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-1\(\beta\) (IL-1\(\beta\)) 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
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.
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
Subpopulation of interest
- Patients with $B(1) = 1$ (threshold achievers on treatment)

Quantities of interest to estimate
- Survival for treatment threshold achievers on treatment $P(T(1) > t \mid B(1) = 1)$
- Survival for treatment threshold achievers on placebo $P(T(0) > t \mid B(1) = 1)$

| $B(0) = 1$ | $B(0) = 0$
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<td>$hsCRP &lt; 2mg/dL$</td>
<td>$hsCRP \geq 2mg/dL$</td>
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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 $z$

The outcome is survival with respect to MACE.
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

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Identification and estimation:
\[ P(T(0) > t \mid B(1) = 1) \]

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

by conditional independence

Obtain averaged placebo survival of treatment responders using their covariates

Predict placebo survival for responders on treatment
Identification and estimation: 
\[ P(T(0) > t \mid B(1) = 1) \]

- Using the same assumptions: \[ T(0) \perp B(1) \mid X \]
- We utilize covariates \( X \) predictive of \( B(1) \)

\[ dX \]

Compare to observed placebo survival weighting placebo patients with 

\[ P(B=1 \mid Z=1, X) \]

Either weighted survival or weighted regression for survival outcomes
Simulation experiment to evaluate performance

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

- We evaluate 3 Scenarios

Scenario 1

Scenario 2

Scenario 3
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

NAIVE_THRES
NAIVE_FULLPBO
MEA(delta=50)
MEA(delta=0.05)
WPP
PPR

Estimation Error for Difference in RMST (t=5)
Results: hazard ratio scale
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