Model Based Meta Analysis for comparative effectiveness and endpoint to endpoint relationships

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Model-based Meta-analyses – WHAT?

• Model-based meta-analysis is different from ‘conventional’ meta-analysis
  – *Meta-analysis* is the statistics practice of combining the results of a number of studies for the purpose of integrating the findings
  – *Model-based meta-analysis* is a meta-analysis that incorporates parametric models for the effect of treatment, time, and patient population characteristics on the outcomes: meta regression
  – *Model-based meta-analysis* builds Knowledge by integrating relevant pre-clinical, bio-marker, clinical safety/efficacy data of competing treatment options in a certain disease area
Model-based Meta-analyses – WHY?

• Comparative safety and efficacy
  – There is a need to evaluate new treatment options against other existing or emerging treatment options for go-no go decisions, dose selection, and trial strategy
  – Lack of active comparator trials in drug development; Meta-analyses can provide an indirect comparison

• Endpoint-to-Endpoint relationships
  – Biomarker to clinical endpoint predictions
  – Bridging across indications

• Leveraging existing information
  – Similar shape of dose response relationships of drugs within class
  – Similar impact of disease severity on treatment effect

• Optimize Trial design
  – Impact of trial design features on placebo, treatment effect and variability
Integrate data across trials & account for differences in patient/ trial characteristics

- Some variability between trials is expected due to the fact that a random sample of the patient population is evaluated
- If there is more variability than expected based on sample size and by chance alone, this is called heterogeneity
  - Study level covariates could explain between trial differences and normalize the outcomes for those differences, i.e. baseline disease severity
  - Random effects model can be used to account for unexplained between trial differences
- Understanding heterogeneity is crucial as trials are not randomized across potential treatment modifiers
Osteoporosis

• Bone mineral density (BMD) changes in postmenopausal women
  – 72 trials,
  – >96,000 patients,
  – 11 drugs
  – 5 drug classes: bisphosphonates, SERMs, PTH, RANKL, HRT

• Endpoints: time course of BMD change at lumbar spine or total hip
Questions

• Comparative effectiveness:
  – What are the differences in BMD dose response relationship between drug classes and drugs within class?
  – What are the differences in speed of onset of BMD changes across drug classes

• Trial design:
  – What are important treatment modifiers explaining between trial difference in treatment effect
General Analysis Methodology - 1

• The mean percent change from baseline in BMD for the $k^{th}$ endpoint (total hip or lumbar spine) in the $i^{th}$ arm in the $j^{th}$ trial at time $t$ ($\Delta BMD_{ij}$) is a function of a placebo response for that endpoint in that trial at time $t$ ($Eo_{jtk}$) and a dose response relationship for the time course of the treatment effect for the endpoint $f(t, \theta_{kj}, X_{ij})$, including covariates $X_{ij}$

$$\Delta BMD_{ijtk} = Eo_{jtk} + f(t, \theta_{kj}, X_{ij}) + \eta_{ijk} + \epsilon_{ijtk}$$

• The trial specific model parameters $\theta_{kj}$ are assumed to be normally distributed with between trial variance $\Omega$ (heterogeneity)

$$\theta_{kj} \sim N(\theta_k, \Omega_{trial})$$
\[ \Delta BMD_{ijtk} = Eo_{jtk} + f(t, \theta_{kj}, X_{ijk}) + \eta_{ijk} + \varepsilon_{ijtk} \]

- \( \eta_{ijk} \) reflects the variability in mean response due to between subject variability. The random effects are assumed to be multivariate normally distributed with variances \( \omega^2_{\text{spine}}/N_{ij} \) and \( \omega^2_{\text{hip}}/N_{ij} \) and correlation \( \rho_{\text{hip,spine}} \).
- \( \varepsilon_{ijtk} \) reflects the residual variability in mean response due to within subject variability assumed to be normally distributed with variance \( \sigma_k^2/N_{ij} \).
- accounts for the correlation between the mean response in total hip BMD and lumbar spine BMD observed in the same group of patients and for the serial correlation of the mean response in the same group of subjects over time.
Example of fit to time course data in 1 trial
Estimated Dose response relationship for bisphosphonates at 24 months symbol represents one arm in trial with size related to precision.

Lumbar Spine

Total Hip

BMD (% change from baseline)

Dose/ED50

placebo
alendronate oral
ibandronate iv
ibandronate oral
risedronate oral
zoledronic acid iv

Dose/ED50
Importance of correcting for between trial differences in baseline disease severity
Impact of baseline BMD on the bisphosphonate response at 24 months (spine) normalized to 10 mg/day alendronate
Summary Osteoporosis

• Quantified relative effectiveness of treatment options for osteoporosis for hip and spine BMD changes
• Quantified differences in speed of onset of BMD changes between different mechanisms of action
• Quantified dependency of treatment effect on between trial differences in baseline BMD
Dyslipidemia

Database with about 450 trials that captures summary level data from publicly available data sources for the following outcomes:

• atherogenic lipid profile and inflammatory biomarkers: LDL, Triglycerides, HDL, total cholesterol, ApoA1, ApoB, CRP, nHDL.

• adverse events: dropout, dropout due to AEs, risk in ALT/AST elevation, CPK elevation, myalgia, myopathy, etc.

• progression of atherosclerosis (QCA, Bmode, or IVUS): mean and min lumen diameter, % stenosis; mean and max IMT, plaque volume, plaque burden, etc.

• cardiovascular outcomes: major coronary events, cardiovascular events, stroke, MI, hospitalization due to UA, PCI, etc.
After adjusting for differences in potency (ED50) all statins share a common dose response relationship for LDL
Statin Dose response relationship for AE related dropouts

[Graphs showing dose response relationship for different statins: Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin, Pravastatin, and Rosuvastatin. Each graph plots dose on the x-axis and dropout due to AEs (%) on the y-axis.]
The Statins differ with respect to their benefit/risk ratio

<table>
<thead>
<tr>
<th>Drug</th>
<th>ALT/ AST Elevations</th>
<th>AE dropout</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ED50 LFT/ ED50 LDL</td>
<td>ED50 dropout/ ED50 LDL</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>0.48 [0.27 to 0.88]</td>
<td>0.75 [0.47 to 1.2]</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>0.83 [0.41 to 1.7]</td>
<td>2 [0.69 to 6]</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>1.3 [0.86 to 1.9]</td>
<td>2.6 [1.7 to 4]</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>2.6 [0.79 to 8.4]</td>
<td>4.7 [0.94 to 24]</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>3.6 [2.7 to 4.9]</td>
<td>13 [8.8 to 20]</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>4.3 [2.9 to 6.6]</td>
<td>14 [6.3 to 32]</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>13 [8.3 to 22]</td>
<td>24 [15 to 38]</td>
</tr>
</tbody>
</table>

- For drugs with the same $E_{\text{max}}$, the ratio of the $ED_{50}$ for safety and efficacy is a good measure to compare their therapeutic index (TI)
- Rosuvastatin provides the widest safety margin and Fluvastatin the smallest
Importance of correcting for between trial differences in baseline dyslipidemia: LDL effect of Fibrates as function of baseline triglycerides
A meta-analysis was used to characterize the interaction between fenofibric acid and statins.
What is the benefit of Triglyceride lowering on top of LDL lowering?

• Database was used to characterize the multivariate relationship between changes in LDL, HDL and triglycerides and risk for major coronary events after treatment with statins, fibrates or niacin.
Primary response variable was number of patients with a cardiovascular event during the treatment period. Patient variability follows a binomial distribution:

\[ N_{\text{event,ij}} \sim \text{binomial}(P(\text{event})_{ij}, N_{ij}) \]

Probability of a patient having an event in a treatment arm (j) of a trial (i) is a function of a placebo response in that trial \((E_{0,i})\) and \(f(x)\) represent the functional relationship between the difference in on-treatment lipid values between the control and active arms \((\text{Lipids}_{ij})\) and the log of the odds-ratio for a cardiovascular event including model parameters \(\theta_i\) and covariates \(X_{ij}\)

\[ P(\text{event})_{ij} = g\{E_{0,i} + f(\text{Lipids}_{ij}, \theta_i, X_{ij})\} \]

The trial specific model parameters \(\theta_i\) are assumed to be normally distributed with between trial variance \(\Omega\) (heterogeneity)

\[ \theta_i \sim N(\theta, \Omega) \]
• The risk reduction (difference in log of odds-ratio) for cardiovascular events was found to be statistically significantly dependent (p<0.001 for each variable) on the absolute difference in on treatment LDL-C between active and control arm ($\Delta LDL_i$), the absolute difference in on-treatment TG between active and control arm ($\Delta TG_i$) and treatment duration (time) according to the following relationship

$$f(x) = (\theta_1 \cdot \Delta LDL_i + \theta_2 \cdot \Delta TG_i) \cdot (1 - e^{-\theta_3 \cdot time})$$
The meta-analysis found a significant contribution of lowering triglycerides on top of reducing LDL-C to the risk reduction for a major coronary event after treatment with statins, fibrates or niacin (p<0.001).

- The risk reduction for major coronary events was estimated to be 18.5% [14.1 to 22.7%] for every 1 mmol/L (38.7 mg/dL) reduction in LDL-C and 27.5% [15.7 to 37.7%] for every 1 mmol/L (88.6 mg/dL) reduction in triglycerides.

- The reduction in triglycerides was found to explain most (84%) of the risk reduction for treatment with fibrates. For statins, the reduction in LDL-C was found to explain most (71%) of their benefit.
**Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus**

The ACCORD Study Group*

**ABSTRACT**

**BACKGROUND**

We investigated whether combination therapy with a statin plus a fibrate, as compared with statin monotherapy, would reduce the risk of cardiovascular disease in patients with type 2 diabetes mellitus who were at high risk for cardiovascular disease.

**METHODS**

We randomly assigned 5518 patients with type 2 diabetes who were being treated with open-label simvastatin to receive either masked fenofibrate or placebo. The primary outcome was the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years.

**RESULTS**

The annual rate of the primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group (hazard ratio in the fenofibrate group, 0.92; 95% confidence interval [CI], 0.79 to 1.08; P=0.32). There were also no significant differences between the two study groups with respect to any secondary outcome. Annual rates of death were 1.5% in the fenofibrate group and 1.6% in the placebo group (hazard ratio, 0.91; 95% CI, 0.75 to 1.07; P=0.33). Prespecified subgroup analyses suggested heterogeneity in treatment effect according to sex, with a benefit for men and possible harm for women (P=0.01 for interaction), and a possible interaction according to lipid subgroup, with a possible benefit for patients with both a high baseline triglyceride level and a low baseline level of high-density lipoprotein cholesterol (P=0.057 for interaction).

**CONCLUSIONS**

The combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone. These results do not support the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00000620.)
The meta-analysis predicted results of ACCORD trial of fenofibrate add-on treatments in diabetes and pointed to target patient population that would benefit most.
Summary Dyslipidemia

• Quantified risk/benefit of statins and fibrates
• Characterized the pharmacodynamic interaction between fibrates and statins across all lipid endpoints
• Quantified the relationship between lipid changes and cardiovascular risk reduction
  – Established importance of triglycerides in addition to LDL
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