Communicating Complex Information in Drug Product Labeling

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Division of Cardiovascular and Renal Products
FDA
**Forest plot of effects by subgroup**

![Forest plot diagram](forest_plot_diagram.png)

*Figure 5: Stroke and Symptomatic Tachycardia Hazard Ratios by Baseline Characteristic.*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients</th>
<th>TRADAXA 150</th>
<th>Warfarin</th>
<th>TRADAXA 150 vs Warfarin</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>16119</td>
<td>1730 (1.12)</td>
<td>117 (1.04)</td>
<td>0.65 (0.52-0.83)</td>
<td></td>
</tr>
<tr>
<td>VKA use at entry (yes (41.8%), no (58.2%))</td>
<td>1512</td>
<td>1170 (1.12)</td>
<td>104 (1.04)</td>
<td>0.64 (0.48-0.85)</td>
<td></td>
</tr>
<tr>
<td>African-American (yes (39.8%), no (60.2%))</td>
<td>1512</td>
<td>1170 (1.12)</td>
<td>104 (1.04)</td>
<td>0.64 (0.48-0.85)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60 (15.3%)</td>
<td>2891</td>
<td>1410 (1.02)</td>
<td>225 (1.12)</td>
<td>0.51 (0.36-0.75)</td>
<td></td>
</tr>
<tr>
<td>60-74 (40.6%)</td>
<td>7664</td>
<td>3886 (1.01)</td>
<td>378 (1.03)</td>
<td>0.87 (0.67-1.14)</td>
<td></td>
</tr>
<tr>
<td>≥ 75 (44.1%)</td>
<td>7239</td>
<td>3120 (1.01)</td>
<td>131 (1.01)</td>
<td>0.98 (0.71-1.36)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (62.3%)</td>
<td>11514</td>
<td>6014 (1.11)</td>
<td>115 (1.05)</td>
<td>0.73 (0.54-1.00)</td>
<td></td>
</tr>
<tr>
<td>Female (37.7%)</td>
<td>6518</td>
<td>3500 (1.02)</td>
<td>87 (1.03)</td>
<td>0.89 (0.67-1.18)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60 (17.2%)</td>
<td>1997</td>
<td>1057 (1.03)</td>
<td>168 (1.03)</td>
<td>0.50 (0.32-0.80)</td>
<td></td>
</tr>
<tr>
<td>60-90 (39.0%)</td>
<td>8037</td>
<td>3843 (1.00)</td>
<td>101 (1.01)</td>
<td>0.89 (0.59-1.36)</td>
<td></td>
</tr>
<tr>
<td>≥ 90 (43.8%)</td>
<td>1608</td>
<td>836 (1.01)</td>
<td>34 (1.01)</td>
<td>0.89 (0.59-1.36)</td>
<td></td>
</tr>
<tr>
<td>History of stroke/TIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (68.0%)</td>
<td>16480</td>
<td>8445 (1.00)</td>
<td>136 (1.01)</td>
<td>0.60 (0.45-0.80)</td>
<td></td>
</tr>
<tr>
<td>Yes (32.0%)</td>
<td>1263</td>
<td>651 (1.01)</td>
<td>65 (1.02)</td>
<td>0.69 (0.50-1.02)</td>
<td></td>
</tr>
<tr>
<td>Diabetes at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (67.7%)</td>
<td>15094</td>
<td>7517 (1.02)</td>
<td>130 (1.01)</td>
<td>0.67 (0.51-0.87)</td>
<td></td>
</tr>
<tr>
<td>Yes (32.3%)</td>
<td>4229</td>
<td>2212 (1.00)</td>
<td>64 (1.02)</td>
<td>0.60 (0.41-0.85)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (70.0%)</td>
<td>15094</td>
<td>7517 (1.02)</td>
<td>130 (1.01)</td>
<td>0.67 (0.51-0.87)</td>
<td></td>
</tr>
<tr>
<td>Yes (30.0%)</td>
<td>4229</td>
<td>2212 (1.00)</td>
<td>64 (1.02)</td>
<td>0.60 (0.41-0.85)</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 3 (1.4%)</td>
<td>7545</td>
<td>3871 (1.00)</td>
<td>41 (1.01)</td>
<td>0.64 (0.48-0.86)</td>
<td></td>
</tr>
<tr>
<td>&gt; 3 (25.4%)</td>
<td>14583</td>
<td>7299 (0.98)</td>
<td>101 (1.02)</td>
<td>0.89 (0.65-1.23)</td>
<td></td>
</tr>
<tr>
<td>CrCl (mL/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 30 (3.9%)</td>
<td>77</td>
<td>4 (0.87)</td>
<td>2 (0.75)</td>
<td>0.38 (0.16-0.89)</td>
<td></td>
</tr>
<tr>
<td>15-29 (30.3%)</td>
<td>5246</td>
<td>2685 (1.00)</td>
<td>58 (1.05)</td>
<td>0.45 (0.31-0.65)</td>
<td></td>
</tr>
<tr>
<td>9-14 (31.2%)</td>
<td>4297</td>
<td>2147 (1.00)</td>
<td>58 (1.05)</td>
<td>0.45 (0.31-0.65)</td>
<td></td>
</tr>
<tr>
<td>&lt; 9 (44.2%)</td>
<td>2996</td>
<td>1590 (1.00)</td>
<td>42 (1.04)</td>
<td>0.45 (0.31-0.65)</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA (50.7%)</td>
<td>5535</td>
<td>2665 (1.00)</td>
<td>81 (0.87)</td>
<td>0.68 (0.47-0.97)</td>
<td></td>
</tr>
<tr>
<td>Canada (49.3%)</td>
<td>3270</td>
<td>1635 (1.00)</td>
<td>73 (0.87)</td>
<td>0.68 (0.47-0.97)</td>
<td></td>
</tr>
<tr>
<td>ASA use at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (91.0%)</td>
<td>5890</td>
<td>2930 (1.00)</td>
<td>110 (1.00)</td>
<td>0.83 (0.68-1.00)</td>
<td></td>
</tr>
<tr>
<td>Yes (9.0%)</td>
<td>113</td>
<td>60 (0.53)</td>
<td>10 (1.00)</td>
<td>0.67 (0.43-1.03)</td>
<td></td>
</tr>
</tbody>
</table>

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Forest plot of effects by subgroup

Figure 5  Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients</th>
<th>PRADAXA 150</th>
<th>Warfarin</th>
<th>PRADAXA 150 vs Warfarin</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total no.</td>
<td>n</td>
<td>N(%) per yr</td>
<td>n</td>
<td>N(%) per yr</td>
</tr>
<tr>
<td>All patients</td>
<td>16113</td>
<td>135</td>
<td>6976 (1.12)</td>
<td>203</td>
<td>6022 (1.72)</td>
</tr>
<tr>
<td>VKA use at entry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naive (50.4%)</td>
<td>9126</td>
<td>62</td>
<td>3026 (1.09)</td>
<td>97</td>
<td>3093 (1.69)</td>
</tr>
<tr>
<td>Experienced (49.6%)</td>
<td>8984</td>
<td>73</td>
<td>3047 (1.15)</td>
<td>106</td>
<td>2929 (1.75)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 (15.5%)</td>
<td>2981</td>
<td>14</td>
<td>1030 (0.69)</td>
<td>25</td>
<td>953 (1.35)</td>
</tr>
<tr>
<td>≥ 65 and ≤ 75 (43.6%)</td>
<td>7984</td>
<td>51</td>
<td>2580 (0.98)</td>
<td>77</td>
<td>2646 (1.47)</td>
</tr>
<tr>
<td>≥ 75 (40.0%)</td>
<td>7236</td>
<td>70</td>
<td>2466 (1.46)</td>
<td>101</td>
<td>2423 (2.15)</td>
</tr>
<tr>
<td>ASA use at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (60.5%)</td>
<td>10960</td>
<td>76</td>
<td>3738 (1.01)</td>
<td>113</td>
<td>3591 (1.57)</td>
</tr>
<tr>
<td>Yes (39.5%)</td>
<td>7153</td>
<td>59</td>
<td>2338 (1.31)</td>
<td>90</td>
<td>2431 (1.96)</td>
</tr>
</tbody>
</table>
Forest plot of effects by subgroup

• Good
  – Consistency, usually
  – Disclaimer re overinterpretation
  – Supports “personalized medicine”
  – Works as well for prominent safety findings

• Bad
  – Despite disclaimer, hard to ignore discrepancies
  – Based on naïve subgroups; you cannot use to estimate response in a patient whose corresponding factor levels you know
  – No multiplicity adjustment
Figure 2. Impact of Coadministered Drugs on the Pharmacokinetics of Corlanor

- **Strong CYP3A4 Inhibitors**
  - Ketoconazole 200 mg QD
  - AUC

- **Moderate CYP3A4 Inhibitors**
  - Diltiazem 120 mg BID
  - AUC
  - AUC

- **CYP3A4 Inducers**
  - St. John’s Wort 500 mg TID

- **Other**
  - Sildenafil 100 mg
  - AUC
  - AUC

**PK Measures**
- Cmax
- AUC

**Recommendation**
- **Contraindicated**
- **Avoid Use**
- **Avoid Use**
- **Avoid Use**
- **Avoid Use**
- **Avoid Use**
- **No Dose Adjustment**
- **No Dose Adjustment**
- **No Dose Adjustment**
- **No Dose Adjustment**
- **No Dose Adjustment**
- **No Dose Adjustment**

**Change Due to**
- **0.25**
- **0.5**
- **1.0**
- **2.0**
- **4.0**
- **8.0**

**Fold Change and 90% Confidence Intervals**

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**Figure 5.2** Effect of Non-P-gp Inhibitor or Inducer, Other Drugs, on Peak and Total Exposure to Dobutamine (Cmax and AUC). Shown are the Geometric Mean Ratios (Ratio) and 90% Confidence Interval (90% CI). The Perioperative and Dobutamine Exclusions Dose and Dosing Frequency are given as well as the Time of Perioperative Dosing in Relation to Dobutamine Exclusions Dose (Time Difference).

- **Interacting Drug, Time Difference**
  - Atorvastatin 80 mg QD
  - AUC
  - Cmax

- **PK Measures**
  - AUC
  - Cmax

- **Fold Change and 90% CI**
  - 0.5
  - 1.0
  - 1.5
  - 2.0

- **Change Relative to Reference**
  - 0.5
  - 1.0
  - 1.5
  - 2.0

- **Interacting Drug, Time Difference**
  - Captopril 20 mg QD
  - AUC
  - Cmax

- **PK Measures**
  - AUC
  - Cmax

- **Fold Change and 90% CI**
  - 0.5
  - 1.0
  - 1.5
  - 2.0

- **Change Relative to Reference**
  - 0.5
  - 1.0
  - 1.5
  - 2.0

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Forest plot for drug interactions

• Good
  – Compact DDI information
  – Each section is separate study
    • No confounding
    • No multiplicity issue
  – Accommodates advice

• Bad
  – Hides study details
  – Can’t tell how much of the variability is related to sample size
Distribution of responses—waterfall

Figure 1: Percent Change from Baseline in Spleen Volume at Week 24 or Last Observation for Each Patient (Study 1)
Distribution of responses—waterfall

**Good**
- Individuals resolvable
- Works for any continuous data
- Can mark a clinically important or responder level

**Bad**
- Side-by-side makes comparison difficult of distributions are similar
Distribution of responses—cumulative

Figure 1: Patients Achieving Various Levels of Improvement in Pain Intensity – Study DPN 1
Distribution of responses—cumulative

• Good
  – Similar patterns easier to distinguish
  – Works for any continuous data
  – Can mark a clinically important or responder level

• Bad
  – Not intuitive?
Modeled response

Likelihood of getting to some BP goal as a function of baseline BP on
Placebo
One drug
Combo

Figure 1: Probability of Achieving Systolic Blood Pressure <140 mmHg at Week 8

Figure 2: Probability of Achieving Diastolic Blood Pressure <90 mmHg at Week 8

Figure 3: Probability of Achieving Systolic Blood Pressure <130 mmHg at Week 8

Figure 4: Probability of Achieving Diastolic Blood Pressure <80 mmHg at Week 8
Modeled response

• Good
  – Based on factorial trial data
  – Intended to advise on when starting two drugs is useful

• Bad
  – Model
  – Hides assumptions
  – Hides confidence intervals
  – Suspect interpretability

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General concerns

• No testing of comprehension by target audience
• Potential misfit of analytic approach with intended use
• Complex graphics not compatible with
  – Portable devices
  – Decision support systems