Quality in clinical trials: what really matters?

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Put greater reliance on design strengths inherent in randomized-controlled trials

- Randomization: unbiased comparison of patient groups that differ randomly

- Control group: unbiased ascertainment of outcomes in study treatment groups

Yields unbiased assessment of treatment (which will only be reliable if large enough)

Proper randomized comparison

- No foreknowledge of likely study treatment allocation
- Minimise post-randomization withdrawals (i.e. intent-to-treat)
- Minimise losses to follow-up (e.g. after primary event occurs or study treatment stops)

Ensures patient groups differ only randomly: allowing unbiased assessment of treatment

Sufficient numbers of relevant events

- Number of events, not patients, is chief determinant of power (i.e. 1º prevention trials are inefficient 2º prevention trials)
- Composite outcomes that combine events which may involve different directions of effect are less sensitive and generalizable (e.g. total versus cause-specific mortality, or total versus site-specific cancer)

EMEA: Guideline on the evaluation of medicinal products for cardiovascular disease prevention

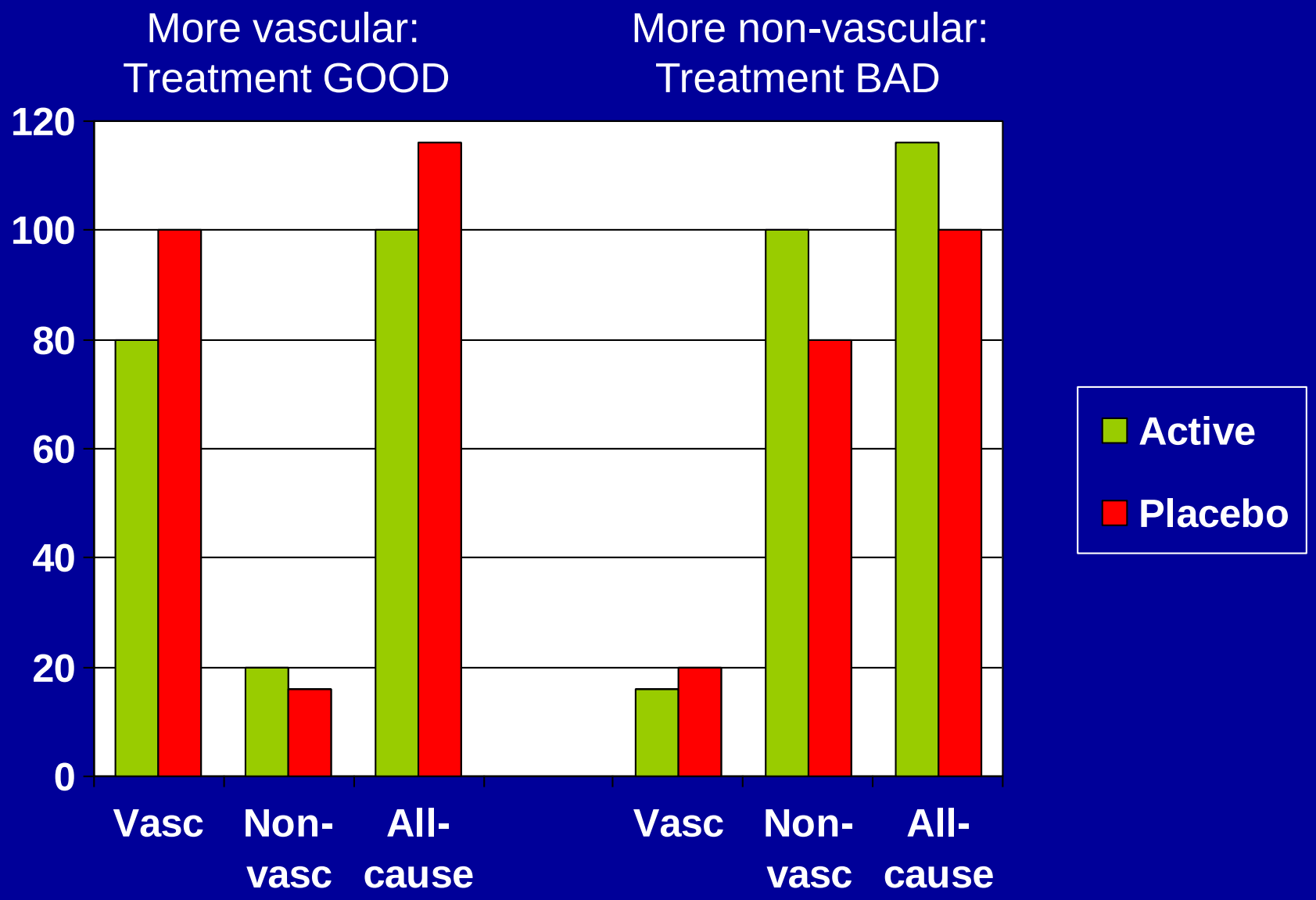
"Primary efficacy endpoints…..

All-cause mortality is preferred over cardiovascular mortality…. Cardiovascular mortality, if objectively and conservatively defined, may also be acceptable..

...Composite outcomes may be appropriate in trials of CV prevention when including hard clinical endpoints (e.g. nonfatal myocardial infarction, stroke)."

This is irrespective of the likelihood of study treatment affecting different causes of death, or different types of vascular event, differently!

Different direction of effect on all-cause mortality depending on split of vascular and non-vascular death



Review underlying assumptions for statistical power during the trial

- Assess overall rates of the main clinical outcomes (blinded to allocated treatment)
- Assess impact of compliance to allocated treatment on risk factor levels (for example unblinded differences in lipids or BP)
- Modify study duration, number of events and/or pre-specified outcomes (blinded to effects of allocation on clinical outcomes)

Potential for false negative findings if power assumptions are not assessed during trials

Treatment effect on biomarker	Anticipated relative risk reduction	Active (n=4000)	Control (n=4000)	Power at p=0.01
1.0	20%	480 (12.0%)	600 (15.0%)	91%
0.7	14%	516 (12.9%)	600 (15.0%)	54%

Not to check these assumptions may have adverse public health implications

FDA draft guidance: Adaptive design clinical trials for drugs and biologics

"Statistical bias can be introduced into adaptive design studies that make modifications based on interim analyses of a biomarker … even though the final study analysis uses a clinical efficacy endpoint. This is because of the correlation between the biomarker and final study endpoint."

FALSE: Assessing the effect on a biomarker (such as blood pressure or cholesterol) does not introduce bias!

Fallacy in FDA draft guidance on unblinding

- Known that a treatment lowers risk factor levels (such as blood pressure or cholesterol)
- Known that risk factors are correlated with risk (such as blood pressure with stroke)
- But NOT known that changing risk factor levels with the treatment is correlated with disease risk (which is the hypothesis being tested in the trial)
- Unblinding the achieved change in the risk factor level provides NO information about correlation between this risk factor change and disease risk
- So, such unblinding does NOT cause any bias

Undue emphasis on data quality

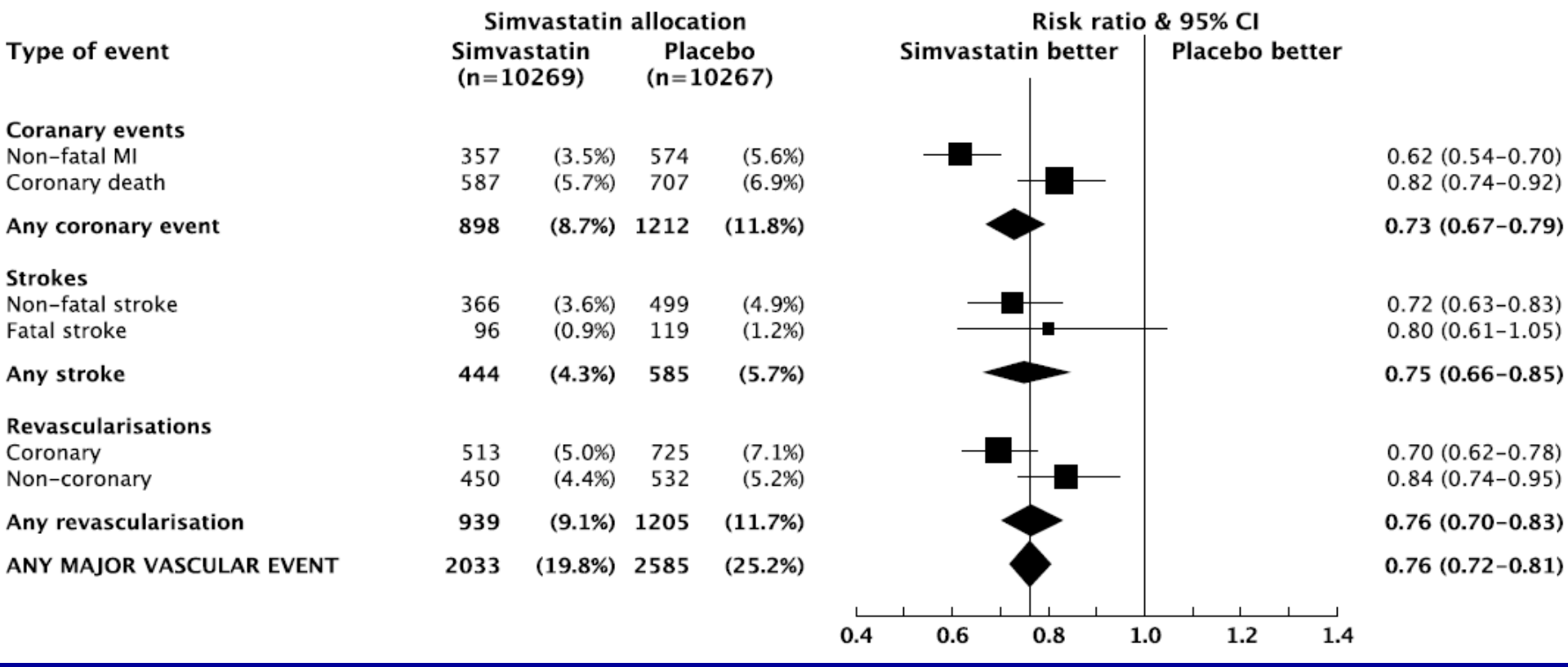
Reliable RESULT ≠ High quality DATA

High quality DATA ≠ Reliable RESULT

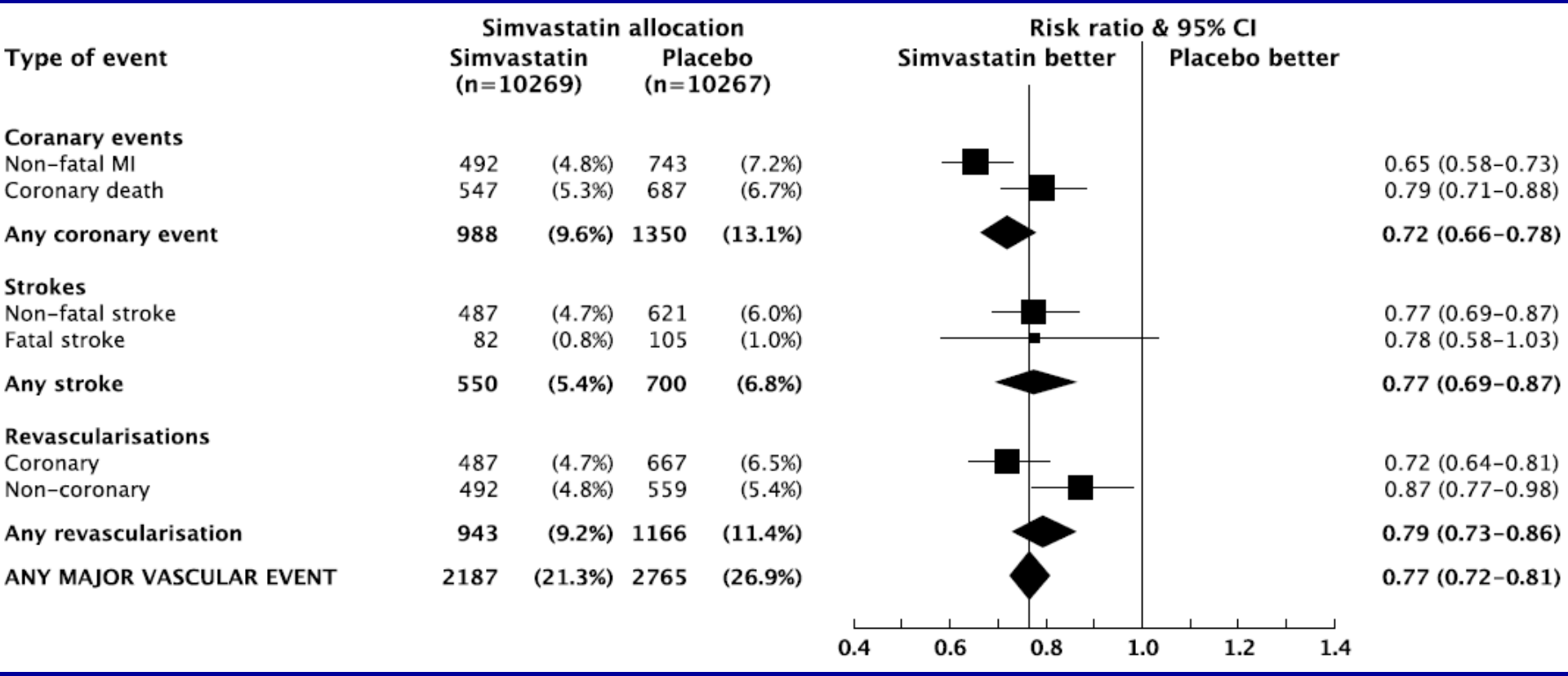
Unbiased ascertainment of major study outcomes

- Put greater reliance on comparison with the randomly-allocated control group
- Missing data have little impact if this is unbiased with respect to allocation
- Adjudication of study outcomes adds substantial cost, but typically little gain

HPS: Effects of simvastatin-allocation on ADJUDICATED major vascular events (Lancet 2002)



HPS: Effects of simvastatin-allocation on UN-ADJUDICATED major vascular events



Minimal impact of adding false events or of missing real events

	Active (10,000)	Control (10,000)	OR (& 95%CI)	Z score
True events	800	1000	0.78 (0.71-0.86)	4.9
Extra false events (evenly distributed)				
+ 10%	890	1090	0.80 (0.73-0.88)	4.7
+ 20%	980	1180	0.81 (0.74-0.89)	4.6
Missing real events (unevenly distributed)				
- 10%	720	900	0.78 (0.71-0.87)	4.7
- 20%	640	800	0.79 (0.71-0.88)	4.4

Statistical monitoring of data (rather than physical monitoring of sites)

- Standard checks of range, consistency and completeness of data
- Checks for unusual distribution of data within and between study sites (e.g. too little variance; lack of outliers; unlikely dates)
- Quality control assessments in random samples of investigators, patients and data items (supplemented by systematic checks of particular sites prompted by other analyses)

ESPS-2: Failure to detect fraud during special audit site visit by Good Clinical Research Practices Ltd

"The auditors were not able to uncover major anomalies in the data collected by this centre."

ESPS-2 report,
June 1996

ESPS-2: Confirmation of problem by central assay of blood samples

Both DIP & ASA were in all samples (rather than expected 25%)

DIP levels were either trace or very high (& different from other centres)

ASA levels were incompatible with low-dose aspirin regimen

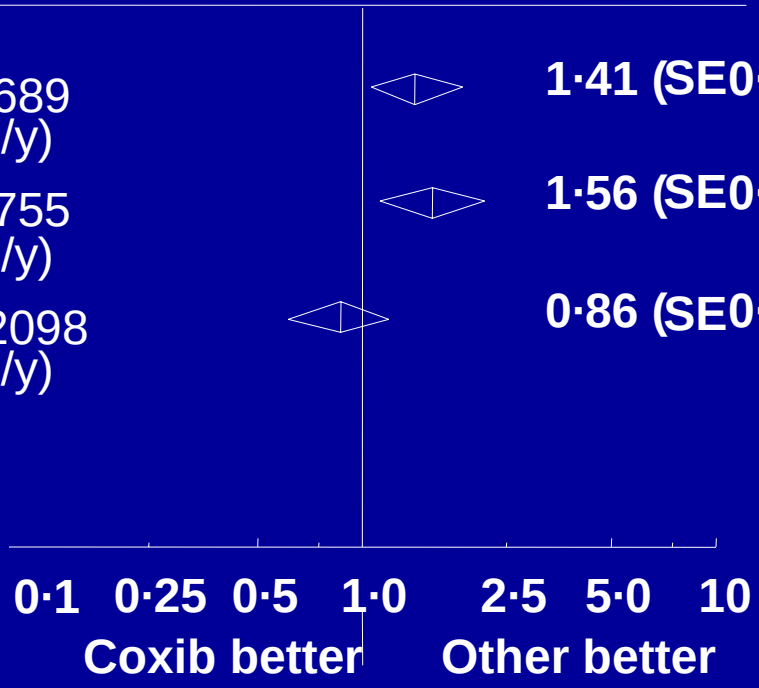
Plasma protein polymorphism measurement showed each of 90 samples was from same mixture of plasma from several persons

Pharmacovigilance in randomized trials

- LARGE effects on RARE outcomes may be detected by the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARS) required in trials by regulations
  - but this does not require randomization
- Reliable assessment of MODERATE effects on COMMON outcomes does, however, need LARGE-SCALE RANDOMIZED evidence
  - and this is best monitored by a DSMB (rather than by reporting masses of adverse events)

RELIABLE assessment of MODERATE hazards: Large-scale randomized meta-analysis of effects of COX-2 inhibitors on major vascular events

Coxib vs.	No. of trials	Events/person-years: Allocated Coxib	Events/person-years: Allocated Other	Ratio of annual event rates Coxib : Other
Placebo	**91**	209/11584 (1·8%/y)	106/8689 (1·2%/y)	**1·41 (SE0·14)**
Naproxen	**38**	180/15980 (1·1%/y)	78/10755 (0·7%/y)	**1·56 (SE0·17)**
Non-naproxen NSAID	**42**	148/16558 (0·9%/y)	127/12098 (1·0%/y)	**0·86 (SE0·12)**



Heterogeneity: χ^2_2 = 12·9; p = 0·002

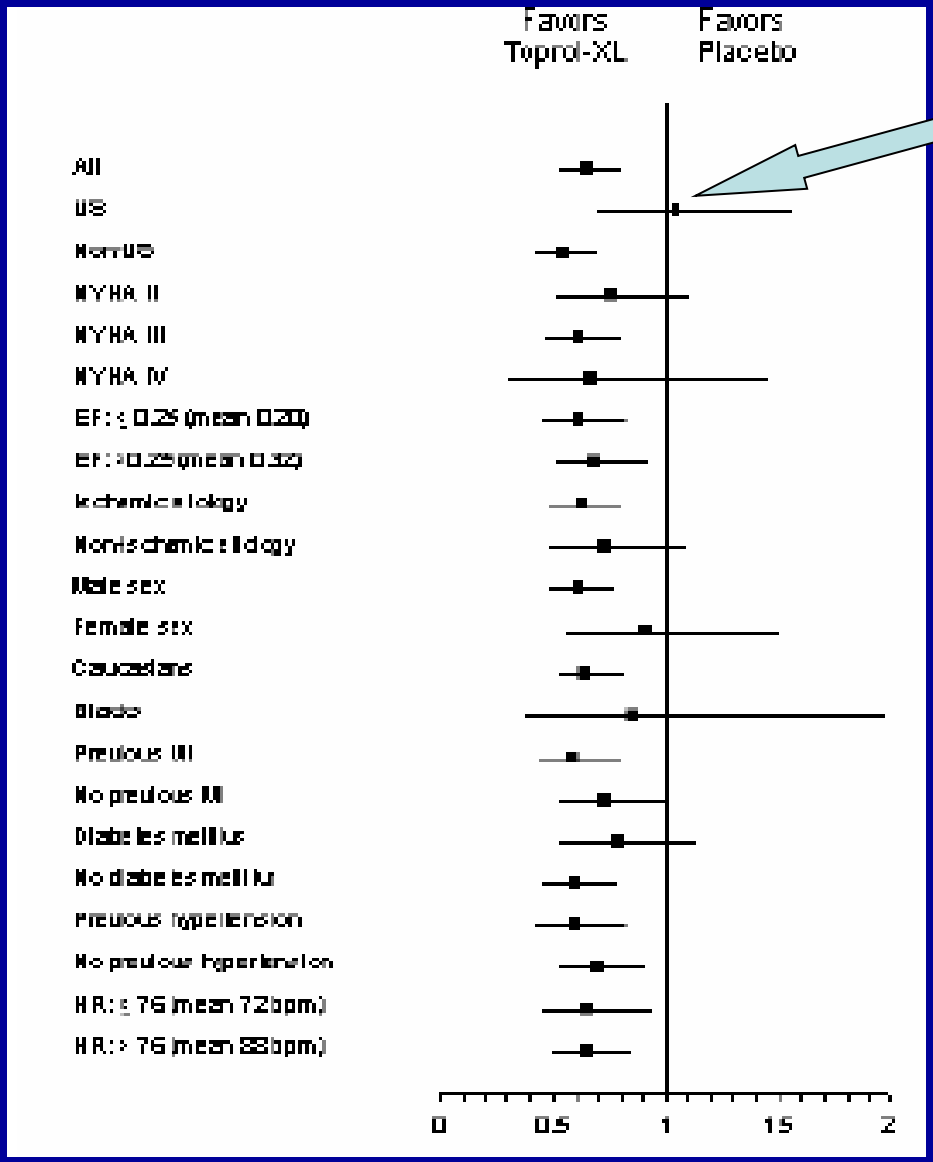
Such moderate effects on common outcomes cannot be reliably detected by non-randomized pharmacovigilance (as is sought by regulatory authorities)

Avoid subgroup and non-randomized "on treatment" analyses

- Emphasis on findings in small subgroups (e.g. North American patients), even when a trial has compelling overall results, may well be seriously misleading

- "On treatment" comparisons of patients who get larger versus smaller response to treatment are **non**-randomized (and so not appropriate when randomization is needed to assess the overall effect reliably)

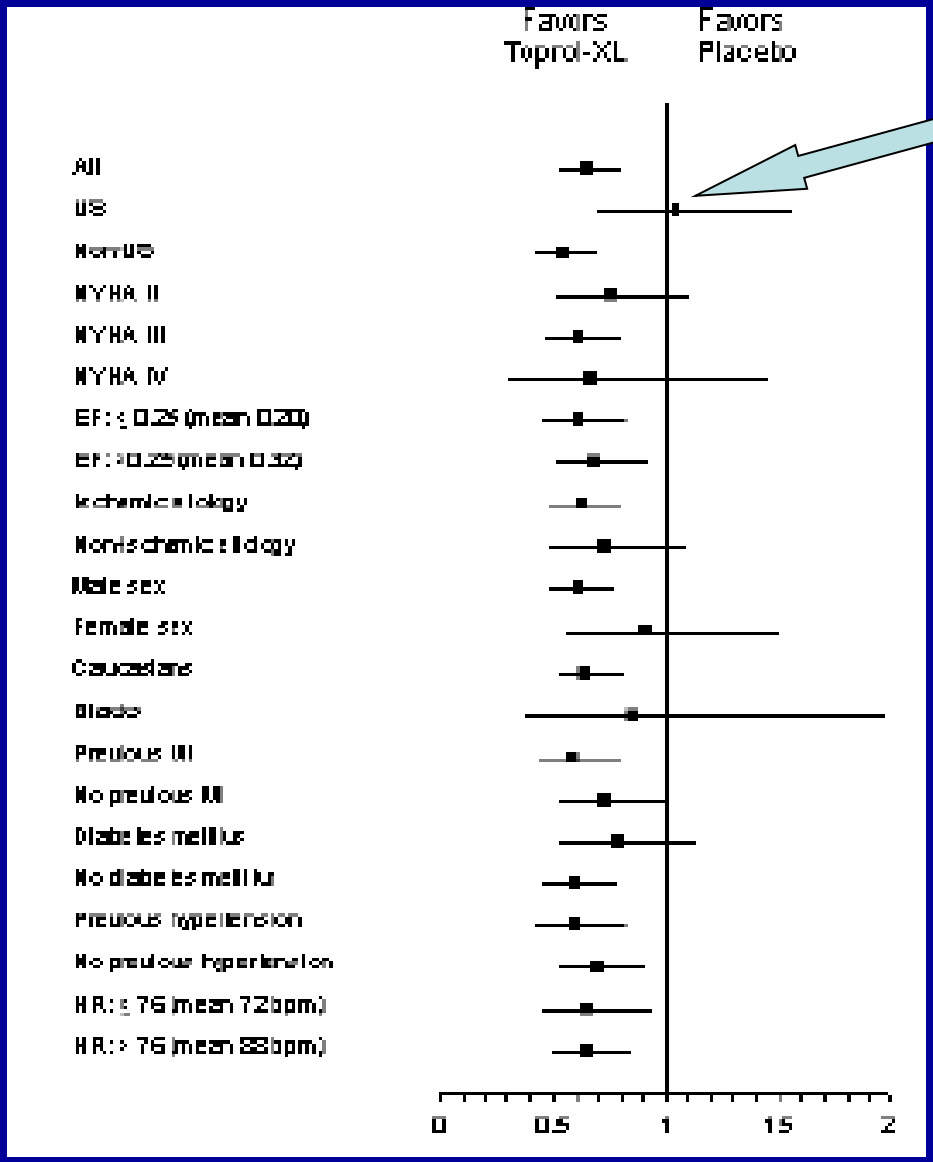
MERIT-HF: Effects on total mortality of beta-blocker in heart failure in various subgroups



US patient subgroup

FDA datasheet: *"..mortality plus heart failure hospitalization showed consistent effects in the overall study population and subgroups, including women and the US population. However, in the US subgroup (n=1071) and women (n=898), overall mortality and cardiovascular mortality appeared less affected."*

MERIT-HF: Effects on total mortality of beta-blocker in heart failure in various subgroups



US patient subgroup

"Analyses of US patients were carried out because they represented about 25% of the overall population."

Why is that justification for post hoc data-dependent emphasis on a subgroup?

JUPITER: Non-randomized comparison of effects of different apparent response (Lancet 2009)

- *"Compared with placebo, participants allocated to rosuvastatin who did not achieve LDL cholesterol less than 1.8 mmol/L had no significant reduction in vascular events …whereas we recorded a 55% reduction in those who did achieve this target"*

- But, patients defined by the difference in post-randomization cholesterol-lowering response to treatment may well not differ only randomly from each other (e.g. factors related to lipid-response might also be related to clinical outcome).

JUPITER: Non-randomized comparison of effects of different apparent response (Lancet 2009)

If pre-specified randomized comparisons are required to detect the overall effects on outcome, then why would analyses based on non-randomized subgroup comparisons be considered appropriate (and, indeed, often required by regulatory authorities)?

PLATO trial: Effect on primary outcome of vascular mortality, MI or stroke in ACS

Region	Patients	Ticr (%)	Clop (%)	HR (95%CI)
Asia/Australia	1714	11.4	14.8	0.80 (0.61-1.04)
Central/South America	1237	15.2	17.9	0.86 (0.65-1.13)
Europe/Middle East/Africa	13859	8.8	11.0	0.80 (0.72-0.90)
North America	1814	11.9	9.6	1.25 (0.93-1.67)
ALL REGIONS	18624	9.8	11.7	0.84 (0.77-0.92)

P-value for interaction = 0.05 (before any adjustment for this being 1 of 33 pre-specified subgroup analyses)

PLATO trial: Effect on primary outcome of vascular mortality, MI or stroke in ACS

Post hoc subgroup analysis based on post-randomisation defined subgroup

FDA ruling: *"Aspirin doses above 100 milligrams daily decrease the effectiveness of the medication."* July 2011

Study team: *"The regional interaction could arise from chance alone."* Circulation 2011

P-value for interaction = 0.05 (before any adjustment for this being 1 of 33 pre-specified subgroup analyses)

Need emphasis to be on the key features for getting reliable results from trials

- Proper randomization (and intent-to-treat analysis)
- Sufficient numbers of relevant clinical outcomes (with efficacy and safety considered separately)
- Unbiased ascertainment of key study outcomes (without excessive checking and adjudication)
- Comparisons with the randomized control group (except for assessing big effects on rare events)
- Avoiding undue emphasis on subgroup findings and on non-randomized “on treatment” analyses

Need emphasis to be on the key features for getting reliable results from trials

And avoid distracting investigators with undue focus on processes (e.g. site monitoring; SUSAR reporting; source data verification) of unproven value


and I say we're lost.
ATLANTIC OCEAN
MOROCCO
ALGERIA
MEDITERRANEAN SEA
FEZZAN
LIBYA
RIO DE ORO
MAURITANIA
SAHARA
FRENCH WEST AFRICA
NIGER COLONY
FRENCH SUDAN
SENEGAL
FRENCH GUINEA
IVORY COAST
GOLD COAST
LIBERIA
NIGERIA
CHAD
FRENCH EQUATORIAL AFRICA
UBANGI-SHARI
CAMEROONS
GABON
MIDDLE CONGO
BELGIAN CONGO
ANGLO-EGYPTIAN SUDAN
ABYSSINIA (ETHIOPIA)
UGANDA
KENYA
Gulf of Guinea
Bight of Biafra
SOUTH