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Subgroup Analysis in Clinical Trials: Opportunities and Challenges

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Conflicts of Interest

No financial conflicts of interest

No intellectual conflicts of interest

Note: I am not a statistician

Outline

- Subgroups generally of interest in clinical trials
- Interpretation
- Dichotomization
- Pre-specification
- Safety Analyses

Subgroups Generally of Interest in Clinical Trials

- Demographics (age, sex, race, ethnicity)
- Geography (especially US, non-US), region, country
- Body mass, or body mass index (BMI)
  - Particularly important if drug dose is not weight-adjusted
- Baseline disease characteristics, especially when they are prognostic
- Concomitant diseases (when they might impact disease outcomes or affect drug levels)
- Concomitant drugs (when they might impact the disease or affect drug levels)
- Other

Interpretation of Analyses of Numerous Subgroups Can be Challenging

Exploration is the goal; there is usually no formal hypothesis testing.

- Limitations to consider:
  - When results in subgroups are generally consistent with the overall result, we may feel reassured—even if the study is underpowered to examine subgroups.
  - There is always the danger of overinterpreting differences, even large differences, with respect to outliers.

Factors that lend credibility to findings in subsets:

- Similar findings in independent studies.
- Strong relationship across continuous variables, i.e., effect size increases/decreases across quartiles.
- Strong mechanistic plausibility.

Dichotomization of Continuous Variables

- Dichotomization for some continuous variables is common, e.g., age (>65; >75); creatinine clearance (<30).
- Some of these cut-offs are well standardized and there may be value in continuing to use them, but expression in quartiles or quintiles may aid in interpretation:

Table 5: SHIFT – 1° Endpoint by Subgroups

		% of population	% with Primary Endpoint Event		Δ Absolute %	RR (95% CI)
			Ivabradine	Placebo		
All		100%	24.5%	28.7%	4.2%	0.85 (0.78, 0.92)
Age quartile	<54	26.6%	17.4%	25.4%	8.0%	0.69 (0.57, 0.83)
	55 to 60	23 9%	23.0%	24.7%	1.7%	0.93 (0.78, 1.11)
	61 to 69	26 5%	27.7%	30.6%	2.9%	0.91 (0.79, 1.05)
	>69	23.1%	29.9%	35.1%	5.2%	0.85 (0.73, 0.98)
Age	≥ 65	38 0%	30.5%	33 9%	3.4%	0.9 (0.8, 1.01)
	≥ 75	11.1%	33.9%	37.7%	3.8%	0.9 (0.74, 1.09)

Ivabradine Office Director Review:
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206143Orig1s000ODMemo.pdf

Pre-specification

Three possibilities:

1. Subgroup analysis with formal test of hypothesis (unusual, but it is done)
2. Pre-specified subgroup analysis
3. Non-pre-specified subgroup analysis

In my opinion, there is no difference between #2 and #3:

- If no alpha is allocated, I don't care whether subgroup analysis was prespecified or not
- One could prespecify 10,000 analyses

Safety Analyses by Subgroup

When there are safety issues, a critical question is “Who gets into trouble?”

- Subgroup analyses for safety are grossly underpowered because only relatively small numbers of patients have the adverse event of interest.
- Nevertheless, such analyses can be worthwhile.

Safety Analyses by Subgroup

Table 8: SHIFT – Adverse Events by Subgroup

		% of subjects	↓ HR Ivab	↓ HR Placebo	RR	↑ BP Ivab	↑ BP Placebo	RR	A Fib/Flutter Ivab	A Fib/Flutter Placebo	RR	Phosphenes Ivab	Phosphenes Placebo	RR
All			10.1%	2.4%	4.2	9.0%	8.0%	1.1	10.3%	8.8%	1.1	2.8%	0.5%	5.3
Age quartile	<54	27%	8.5%	1.0%	8.4	7.1%	7.5%	0.9	5.8%	5.8%	0.9	3.4%	0.8%	4.2
	55 to 60	24%	9.9%	2.8%	3.5	8.9%	8.1%	1.1	9.5%	5.9%	1.5	2.8%	0.5%	5.4
	61 to 69	27%	9.1%	2.8%	3.2	9.0%	8.3%	1	11.6%	10.4%	1.1	3.4%	0.4%	9.8
	>69	23%	13.1%	3.2%	4.1	11.1%	8.0%	1.3	14.6%	13.8%	1	1.4%	0.4%	3.4
Age	> 65	38%	12.2%	3.1%	3.8	10.4%	8.8%	1.1	13.3%	12.7%	1	2.0%	0.4%	4.7
	> 75	11%	13.0%	3.1%	4.1	11.1%	7.6%	1.4	16.0%	13.9%	1.1	1.9%	0.6%	3.3
Sex	Male	76%	9.6%	2.6%	3.6	8.3%	7.7%	1	10.5%	9.3%	1.1	2.6%	0.4%	7.3
	Female	24%	11.6%	1.6%	7.2	11.2%	9.0%	1.2	9.8%	7.4%	1.3	3.2%	1.1%	3
Race	Caucasian	89%	10.3%	2.6%	3.9	9.7%	8.6%	1.1	11.0%	9.3%	1.1	2.9%	0.6%	5.2
	Black	1%	9.4%	0.0%	-	9.4%	4.7%	-	12.5%	7.0%	1.7	0.0%	0.0%	-
	Asian	8%	8.6%	0.8%	11.3	2.6%	2.3%	1.1	4.1%	4.5%	0.9	2.2%	0.4%	5.9
	Other	2%	8.1%	0.0%	-	1.6%	6.2%	-	3.2%	6.2%	0.5	0.0%	0.0%	-
Modal dose	2.5 mg	5%	32.6%	2.4%	13.6	10.3%	8.0%	1.3	8.9%	8.8%	1	4.6%	0.5%	8.9
	5 mg	16%	16.6%	2.4%	6.9	7.7%	8.0%	1.0	10.7%	8.8%	1.2	4.2%	0.5%	8.1
	7.5 mg	79%	4.8%	2.4%	2	9.3%	8.0%	1.2	10.4%	8.8%	1.1	2.0%	0.5%	3.9
	<60 Kg	25%	11.3%	2.3%	4.9	5.5%	6.3%	0.8	10.7%	6.1%	1.7	1.7%	0.4%	4.7

From the Ivabradine Office Director Review:
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206143Orig1s000ODMemo.pdf

Thanks for Listening!

Questions entertained…