

Causality Matters

Some examples from clinical development

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Overview

Two examples from Clinical development

- Is inhibition of cholesteryl ester transfer protein (CETP) causing an increased risk for CardioVascular (CV) events?
 - Using the development of Torcetrapib as an example
- Are intensive glycemic control leading to increased risk for CV events?
- All results presented are publically available.
- This is not an evaluation of the clinical development programs, but serves to illustrate the challenges with assessing causality in clinical trials.



Background to development of CETP inhibitors

- Reductions in low-density lipoprotein cholesterol (LDL-C) through the use of statins have been observed to decrease the risk for CV events in clinical trials.
 - *“Further reductions in LDL cholesterol safely produce definite further reductions in the incidence of heart attack, of revascularisation, and of ischaemic stroke, with each 1.0 mmol/L reduction reducing the annual rate of these major vascular events by just over a fifth”, Lancet 2010*
- There are data illustrating a relationship between low levels of HDL and high risk for CV events, but clinical trials have not directly shown that increasing HDL decreases the risk for CV events.
- *“In early-phase studies in humans, the drug (torcetrapib) increased HDL cholesterol by 60 to 100% at the same time that it lowered LDL cholesterol by up to 20%.” NEJM 2007.*
- Several large (>10 000 patients) clinical trials ongoing to evaluate if CETP inhibitors can reduce the risk for CV events.

1. *Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. CTCT, Lancet 2010, 13.*
2. *Effects of Torcetrapib in Patients at High Risk for Coronary Events. Barter NEJM 2007*



The design of the ILLUMINATE trial

- A randomized, double-blind study involving 15,067 patients at high CV risk.
- The patients received either torcetrapib plus atorvastatin or atorvastatin alone.
- The primary outcome was the time to the first major cardiovascular event, which was defined as death from coronary heart disease, nonfatal myocardial infarction, stroke, or hospitalization for unstable angina.



The results of the ILLUMINATE trial

- At 12 months in patients who received torcetrapib there was,
 - an increase of 72.1% in HDL vs. 1.8% in the comparator arm (P<0.001),
 - a decrease of 24.9% in LDL vs. 3.0% in the comparator arm (P<0.001)
- There was an increase of 5.4 mm Hg in systolic blood pressure, a decrease in serum potassium, and increases in serum sodium, bicarbonate, and aldosterone (P<0.001 for all comparisons).
- There was an increased risk of cardiovascular events (hazard ratio, 1.25; 95% confidence interval [CI], 1.09 to 1.44; P = 0.001) and death from any cause (hazard ratio, 1.58; 95% CI, 1.14 to 2.19; P = 0.006).



Questions raised by the ILLUMINATE trial

- Is the higher frequency of CV events seen with torcetrapib specific to the compound or is it a class effect due to the mechanism of CETP inhibition?
 - Did the effect of torcetrapib on heart rate drive the increased incidence of CV events?
 - If so, new CETP inhibitors could evaluate the effect on blood pressure prior to initiating large expensive outcome trials
- Prior to looking at statistical methods used, there is another example.



Is lowering of blood glucose increasing the risk for CV events?

The ACCORD study

- Lowering of high blood glucose levels in patients with T2DM have been shown to lead to decreased risk for microvascular complications.
- It is less known if lowering the blood glucose leads to decreased risk for macrovascular events.
- Glycated hemoglobin, HbA1c, is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time.
- Hypoglycemia is a medical emergency that involves an abnormally diminished content of glucose in the blood.
- The ACCORD study was a factorial design but for simplicity we can focus on patients randomised to intensive glucose control vs standard glucose control. The primary outcome was myocardial infarction, stroke, or cardiovascular death.

1. *Effects of Intensive Glucose Lowering in Type 2 Diabetes. NEJM 2008*



Is lowering of blood glucose increasing the risk for CV events?

The ACCORD study

- All 10,251 patients were randomly assigned to receive comprehensive intensive therapy targeting a HbA1c level of less than 6.0% or to receive standard therapy targeting a level of 7.0 to 7.9%.
- Patients were eligible for the ACCORD study if they had type 2 diabetes, a HbA1c concentration of at least 7.5% and fulfilled some additional criteria.
- The intensive glycaemia intervention was stopped early owing to increased mortality in the intensive glycaemia control arm, and all participants were transitioned to the standard glycaemia control intervention.
- The mean duration of follow-up at the time the data and safety monitoring committee recommended the discontinuation of the intensive regimen was 3.5 years.

1. *Effects of Intensive Glucose Lowering in Type 2 Diabetes. NEJM 2008*



Is lowering blood glucose increasing the risk for CV events?

ACCORD study results

- The crude, annualized mortality rate was 1.14% a year in the standard glycemia control arm and 1.42% a year in the intensive glycemia control arm.
- Within 4 months after randomization, the median HbA1c level had fallen from 8.1% at baseline to 6.7% in the intensive-therapy group and to 7.5% in the standard therapy group. Stable median levels of 6.4% and 7.5%, respectively, were achieved in the two groups at 1 year and were maintained throughout the follow-up period.



Is lowering blood glucose increasing the risk for CV events?

ACCORD study results

- *“Our findings indicate that a comprehensive, customized, therapeutic strategy targeting HbA1c levels below 6.0% increased the rate of death from any cause after a mean of 3.5 years, as compared with a strategy targeting levels of 7.0 to 7.9% in patients with a median HbA1c level of 8.1% and either previous cardiovascular events or multiple cardiovascular risk factors.”*
- For the purpose of this presentation, the question can be
 - Is lowering glucose levels causing an increased risk for death?
 - Is Hypoglycemia causing an increased risk for death?



Methods used for evaluating causality in clinical trials

- Descriptive comparison between patients experiencing the events and patients not experiencing the event
 - Blood pressure for patients with CV events by treatment arm in ILLUMINATE
 - “Paradoxically, there was an increased risk of death and major cardiovascular events in patients whose increase in systolic blood pressure was less than the median. It should be emphasized that the results shown in Table 5 were both exploratory and post hoc...” (Barter et al)
 - “In conclusion, our study neither validates nor invalidates the hypothesis that raising levels of HDL cholesterol by the inhibition of CETP may be cardioprotective.” (Barter et al)
- Cox regression
 - Time to event (e.g. death) using time dependent covariates (e.g. blood pressure or blood glucose)
 - The evaluation of “” Whether hypoglycemia leads to death in critically ill patients...” by the NICE-SUGAR investigators was done by “...the hazard ratio adjusted for treatment assignment, baseline characteristics, and time-dependent factors that occurred after randomization and that may influence the probability of death.”¹
- Various more complex modeling approaches
 - Structural equation modelling. Rarely used.

1. *NICE-SUGAR Study Investigators. NEJM 2012*



The use of Cox regression

What are the problems?

- The partial log-likelihood function being optimized with time dependent covariates can be written as:

$$\sum_{i=1}^n \delta_i \left\{ \sum_{j=1}^p \beta_j x_{ji}(t_i) - \log \sum_{l \in R(t_i)} \exp \left(\sum_{j=1}^p \beta_j x_{jl}(t_i) \right) \right\}$$

- where delta is the event indicator and $R(t)$ is the risk set at time t
- Hence, this requires that all covariate values are available for the patients at risk at each time point for an event.
- In CV outcome trials, $x(t)$ is generally not available
 - E.g. Blood glucose, blood pressure are measured at scheduled visits while CV events do occur between visits.
- If an approximation is used, a less fluctuating measure is generally preferable.
 - HbA1c as compared to fasting plasma glucose.



The use of Cox regression

- Joint modeling of covariate and time to event can address this issue, but introduces additional assumptions. These methods generally use a model to predict the values missing, but what model to use?
 - “Joint models for Longitudinal and Time-to-Event data” D. Rizopoulos 2012.
- Even if continuous measures of the covariates are available, there is still the issue of including a covariate post randomization that is known to be influenced by the randomized treatment...



Summary and possible next steps

- Development of torcetrapib was stopped, does it matter why it failed?
 - Constrained resources to bring new effective and safe drugs to patients.
- The pre-specified analysis of clinical trials are often more rigorous than evaluation of unexpected findings.
- Commonly used methods to evaluate causality are not fit for purpose, and alternatives exist. Though we need to be mindful to not introduce complexity and further assumptions without gaining something.
- There is still work to be done in this area to improve the way new potential drugs are being evaluated, and the way we present the evaluation of the statistical methods used.



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