ICH-E17
MULTI-REGIONAL CLINICAL TRIALS

YOKO TANAKA

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OUTLINE

- HISTORY OF MRCT CONCEPT – ICH E5
- 2017 ICH-E17 DRAFT GUIDELINE
- STATISTICAL CONSIDERATIONS
  - REGIONAL SAMPLE SIZE
  - CONSISTENCY ASSESSMENT
- CONCEPT OF SUBPOPULATION
  - INTRINSIC & EXTRINSIC FACTORS
  - REAL EXAMPLE
- MODERN PLANNING

MULTI-REGIONAL CLINICAL TRIAL

- A trial designed for worldwide development of a new drug and gaining approval from regulatory agencies globally
- Multiple countries/regions participating concurrently in accordance with a common clinical trial protocol

ICH-E5: ETHNIC FACTORS IN THE ACCEPTABILITY OF FOREIGN CLINICAL DATA

- Bridging concept
  - Bridge the ‘foreign’ clinical data to the local population
- E5 addresses points to consider in extrapolating ‘foreign’ to local

ICH-E5: Q&A11

- It may be desirable in certain situations to achieve the goal of bridging by conducting a multi-regional trial under a common protocol that includes sufficient numbers of patients from each of multiple regions ……

PERCEIVED PROBLEM

- Drug development has rapidly been globalized recently, and MRCT for regulatory submission has widely been conducted
- Regulatory agencies face challenges in evaluating data from MRCTs for drug approval
- However, there was currently no harmonized ICH Guideline on MRCTs, especially focusing on scientific issues in planning/designing MRCTs
- An international guideline will be needed to promote conducting MRCTs appropriately

E17 BRIEF DEVELOPMENT HISTORY

- 2014 June
  - E17 Expert Working Group formed
  - Rapporteur: PMDA
- 2016 June-Sep
  - Public comments collected
- 2017 4Q
  - Finalization expected

MEMBERS / OBSERVERS OF ICH-E17 WORKING GROUP

EU	EMA	Canada	Health Canada
	EFPIA	WHO	WHO
Japan	PMDA	GCC	Saudi Food and Drug Authority
	JPMA	Brazil	Brazilian Health Surveillance Agency
US	FDA	Singapore	Health Sciences Authority (HSA)
	PhRMA	Korea	Ministry of Food and Drug Safety (MFDS)
		Chinese Taipei	Center for Drug Evaluation (CDE)

ICH E17

- Title:

General principles on planning and designing multi-regional clinical trials

- Objective:

To increase the acceptability of multi-regional clinical trials (MRCTs) in global regulatory submissions

E17 PROMOTES CONDUCT OF MRCTS

MRCTs are generally the preferred option for investigating a new drug for which regulatory submission is planned in multiple regions.

- The treatment effect is clinically meaningful and relevant to all regions being studied.
- The study is intended to describe and evaluate this treatment effect.
- Some sensitivity of the drug to intrinsic and/or extrinsic factors may be expected in different regions (This should not preclude consideration of MRCTs).

KEY STATISTICAL CONSIDERATIONS
- Sample Size to Regions -

Sample Size to Regions	1) Treatment effect preservation 2) Similar directional trend 3) Proportional to region population 4) Local statistical significance 5) Fixed minimum per region

TREATMENT EFFECT PRESERVATION

Estimated treatment effect D_{all} and D_J for all patients and Japanese cohort, respectively.

Results are considered consistent if { $D_J / D_{all} > \pi$}.

Determine the number of Japanese subjects so that

- $D_J / D_{all} > \pi$ will occur with a probability of 80 % or higher.
- π: 0.5 or higher in Japanese guidance*.

* : Basic Concepts for Global Clinical Trials. September 28, 2007. Ministry of Health, Labour and Welfare of Japan.

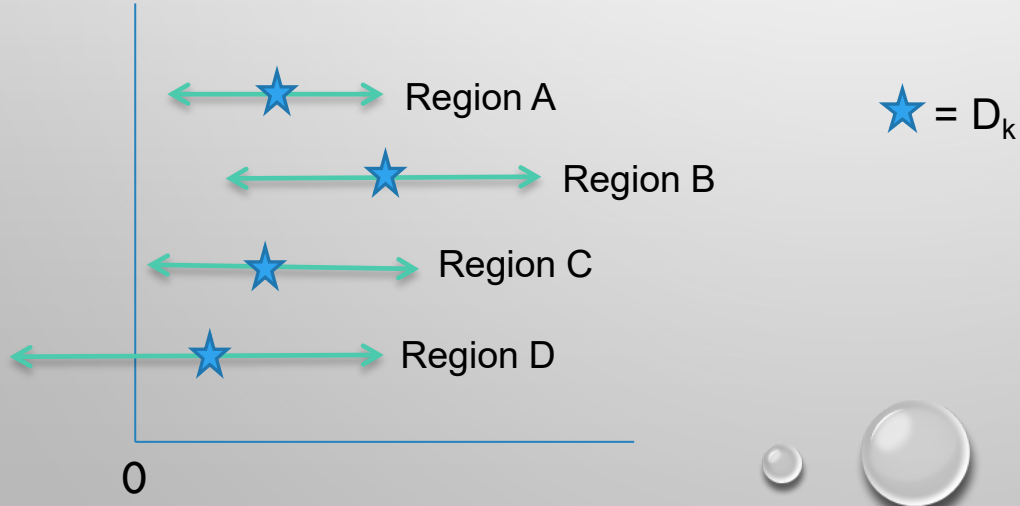
SIMILAR DIRECTIONAL TREND

Positive trend in all regions.

Estimated treatment effect D_{all} for all patients and D_k , k=1, …, *k* for region *k*, respectively.

Results are considered consistent if { $D_k > 0$, k=1, …, *k* }.

- Number of subjects is determined so that each of the D_k will exceed 0 with a probability of 80 % or higher.



PROPORTIONAL TO REGION / DISEASE POPULATION

- Enroll subjects in proportion to region size and disease prevalence without a fixed allocation for regions

- Stomach cancer is much more prevalent in Asia than North America.

LOCAL STATISTICAL SIGNIFICANCE

- Determine the regional sample size to achieve statistically significant result within a region of interest

[E17 Quote]

This allocation strategy brings into question the reasons for conducting MRCTs and should be discouraged.

FIXED MINIMUM PER REGION

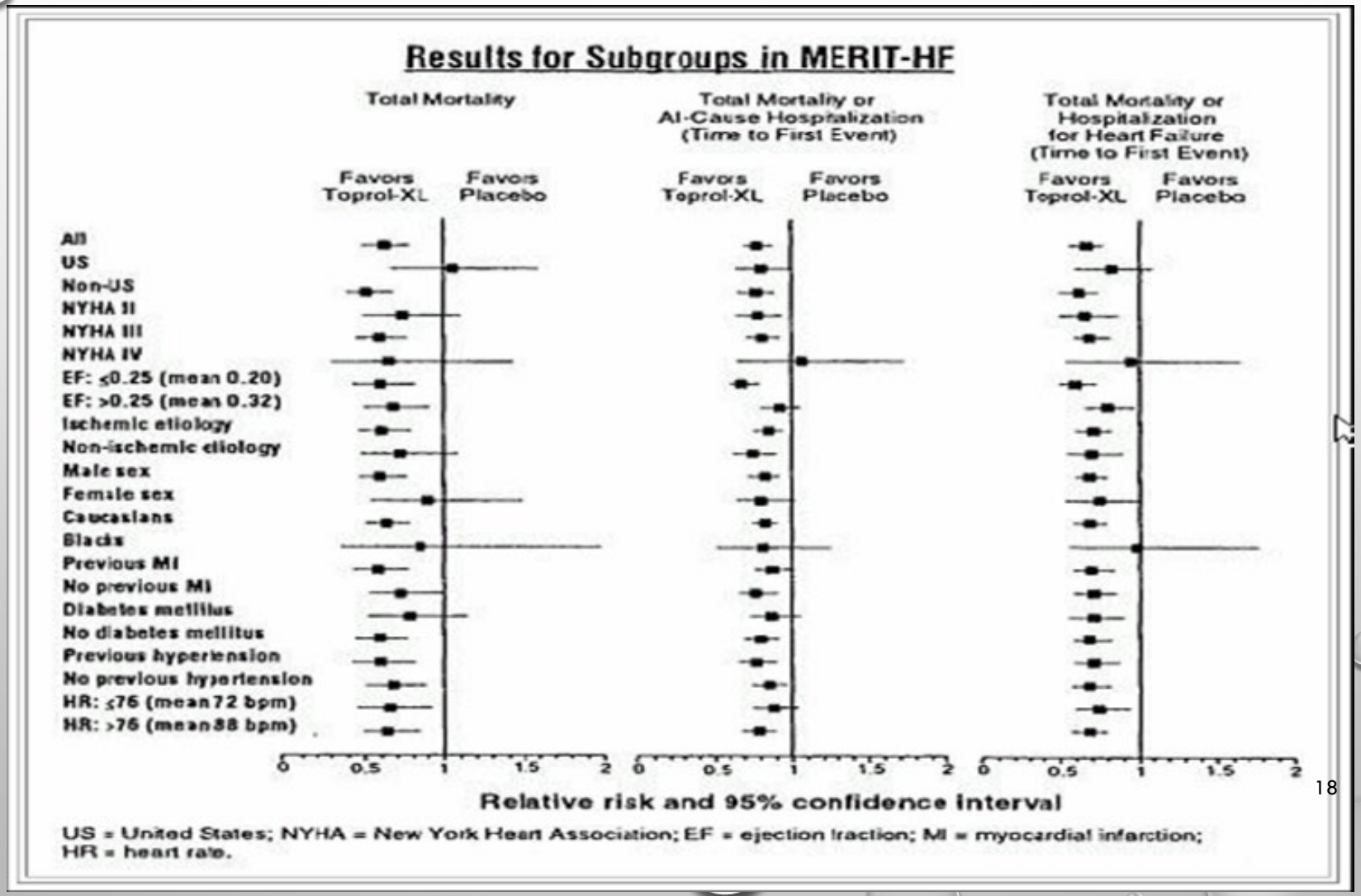
- Require a fixed minimum number of subjects in one or more regions

- Small country / region may not be able to afford many patients. Some authorities set a precedent number of local subjects.

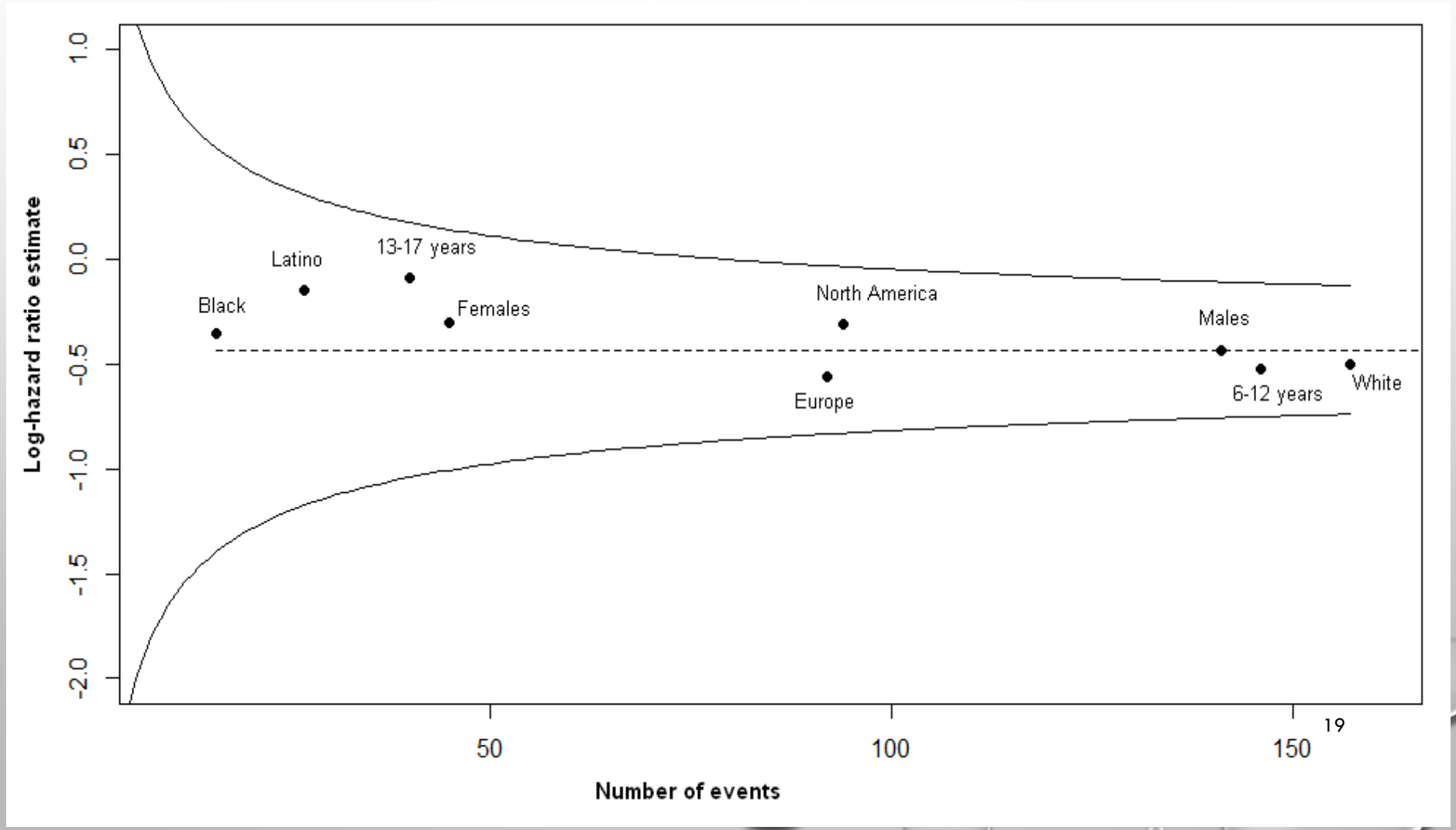
KEY STATISTICAL CONSIDERATIONS
- Consistency Evaluation -

Consistency Evaluation To be evaluated & described -- Not to be tested --	a) Visual displays (forest plots, funnel plots) b) Descriptive summaries c) Model-based estimation including covariate-adjusted analysis d) Test of treatment by region interaction

FOREST PLOT


Results for Subgroups in MERIT-HF
Total Mortality
Total Mortality or All-Cause Hospitalization (Time to First Event)
Total Mortality or Hospitalization for Heart Failure (Time to First Event)
Favors Toprol-XL
Favors Placebo
All
US
Non-US
NYHA II
NYHA III
NYHA IV
EF: ≤0.25 (mean 0.20)
EF: >0.25 (mean 0.32)
Ischemic etiology
Non-ischemic etiology
Male sex
Female sex
Caucasians
Blacks
Previous MI
No previous MI
Diabetes mellitus
No diabetes mellitus
Previous hypertension
No previous hypertension
HR: ≤76 (mean 72 bpm)
HR: >76 (mean 88 bpm)
0
0.5
1
1.5
2
Relative risk and 95% confidence interval
US = United States; NYHA = New York Heart Association; EF = ejection fraction; MI = myocardial infarction; HR = heart rate.

FUNNEL PLOT


Log-hazard ratio estimate
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Black
Latino
13-17 years
Females
North America
Europe
Males
6-12 years
White
50
100
150
Number of events

MODEL-BASED ESTIMATION

Example: Empirical shrinkage Estimator

- Random effect model incorporates between-region variability in the analysis and controls the type I error rate.
- The empirical shrinkage estimators of treatment effects for individual regions borrowing information from other regions are more efficient estimators.
- It may provide more generalizable trial results.

Empirical Shrinkage Estimator

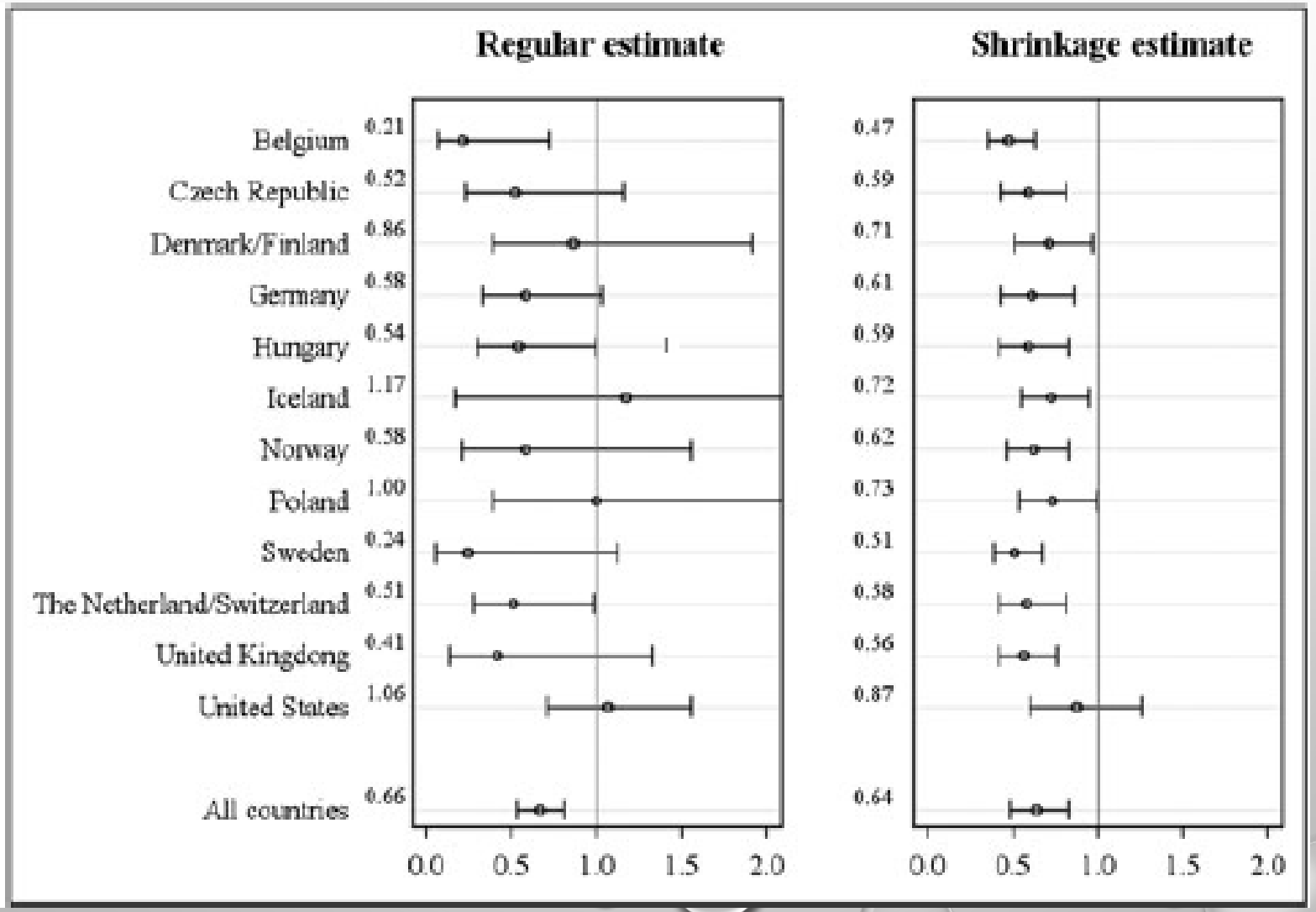
Metoprolol Controlled-Release Randomized Intervention Trial in Heart Failure (MERIT-HF)

Table IV. Data of mortality from MERIT-HF.

	Sample size		Number of events	
Country	Meto CR/XL	Placebo	Meto CR/XL	Placebo
Belgium	68	66	3	13
Czech Republic	123	124	9	17
Denmark/Finland	141/20	150/14	11/0	11/2
Germany	252	247	19	31
Hungary	211	212	16	29
Iceland	19	22	2	2
Norway	97	105	6	11
Poland	102	102	8	8
Sweden	39	46	2	9
The Netherland/Switzerland	278/21	270/21	14/0	25/1
UK	87	83	4	9
USA	532	539	51	49

Empirical Shrinkage Estimator

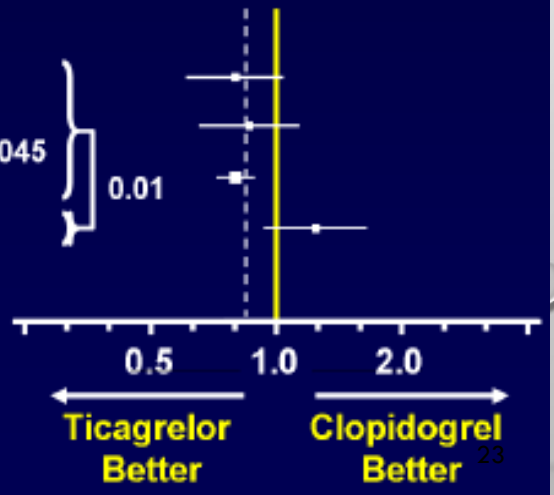
Hazard ratio (95% confidence interval) on mortality by region for MERIT-HF



Treatment by Region Interaction

- Evaluate ticagrelor versus clopidogrel in patients with acute coronary syndromes
- The study showed an overall statistically significant efficacy effect. However, results in North America and, in particular, in the United States showed a trend in the opposite direction

Characteristic	Total Patients	# of Events Tic	# of Events Clop	HR (95% CI)	Interaction p-value
Geographic Region					
Asia / Australia	1714	95	116	0.80 (0.61, 1.04)	0.045
Cent / Sth America	1237	91	104	0.86 (0.65, 1.13)	
Euro / Md E / Afr	13859	576	712	0.80 (0.72, 0.90)	
North America	1814	102	82	1.25 (0.93, 1.67)	0.01



Totality of Evidence

E17 quote:

- Credibility of regional findings should also take into consideration **biological plausibility**, **consistency (internal and/or external) of findings**, the **strength of evidence**, as well as the **statistical uncertainty**.

Hill's criteria (established in 1965 by the English epidemiologist in establishing evidence of a causal relationship)

Careful Consideration of Intrinsic/Extrinsic Factors

To increase an acceptability of MRCT data in the review by multiple regulatory agencies for drug approval, a sponsor should carefully consider the planning and design of MRCTs in advance.

- Intrinsic and extrinsic factors are a major point of consideration

INTRINSIC & EXTRINSIC FACTORS

- Intrinsic factors are the subject's characteristics represented **within themselves** such as age, gender, race, gene, height, weight.
- Extrinsic factors are the subject's **environment and culture** (something outside themselves) which could influence the subject's behavior, practice, and preferences such as tobacco/alcohol use, diet, socio-economic status, and medical practice/standard of care.

ICH-E5:
INTRINSIC & EXTRINSIC FACTORS

Classification of intrinsic and extrinsic ethnic factors

INTRINSIC		EXTRINSIC
Genetic	Physiological and pathological conditions	Environmental
Gender	Age (children-elderly)	Climate Sunlight Pollution
Height Bodyweight		
	Liver Kidney Cardiovascular functions	**Culture** Socioeconomic factors Educational status Language
ADME Receptor sensitivity		
Race		Medical practice Disease definition/Diagnostic Therapeutic approach Drug compliance
Genetic polymorphism of the drug metabolism		
		Smoking Alcohol
		Food habits Stress
Genetic diseases	Diseases	Regulatory practice/GCP Methodology/Endpoints

SUBPOPULATION – NEW CONCEPT

- A subset of subjects across the regions who are thought to be similar with respect to intrinsic and/or extrinsic factors **relevant to the disease area and/or drug under study**

SUBPOPULATION

- Subpopulation should be defined with the consideration of the outcome of the study.
- If the objective is to study the pharmacokinetics of the drug (i.e. PK study), intrinsic factors such as race and genetics may be more important than the extrinsic factors to understand how the drug is processed in the subject's body.
- If the objective is to evaluate efficacy and safety of the drug, extrinsic factors may be more important since local clinical guideline and medical practice, and culture may have more impact on the subject's response to the certain drug of investigation.

EXAMPLE – PLATO TRIAL

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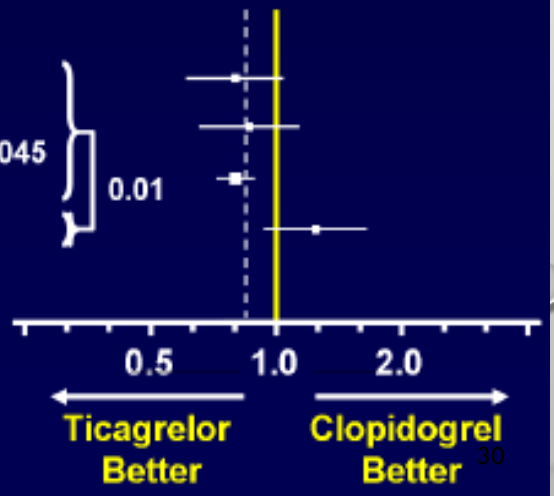

ASPIRIN DOSE

- One potential confounder based on post hoc analysis was the dose of maintenance aspirin which was used at much higher dosage in the US than in the rest of the world.
- Analyses controlling for aspirin dose (low, medium, high) revealed that what was initially discovered as a region effect could be attributed to differences in aspirin doses being confounded with region.
- Having considered aspirin dose in the design of the study may have avoided much work to try to explain the regional finding.

PLATO CONCLUSION

- This "North American" anomaly is widely believed to be one of the main reasons that the US FDA has delayed the approval of ticagrelor; in December (2010) it delayed a decision on ticagrelor for a second time.

- FDA approved blood-thinning drug Brillinta to treat acute coronary syndromes , Boxed warning says daily aspirin doses above 100 mg decreases effectiveness. July, 2011

SUBPOPULATION EXAMPLES

- Diagnosis of ADHD type
  - Subtype (inattention, hyperactivity, combined) is an important factor to understand the magnitude of responses to treatment in evaluating the ADHD medications.
  - Patients with inattentive type typically exhibits much smaller response relative to the hyperactive subtype.

➢ In defining subpopulation, diagnosis of ADHD subtype maybe more important than geographic regions.

SUBPOPULATION EXAMPLES

- Heart disease in medical practice and disease management
  - More invasive/advanced care in North America
  - Trial population – much higher risk patients from eastern EU

➢ Optimal patient allocation to Eastern EU vs NA; subpopulation defined by medical practice maybe more important than geographic regions

Contrast from Pooled Regions

- **Pooled regions** are defined as a subset of subjects pooled across **geographical** regions, countries or regulatory regions for purpose of regulatory decision-making.
- Here, the focus is more for the regulatory review and approvability in the region where the regulatory authority is responsible.

Geographic Region

Contrast from Pooled Regions

- Regions in the completed trial data can be pooled to provide more sample size, or if the characteristics of pooled regions defined by intrinsic and extrinsic factors that are considered similar to the concerned region, the data from the pooled regions can be a basis for the regulatory review for the concerned region.
- Pooled data from Japan and Taiwan can possibly be submitted to Korea if the patient population is considered similar with respect to intrinsic/extrinsic factors.

Contrast from Subgroup

- Subgroup analysis is to assess **consistency of the primary trial result** performed among different subset of subjects defined by patient demographics (ex. age, gender) or baseline clinical characteristics (ex. different severity).
- There may be an **overlap** when trying to distinguish between subgroup and subpopulation.
- Subpopulation is a **specific type of subgroup** that is a pooled subset of the subjects across regions sharing one or more intrinsic or extrinsic factors that may be associated with differential treatment response.

Contrast from Subgroup

- In the PLATO example, both **geographic region and aspirin dose were subgroups**, but the **aspirin dose** perhaps could have been considered more as a **subpopulation** since the determination of aspirin dose is related to local clinical practice in different regions, can be recognized at the design stage, can be pooled across regions, and the effect on the treatment response has biological plausibility.

MODERN TRIAL PLANNING

- Early protocol design should be **accompanied by** intrinsic/extrinsic factor assessment

[Easier said than done !]

- Assess regional imbalance in influential intrinsic and extrinsic factors (subpopulation) in treatment response
- Sample size strategy to account for subpopulation

MODERN TRIAL PLANNING

- Agreement with the regulatory authorities
  - Sample size and subpopulation
- Clinical Operation
  - Optimal patient allocation implementation
- Trial Monitoring
  - Region data review
- Consistency Evaluation
  - By region – authority's jurisdiction
  - By subpopulation – science driven