How predictive is short-term body-weight loss in the longer term for decision making during clinical drug development?

Motivation

Why is research in the area of obesity of interest and highly relevant?

- Worldwide prevalence of obesity has tripled since 1975 and is still rising (Fig. 1) [1].
- Adults: 39% overweight and 13% obese (2016) [2].
- 2.8 million deaths/year resulting from overweight/obesity.
- Obesity is major risk factor for chronic diseases.
  - Weight loss can significantly improve these outcomes.

What are the key challenges?

- High unmet medical need for effective and safe therapy of patients with overweight or obesity.
- Trials without specific duration (T2D).
- Few approved weight-loss compounds with limited efficacy (3%-7% body-weight loss).
- Clinical trials in T2D/obesity are time-consuming and expensive.

Objectives

- What are the objectives of this work?
  - Make use of publicly-available (summary-level) clinical trial data to:
    - Investigate if this relationship is consistent across compounds and populations.
    - Evaluate the effect of potential predictors (e.g. indication) on this relationship.

Methods

- Randomised, controlled Phase IV & V clinical trials:
  - Patients with obesity or T2D
    - Receiving incretin-based therapies (GLP-1 agonists, DPP-4 inhibitors, dual GLP/GIP agonists)
    - Weight loss endpoints (incl. baseline weight).
  - Published from 01/2010 until 11/2018.

Clinical database

- Mainly parallel, double-blind phase 3 studies in peer-reviewed journals.
- Reported weight-loss endpoints:
  - Absolute weight loss or relative change from baseline (including baseline weight).
  - Patients ≥18 years were excluded (n=9).
  - Baseline Arm Characteristics stratified by indication revealed distinct differences between patients with/without T2D (Tab. 1).
  - Trials arms comprised (in descending order) GLP-1 agonists, placebo, DPP4 inhibitors and dual agonists.

Regression-based meta analysis

- Regression-based meta-analysis [5] was performed on summary-level data (using 90% of available data → “development dataset”), influence of potential additional predictors (baseline BMI/age, indication, drug class) was tested.
  - To account for differences in trials sizes, weighting according to trial arm size was used.
    - Strong correlation between of ΔWT, t=4 weeks and ΔWT, t=14 weeks was identified (Fig. 3, t=0.87, with 95% confidence interval 0.64-0.89).
  - Evaluation of predictors revealed statistically significant influence of trial arm baseline WT (P = 0.005), additional predictors were not significant (BMI, age, indication, drug class).
  - External model evaluation revealed good model performance using “test dataset”, i.e. the remaining 10% of available data (Fig. 4, red data points).

Results

Exploratory analysis

- Key aspect is reduction in mean body weight relative to baseline (ΔWT, %) after 12, 24 or 52 weeks (Fig. 2).
  - Most data available up to 24-26 weeks.
  - Pronounced differences between placebo and treatment arms (Fig. 2).
  - For trial arms comprising placebo and DPP4-agonists, ΔWT was relatively small, but for GLP-1 and dual GLP/GIP agonists maximum ΔWT was 10%-20%.
  - Linear relation between short-term ΔWT, t=4 and long-term ΔWT, t=14 weeks identified (Fig. 3).

In the following, exemplary for the applied workflow, the analysis of ΔWT, t=4 weeks versus ΔWT, t=14-weeks is shown:

Conclusions and Perspectives

- Analysis revealed high correlation between ΔWT, t=4 weeks and ΔWT, t=14 weeks for all investigated treatments independent of mechanism of action or dosing regimen.
- Further exploration of correlations including potential predictors, e.g. baseline WT/BMI/age, induction or drug class revealed significant influence of trial arm baseline WT, which was illustrated using 50% (90 kg) and 95% percentile (110 kg) of baseline WT distribution.
- Results of this analysis can be easily visualised, interpreted and communicated.
- Strong relation between ΔWT, t=4 weeks and ΔWT, t=14 weeks can be used to inform and optimise clinical trial design, e.g. perform early interim data analyses or reduce trial length.
- The presented workflow was successfully applied and integrated into a clinical project.

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References


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