Meta Analysis for All-cause Death for Apixaban vs. Placebo Or Control in SPAF Trials

Li Wang, Ph.D, Weihua Tang, Ph.D
Bristol-Myers Squibb Company, Hopewell, NJ 08534

BACKGROUND

- Apixaban was superior to warfarin for reduction of all-cause death in ARISTOTLE SPAF trial
- Apixaban reduced the incidence of all-cause death comparing to aspirin (ASA) although it was not statistically significant in AVERROES SPAF trial
- It is of great interest to identify the effect of apixaban vs. placebo or control (other than warfarin and ASA) in terms of reducing all-cause death in SPAF trials

DATA AVAILABILITY

- Apixaban vs. warfarin
- Apixaban vs. ASA
- Warfarin vs. placebo or control
- ASA vs. placebo or control

METHODOLOGY

- Indirect Comparison:
  - When head to head direct comparison data is not available, indirect comparison is a very useful tool to make inferences
  - Naïve indirect comparison should be avoided
  - Adjusted indirect comparison usually gives consistent results with direct comparison
- Meta Analysis:
  - When there are more than one trial with the same comparators, Meta-analysis is often used to combine findings from these independent trials to provide a more precise estimate of the treatment effect, weighted by the size of the studies
  - Heterogeneity between trials should be explored

STATISTICAL ANALYSIS DETAILS

<table>
<thead>
<tr>
<th>Treatments Compared</th>
<th>Odds Ratio</th>
<th>Odds Ratio 95% CI</th>
<th>Nominal P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISTOTLE Hart et al. 2007</td>
<td>W vs. A</td>
<td>0.89</td>
<td>(0.79, 1.00)</td>
</tr>
<tr>
<td>AVERROES Hart et al. 2007</td>
<td>ASA vs. P</td>
<td>0.74</td>
<td>(0.57, 0.97)</td>
</tr>
<tr>
<td>Meta Analysis Combining Two Indirect Comparisons</td>
<td>A vs. P</td>
<td>0.66</td>
<td>(0.50, 0.88)</td>
</tr>
</tbody>
</table>

STATISTICAL ANALYSIS DETAILS (cont.)

- Indirect Comparison for Odds Ratio:
  - ln(OR_{i1}) = ln(OR_{w1}) - ln(OR_{w2})
  - Var(\ln(OR_{w1})) = Var(\ln(OR_{w2})) + Var(\ln(OR_{w3}))
- Meta analysis with random effect model:
  - \bar{\theta}_i = \theta_i + v_i + e_i
  - \bar{\theta}_i \sim N(\theta, \Sigma)^e \sim \chi^2
- DerSimonian and Laird (1986): to estimate random variance \(v_{w1}\) and standard error of \(m_w\) on natural log of OR:
  - \(m_w = \sum_{i=1}^{n} \frac{w_i y_i}{w_i + 1}\)
  - s.e.\((m_w) = 1 / \left(\sum_{i=1}^{n} w_i \right)^{1/2}

CONCLUSION AND DISCUSSION

- In this meta analysis, apixaban reduced all-cause death comparing to placebo or control
- Each indirect comparison shows that apixaban reduced all-cause death by at least 33% when compared to placebo or control with a 95% CI with upper bound < 1
- Apixaban effect is highly consistent in two indirect comparisons
- This meta analysis combining two indirect comparisons shows that apixaban reduced all-cause death by 34% when compared to placebo/control with a 95% CI with upper bound < 1
- Caveat:
  - The result depends on the assumption of similarity of treatment effect in indirect comparison, which is not testable
  - Only two trials were used to assess between study variation in this meta analysis

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REFERENCES