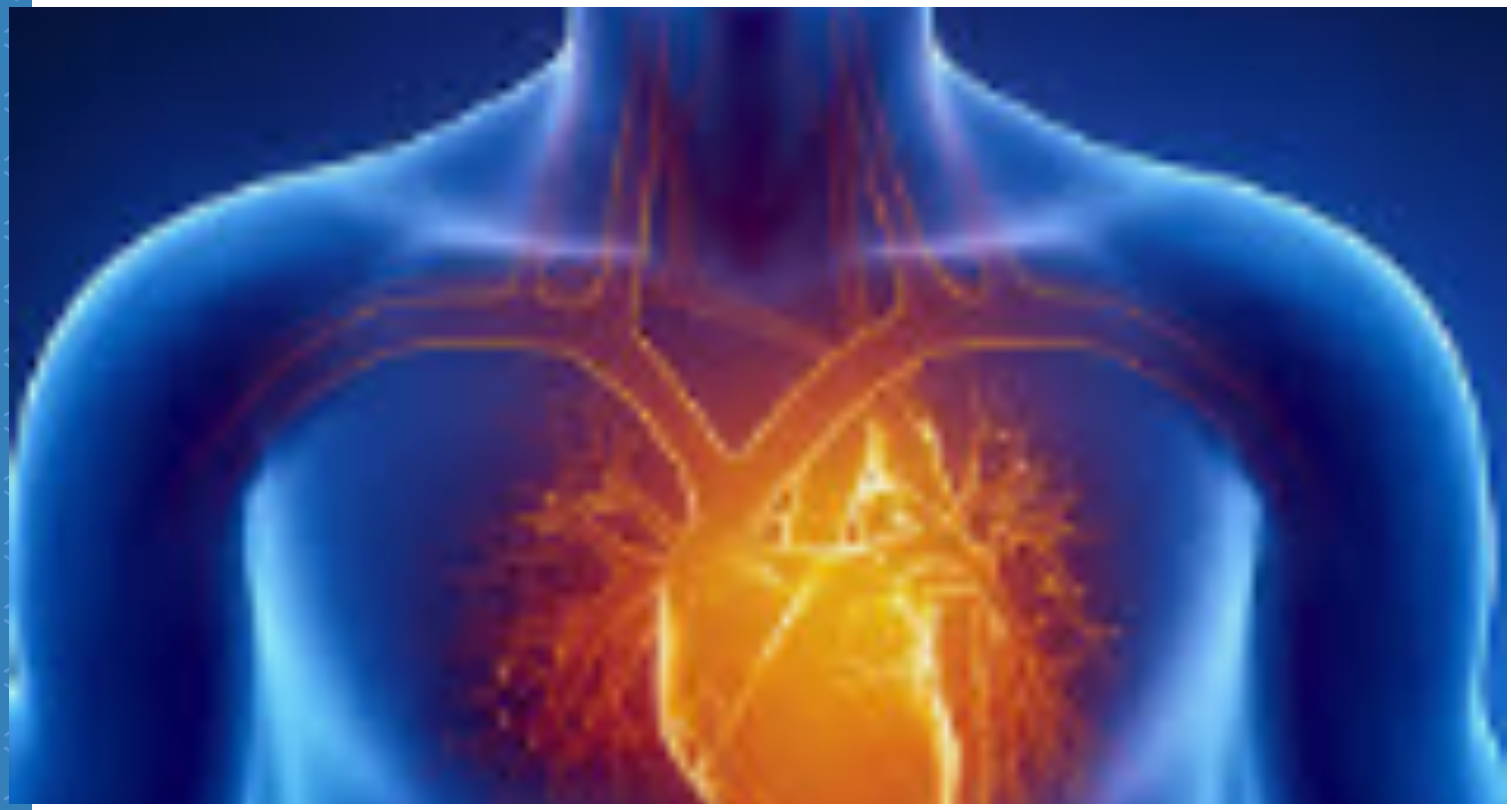

Cardiovascular medicine: approaches to the use of early biomarker response to identify a patient subgroup with enhanced therapeutic benefit

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Background: the CANTOS trial

- CANTOS trial
  - Tested whether reducing inflammation with canakinumab leads to reduction in the risk of CV events
  - Canakinumab blocks Interleukin-1β (IL-1β) a cytokine that modulates inflammatory response
    - The downstream marker of inflammatory risk and also of treatment activity was high-sensitivity C-Reactive Protein (hsCRP)
    - Observational data establish that it is prognostic of cardiovascular risk
- Population:
  - previous myocardial infarction and hsCRP > 2 mg per liter
- Treatment
  - Three dosing regimens vs placebo
    - 50mg, 150mg, 300mg every 4 weeks (+ loading for the 300mg group)
- Primary outcome: Time to first major adverse cardiovascular events (MACE)
  - cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke
- Results:
  - Only 150mg significant after adjusting for multiplicity with a hazard ratio of 0.85

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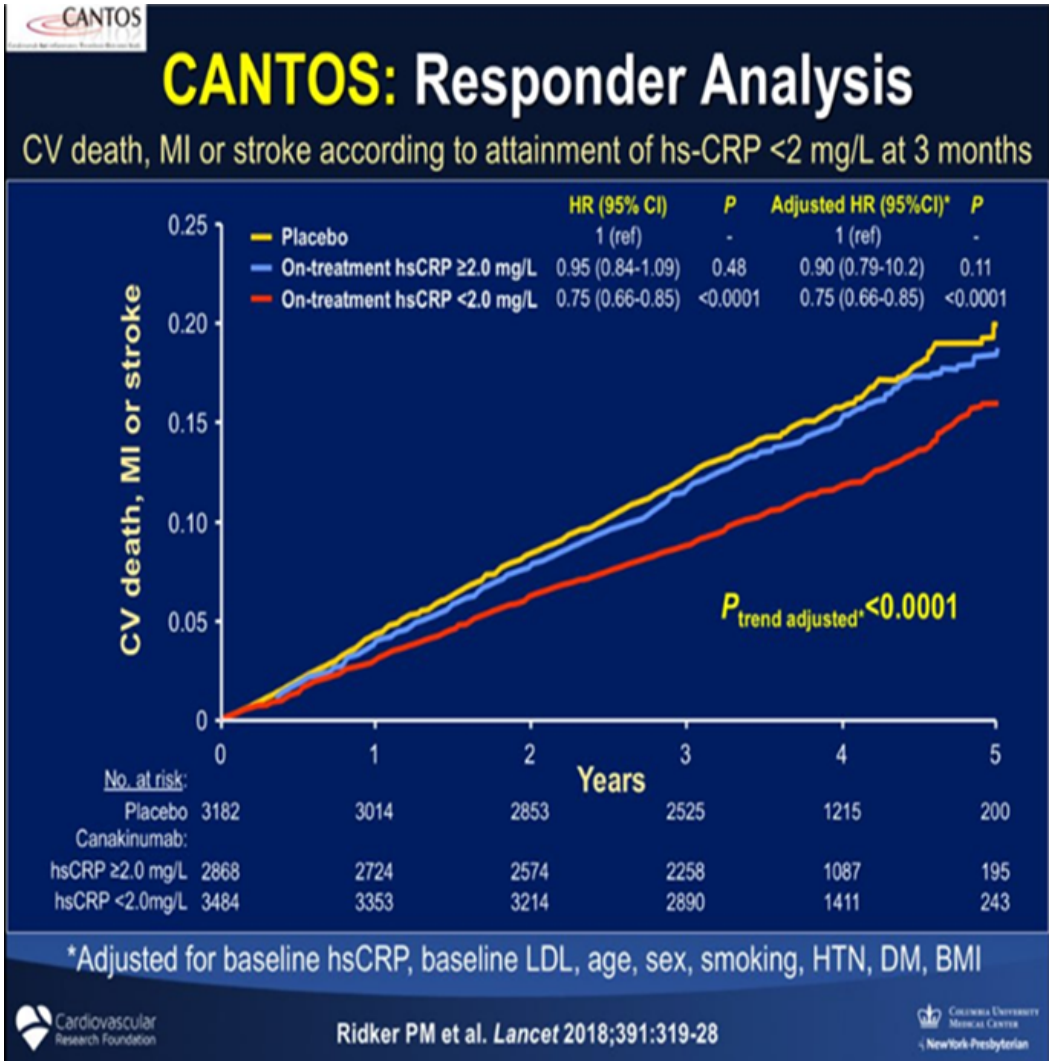
Responder subgroup in the CANTOS trial

- It suggested a larger benefit in this subpopulation than in the overall trial population
- The comparison implemented compared responders pooling all 3 canakinumab groups, to all placebo regardless of their month 3 hsCRP levels



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What is the estimand that captures the effect of treatment?

- Estimand: Treatment effect on MACE in the population of patients that would at month 3 reach hsCRP < 2.0 mg/L if assigned to treatment
- Attainment of hsCRP levels < 2 mg/L on active treatment is an event arising post-randomization
- Identification of this estimand requires strong assumptions in a parallel groups trial
  - Not immediately clear how survival for treatment threshold achievers would have been if treated with placebo
  - & vice versa which patients on placebo would have achieved the threshold if they had received treatment

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Principal stratification estimand

Z - indicator of treatment assignment (0: Placebo, 1:Active)

B(z) -potential biomarker outcome for treatment Z=z

T(z) –Survival outcome on treatment z

	Placebo **B(0) = 1** *hsCRP<2mg/dL*	**Placebo** **B(0) = 0** *hsCRP≥2mg/dL*
Treatment **B(1) = 1** *hsCRP<2mg/dL*		
Treatment **B(1) = 0** *hsCRP≥2mg/dL*		

The outcome is survival with respect to MACE

- Subpopulation of interest
  - Patients with B(1) = 1 (threshold achievers on treatment)
- Quantities of interest to estimate
  - Survival for treatment threshold achievers on treatment P(T(1) > t | B(1) = 1)
  - **Survival for treatment threshold achievers on placebo P(T(0) > t | B(1) = 1)**

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Potential outcomes

- Each patient has 2 potential outcomes related to treatment assignment
  - Biomarker levels on treatment, B(1) and on placebo B(0)
  - Survival on treatment, T(1), and survival on placebo T(0)
- In a parallel arm clinical trial only one of these combinations can be observed

	B(0) = 1	B(0) = 0
B(1) = 1	T(1) T(0)	T(1) T(0)
B(1) = 0	T(1) T(0)	T(1) T(0)

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Identification and estimation:
P(T(0) > t | B(1) = 1)

- Requires additional assumptions: T(0) B(1) | X
- We utilize covariates X predictive of T(0) and B(1)

by conditional independence

Predict placebo survival for responders on treatment

Obtain averaged placebo survival of treatment responders using their covariates

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Identification and estimation: P(T(0) > t | B(1) = 1)

- Using the same assumptions: T(0) B(1) | X
- We utilize covariates X predictive of B(1)

dX

Compare to observed placebo survival weighting placebo patients with

P(B=1|Z=1,X)

Either weighted survival or weighted regression for survival outcomes

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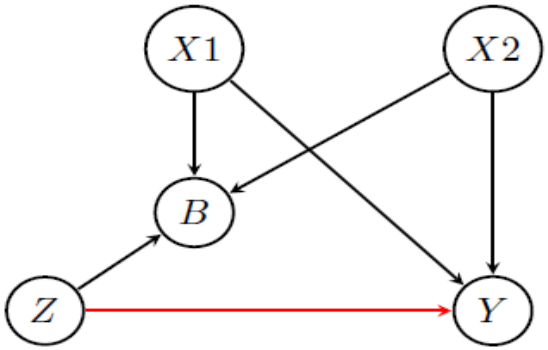
Simulation experiment to evaluate performance

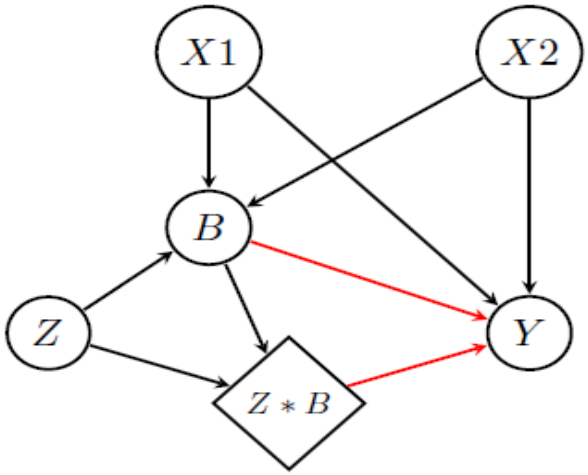
- Survival outcome trials from
  - Biomarker values (Z,)
  - Survival outcomes with

- We evaluate 3 Scenarios

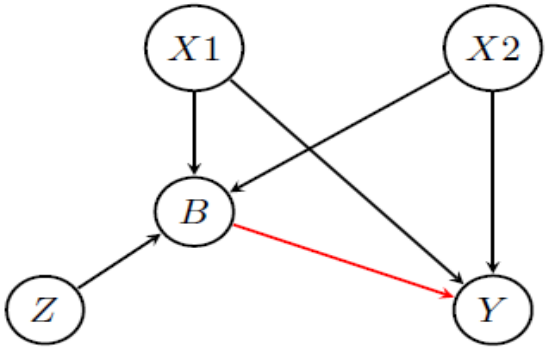
Scenario 1



Scenario 3



Scenario 2



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Issue of the measure for survival outcomes

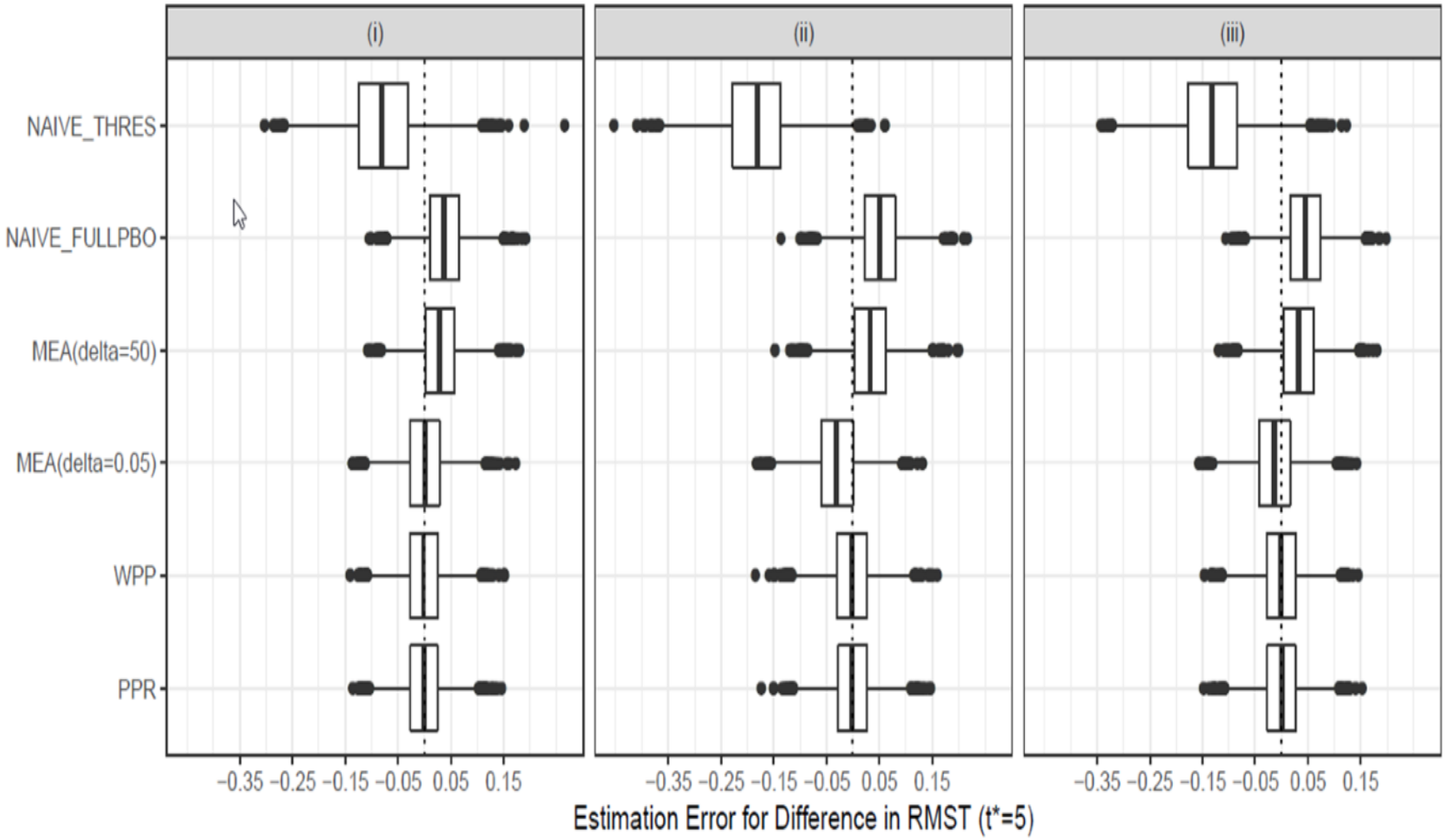
- The simulations evaluate the **difference** in **restricted mean survival time (RMST)**
- Reluctance to use the hazard ratio was due to
  - non-collapsibility
  - lack of causal interpretation specifically of the estimate from Cox regression even in a randomized clinical trial (Aalen et al 2015).
- However, we mention that
  - *if the cumulative hazard functions are approximately linear, a simple exponential model could be derived to estimate the hazard, and calculate the hazard ratio as the ratio of the hazards.*
- Main difference:
  - A difference in survival can be estimated non-parametrically (e.g. using the difference in RMST)
  - The hazard rate requires additional modelling assumptions to obtain a single estimate that represents the average hazard rate used to calculate the ratio between treatments

Performance evaluation

- **Comparison of survival:**
  - *Predicted Placebo Response* (PPR) and *Weight Placebo Patients* (WPP) difference in restricted mean survival time at a pre-specified time point
- **Comparison based on the hazard rates:**
  - *Predicted Placebo (PP)*
    - Same as survival for PPR above. We use a nonlinear regression fit to the survival functions that follows an exponential or Weibull parametrization, and fitting a weighted linear regression model to the cumulative survival function
  - *Weight Placebo (WP)*
    - With weighted Cox regression including treatment only, and X1 and X2 (DR)
- We also compare with 2 “naive“ approaches:
  - NAIVE_THRES- compares to placebo patients reaching the threshold (on placebo)
  - NAIVE_FULLPBO- compares to all placebo patients regardless of whether they would have been responders if given treatment or not

Results: survival difference scale

(i) Only main effect of Z	(ii) Only main effect of B	(iii) Main effect of B and Z* B



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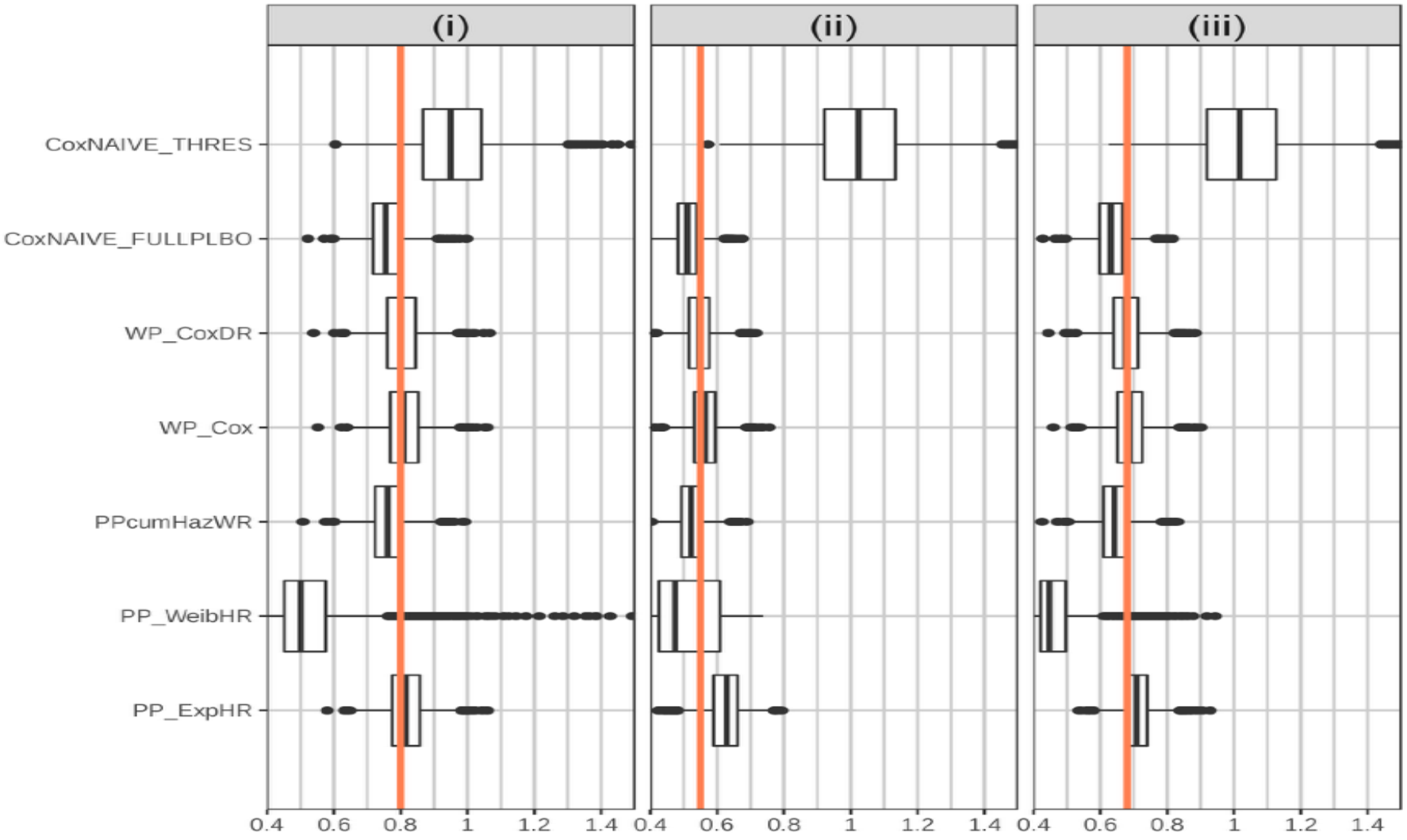
Results: hazard ratio scale



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Summary

- These are approaches to derive the magnitude of treatment benefit in a patient subpopulation defined by an early biomarker response
  - They are not meant as mediation analysis
  - They do not fall in the surrogacy field
  - We do not account for inter-current events. Their treatment requires additional assumptions.
  - We keep **survival risk between treatments equal to risk at the time of randomization assuming all patients have biomarker measurements**
- **Survival difference scale:** both approaches perform well regardless of the path through which treatment impacts survival
- **Hazard ratio scale:** only the weighted placebo applied to Cox regression including covariates performs well regardless of treatment path

Is this useful for cardiovascular drug development?

- An early response to treatment can be used for treatment optimization strategies or treatment selection
  - This framework cannot replace a randomized comparison, but may be useful for planning future targeted randomized trials
- Cardiovascular outcome trials build on the premise of homogeneous patient responses
  - but the long treatment horizon with competing events dilutes treatment impact in some patient segments
  - This causal inference framework can enhance understanding of patient responses
  - Protocol defined follow up treatment strategies might be a way of optimizing the conduct of these trials