Communicating Complex Information in Drug Product Labeling

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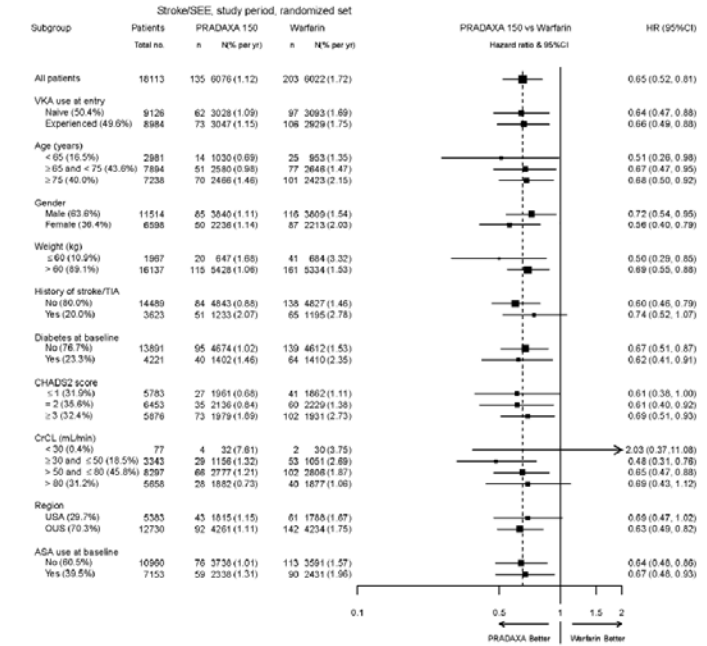
Forest plot of effects by subgroup

Figure 5 Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics*

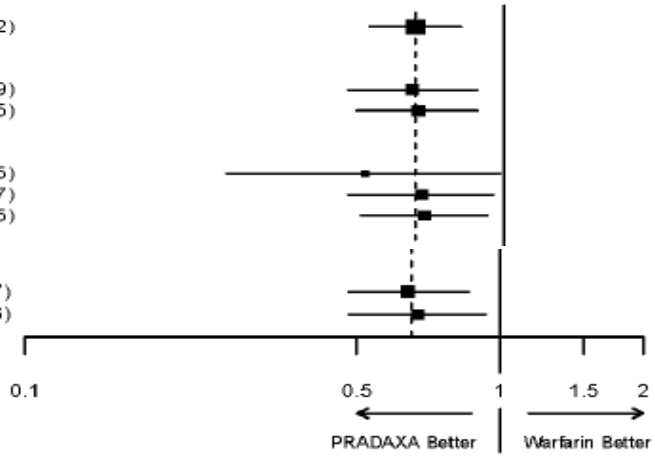


Forest plot of effects by subgroup

Figure 5 Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics*

Stroke/SEE, study period, randomized set

Subgroup	Patients	PRADAXA 150		Warfarin		PRADAXA 150 vs Warfarin	HR (95%CI)
	Total no.	n	N(% per yr)	n	N(% per yr)	Hazard ratio & 95%CI	
All patients	18113	135	6076 (1.12)	203	6022 (1.72)		0.65 (0.52, 0.81)
VKA use at entry							
Naive (50.4%)	9126	62	3028 (1.09)	97	3093 (1.69)		0.64 (0.47, 0.88)
Experienced (49.6%)	8984	73	3047 (1.15)	106	2929 (1.75)		0.66 (0.49, 0.88)
Age (years)							
< 65 (16.5%)	2981	14	1030 (0.69)	25	953 (1.35)		0.51 (0.26, 0.98)
≥ 65 and < 75 (43.6%)	7894	51	2580 (0.98)	77	2646 (1.47)		0.67 (0.47, 0.95)
≥ 75 (40.0%)	7238	70	2466 (1.46)	101	2423 (2.15)		0.68 (0.50, 0.92)
ASA use at baseline							
No (60.5%)	10960	76	3738 (1.01)	113	3591 (1.57)		0.64 (0.48, 0.86)
Yes (39.5%)	7153	59	2338 (1.31)	90	2431 (1.96)		0.67 (0.48, 0.93)



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

Forest plot for drug interactions

Figure 2. Impact of Coadministered Drugs on the Pharmacokinetics of Corlanor

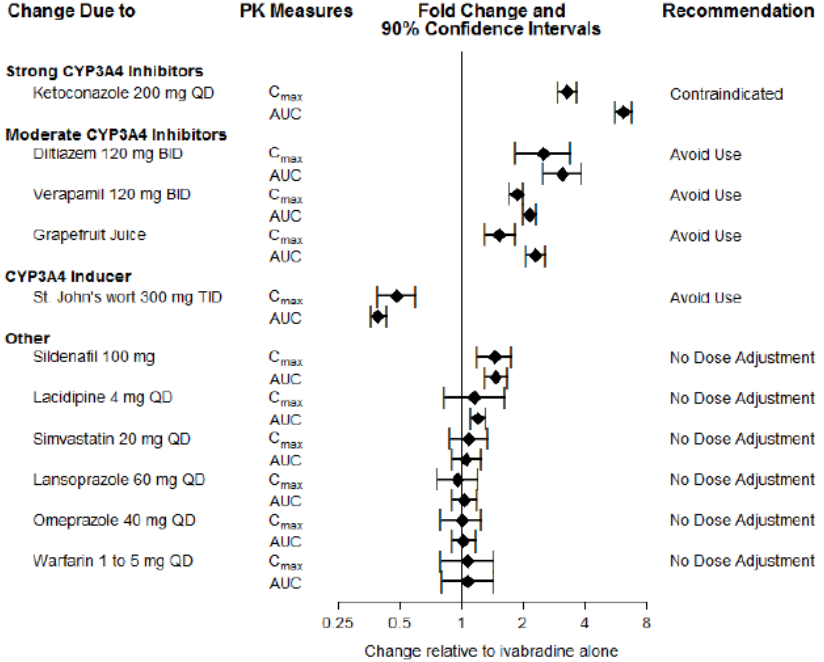
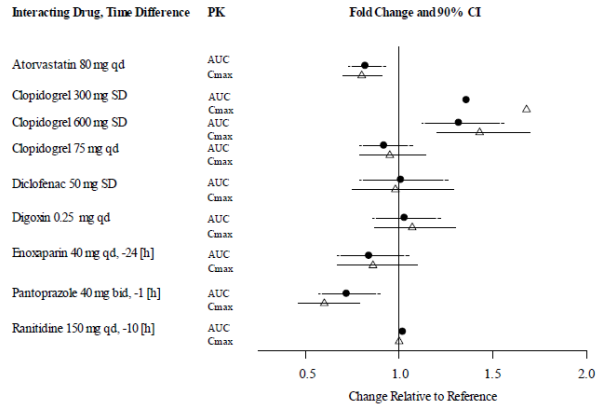


Figure 3.2 Effect of Non-P-gp Inhibitor or Inducer, Other Drugs, on Peak and Total Exposure to Dabigatran (Cmax and AUC). Shown are the Geometric Mean Ratios (Ratio) and 90% Confidence Interval (90% CI). The Perpetrator and Dabigatran Etexilate Dose and Dosing Frequency are given as well as the Time of Perpetrator Dosing in Relation to Dabigatran Etexilate Dose (Time Difference)

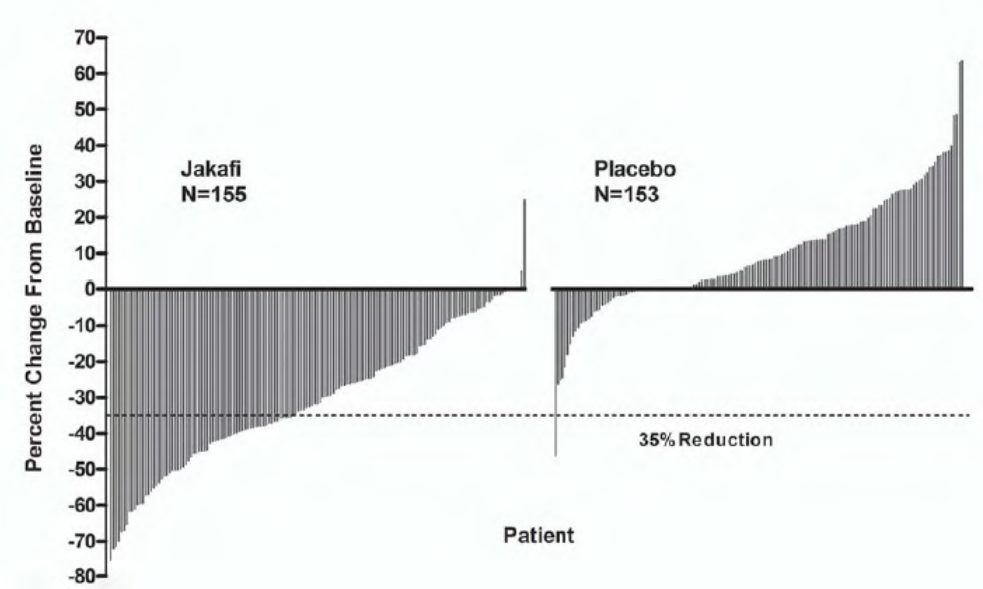


Forest plot for drug interactions

- 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)**

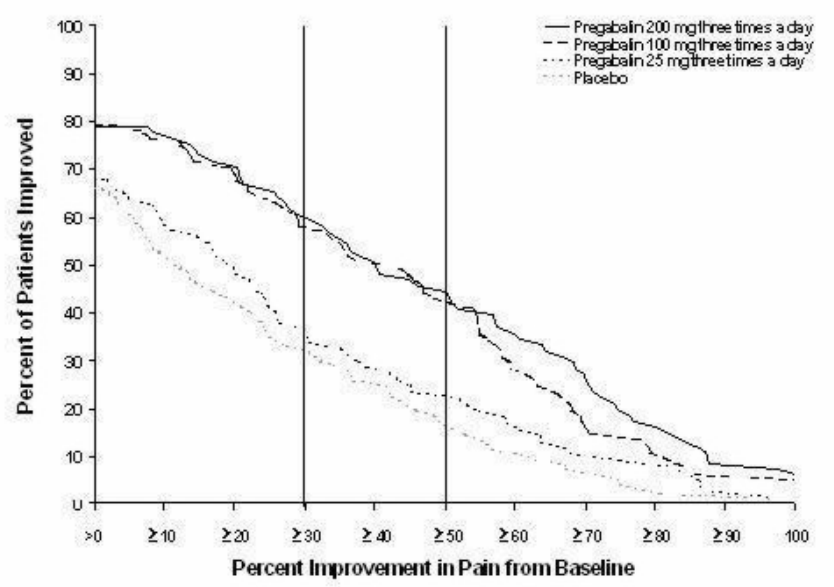


Distribution of responses—waterfall

- 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

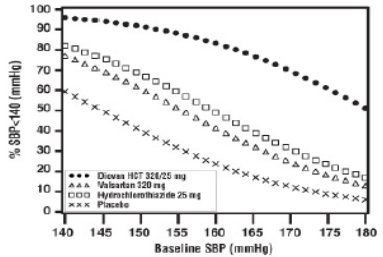


Figure 1: Probability of Achieving Systolic Blood Pressure <140 mmHg at Week 8

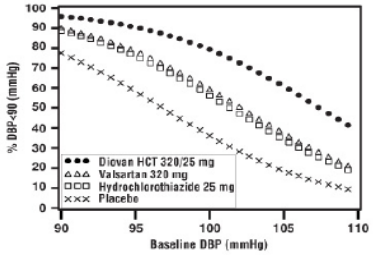


Figure 2: Probability of Achieving Diastolic Blood Pressure <90 mmHg at Week 8

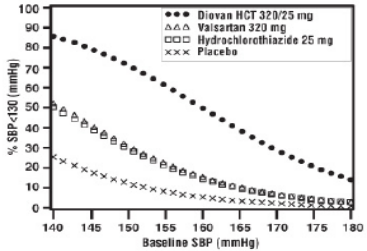


Figure 3: Probability of Achieving Systolic Blood Pressure <130 mmHg at Week 8

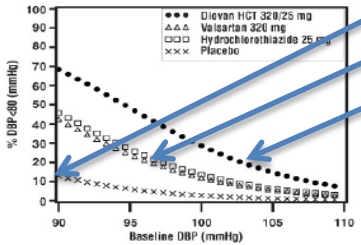


Figure 4: Probability of Achieving Diastolic Blood Pressure <80 mmHg at Week 8

Likelihood of getting to some BP goal as a function of baseline BP on

- Placebo
- One drug
- Combo

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

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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