Efficacy and Safety of DOACs vs. Warfarin by Background Antiplatelet Therapy

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BACKGROUND

- Efficacy and safety of DOACs vs. W may differ in AF pts receiving antplatelet therapy (APT).
- Prior individual-trial-specific analyses examining Rx effect of DOAC vs. W by baseline APT are underpowered for interaction testing.

METHODS

- Pt-level data from COMBINE-AF (RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE-AF-TIMI 48) analyzed.
- Lower-dose DOACs (Dabi 110, Edox 110) not globally approved for clinical use excluded.
- Pts grouped by use of APT at baseline.
- Outcomes examined using Cox models adjusted for age, sex, wgt, CrCl, smoking status, HTN, DM, CAD, prior MI, PAD and prior stroke, with interaction testing for APT*treatment allocation.

RESULTS

- Among 57,598 pts, 19,774 (34%) on APT at baseline (92% aspirin only, 5% P2Y12 only, 3% DAPT) (Table 1).
- Pts receiving APT had ↑ event rates (Figure 1), in context of baseline ↑ risk.
- Differences ↑ for major bleeding (incl. GIB) and mortality.
- Relative Rx effect (HR) of DOAC vs. W for all 6 outcomes was consistent irrespective of baseline APT (p-interaction [aHR] for each ≥0.20; Figure 1).
- However, direction & magnitude of ARR differed for ICH and major GI bleeding by baseline APT:
  - For ICH, ↑ absolute benefit w/ DOAC vs. W in those on APT at baseline (ARR 0.6% vs. 0.3%; p = 0.007).
  - For major GI, ↑ risk of bleed w/ DOAC vs. W in those on APT (ARR 0.6% vs. -0.2%; p = 0.04).
- Limitation: APT assessed at baseline, which may underestimate reported effects owing to changes in APT use during f/u.

RESULTS (Continued)

- Those on APT were less likely to be female, with ↑ CAD, prior MI, PAD and stroke (p < 0.001 for each; Table 1).
- No differences when further stratified by DOAC vs. W.
- Pts receiving APT had ↑ event rates (Figure 1), in context of baseline ↑ risk.

- Differences ↑ for major bleeding (incl. GIB) and mortality.
- Relative Rx effect (HR) of DOAC vs. W for all 6 outcomes was consistent irrespective of baseline APT (p-interaction [aHR] for each ≥0.20; Figure 1).
- However, direction & magnitude of ARR differed for ICH and major GI bleeding by baseline APT:
  - For ICH, ↑ absolute benefit w/ DOAC vs. W in those on APT at baseline (ARR 0.6% vs. 0.3%; p = 0.007).
  - For major GI, ↑ risk of bleed w/ DOAC vs. W in those on APT (ARR 0.6% vs. -0.2%; p = 0.04).
- Limitation: APT assessed at baseline, which may underestimate reported effects owing to changes in APT use during f/u.

CONCLUSIONS

- Pts receiving APT have ↑ event rates owing to higher baseline risk.
- DOACs ↓ S/SEE and major bleeding irrespective of baseline APT.
- Given ↑ bleeding in AF pts treated w/ both APT and AC in absence of findings, support recent GL recommendation to avoid routine APT + AC.
- In pts treated with APT, DOAC vs. W has greater absolute safety benefit for ICH, though with greater absolute risk for GI bleeding.

Table 1: Selected Baseline Characteristics by Group

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>No Antiplatelet Therapy (N=37,824)</th>
<th>Antiplatelet Therapy (N=19,774)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>72 (65-77)</td>
<td>71 (65-77)</td>
<td>0.63</td>
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<tr>
<td>Female (%)</td>
<td>38.4</td>
<td>35.1</td>
<td>&lt;0.001</td>
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<td>Weight (kg)</td>
<td>81 (70-95)</td>
<td>80 (69-94)</td>
<td>0.003</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>23.7</td>
<td>40.5</td>
<td>&lt;0.001</td>
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<tr>
<td>Prior MI (%)</td>
<td>11.1</td>
<td>21.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAD (%)</td>
<td>4.1</td>
<td>5.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>18.7</td>
<td>20.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figures

Figure 1: Clinical Outcomes by DOAC vs. Warfarin Stratified by Baseline Antiplatelet Therapy

- DOAC w/o APT
- Warfarin w/o APT
- DOAC + APT
- Warfarin + APT

- Stroke/SEE
- Ischemic Stroke
- Major Bleeding
- Intracranial Hemorrhage
- Major GI Bleeding

- p-int (ARR) = 0.13 p-int (ARR) = 0.27
- p-int (ARR) = 0.51 p-int (ARR) = 0.60
- p-int (ARR) = 0.12 p-int (ARR) = 0.23
- aHR 0.5% aHR 0.7% aHR 0.8% aHR 0.6% aHR 0.2% aHR 0.5% aHR 0.2% aHR 0.5% aHR 0.2%
- ARR 0.3% ARR 0.2% ARR 0.5% ARR 0.6% ARR 0.5% ARR 0.5% ARR 0.6% ARR 0.5% ARR 0.5% ARR 0.5% ARR 0.5%
- p = 0.007 p = 0.007 p = 0.001 p = 0.001 p = 0.001 p = 0.001 p = 0.001 p = 0.001 p = 0.001 p = 0.001

DISCLOSURE OF FACULTY RELATIONSHIPS:


Figure 1: Clinical Outcomes by DOAC vs. Warfarin Stratified by Baseline Antiplatelet Therapy

- DOAC w/o APT
- Warfarin w/o APT
- DOAC + APT
- Warfarin + APT

- Stroke/SEE
- Ischemic Stroke
- All-Cause Mortality

- p-int (ARR) = 0.52 p-int (ARR) = 0.35
- p-int (ARR) = 0.12 p-int (ARR) = 0.23
- p-int (ARR) = 0.07 p-int (ARR) = 0.20
- p-int (ARR) = 0.29
- aHR 0.5% aHR 0.5% aHR 0.6% aHR 0.6% aHR 0.2% aHR 0.6%
- ARR 0.5% ARR 0.5% ARR 0.6% ARR 0.6% ARR 0.5% ARR 0.6%
- p = 0.007 p = 0.007 p = 0.001 p = 0.001 p = 0.001 p = 0.001

Table 1: Selected Baseline Characteristics by Group

- Major Bleeding
- Intracranial Hemorrhage
- Major GI Bleeding

- Event Rate (%/y)

- Event Rate (%/y)

- Event Rate (%/y)