Using Group Data to Treat Individuals:
Understanding heterogeneous treatment effects in the age of precision medicine and patient centered care

David M. Kent, MD, MSc
Professor of Medicine, Neurology, Clinical and Translational Science,
Director, Predictive Analytics and Comparative Effectiveness (PACE) Center,
Institute for Clinical Research and Health Policy Studies, Tufts Medical Center

- Person-level heterogeneity of treatment effects (HTE) are ubiquitous
- Group-level HTE is rarely reliably identifiable in clinical trials.

Problems with conventional subgroup analysis

- Weak Theory (poor prior knowledge about effect modifiers)
- Noisy Data (Low power)
- Patients have too many attributes

Why Risk Based Subgroup Analysis Should be Routine

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Why privilege risk-based HTE analysis?

- Risk is a known mathematical determinant of treatment effect.

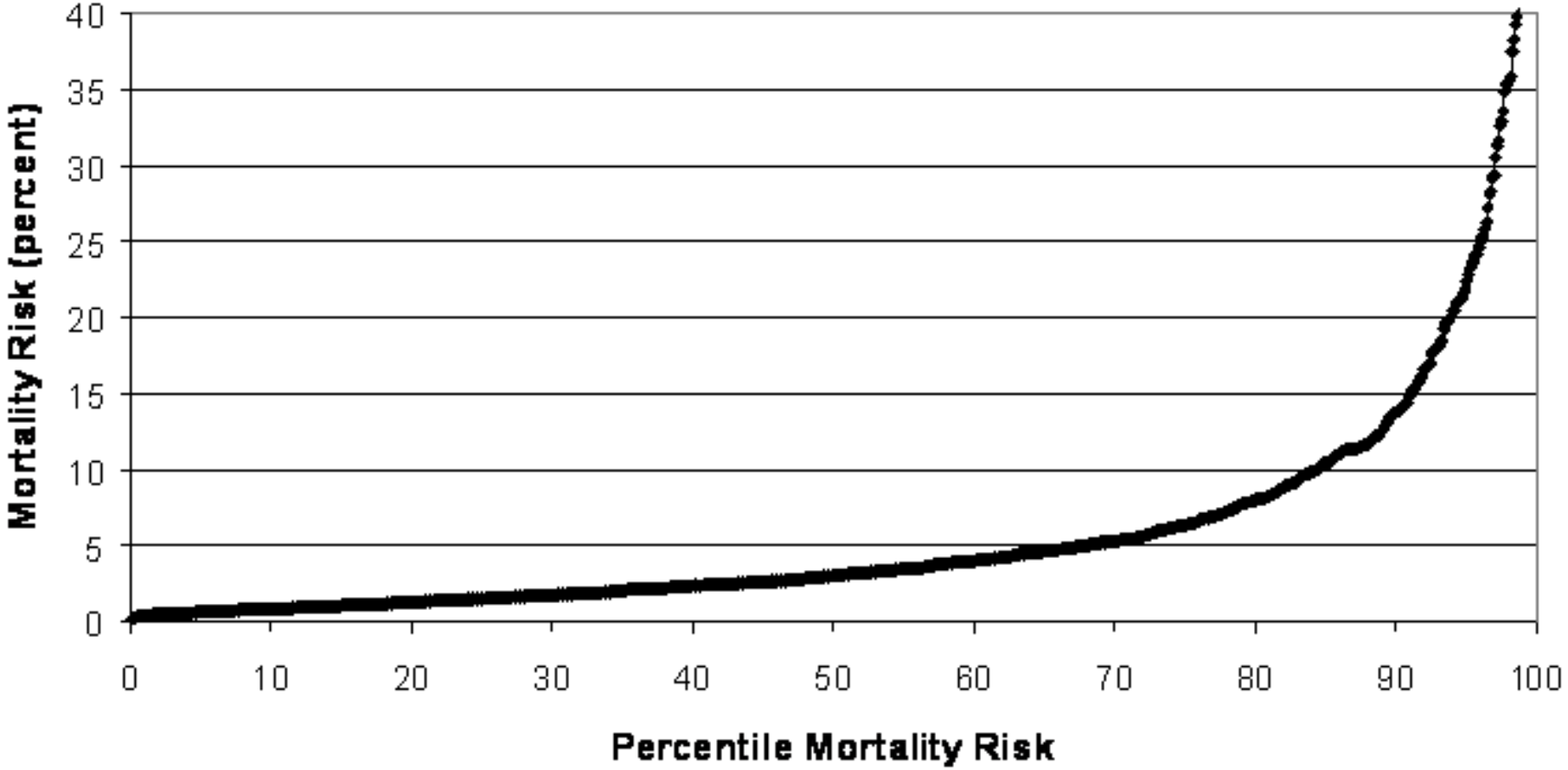
Common measures of treatment effect

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	

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.
- Risk provides a summary measure that takes into account multiple variables that are relevant; provides "patient-centered" evidence.

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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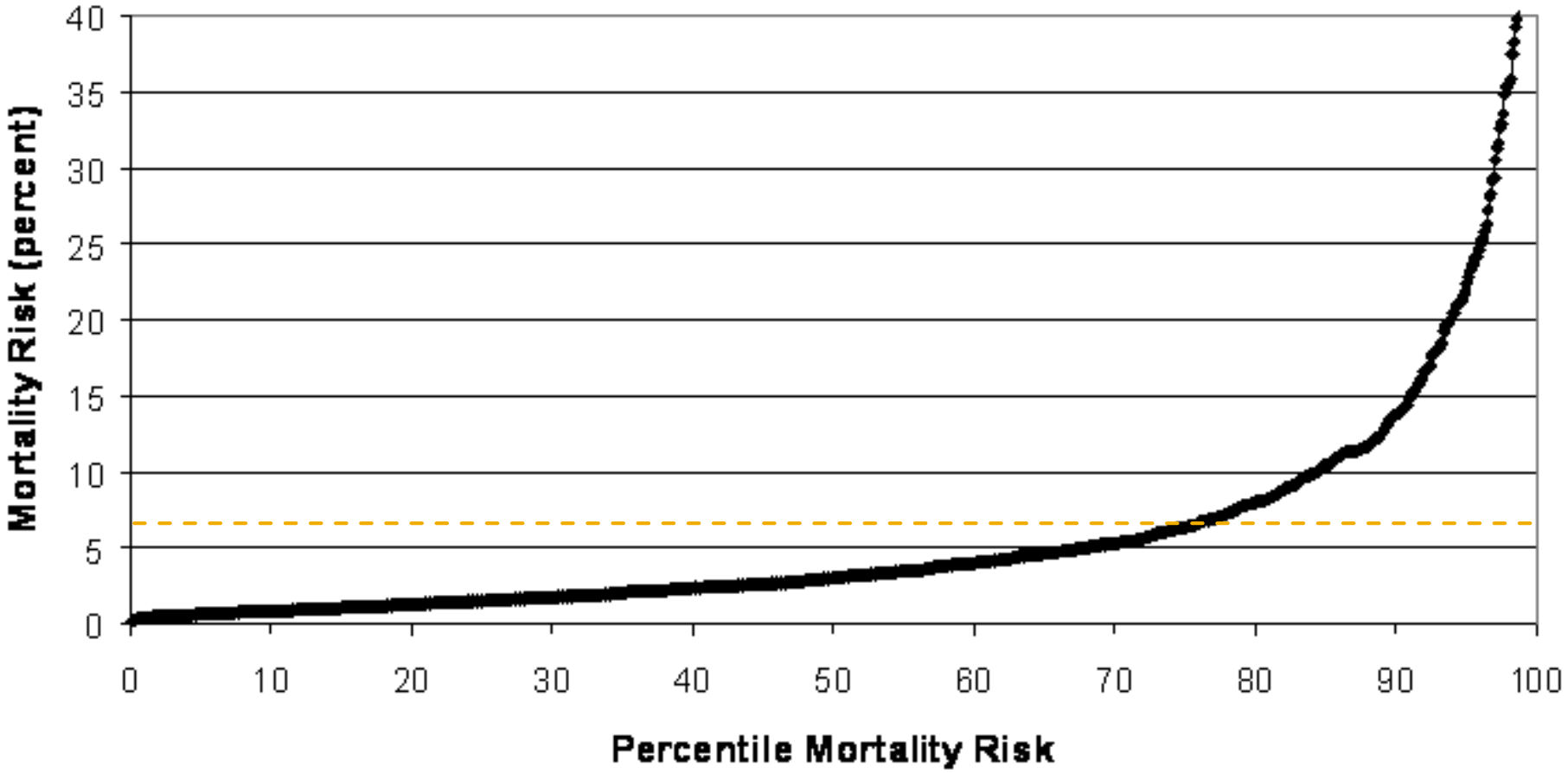

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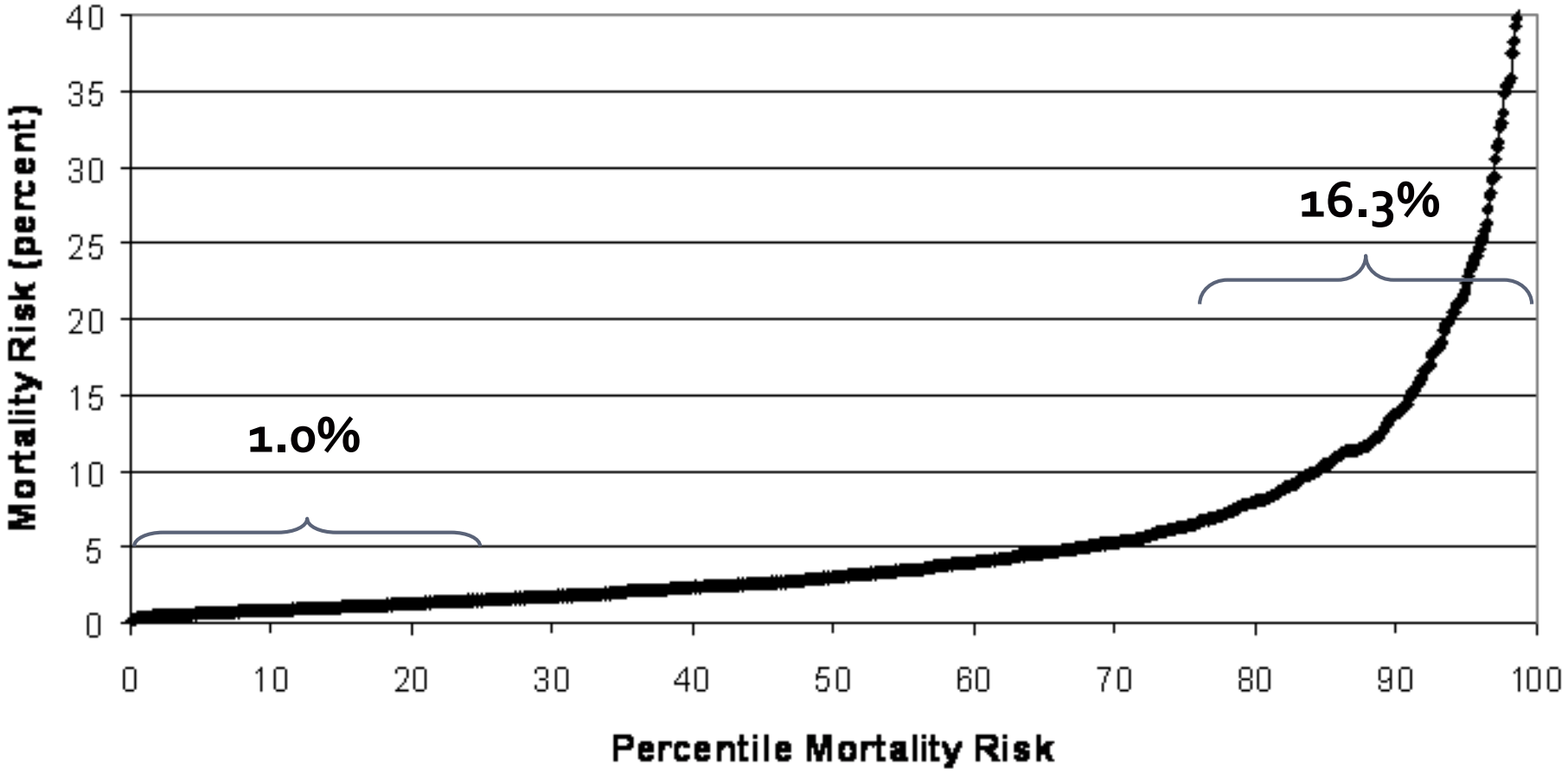

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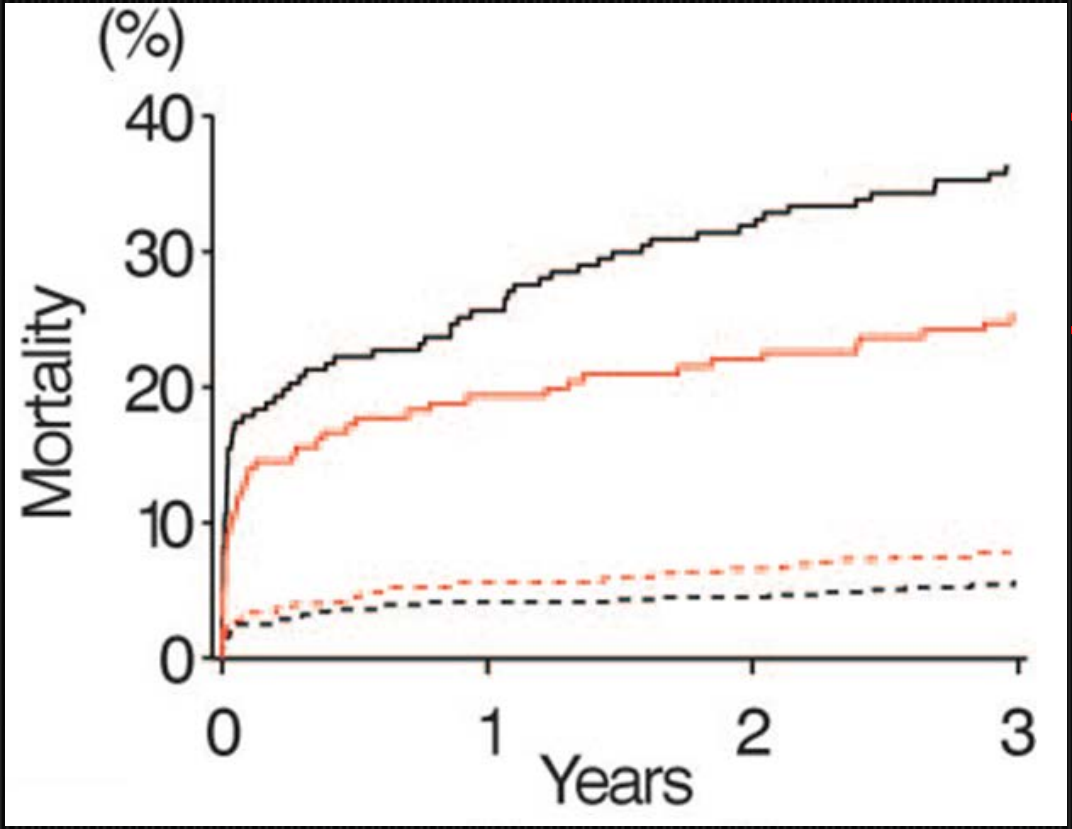
DANAMI-2

PCI
Medical Therapy



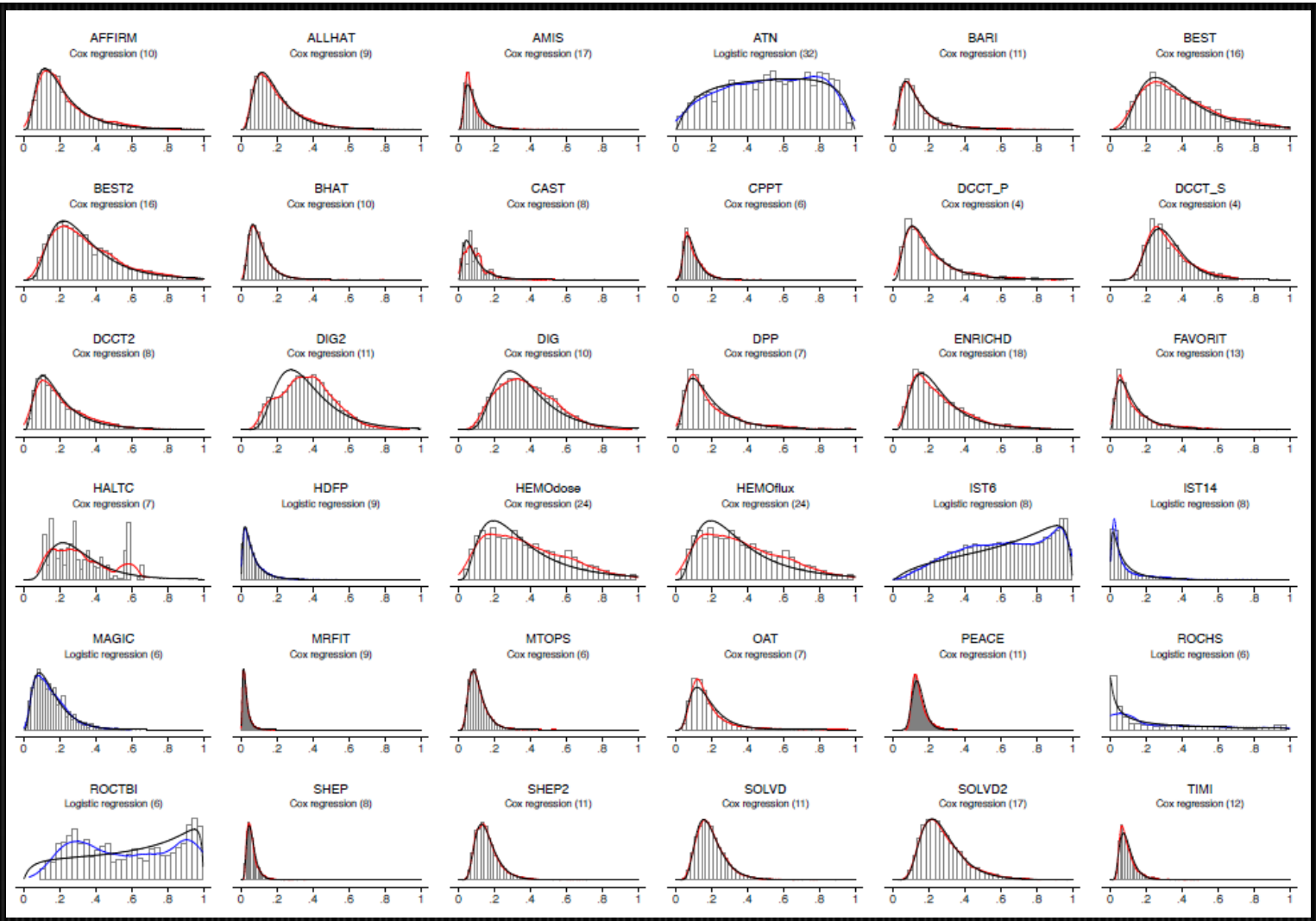
High Risk

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

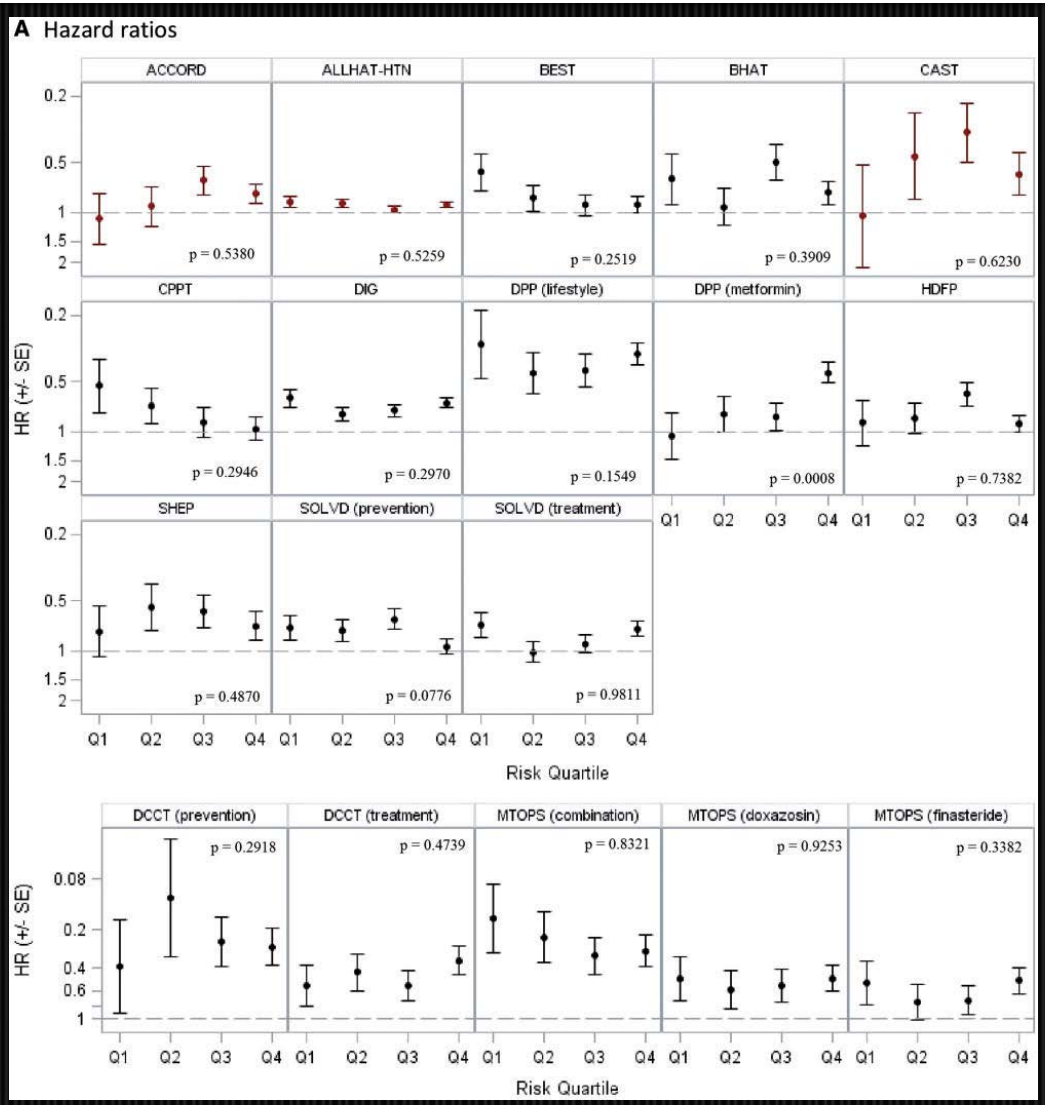
Thune JJ, et al. *Circulation* 2005,112:2017-2021.

Predicted risk distributions in RCTs



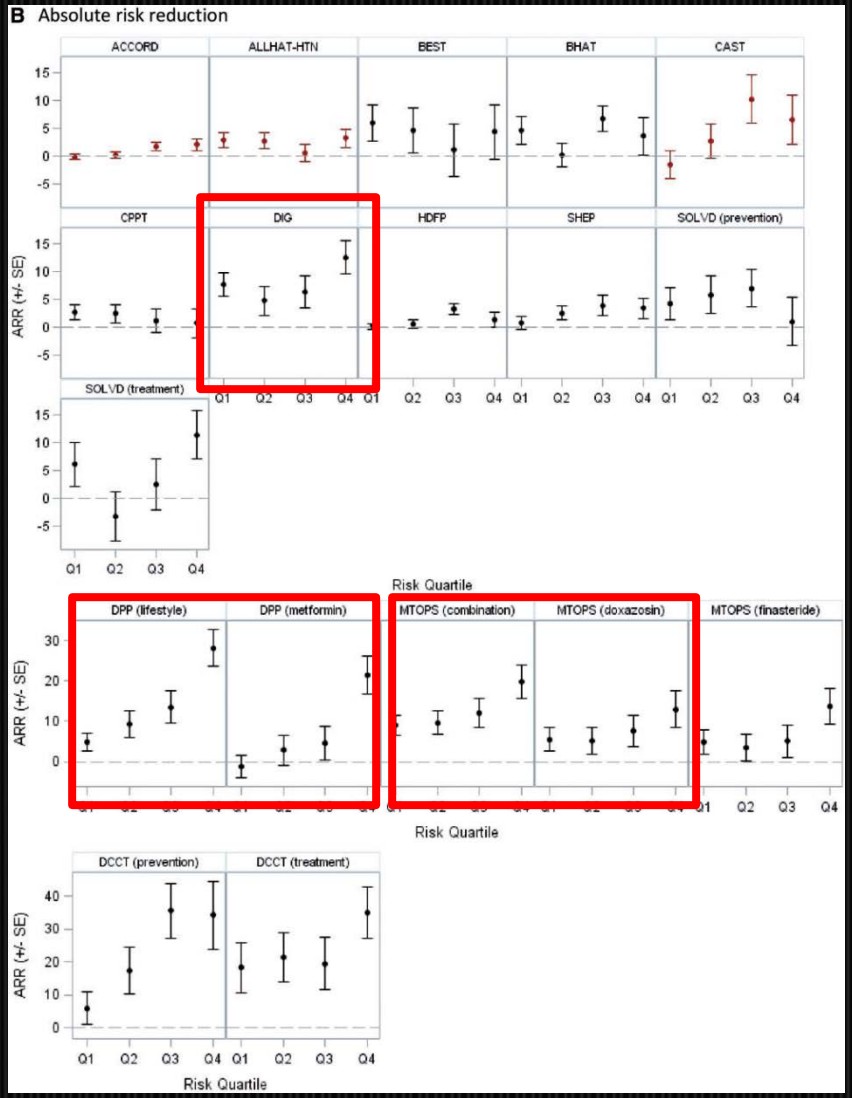
Kent DM et al. Int J Epidemiol. 2016 Jul 3. pii: dyw118.

Relative risk reduction across risk quartiles



Treatment effect heterogeneity on the proportional scale across patients at different baseline risk was rare

Absolute risk reduction across risk quartiles



Substantial differences in absolute treatment effects were common

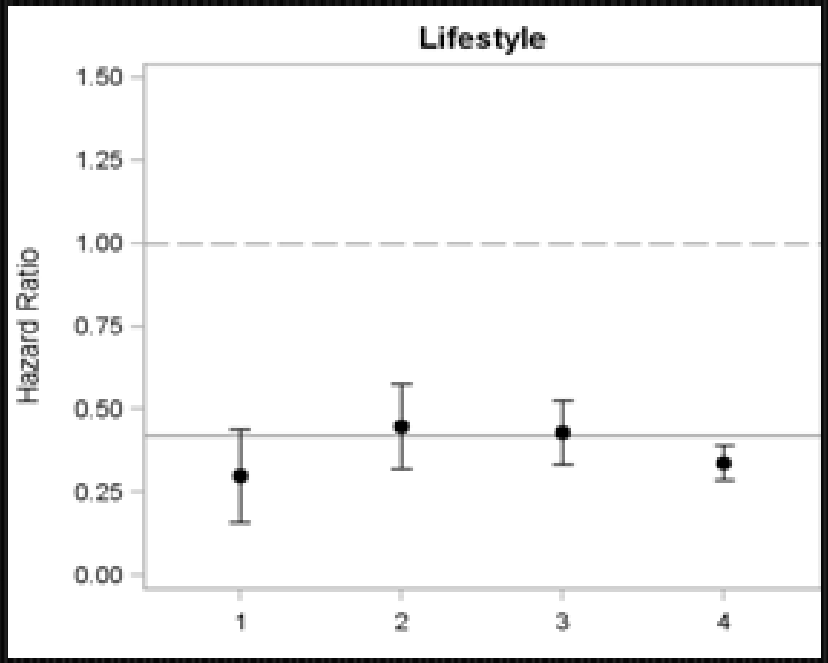
Displaying results across subgroups defined by risk is feasible and can lead to clinically important findings

Diabetes Prevention Program (DPP) Randomized Controlled Trial

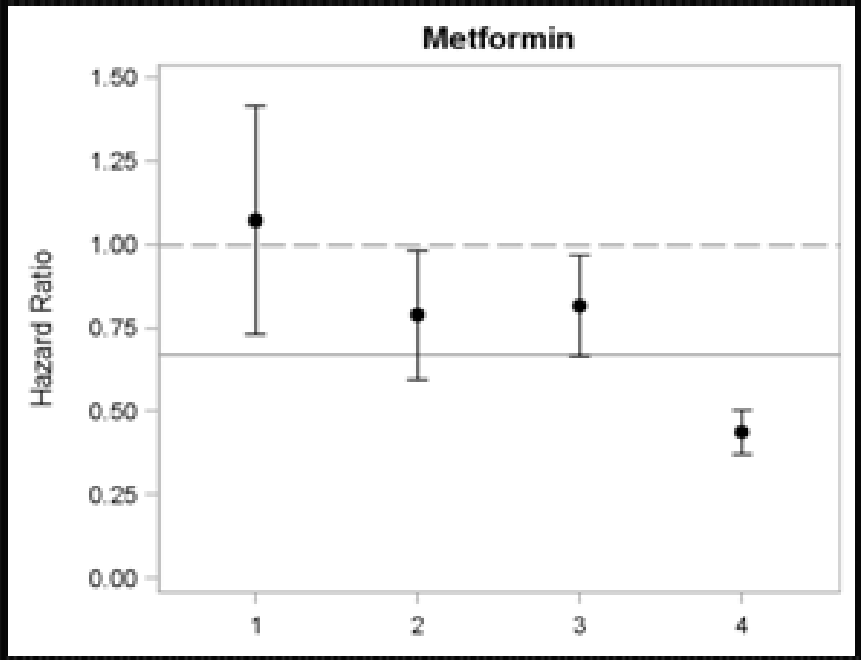
- Participants: 3060 nondiabetic persons with evidence of impaired glucose metabolism.
- Intervention: Intervention groups received metformin or a lifestyle-modification program.
- Main Outcome Measure: Development of diabetes

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



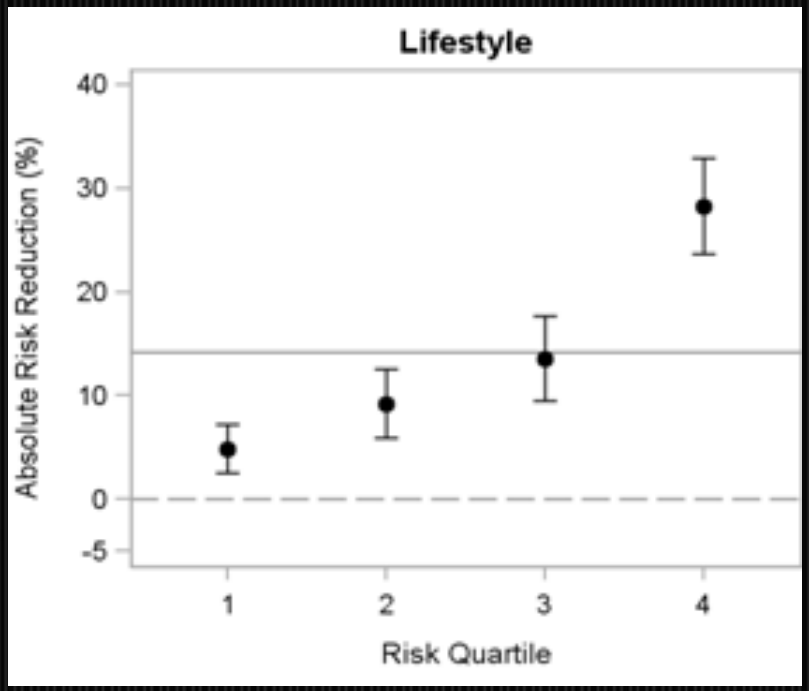
p value = NS

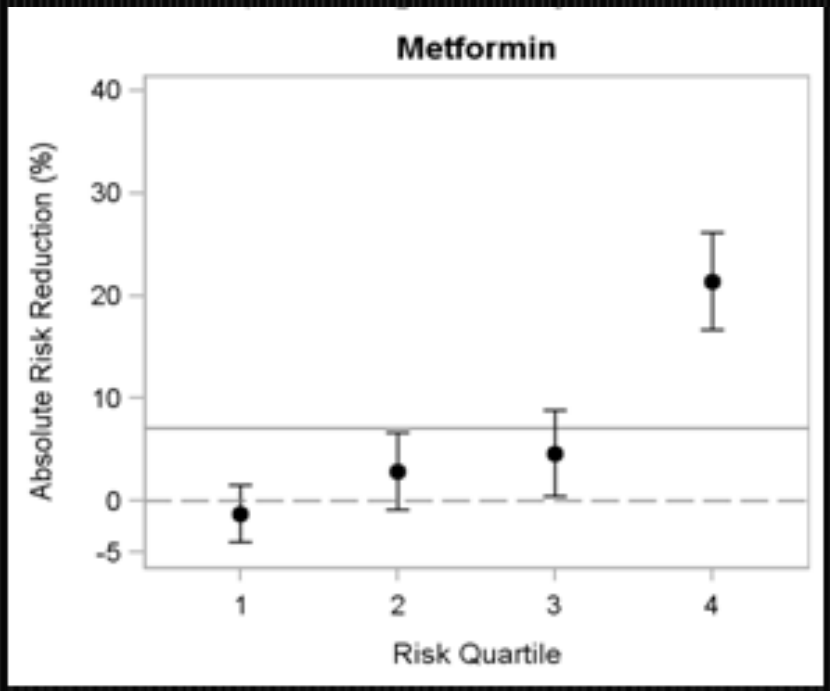


p value = 0.0008

Sussman JB et al. BMJ. 2015 Feb 19;350:h454.

DPP Risk Stratified Results



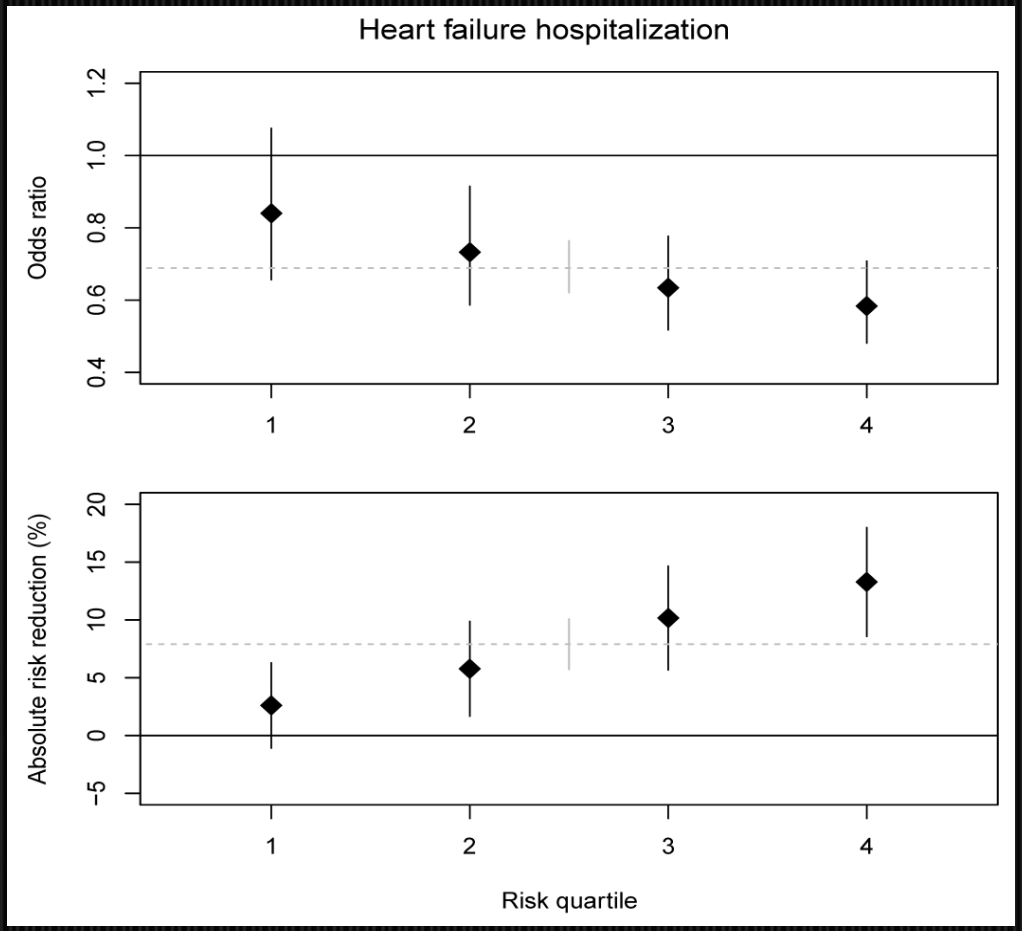


Sussman JB et al. BMJ. 2015 Feb 19;350:h454.

Digitalis Investigator Group (DIG) Study

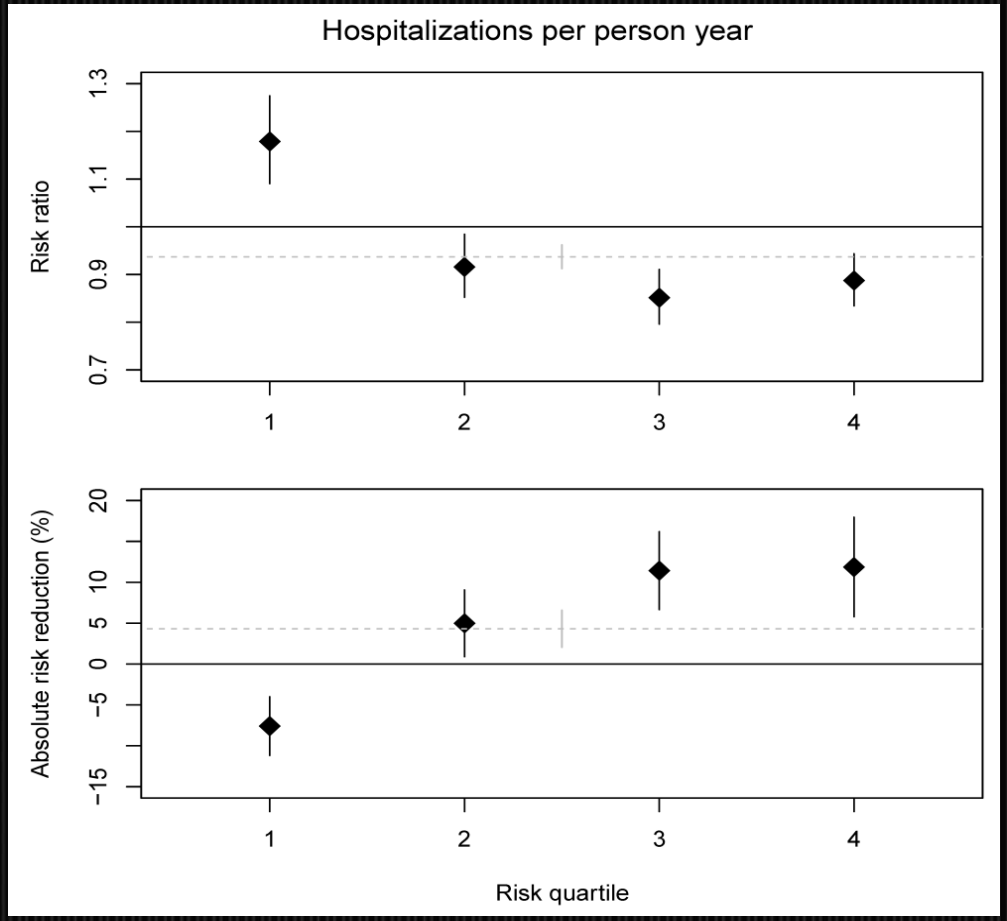
- Participants: Participants with HF and LVEF less than or equal to 45% (main DIG study, n=6800) or LVEF >45% (ancillary DIG study, n=988).
- Intervention: digoxin versus placebo
- Main Outcome Measure: Hospitalization due to worsening HF, all cause hospitalization

DIG Risk Stratified Results



Upshaw JN et al. Am J Med. 2018 Jun;131(6):676-683.e2.

DIG Risk Stratified Results

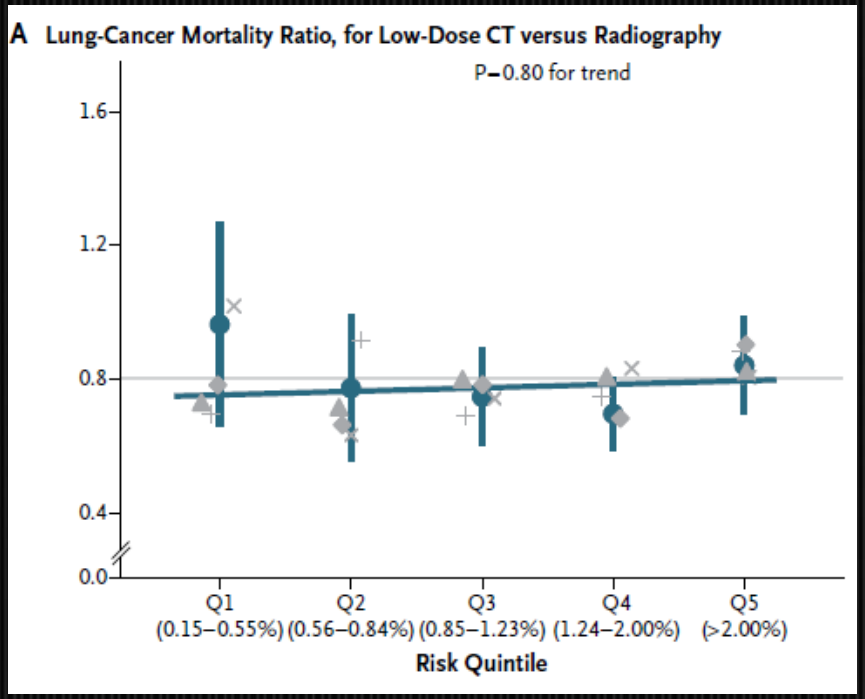


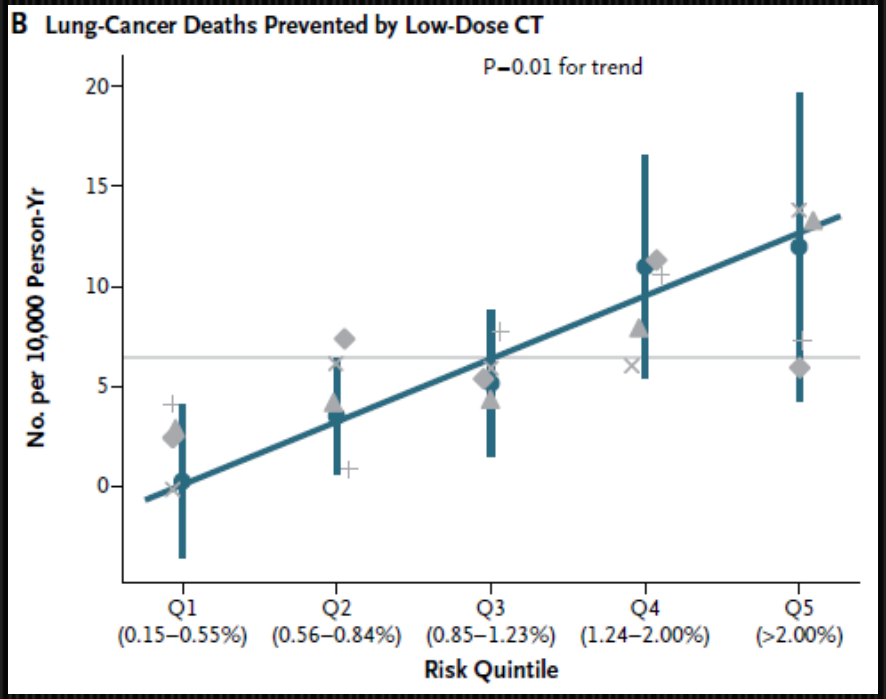
Upshaw JN et al. Am J Med. 2018 Jun;131(6):676-683.e2.

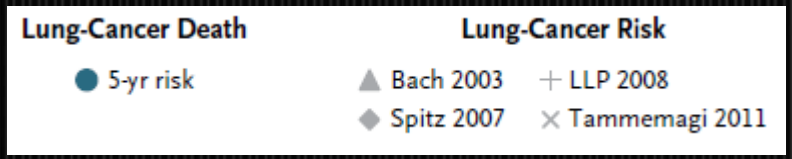
National Lung Screening (NLST) Trial

- Participants: Smokers between the ages of 55 and 74 years with a minimum of 30 pack-years of smoking and no more than 15 years since quitting
- Intervention: Low-dose CT screening or chest radiography
- Main Outcome Measure: Lung-cancer deaths

NLST Risk Stratified Results







Kovalchik SA et al. N Engl J Med 2013; 369: 245-54

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

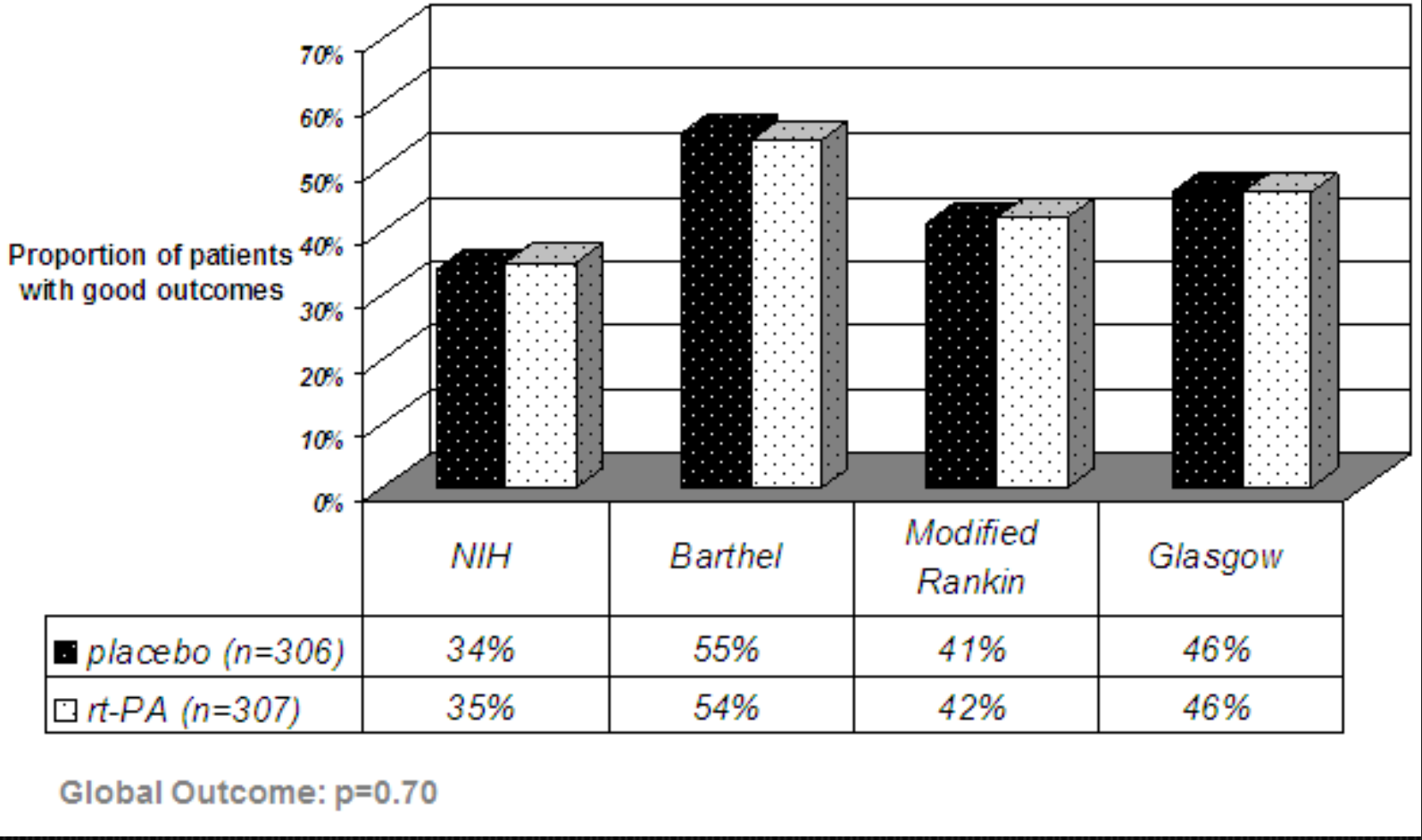
Kent DM, et al. *Trials* 2010;11:85.

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.

Treatment-related Harm

Overall outcomes in ATLANTIS B trial



Kent DM, et al. *Stroke* 2003;34:464-7.

Thrombolytic-related ICH-risk in Myocardial Infarction

- Age
- Sex
- Race (white, black or other)
- History of prior stroke
- Systolic blood pressure
- Diastolic blood pressure
- Interaction term: age* gender* history of prior stroke

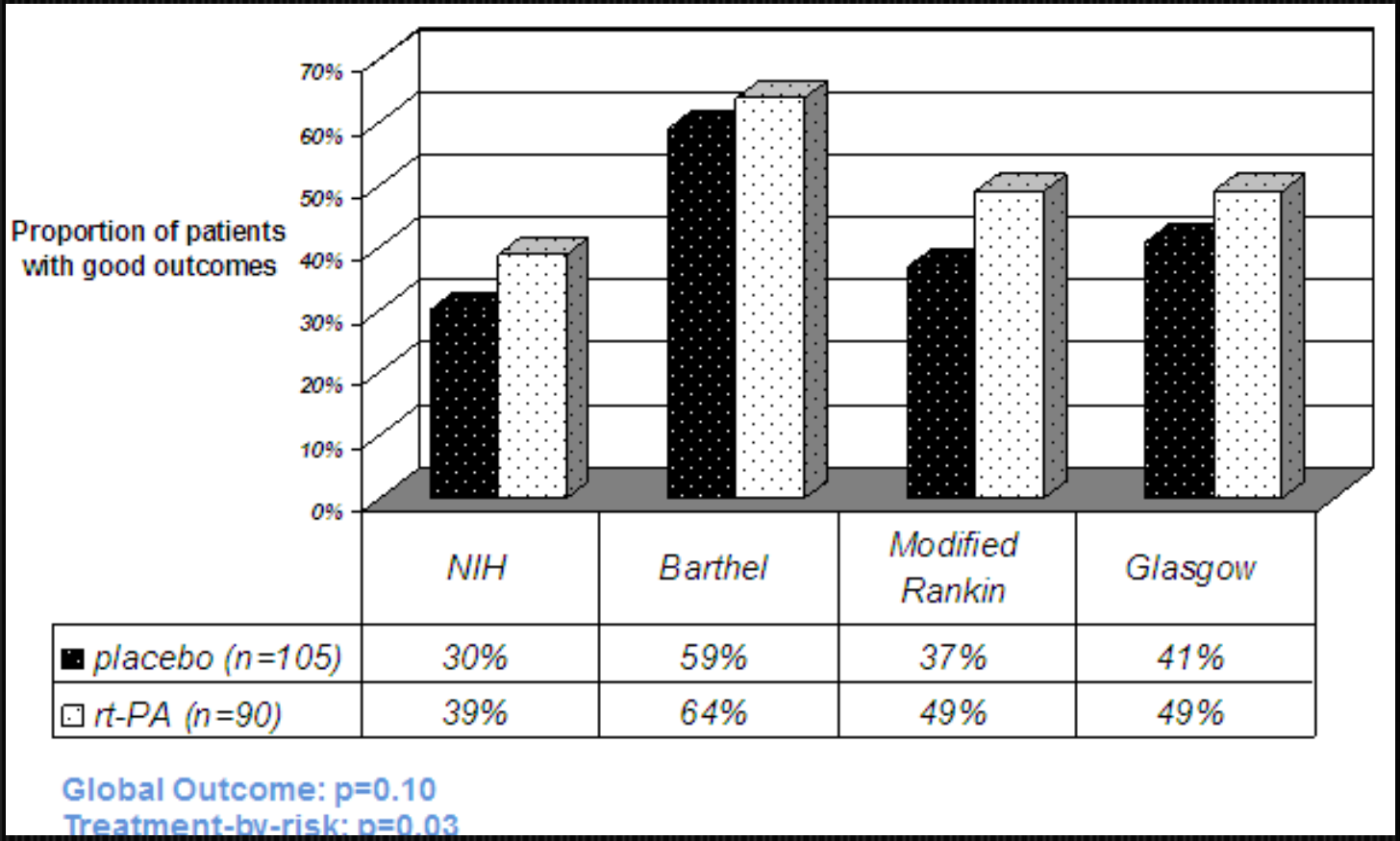
Gurtwiz JH, et al. *Ann Intern Med* 1998;129(8):97-604.

Rate of Intracranial Hemorrhage with Thrombolytic Therapy

Outcome	Low risk	Medium/high risk
	n=90	n=196
Symptomatic ICH	2.2%	9.2%

Kent DM, et al. *Stroke* 2003;34:464-7.

Outcomes: Low-risk group in ATLANTIS B Trial



	NIH	Barthel	Modified Rankin	Glasgow
placebo (n=105)	30%	59%	37%	41%
rt-PA (n=90)	39%	64%	49%	49%

Global Outcome: p=0.10
Treatment-by-risk: p=0.03

Kent DM, et al. *Stroke* 2003;34:464-7.

ORIGINAL ARTICLE

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

W.N. Kernan, C.M. Viscoli, K.L. Furie, L.H. Young, S.E. Inzucchi, M. Gorman, P.D. Guarino, A.M. Lovejoy, P.N. Peduzzi, R. Conwit, L.M. Brass,* G.G. Schwartz, H.P. Adams, Jr., L. Berger, A. Carolei, W. Clark, B. Coull, G.A. Ford, D. Kleindorfer, J.R. O'Leary, M.W. Parsons, P. Ringleb, S. Sen, J.D. Spence, D. Tanne, D. Wang, and T.R. Winder, for the IRIS Trial Investigators†

Background

- Primary outcome (stroke and MI) at 4.8 years:
  - Pioglitazone: 9.0%
  - Placebo: 11.8%
  - HR: 0.76; P=0.007
- Pioglitazone was associated with serious bone fracture (5.1% vs. 3.2%, P=0.003).
- For each 100 patients treated,
  - 2.8 primary events (stroke or MI) were averted
  - 1.9 fractures
  - primary events averted: fractures caused ratio =~1.5

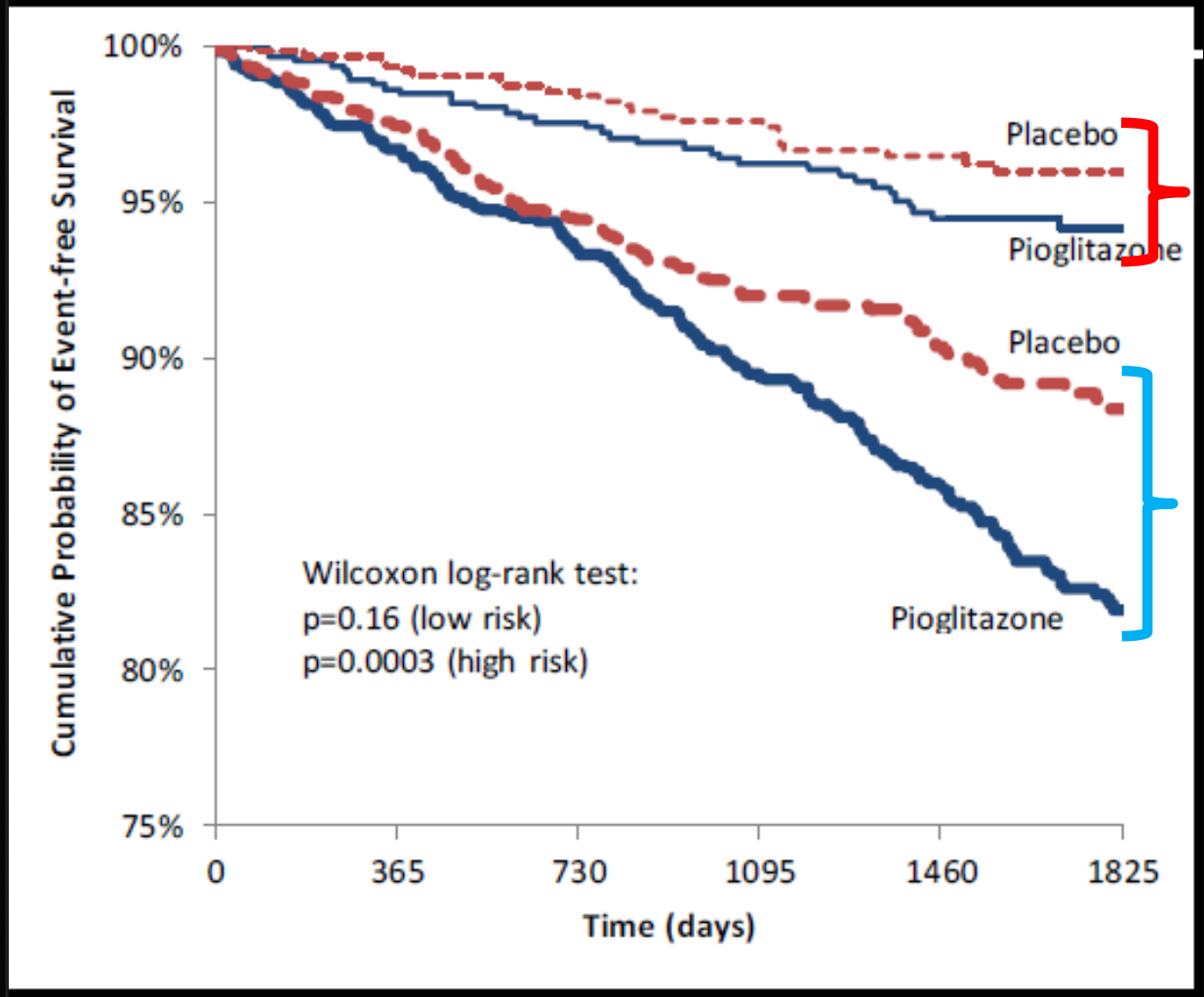
IRIS Fracture Risk Model

Feature	Hazard Ratio	P value	Points
Female sex	1.72	<0.0001	1
Age 65-69	1.51	0.01	1
70-79	1.72	<0.0001	
80+	2.90	<0.0001	3
Non-black race	2.60	0.0002	2
Non-hispanic ethnicity	3.71	0.02	3
Modified Rankin grade 3+*	1.61	0.003	1
Body mass index < 25 kg/m^2	1.44	0.004	1
Antidepressant	1.57	0.0002	1
Epilepsy drug	2.35	<0.0001	2

*moderate or greater disability (i.e., requires at least some help in walking or daily activities)

Viscoli C et al. Stroke 2019 (In Press)

IRIS



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Outcome / Risk Strata	Patients	Pioglitazone Risk	Placebo Risk	Hazard Ratio (95% CI)	Risk Difference (95% CI)
Fracture Overall	1939	13.6%	8.8%	1.53 (1.24, 1.89)	4.9% (2.6%, 7.1%)
Low (0-5)	680	5.8%	4.0%	1.46 (0.86, 2.48)	1.8% (-0.7%, 4.3%)
High (6+)	1214	18.0%	11.6%	1.53 (1.21, 1.92)	6.4% (3.2%, 9.6%)
Stroke or MI					
Low	52	8.3%	12.0%	0.73 (0.51, 1.05)	-3.7% (-7.2%, -0.2%)
High	120	11.6%	15.1%	0.76 (0.60, 0.96)	-3.5% (-6.5%, -0.5%)

Viscoli C et al. Stroke 2019 (In Press)

METHODOLOGY Open Access

Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal

TRIALS

David M Kent[1*], Peter M Rothwell[2], John PA Ioannidis[1,3], Doug G Altman[4], Rodney A Hayward[5]

1. Evaluate and **report on the distribution of risk** in the overall study population and in the separate treatment arms of the study by using a risk prediction model or index.
2. Primary subgroup analyses should include reporting how relative and absolute risk reduction varies in a **risk-stratified analysis**.
3. Any additional **primary subgroup analysis should be pre-specified** and limited to patient attributes with strong a prior pathophysiological or empirical justification.
4. Conduct and **report on secondary (exploratory) subgroup analyses separate** from primary subgroup comparisons.
5. All analyses conducted must be reported and statistical testing of HTE should be done using **appropriate methods** (such as interaction terms) and avoiding over-interpretation.

Predictive Approaches to Treatment Effect Heterogeneous (PATH): Technical Expert Panel

David Kent, MD,	Tufts Medical Center	**Sally Morton, PhD**	Virginia Tech
Ewout Steyerberg, PhD	Leiden University MC	**Sharon-Lise Normand, PhD**	Harvard Medical School
Naomi Aronson, PhD	Blue Cross and Blue Shield Association;	**Michael Pencina, PhD**	Duke University
Ralph D'Agostino, PhD	Boston University	**Joseph Ross, MD**	Yale University
Steven Goodman, MD,	Stanford University	**Harry Selker, MD MSPH**	Tufts Medical Center
Rodney Hayward, MD	University of Michigan	**Ravi Varadhan, PhD**	Johns Hopkins University
John P.A. Ioannidis, MD,	Stanford University	**Andrew Vickers, PhD**	Memorial Sloan Kettering
Bray Patrick-Lake, MFS	Duke University	**John B. Wong, MD**	Tufts Medical Center