Win Ratio Application for a Composite Outcome in a Randomized Cardiovascular Trial

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Background – Common practice

- Cardiovascular clinical trials often use survival analysis on composite outcomes (time-to-first-event).
- If severity of event types differ or there is a temporal relationship among events, this may underrepresent more severe, later occurring events by taking the first event and censoring the rest.
  - Example: If outcome is death/stroke/bleeding, could underrepresent death since other events may occur prior to death but not after.
- Combining events known to have associations in opposite directions may cause point estimate to be close to null.
  - Example: Warfarin is associated with fewer strokes (HR < 1), but more bleeding (HR > 1). So, composite endpoint may be about 1.
Background – Win ratio

• While Cox PH first combines events then compares, the win ratio first compares events then combines.
• Win ratio compares events in order of severity among pairs of patients on active and standard treatment.
• Can do matched analysis (one patient on active treatment matched to one patient on standard treatment based on risk factors) or unmatched analysis (every patient on active treatment is compared to every patient on standard treatment).
Background – Win ratio calculation

• Only include events that occur within time neither patient on active/standard treatment was censored
• If patient on standard treatment has most severe event type prior to the patient on active treatment having the same event, active treatment wins and standard treatment loses
• If neither win on most severe outcome, then next severe event type compared
• Continue through all event types and summarize across all pairs
• Win ratio = total wins/total losses
  • Win ratio > 1 favors treatment effect of active therapy
  • Unlike hazard ratio, where HR < 1 favors treatment effect of active therapy
Goal

Compare win ratio analysis to standard Cox proportional hazards model (time-to-first-event) and a modified Cox PH model (time-to-most-severe-event)
Methods

• Used net outcome (death/disabling stroke/life-threatening bleeding) of ENGAGE-TIMI 48 trial
• ENGAGE compared high dose Edoxaban (n = 7035) and low dose Edoxaban (n = 7034) to Warfarin (n = 7036)
• Time-to-first-event and time-to-most-severe event Cox PH models calculated with SAS 9.4
• Unmatched win ratio and confidence intervals calculated in R with WWR package
Methods

• Event severity order:
  1. Death
  2. Disabling stroke
  3. Life-threatening bleeding
### Results

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Win ratio</th>
<th>Time-to-first-event Cox PH</th>
<th>Time-to-most-severe-event Cox PH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>High dose Edoxaban vs. Warfarin</td>
<td>Win/Hazard Ratio</td>
<td>1.122</td>
<td>0.885</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>1.021, 1.233</td>
<td>0.808, 0.969</td>
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<tr>
<td></td>
<td>P-value</td>
<td>0.0173</td>
<td>0.0084</td>
</tr>
<tr>
<td>Low dose Edoxaban vs. Warfarin</td>
<td>Win/Hazard Ratio</td>
<td>1.184</td>
<td>0.834</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>1.076, 1.303</td>
<td>0.761, 0.915</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>0.0005</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Win ratio > 1 favors treatment effect of active therapy (Edoxaban)

Hazard ratio < 1 favors treatment effect of active therapy (Edoxaban)
Results – Contribution Indices

Contribution index = total number of wins or losses due to event type / total wins and losses

*Ex. 46% of wins and losses for HDER compared to warfarin were wins due to death
Conclusion

• High dose edoxaban “wins” 12% more often than Warfarin and has 11% less risk of death/disabling stroke/life-threatening bleeding (first/most severe)
• Low dose edoxaban “wins” 18% more often than Warfarin, has 17% less risk of first event, and 18% less risk of most severe event of death/disabling stroke/life-threatening bleeding
• Win ratio, time-to-first-event Cox PH, and time-to-most-severe-event Cox PH provided similar conclusions for net benefit in ENGAGE-TIMI 48
References & Acknowledgements


