Subgroup Analysis in Drug Development

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Subgroup analysis

- An analysis of treatment effects within subgroups of patients enrolled on a clinical trial
- The majority of reports of randomized clinical trials contain subgroup analysis
- Deciding on analysis after looking at the data is "useful, often done, and can be problematic"

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Guideline on the investigation of subgroups in confirmatory clinical trials

DRAFT

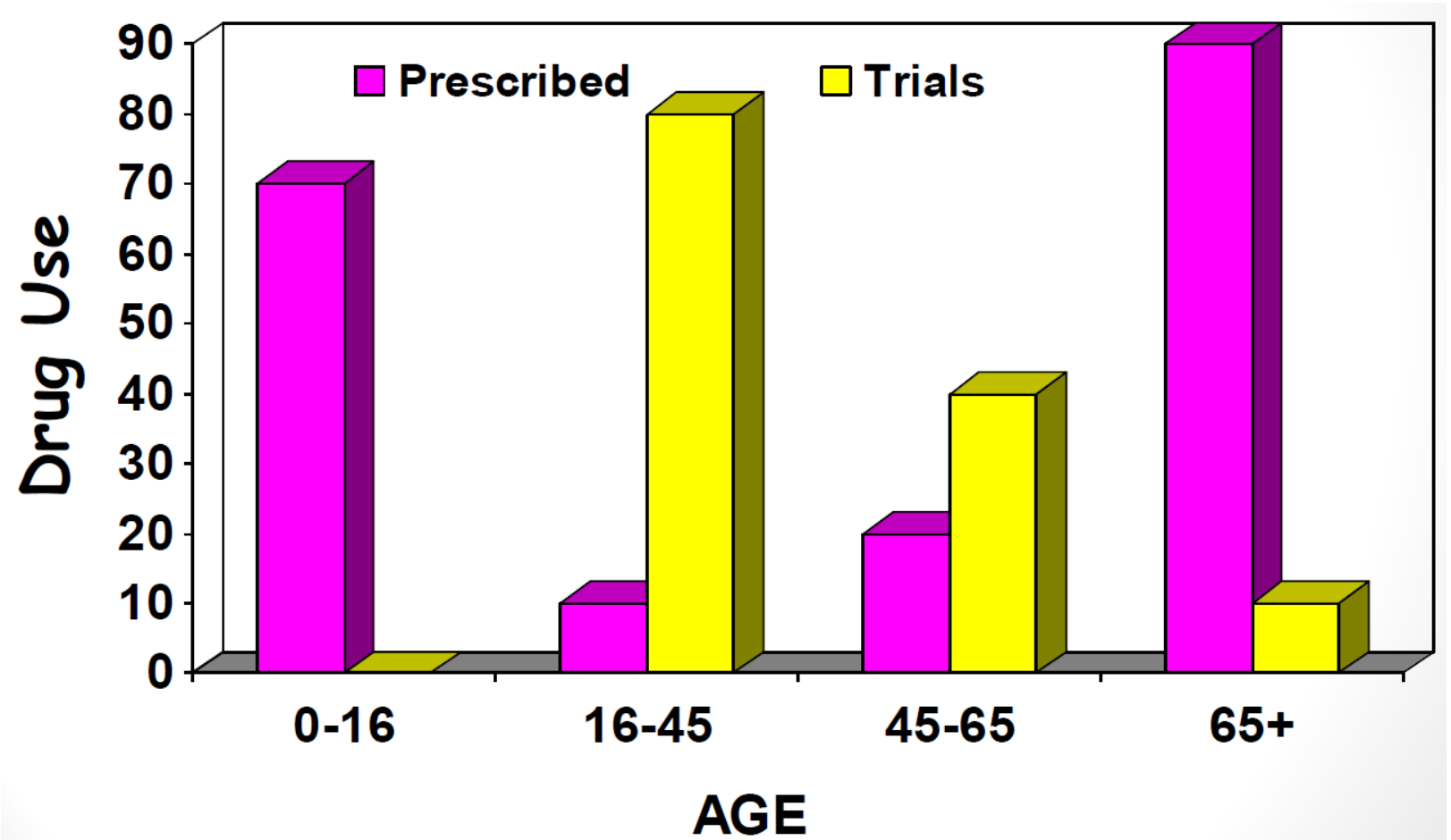
Different scenarios that call for subgroup analysis

Scenario 1: The clinical data presented are overall statistically persuasive with therapeutic efficacy demonstrated globally. It is of interest to verify that the conclusions of therapeutic efficacy (and safety) apply consistently across subgroups of the clinical trial population

Scenario 2: The clinical data presented are overall statistically persuasive but with therapeutic efficacy or benefit/risk which is borderline or unconvincing and it is of interest to identify post-hoc a subgroup, where efficacy and risk-benefit is convincing

Scenario 3: The clinical data presented fail to establish statistically persuasive evidence but there is interest in identifying a subgroup, where a relevant treatment effect and compelling evidence of a favourable risk-benefit profile can be assessed

Are we testing medicine on a relevant group of patients?



Defining subgroups

- Based on pre-randomization information
- Post-baseline variables may be affected by treatment $\Longrightarrow$ usually not be appropriate to define subgroups for investigation

- Dichotomous factors (e.g. men / women),
- Categorical factors (e.g. region),
- Ordered categorical factors (e.g. disease score at baseline)
- Continuous variables (e.g. age).
- Argumentation for cut-off points for continuous variables and grouping of categories
- Subgroups can be defined by a combination of the above (consider group size)

Multiplicity

- Initial results should be based on analysis of a primary endpoint in a primary analysis population
- Multiple subgroups considered $\Longrightarrow$ increased probability of false-positive findings
- ICH E9: any conclusion of treatment efficacy (or lack thereof) or safety based solely on exploratory subgroup analyses are unlikely to be accepted
- Multiplicity adjustment not recommended because the subgroup analyses are triggers for further investigation

Testing for differential treatment effect

- Is the depression severity different for men and women? versus Is the treatment effect different for men and women?
- Main effect versus interaction effect
- The test for interaction will be associated with a p-value
- The test for interaction cannot be considered adequate. It is recommended to add estimates and corresponding confidence intervals

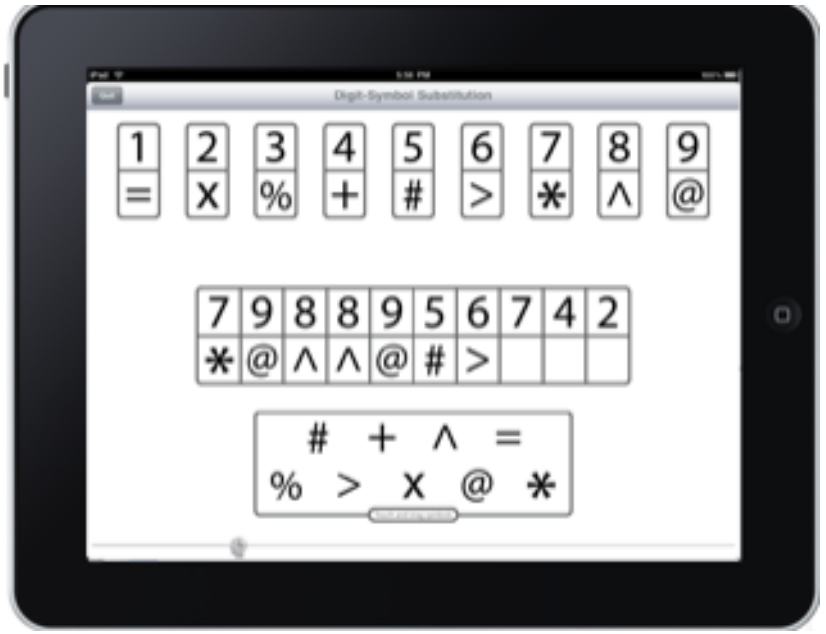
Other issues

- Importance of subgroup analyses depend on homogeniety of the studied population
- The more homogeneous the lower the importance
- Highly relevant in integrated analyses
- Subgroup analyses can not be used to rescue a failed trial

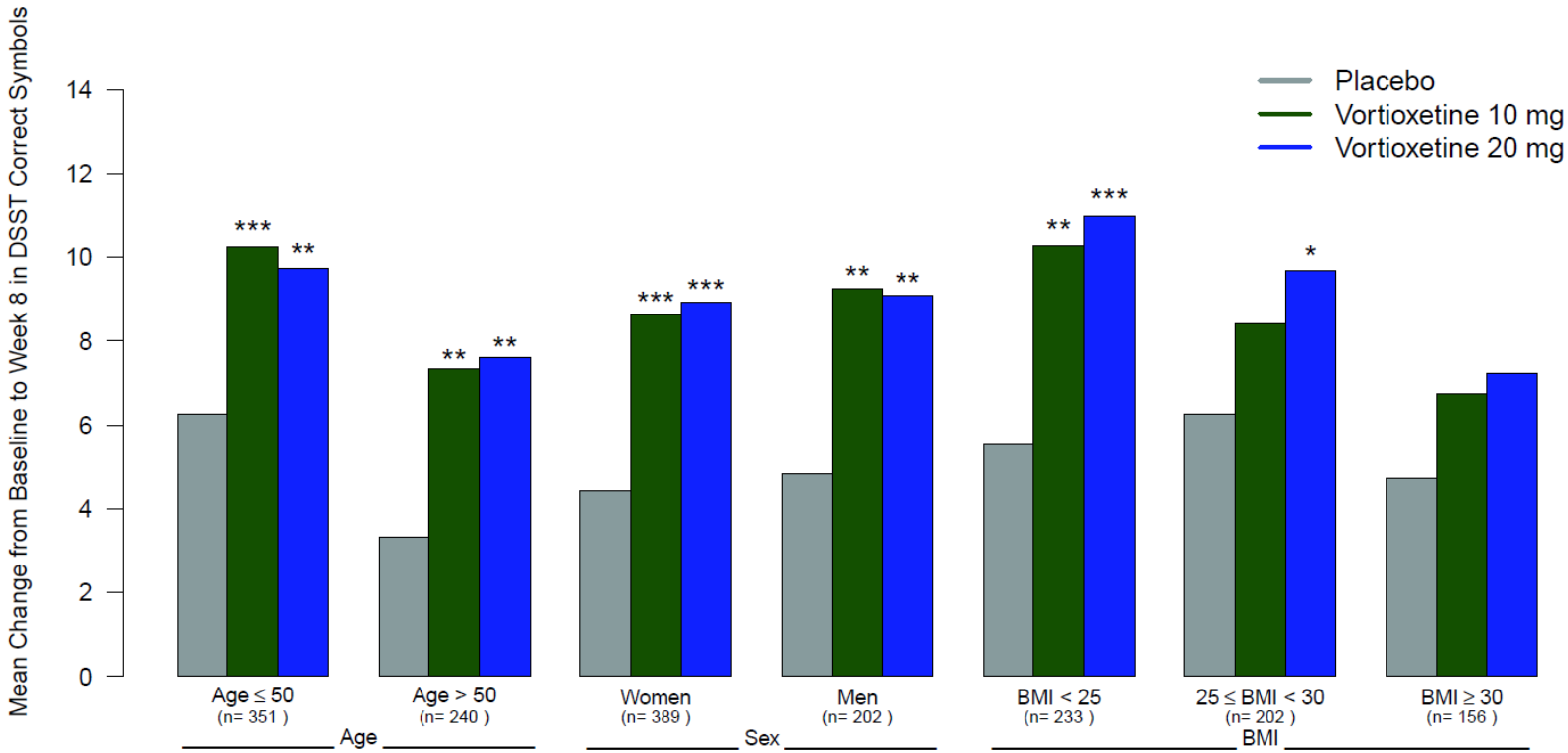
Subgroup analysis in depression study

Overall the effect of treatment with VOR against placebo on the change from baseline to week 8 in DSST number of correct symbols was 4.20 ($p<0.0001$) for 10 mg/day and 4.26 ($p<0.0001$) for 20 mg/day.

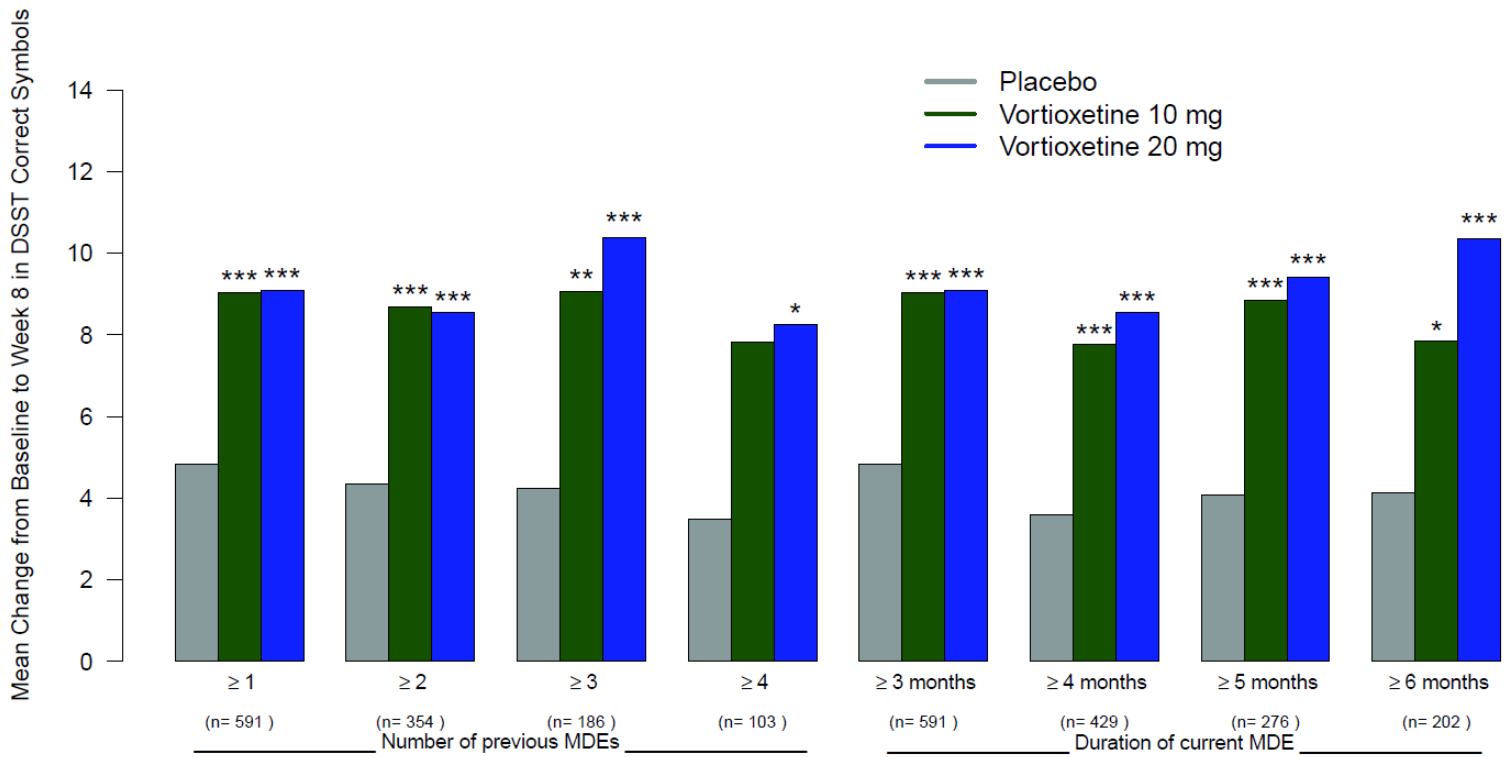
In general, the overall treatment effects were confirmed within subgroups



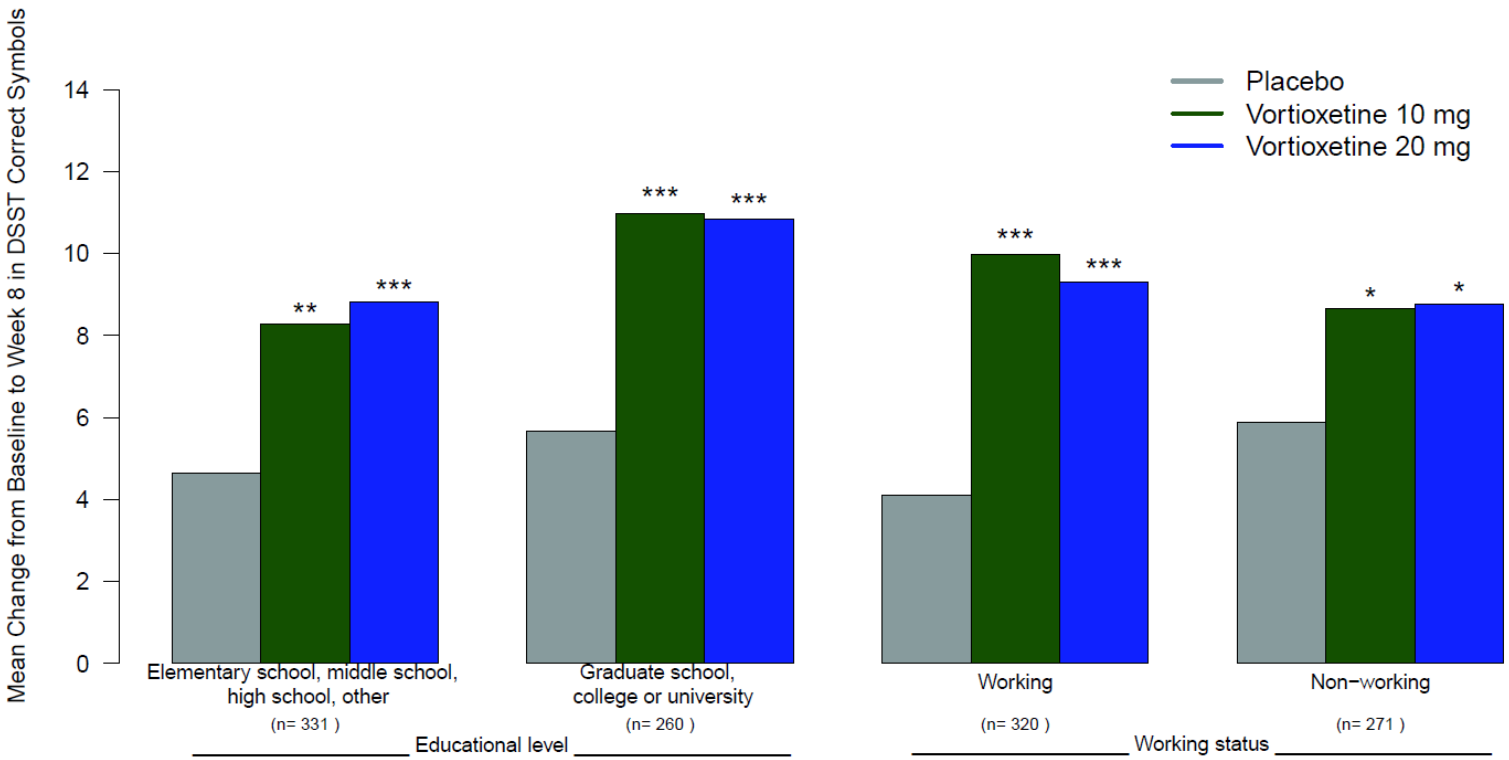
Subgroup analysis in depression study



Subgroup analysis in depression study

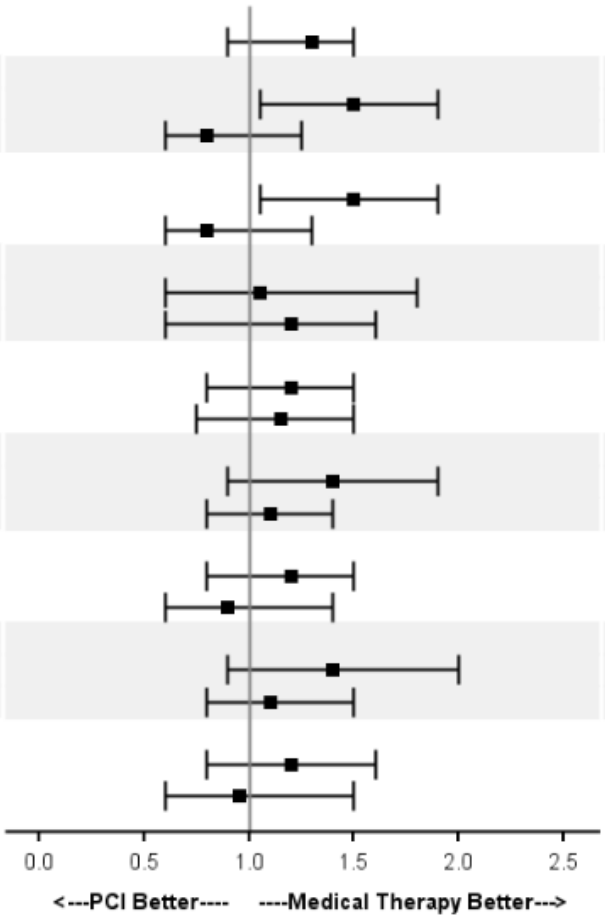


Subgroup analysis in depression study



Forest (Fishbone) plot

Subgroup	No.of Patients (%)	Hazard Ratio	4-Yr Cumulative Event Rate		P Value
			PCI group	Medical Therapy group	
Overall	2166(100)		17.2	15.6	
Age					0.05
<= 65 Yr	1534(71)		17	13.2	
> 65 Yr	632(29)		17.8	21.3	
Sex					0.13
Male	1690(78)		16.8	13.5	
Female	476(22)		18.3	22.9	
Race or ethnic group					0.52
Nonwhite	428(20)		18.8	17.8	
White	1738(80)		16.7	15	
From MI to Randomization					0.81
<= 7 days	963(44)		18.9	18.6	
> 7 days	1203(56)		15.9	12.9	
Infract-related artery					0.38
LAD	781(36)		20.1	16.2	
Other	1385(64)		15.6	15.3	
Ejection Fraction					0.48
< 50%	1151(54)		22.6	20.4	
>= 50%	999(46)		10.7	11.1	
Diabetes					0.41
Yes	446(21)		29.3	23.3	
No	1720(79)		14.4	13.5	
Killip class					0.39
I	1740(81)		15.2	13.1	
II-IV	413(19)		25.3	26.9	



Breast cancer screening and subgroup analysis

- At present, BC screening is offered as a "one-model-fits-all-women"
- Identify subgroups of women for whom breast cancer screening has particularly good benefits or undesirable harmful side-effects
- Future personalised, risk-based cancer screening