Understanding treatment effects in clinical survival trials - A causal approach

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Motivation

- Integrating longitudinal data and time-to-event data
- Clinical trials:
  - Focus on survival outcome
  - Measurements of important parameters at multiple occasions but those are rarely used for standard analysis
- How can this information be used for gaining better understanding of treatment effects?

Outline

Background
The IDEAL Study

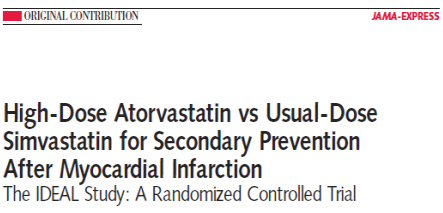
How to handle non-compliance with prescribed treatment ?
Inverse Probability of Censoring Weights
Results

Mediation and time
Dynamic Path Analysis
Weighted Dynamic Path Analysis
Illustrations

Comments

Main publication by Pederson et al. 2005

IDEAL = **I**ncremental **D**ecrease in **E**nd Points Through **A**ggressive **L**ipid Lowering

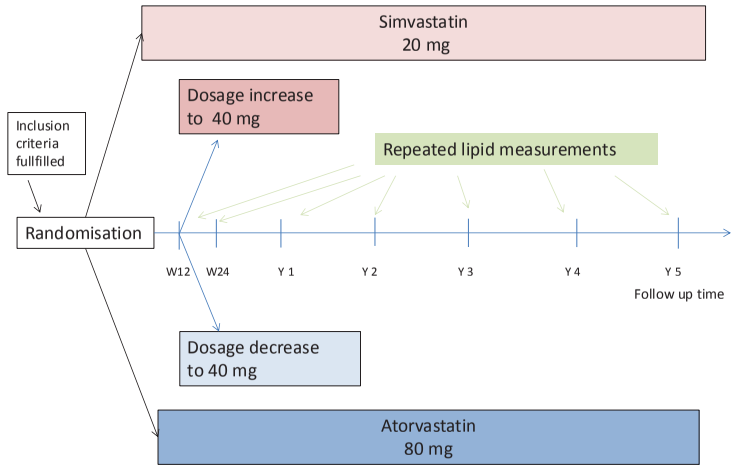

ORIGINAL CONTRIBUTION JAMA-EXPRESS

High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction
The IDEAL Study: A Randomized Controlled Trial

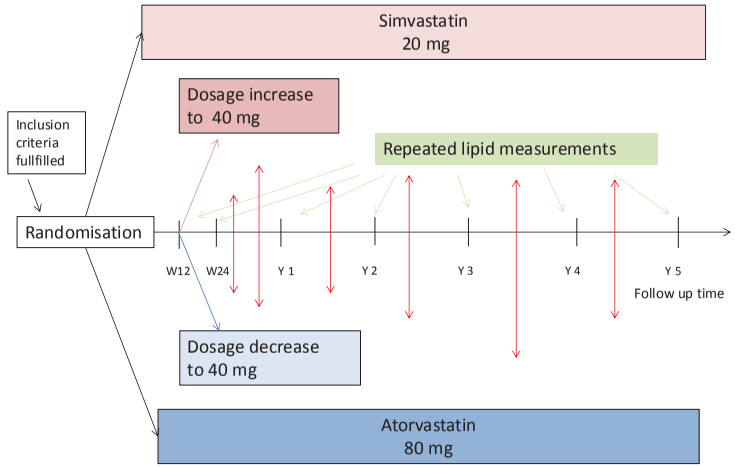
Overall more than 20 publications

- **Hypothesis**
  Intensive lowering of LDL-C with atorvastatin at the highest recommended dose would yield incremental benefit compared with the moderate, most widely used dose of simvastatin
- **Objective**
  To compare the effects of these 2 strategies of lipid lowering on the risk of cardiovascular disease among patients with a previous myocardial infarction (MI)
  - Primary outcome:
    Time to first occurrence of a major coronary event
  - Various prespecified composite secondary outcomes:
    e.g. any CHD event:

Study protocol and available measurements



Study protocol and available measurements - Reality



Protocol violations

- **Patients included**
  - In total $n = 8888$ patients ($n_s = 4449$ simvastatin, $n_a = 4439$ atorvastatin)
- **According to the original dosage file**
  - $n_v = 2826$ patients have records that indicate that they have not constantly been on study medication
- **...but main survival analysis was still based on the Intention-to-Treat (ITT) princple**

How to handle non-compliance with prescribed treatment ?

- **Study medication exposure as percentage of follow-up time for all-cause death**
  - Holme et al. (2009) Adherence-adjusted efficacy with intensive versus standard statin therapy in patients with acute myocardial infarction in the ideal study. *Eur J Cardiovasc Prev Rehabil*
- **Per-protocol analysis**
  - Censor patients who deviate from their randomly allocated treatments at time of deviation
  - Perform a standard analysis using the modified time-to-event and event indicator variable
    - Possibly introduces selection bias, as prognosis might be different in those who deviate from protocol

How to handle non-compliance with prescribed treatment ?

- Attempt to reduce that selection bias: **Inverse Probability of Censoring Weights (IPCW)**, introduced by Robins (1993)
  - Patients are again artificially censored at the time of deviation
  - A model needs to be constructed to predict this artificial censoring
    - This model should include all baseline and time-dependent covariates that predict both outcome and deviation ("no unmeasured confounders")
  - Model is used to assign weights to individuals that have not deviated yet
  - Weights should recreate the population one would have seen with no deviation from allocated treatment
  - Perform desired survival analysis in the re-weighted data.

More formally

- Stabilized censor weights (see e.g. Hernan (2000) for MSM)

$$w_i(t) = \prod_{k=0}^{t} \frac{P(C(k)=0|\bar{C}(k-1)=0, \mathbf{Z}=\mathbf{z}_i)}{P(C(k)=0|\bar{C}(k-1)=0, \mathbf{Z}=\mathbf{z}_i, \bar{\mathbf{L}}(k-1)=\bar{\mathbf{l}}_i(k-1))},$$

,

- where $C(t)=1$ if deviated at time t, $\mathbf{Z}$ denotes a vector of baseline covariates, $\mathbf{L(t)}$ a vector of time-dependent covariates at time t and crossbars represent the respective covariate histories up to time t.
- For each time point up to the time of deviation within each patient the denominator can be estimated using a Cox model

$$\lambda_C[t|\mathbf{L(t)}, \mathbf{Z}, C(t^- = 0)] = \lambda_0(t)\exp(\mathbf{b}_1^T\mathbf{L}(t) + \mathbf{b}_2^T\mathbf{Z})$$

- a similar model can be used for the numerator without $\mathbf{L}(t)$

Model fitting in practice

- Create a data file that includes as detailed and accurately updated information as possible
- For the present data information was available on
  - the dosage/treatment protocol to create the deviation indicator variable and an updated version for the event indicator
  - various baseline covariates
  - repeated lipid measurements at the 7 scheduled measurement times
  - the record of all adverse event including severity and date
- Actual weight estimation can be performed using the *ipw* package in R, described in van der Wal and Geskus (2011)

Results

- Composite secondary outcome: time until any CHD event
- IPCW model included:
  gender, age, usage of aspirin or beta blockers, previous usage of statins, current smoking status and smoking history,
  LDL - cholesterol and apolipoprotein B (for patient with missing values but still at risk the last observation was carried forward),
  number of AEs until time t, severity of the last AE

Method	Cases	HR	95% CI
ITT	1903	0.835	0.763 - 0.914
PP	1426	0.828	0.746 - 0.919
re-weighted	1426	0.812	0.732 - 0.901

Table : Effect of treatment obtained by Cox regression and weighted Cox regression model respectively

Can we understand a little bit more?

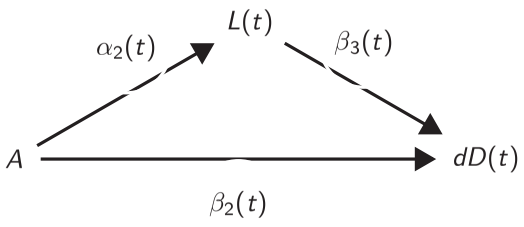
- Boeckholdt et al. Association of ldl cholesterol, non-hdl cholesterol, and apolipoprotein b levels with risk of cardiovascular events among patients treated with statins. A meta-analysis. *JAMA 2012*
  - Assessment of treatment effect explained by different lipid measures
  - Applied methods so far only use one of the various available repeated measurements (1-year measurement)
- **But...**
  could not information from measurements at various time points be used to learn more about the mechanisms of treatment?

Dynamic path analysis

- **Dynamic path analysis**, proposed by Fosen et al. (2006), is a useful tool to illustrate direct and indirect effects as a functions of time
- Generalization of traditional path analysis (Wright 1921)
  - to a time-dependent concept
  - for survival outcomes
- Series of DAGs defined for each jump in a counting process
  - Carry out a set of linear and additive regression analyses at each event time
  - Find direct and indirect effects by multiplying estimated coefficients along each path
  - Sum up, as effects are analysed locally

Again more formally

Consider the path diagram



with structural equations

$$\begin{aligned} L(t) &= \alpha_1(t) + \alpha_2(t)A + \epsilon(t) \\ dD(t) &= Y(t)(\beta_1(t) + \beta_2(t)A + \beta_3(t)L(t-))dt + dM(t), \end{aligned}$$

where $dD(t)$ denotes the infinitesimal change in the event process, $\alpha_j(t)$ are regression coefficients at time t and $\beta_k(t)$ are regression functions.

Cumulative path effects

- Substituting the equation for $L(t)$ suggests the following cumulative path effects

cumulative direct effect

$$A \to D \quad : \quad \int_0^t \beta_2(s)ds$$

cumulative indirect effect

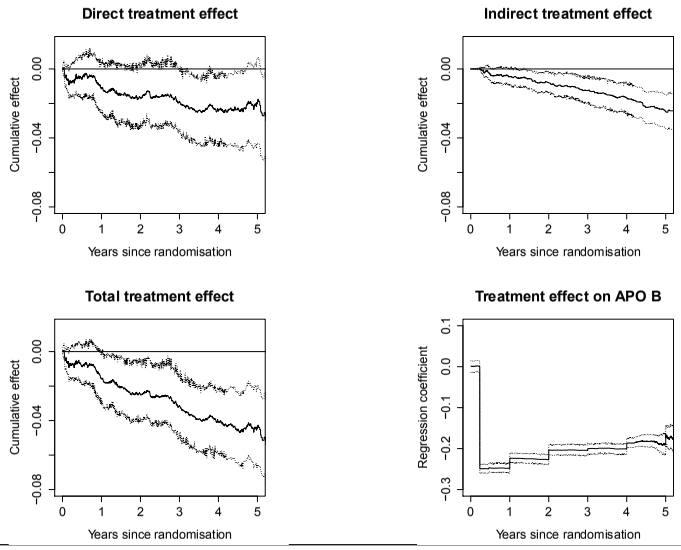
$$A \to L \to D \quad : \quad \int_0^t \alpha_2(t)\beta_3(s)ds,$$

where the the parameters $\boldsymbol{\alpha(t)} = (\alpha_1(t), \alpha_2(t))$ are obtained by solving the normal equation corresponding to a ordinary linear regression at each event time t and $\boldsymbol{\beta(t)} = (\beta_1(t), \beta_2(t), \beta_3(t))$ by solving the estimation equations corresponding to the additive hazard model (for details see Aalen et al.(2008))

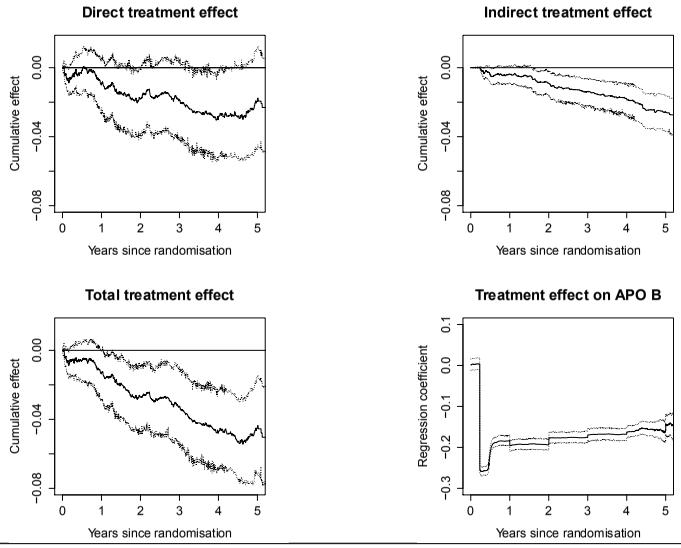
Weighted dynamic path analysis

- Røysland et al. (2010) suggested and extension to dynamic path analysis that allows to incorporate weights, in particular IPCW to adjust for dependent censoring
- Incorporate a diagonal matrix $\mathbf{W}(t)$ containing the censoring weights for each individual i at time t in the normal equation for linear regression and estimating equations for the additive hazard regression

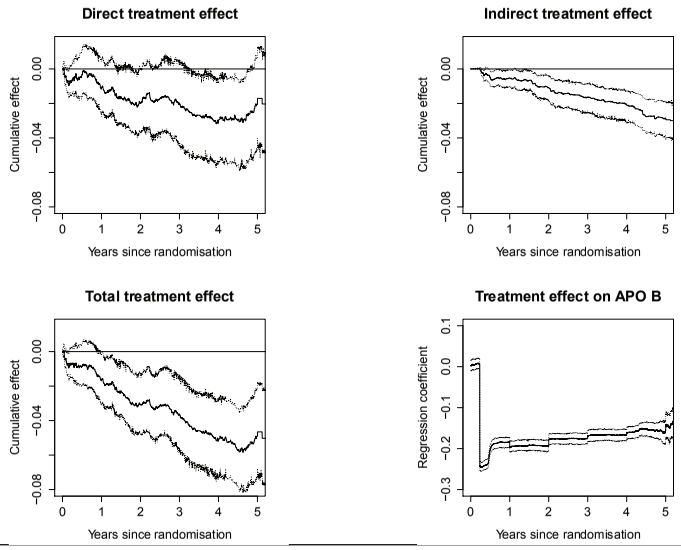
Results based on intention-to-treat analysis



Results based on per-protocol analysis



Results based on re-weighted data set



Comments

- **IPCW**
  - Although data handling can get nasty, still worthwhile to incorporate more detailed information
  - Other possibilities for weight estimation, e.g. applying the additive model (Satten et al. (2001))
  - The R package *ipw* is quite useful though
- **Dynamic path analysis**
  - Useful tool for estimating and illustrating mediation over time
  - No unmeasured confounder assumptions between treatment and outcome and mediator and outcome
  - Lacking causal justification in the counterfactual framework - under construction

THANKS....

- to the audience
- my supervisor team and the causality research group