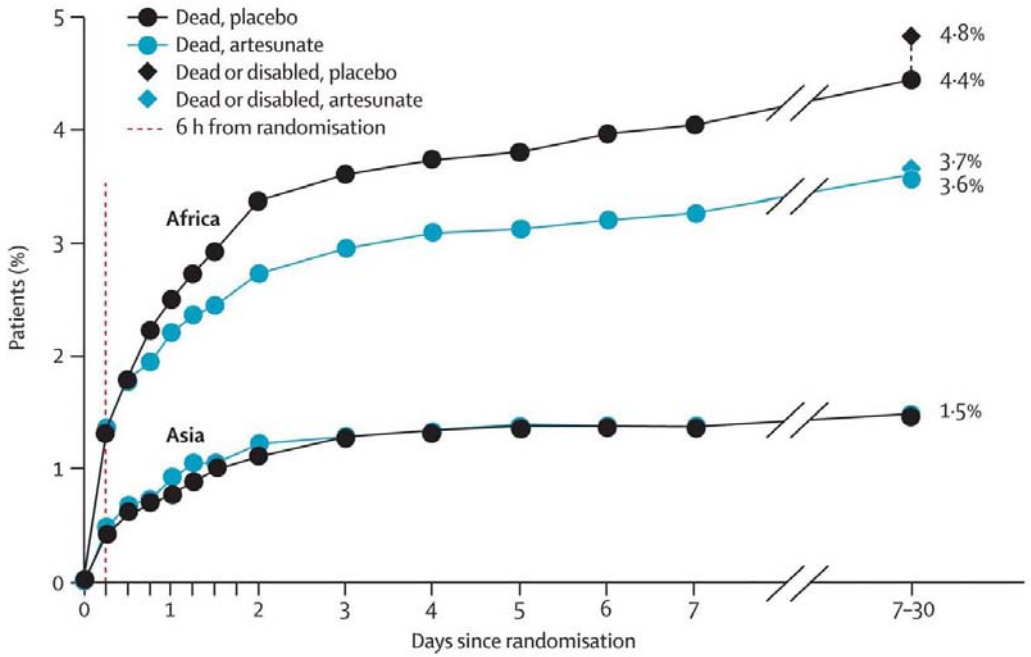
Multiregional Clinical Trials: To Whom Do Their Results Apply?

Janet Wittes
Statistics Collaborative

Artesunate rectal suppository

- 17,826 patients with acute malaria
  - Cannot take medication by mouth
  - Parenteral antimalarial treatment is not available
  - Followed by effective therapy ASAP
- 3 protocols in “Asia” and “Africa”
  - Africa: Ghana and Tanzania
  - Asia: Bangladesh
- Overall it showed benefit

Overall benefit – all in “Africa”



Outline

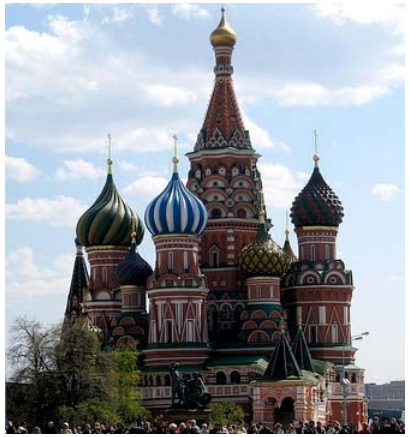
- Some examples of US vs. other
- Why do we go outside US?
- Is region just another subgroup?
- If not, why not?
- What do we do to allow applying results to US?

- “I used to be ambivalent, but now I’m not so sure.” – pace my son Ben

Lesson from an Alzheimer-Drug Failure: Beware Russian Clinical Trial Data

- "Phase III failure of **Dimebon** (latrepirdine) Another reminder to be wary of Russian clinical-trial data."

Trista Morrison | March 5, 2010|BNET



PLATO – Wallentin et al. N Engl J Med 2009;361.

- ticagrelor vs clopidogrel
- Total population: 18,000
- North American: 1,800

"The results regarding the primary end point did not show significant heterogeneity in analyses of the 33 subgroups, with three exceptions: The benefit of ticagrelor appeared to be attenuated in patients weighing less than the median weight for their sex (P = 0.04 for the interaction), those not taking lipid-lowering drugs at randomization (P = 0.04 for the interaction), and those enrolled in North America (P = 0.045 for the interaction)."

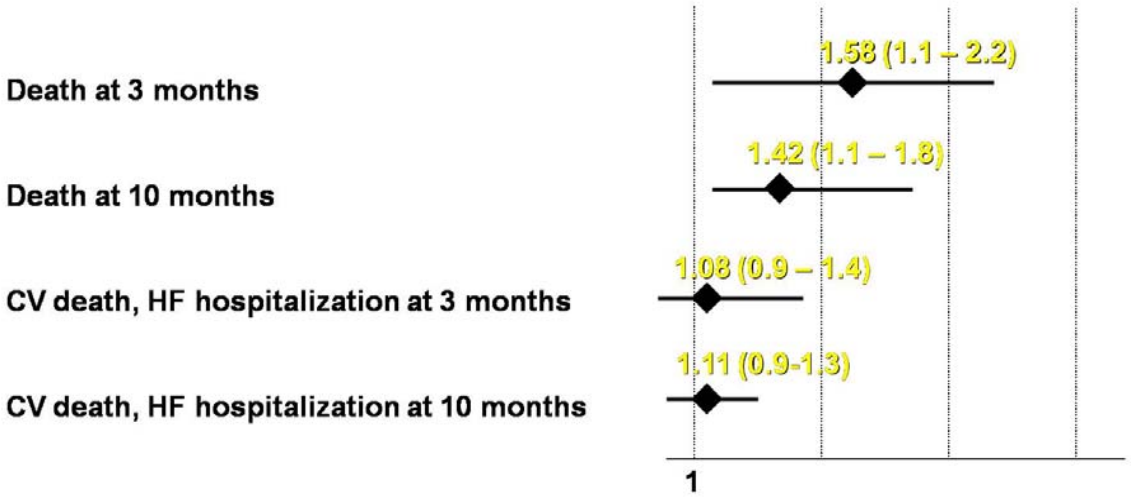
The trend was in the opposite direction.

•Figure 3.

EVEREST TRIAL- **Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure**

EVEREST Trial
Regional differences in outcomes

South America vs. North America
Adjusted outcomes



Adjusted for age, race, etiology, prior myocardial infercion, history of HF hospitalization, NYHA class, chronic renal failure, atrial arrhytmia, SBP, LVEF, BUN, BNP, sodium, ARB-ACEI blockers, B blockers

Blair. *J Am Coll Cardiol 2008;52:1640-1648.*

Belimumab for lupus

Response Rate
(SELENA-SLEDAI improvement 4 or more points, no clinically significant worsening in BILAG or Physician's Global)

Placebo (N=275)	Hi (N=273)
34%	43%

FDA briefing document 19-Oct-10

Belimumab for lupus

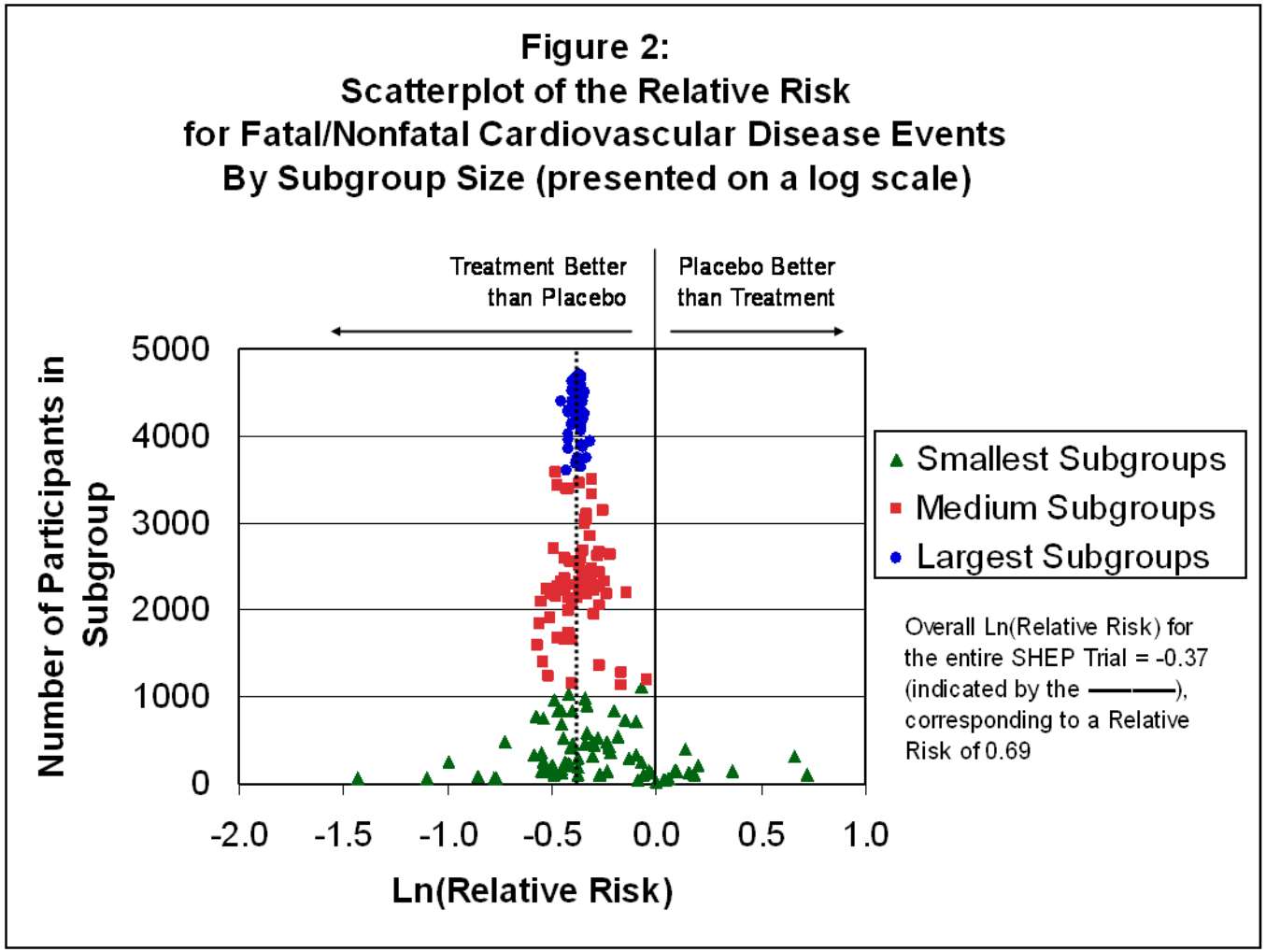
		Placebo (N=275)	Hi (N=273)
Overall		**34%**	**43%**
USA/Can	(300)	32%	35%
W Eur/Isr	(200)	23%	51%
E. Eur	(60)	42%	53%
LA/SA	(60)	57%	53%

FDA briefing document 19-Oct-10

Why do we go outside the US?

- We believe in homogeneity of effect
- We are interested in population heterogeneity
- We want to do trials where it is cheap
  - Recruitment easy
  - People will adhere
  - Costs low
- We want to study people without other meds

But we know to worry about subgroups

- 

Why is this subgroup different from all other subgroups?

- US vs. ROW
- But US is not homogeneous (e pluribus unum)
- And study population is not representative

MERIT-HF

- Randomized, double-blind, placebo-controlled trial
  - Symptomatic heart failure
  - Metoprolol (different doses depending on NYHA class)
  - ~2000 participants / group
  - 13 European countries + US
- Co-primary outcomes (time to) - either
  - total mortality OR
  - combined endpoint of total mortality or all-cause hospitalizations
- Randomization February 1997 - April 14, 1998.

Study stopped at 2nd interim analysis

- 50% information; p<0.001
- Mean follow-up: 1 year
- Deaths
  - Metoprolol: 145
  - Placebo: 217
  - Relative risk: 0.66
  - 95% CL: (0.53, 0.81)

FDA statistical review – May 30, 2000

If the mortality endpoint is the most important among all endpoints, the US sub-population should be the most important subgroup in a multinational trial because the goal of the NDA submission is to gain approval for marketing the drug in the US. The efficacy outcome in this population must be examined carefully as part of the evaluation of the totality of the evidence and possible extrapolation of the efficacy evidence from foreign population[s] to [the] US population.

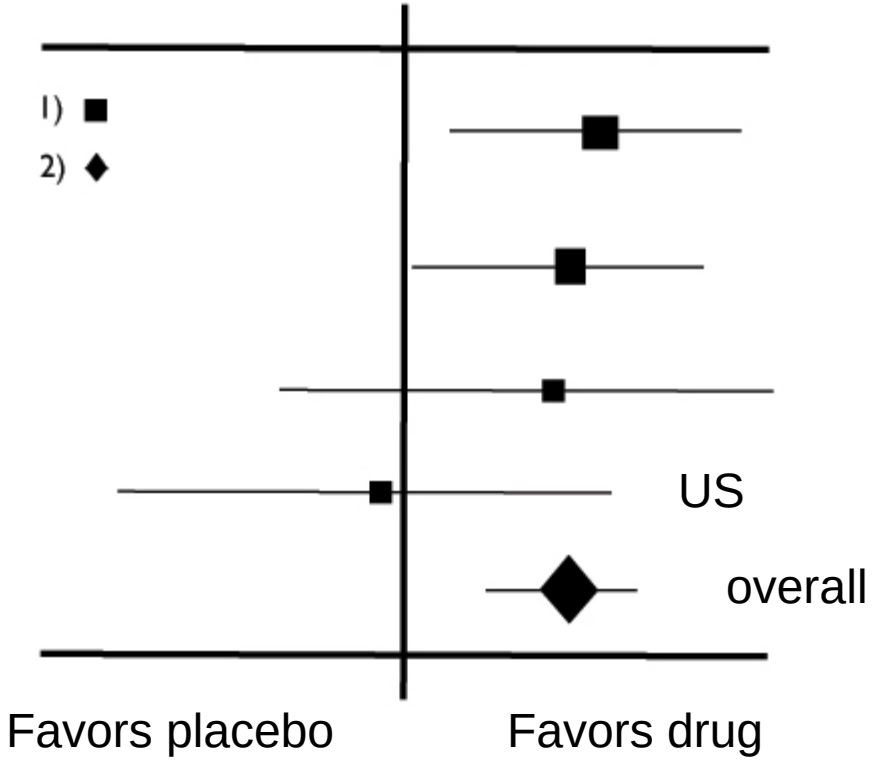
MERIT-HF

Region	Relative Risk	95% CI
Overall	**0.66**	**(0.53, 0.81)**
USA	1.05	(0.71, 1.56)
Ex-US	0.55	(0.43, 0.70)
Interaction p-value: 0.003		

Rephrase: Why is this subgroup (region) different from all other subgroups (or is it)?

- If it's not, we should (nearly) ignore different effects
- But it feels different (US often has different results)
  - Disease factors
  - Population factors
  - Quality of care

Typical forest plot for US and others



Disease factors

- Genetic diseases: different genotypes
- Infectious disease: different organisms
- Chronic disease: different stage of disease
  - cervical cancer in India vs. US
  - invasive breast cancer in Russia vs US
  - heart failure US+W Europe vs Russia+E Eur

How do we split the world? (think df)

- US vs ROW
- US+Canada vs ROW
- US+W Eur+(Israel)+(Australia) vs ROW
- What is “Asia”?
  - Far East (China, Japan, Korea)
  - Subcontinent
  - What about Turkey?
- Africa – does it include the Mahgreb?
- Where does South America go? Mexico?

Population factors

- Diet
- Risk factors
  - Smoking
  - Drinking
  - Comorbidities
- Racial (genetic) and ethnic (cultural) differences

Treatment factors

- Standard of care
  - Time of diagnosis
  - Use of drugs
  - Surgical interventions
- Adherence to protocol

A compromise – think first

CLINICAL TRIALS ARTICLE

Clinical Trials 2010; **7**: 147–156

Regional differences in multinational clinical trials: anticipating chance variation

Ian C Marschner

What are we really asking?

- Narrow regulatory: only interested if we regulate
- Categorize by variables of biological interest
  - That may or may not define regions
  - (Might separate regions within US)

To avoid extrapolation problems

- Think up front
  - Why you are going global (be honest)
  - Think of the extra variability and whether it matters
- Select sample size in US (+Canada?)
  - High power to have effect size in same direction
  - Stratify by region?

A final thought: Recommendation for interim monitoring

- Always report US alone
- Do other regional analyses
- Do other subgroup analyses
- If you stop early, it is what it is