Anticoagulation in atrial fibrillation: the global GARFIELD Registry
INR Control by Region

Based on three most recent INR values (%)

## Novel oral anticoagulants (NOACs)

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand name</strong></td>
<td><strong>Eliquis</strong></td>
<td><strong>Xarelto</strong></td>
<td><strong>Pradaxa</strong></td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor IIa</td>
</tr>
<tr>
<td><strong>T max, h</strong></td>
<td>1-3</td>
<td>2-4</td>
<td>1.25-3</td>
</tr>
<tr>
<td><strong>Half-life, h</strong></td>
<td>8-15</td>
<td>9-13</td>
<td>12-14</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>25%</td>
<td>60%</td>
<td>80%</td>
</tr>
</tbody>
</table>
Meta-analysis: NOAC higher doses
Stroke or systemic embolism

Higher doses of NOACs vs warfarin
Major bleeding

Modified from Ruff CT et al. Lancet 2013
RCTs vs “Real-world” use

- Patient selection
- Relative risk reduction vs. absolute risk reduction
- Personalized approach recommended

Israel:

Dabigatran 150 mg bid – standard dose
Dabigatran 110 mg bid - older patients, high bleeding risk

(Clalit Health Services Pharmacopoeia)
Aims

Primary
• Determine the rates for major bleeding in “real-world” patients with AF beginning treatment with dabigatran, rivaroxaban or warfarin

Secondary
• Determine the organ-specific pattern of bleeding
Clalit Health Services

- >4.3 million members
- >1500 community clinics
- 14 public hospitals
Methods

• Consecutive, unselected patients initiating anticoagulation for AF from 1/2011 to 12/2013

• Charts of patients hospitalized because of bleeding (= bleeding endpoint) reviewed

• Bleeding events calculated as rate per 100 patient-years of treatment

• Organ specific bleeding calculated as rate per 100 patient-years of treatment
Percentage of patients beginning anticoagulants during study period

Jan 2011 – Dec 2013

Percentage of patients

Rivaroxaban  Dabigatran  Warfarin
## Demographic and clinical features

**N=18249**

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran150</th>
<th>Dabigatran110</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>9564</td>
<td>1806</td>
<td>4170</td>
<td>2709</td>
</tr>
<tr>
<td>Patient-years</td>
<td>9451</td>
<td>1079</td>
<td>3215</td>
<td>1086</td>
</tr>
<tr>
<td>Age in years Median (Range)</td>
<td>79 (27-99)</td>
<td>78 (52-89)</td>
<td>82 (55-95)</td>
<td>82 (58-91)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>43.8</td>
<td>45.1</td>
<td>47</td>
<td>38.6</td>
</tr>
<tr>
<td>CHADS$_2$ score Median (Range)</td>
<td>3 (0-6)</td>
<td>3 (1-6)</td>
<td>4 (2-6)</td>
<td>4 (2-6)</td>
</tr>
<tr>
<td>Serum creatinine mg/dL Median (Range)</td>
<td>1.2 (0.3-11.6)</td>
<td>1.0 (0.5-4.4)</td>
<td>1.2 (0.5-4.1)</td>
<td>1.3 (0.5-3.5)</td>
</tr>
<tr>
<td>Anti platelet drug use (%)</td>
<td>52</td>
<td>50</td>
<td>35</td>
<td>55</td>
</tr>
</tbody>
</table>
# Major bleeding rates

<table>
<thead>
<tr>
<th>Rate per 100 patient years (95% CI)</th>
<th>Warfarin</th>
<th>Dabigatran overall</th>
<th>Dabigatran 150</th>
<th>Dabigatran 110</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major bleeding</strong></td>
<td>3.96 (3.64-4.42)</td>
<td>4.24 (3.68-4.89)</td>
<td>2.85 (2.04-3.92)</td>
<td>4.69 (4.03-5.44)</td>
<td>4.10 (3.04-5.32)</td>
</tr>
</tbody>
</table>
Hazard ratios: Warfarin vs NOACs

- Warfarin versus dabigatran overall: HR=0.89, CI=0.73-1.07
- Warfarin versus dabigatran150: HR=1.44, CI=0.99-2.10
- Warfarin versus dabigatran110: HR=0.84, CI=0.69-1.01
- Warfarin versus rivaroxaban: HR=0.97, CI=0.71-1.34
Site-specific bleeding rates:
Intracranial hemorrhage
Site-specific bleeding rates: Gastrointestinal hemorrhage
## Population-based studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Major hemorrhage (per 100 pt years)</th>
<th>Excess bleeding with dabi vs warfarin?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Danish</strong> JACC 2011 (Patient and pharmacy reg.)</td>
<td>Warf=8936 Dabi=4978</td>
<td>Warf=2.9 Dabi150=2.2 Dabi110=2.8</td>
<td>No</td>
</tr>
<tr>
<td><strong>Danish</strong> BMJ Open 2013 (Patient and pharmacy reg.)</td>
<td>Warf=49640 Dabi150=1114 Dabi110=1612</td>
<td>Warf=4.29 Dabi150=3.75 Dabi110=11.05</td>
<td>Yes for dabi110</td>
</tr>
<tr>
<td><strong>Medicare</strong> JAMA Int Med 2014</td>
<td>Warf=8102 Dabi=1302</td>
<td>Warf=5.9% Dabi=9%</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Medicare</strong> Circulation 2014</td>
<td>Warf= 67207 Dabi=67494</td>
<td>Warf= 4.39 Dabi= 4.27</td>
<td>No</td>
</tr>
<tr>
<td><strong>Israeli</strong> (HMO database, individual chart review)</td>
<td>Warf=9564 Dabi150=1806 Dabi110=4170 Riva=2709</td>
<td>Warf=3.9 Dabi150=2.8 Dabi110=4.6 Riva=4.1</td>
<td>No</td>
</tr>
</tbody>
</table>
Conclusions

• Israeli physicians now start over 50% of new AF patients on a NOAC (using dose stratification for dabigatran)

• Major hemorrhage rate was not greater with dabigatran or rivaroxaban compared to warfarin

• Results are consistent with RCTs and some but not all population studies

• High risk versus low risk patients distinguished – plausible reason for greater bleeding risk in dabigatran 110mg group & reduced risk in dabigatran 150 mg group
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