>High Risk</td>
<td>Low Risk</td>
</tr>
<tr>
<td>CrCl &gt; 80 ml/min</td>
<td>&gt; 24 h</td>
<td>&gt; 48 hrs</td>
<td>&gt; 24 hrs</td>
</tr>
<tr>
<td>CrCl 50-80 ml/min</td>
<td>&gt; 36 hrs</td>
<td>&gt; 72 hrs</td>
<td>&gt; 24 hrs</td>
</tr>
<tr>
<td>CrCl 30-50 ml/min</td>
<td>&gt; 48 hrs</td>
<td>&gt; 96 hrs</td>
<td>&gt; 24 hrs</td>
</tr>
<tr>
<td>CrCl 15-30 ml/min</td>
<td>Not Indicated</td>
<td>Not Indicated</td>
<td>&gt; 36 hrs</td>
</tr>
<tr>
<td>CrCl &lt; 15 ml/min</td>
<td>No Official Indication for Use</td>
<td>&gt;= 36 hrs</td>
<td>&gt; 48 hrs</td>
</tr>
</tbody>
</table>

*No Important Bleeding Risk and/or adequate hemostasis possible: Perform surgery at trough level (1.e >12 or 24 hrs after last intake)*
2016 ESC Guidelines: OAC & DAPT

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>After elective coronary stenting for stable coronary artery disease in AF patients at risk of stroke, combination triple therapy with aspirin, clopidogrel and an oral anticoagulant should be considered for 1 month to prevent recurrent coronary and cerebral ischaemic events.</td>
<td>IIa</td>
<td>B</td>
<td>522, 524</td>
</tr>
<tr>
<td>After an ACS with stent implantation in AF patients at risk of stroke, combination triple therapy with aspirin, clopidogrel and an oral anticoagulant should be considered for 1–6 months to prevent recurrent coronary and cerebral ischaemic events.</td>
<td>IIa</td>
<td>C</td>
<td>520</td>
</tr>
<tr>
<td>After an ACS without stent implantation in AF patients at risk of stroke, dual treatment with an oral anticoagulant and aspirin or clopidogrel should be considered for up to 12 months to prevent recurrent coronary and cerebral ischaemic events.</td>
<td>IIa</td>
<td>C</td>
<td>520</td>
</tr>
<tr>
<td>The duration of combination antithrombotic therapy, especially triple therapy, should be kept to a limited period, balancing the estimated risk of recurrent coronary events and bleeding.</td>
<td>IIa</td>
<td>B</td>
<td>520</td>
</tr>
<tr>
<td>Dual therapy with any oral anticoagulant plus clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients.</td>
<td>IIb</td>
<td>C</td>
<td>524, 525</td>
</tr>
</tbody>
</table>
Recommendations for stroke prevention in patients with AF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA2DS2-VASc score of 2 or more.</td>
<td>I</td>
<td>A</td>
<td>38, 318–321, 354, 404</td>
</tr>
<tr>
<td>Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA2DS2-VASc score of 3 or more.</td>
<td>I</td>
<td>A</td>
<td>38, 318–321, 354, 404</td>
</tr>
<tr>
<td>Oral anticoagulation therapy should be considered in male AF patients with a CHA2DS2-VASc score of 1, considering individual characteristics and patient preferences.</td>
<td>IIa</td>
<td>B</td>
<td>371, 375–377</td>
</tr>
<tr>
<td>Oral anticoagulation therapy should be considered in female AF patients with a CHA2DS2-VASc score of 2, considering individual characteristics and patient preferences.</td>
<td>IIa</td>
<td>B</td>
<td>371, 376, 377</td>
</tr>
<tr>
<td>Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.</td>
<td>I</td>
<td>B</td>
<td>274, 435–440</td>
</tr>
<tr>
<td>When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a vitamin K antagonist.</td>
<td>I</td>
<td>A</td>
<td>39, 318–321, 404</td>
</tr>
<tr>
<td>When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored.</td>
<td>I</td>
<td>A</td>
<td>395, 432, 441–444</td>
</tr>
<tr>
<td>AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to NOAC (e.g. prosthetic valve).</td>
<td>IIb</td>
<td>A</td>
<td>39, 318, 319, 404, 408</td>
</tr>
</tbody>
</table>

Eur Heart J. 2016;37(38):2893-2962
### 2016 ESC Guidelines: Who not to Anticoagulate

<table>
<thead>
<tr>
<th>Statement</th>
<th>Grade</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition.</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention.</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.</td>
<td>III</td>
<td>A</td>
</tr>
<tr>
<td>NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C).</td>
<td>III</td>
<td>B, C</td>
</tr>
</tbody>
</table>

Eur Heart J. 2016;37(38):2893-2962
Under-Utilization of OAC

- Approximately 50% of patients eligible for anti-coagulation receive Rx.
- Perceived Bleeding Risk.
  - Age
    - Risk of thromboembolism increases with age.
    - Efficacy of anticoagulation does not decrease with age.
      - Efficacy of Aspirin does decrease with age.
  - Falls & Dementia
  - Frailty
- Failure to Resume OAC following a bleeding episode
  - Retrospective analysis of 442 pts with index GI Bleed.
  - 5.5% vs 0.6% thrombotic episodes @ 90 day follow-up. (p<0.01)
  - 6% vs 10% risk of recurrent GI Bleeding @ 90 days (p=0.09)

Witt DM. Arch Intern Med. 2012;172(19):1484-1491
Conclusions

1. Atrial Fibrillation is a Leading Cause of Stroke
2. Oral Anticoagulation is of proven benefit in Reducing the Risk of Stroke
3. Novel Anti-coagulants compare favorably with Warfarin
   1. Efficacy
   2. Safety Profile
   3. Mortality benefit
4. Reversal Agents are becoming available
   1. Idarucizumab for dabigatran
   2. Adenexanet alpha for factor Xa inhibitors (FDA approval pending ?)
5. Unless absolutely contra-indicated patients at risk for thromboembolism in AF should receive oral anticoagulation.
6. Recent Guidelines reflect this information.