Why Risk Based Subgroup Analysis Should be Routine

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Outline

- Distinguish between "person-level" heterogeneity of treatment effect (HTE) and "group-level" HTE.
- Review why commonly used approaches for describing group-level HTE are poor surrogates for person-level HTE.
- Review why risk-based approaches are better.

Clinical Trial Results

ACTUAL OUTCOME

COUNTER FACTUAL OUTCOME

0 = alive
1 = dead

Subject Name	Without Treatment	With Treatment
SAM	0	
MARY		0
BOB	0	
BEN		0
CHRISTINE		0
NEIL	1	
MOHAMED		1
JENNIFER		1
PAUL	0	
NISHA	1	
MIGUEL	1	
LAYLA		0
PAUL	0	
EMANUEL		1
CHERYL		0
PATRICK	0	
OSCAR		1
JULIANNE	0	
THOMAS	0	
GEORGE		0

Individual Treatment Effects in a Deterministic Framework: Four possibilities

Without Treatment	With Treatment	
0	0	NO EFFECT
0	1	HARM
1	0	BENEFIT
1	1	NO EFFECT

Clinical Trial Results with Counterfactuals

ACTUAL OUTCOME

COUNTER FACTUAL OUTCOME

0 = alive
1 = dead

Subject Name	Without Treatment	With Treatment	
SAM	0	1	← HARM
MARY	0	0	
BOB	0	0	
BEN	1	0	← BENEFIT
CHRISTINE	1	0	← BENEFIT
NEIL	1	1	
MOHAMED	1	1	
JENNIFER	1	1	
PAUL	0	1	← HARM
NISHA	1	1	
MIGUEL	1	1	
LAYLA	1	0	← BENEFIT
PAUL	0	0	
EMANUEL	1	1	
CHERYL	0	0	
PATRICK	0	0	
OSCAR	1	1	
JULIANNE	0	0	
THOMAS	0	0	
GEORGE	1	0	← BENEFIT

Individual Treatment Effects in a Deterministic Framework: Four possibilities

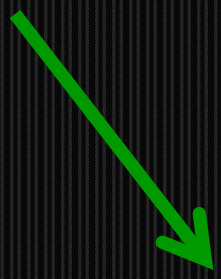
Without Treatment	With Treatment	
0	0	NO EFFECT
0	1	HARM
1	0	BENEFIT
1	1	NO EFFECT

Clinical Trial

0 = alive
1 = dead

Without Treatment	With Treatment
0	1
0	0
0	0
1	0
1	0
1	1
1	1
1	1
0	1
1	1
1	1
1	0
0	0
1	1
0	0
0	0
1	1
0	0
0	0
1	0

BENEFIT



Proportion Dead	11/20 55%)	9/20 45%)

Limitations of conventional (one-variable-at-a-time) subgroup analysis

- Patients have too many attributes.
- One variable-at-a-time subgroup analyses:
  - lead to multiplicity and spurious false positive results.
  - under-represent the degree of heterogeneity across patients.
  - not congruent with the goals of HTE analysis for patient-centered decisions (reference class problem).

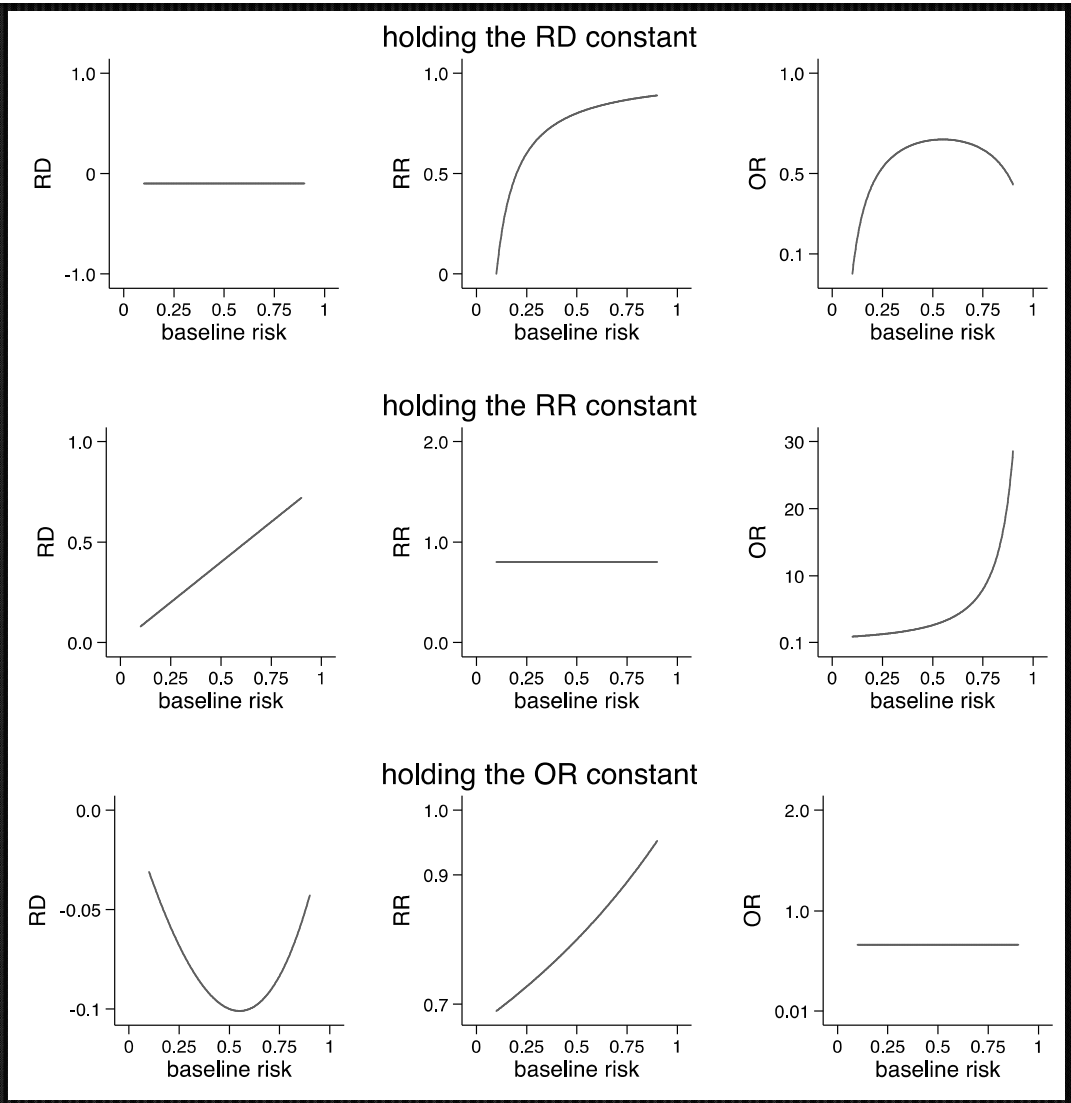
Why privilege risk-based HTE analysis?

- Risk is a known mathematical determinant of treatment effect.

Common Measures of Treatment Effect

Risk Reduction (RR)	Definition
Absolute RR	EER-CER
Relative RR	$1 - \frac{EER}{CER}$
Odds Ratio	$\frac{EER/(1-EER)}{CER/(1-CER)}$
CER=control event rate EER=experimental event rate	

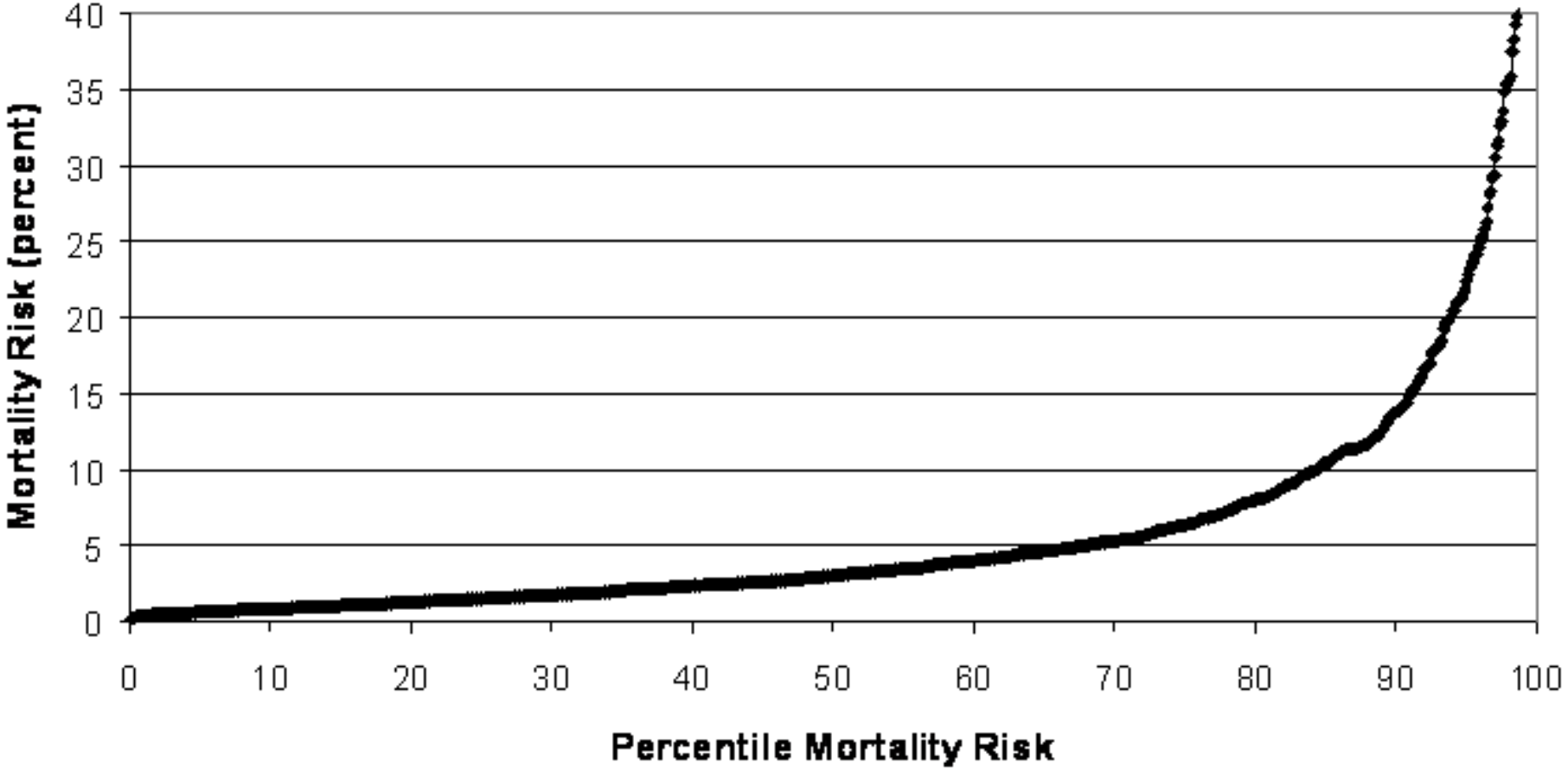
An Illustration of Scale Dependence of HTE over Baseline Outcome Risk



Why privilege risk-based HTE analysis?

- Risk is a known mathematical determinant of treatment effect.
- When baseline risk heterogeneity is present (and the treatment effect is non-zero), there is always HTE.

Figure 1: Distribution of Mortality Risk with Thrombolytic Thearpy in Patients with Acute Myocardial Infarction



Kent DM, et al. *J Gen Intern Med* 2002; 17:887-94.

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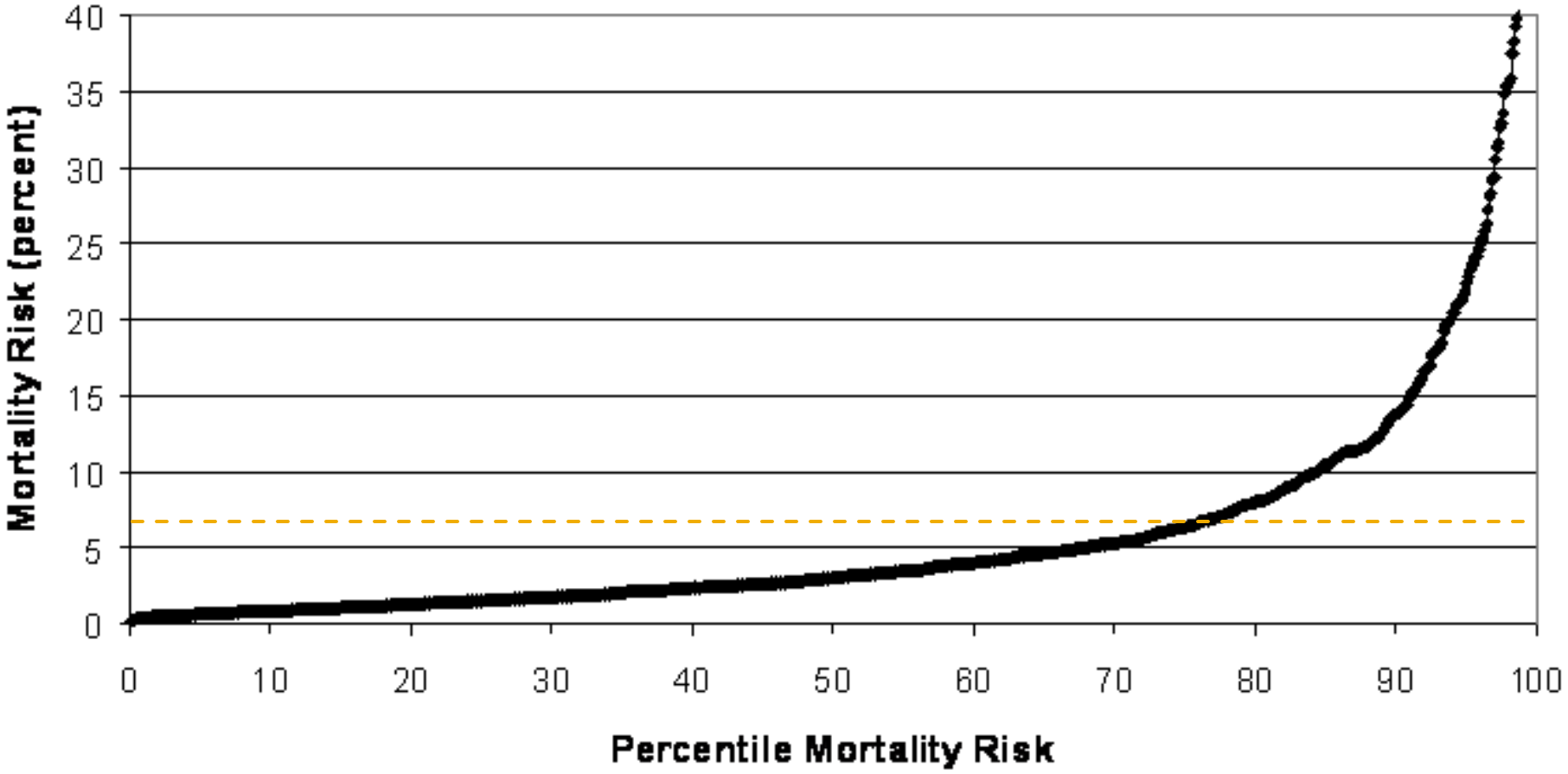

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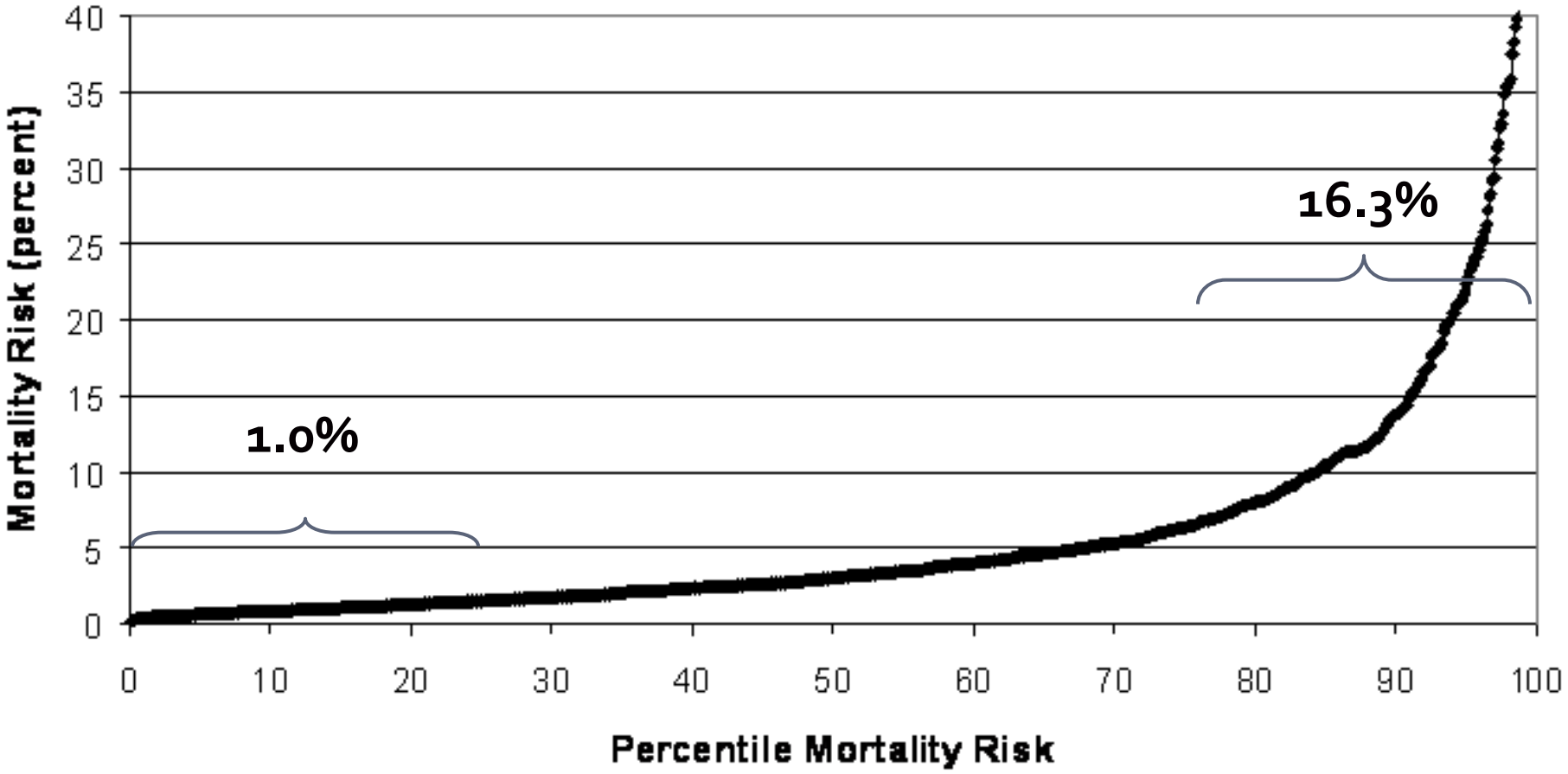

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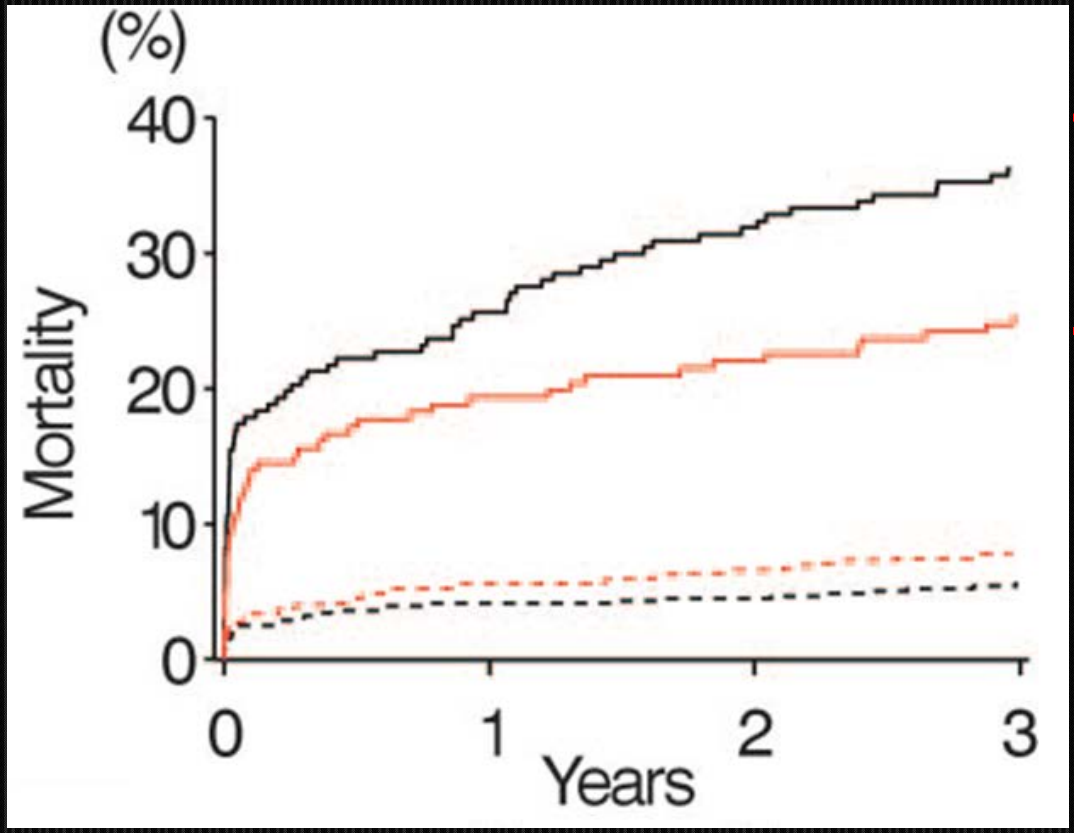
DANAMI-2

PCI
Medical Therapy



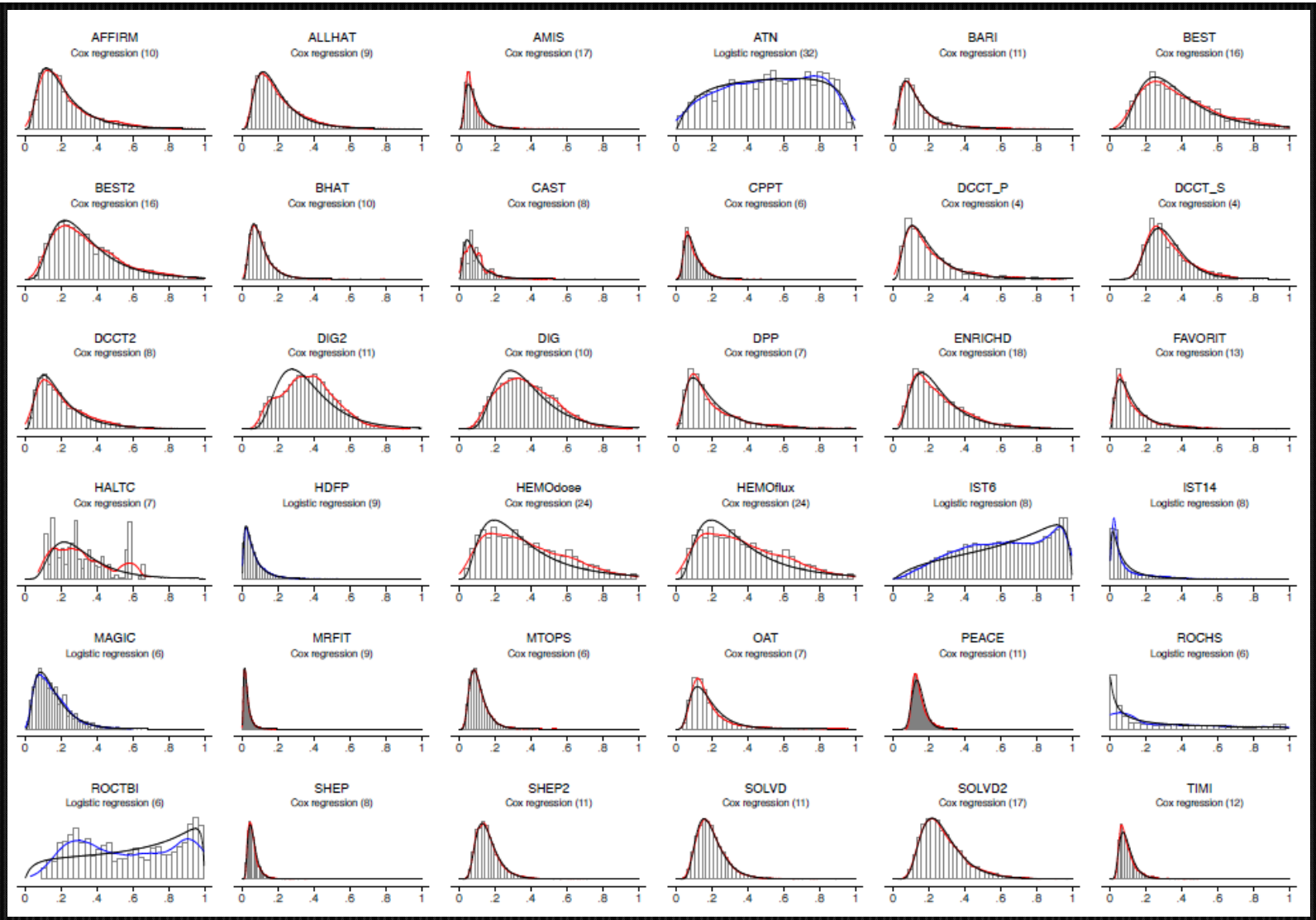
High Risk

Low Risk

Number at risk				
TIMI 0-4	Fx	556	533	531
	PA	578	546	540
TIMI ≥ 5	Fx	207	154	141
	PA	186	150	145

Thune JJ, et al. *Circulation* 2005,112:2017-2021.

Predicted Risk Distributions in RCTs

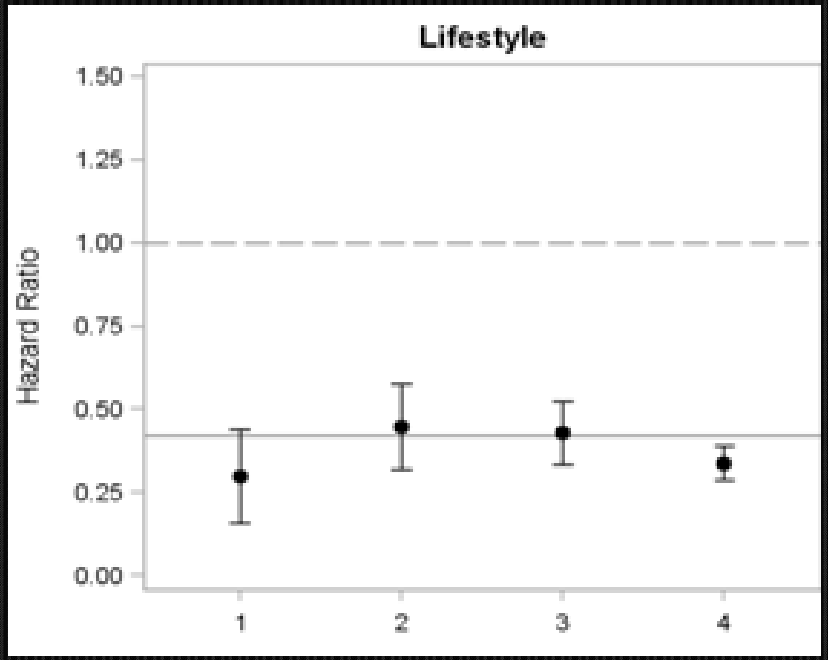


Diabetes Prevention Program (DPP) Randomized Controlled Trial

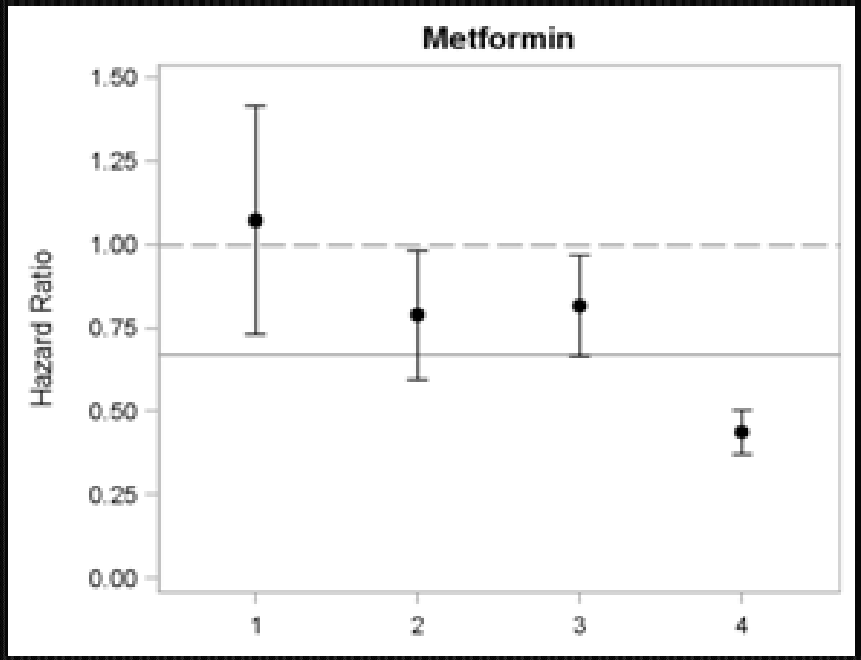
- Participants: 3060 nondiabetic persons with evidence of impaired glucose metabolism.
- Intervention: Intervention groups received metformin or a lifestyle-modification program.
- Main Outcome Measure: Development of diabetes

The DPP study was conducted by the DPP Investigators and supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

DPP Risk Stratified Results

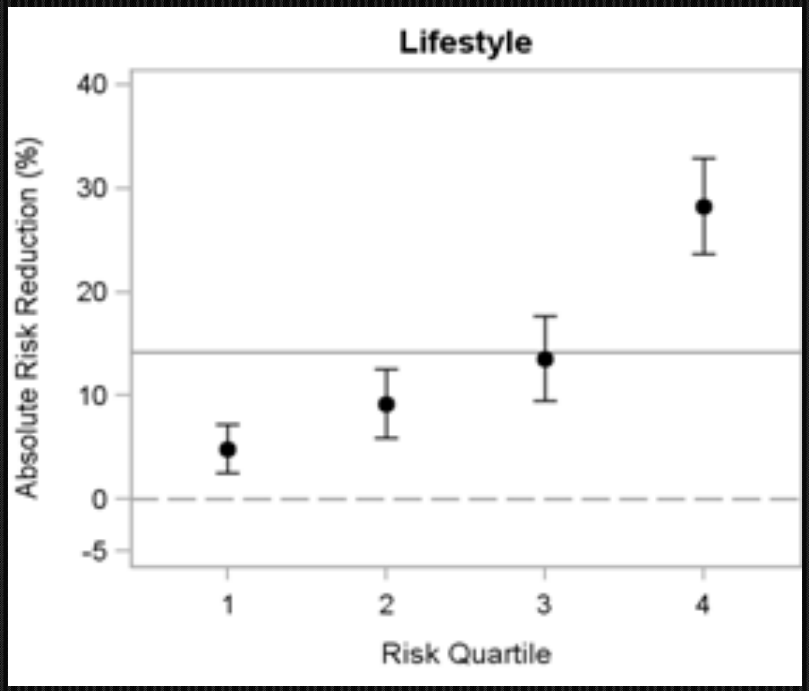


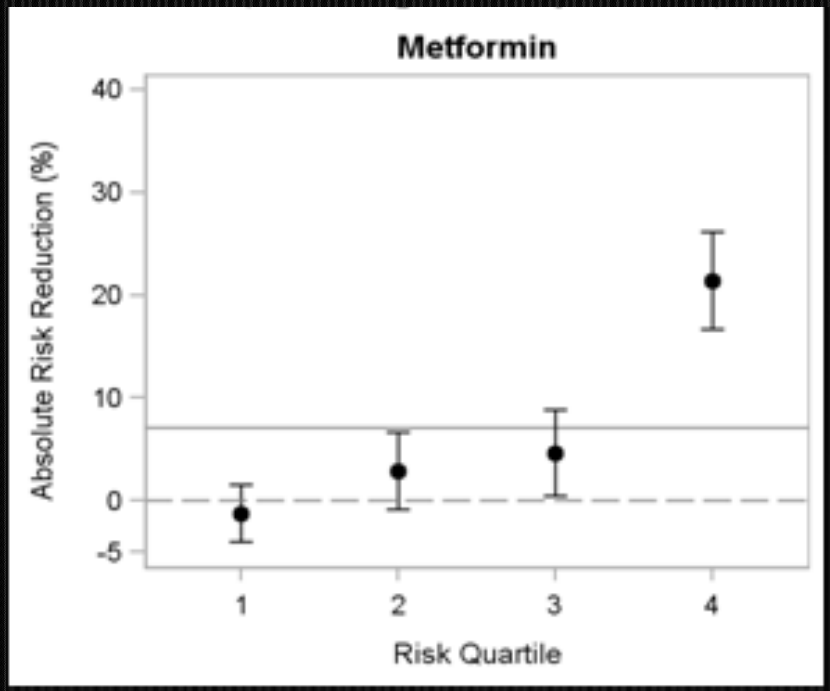
p value = NS



p value = 0.0008

DPP Risk Stratified Results





Risk based analyses can reveal counter-intuitive findings

- Overall effectiveness results may be driven by a relatively small group of influential (typically high risk) patients;
- The typical (median) risk patient is frequently at considerably lower risk than the overall average;
- The average benefit seen in the summary result often over estimates the benefit (on the RD scale) in most patients (and may obscure harm in many).

Clinical Conditions where Outcome Risk is Major Determinant of Clinically-Relevant HTE

CLINICAL CONDITION	INTERVENTION
Symptomatic carotid stenosis	Carotid endarterectomy
Non-valvular atrial fibrillation	Anticoagulation for primary prevention of stroke
Coronary artery disease	Coronary artery bypass grafting
Primary prevention of coronary artery disease	Blood pressure lowering Aspirin Lipid lowering
Acute coronary syndromes	Early invasive strategy (versus conservative) Clopidogrel (versus placebo) Enaxparin (versus unfractionated heparin)
ST-Elevation acute myocardial infarction	tPA (versus streptokinase) Percutaneous coronary intervention (versus thrombolytic therapy)
Severe sepsis	Drotrecogin alfa (activated protein C)
Pre-diabetes	Lifestyle intervention Metformin
Tobacco smoking	Lung cancer screening

Kent DM, et al. *Trials* 2010;11:85.

Summary

- Heterogeneity of outcome risk is ubiquitous.
- Heterogeneity of outcome risk inevitably gives rise to heterogeneity of treatment effect.
- One variable at a time subgroup analyses are inadequate (and prone to spurious false positive results).
- Risk based subgroup analyses can do better.