Diabetes and Hypoglycemia Events

- Diabetes is a disease characterized by elevated blood glucose level.
- Hypoglycemia events, a complication of insulin therapy, are a limiting factor for patients to further titrate insulin to achieve optimal glycemic control.
- It is important to develop new diabetes medication with low hypoglycemia events.
- Statistical analysis of hypoglycemia events is important.

Commonly used statistical models to analyze hypoglycemia events

- Linear regression – hypoglycemia events are not continuous variables and the distribution is very skewed.
- Poisson regression – too strong on model assumption.
- Wilcoxon test – difficult to adjust for baseline covariates and hard to interpret the results.

- Negative binomial regression (1,2) is widely used in current clinical research and publications – the properties of negative binomial regression with different options in analyzing hypoglycemia events are not well studied.

Objectives

- To compare negative binomial models with different options through Monte Carlo simulation and bootstrap simulation and identify the most appropriate and robust method for analyzing hypoglycemia event data with and without baseline adjustment.

We let NBSP denote the negative binomial regression with $\phi$ estimated by the quasi-likelihood approach.

$$z^2 = \sum (y_i - \mu_i)^2 / \phi$$

$$NBSP$$

Let $NBSP$ denote the negative binomial regression with $\phi$ estimated using the quasi-likelihood approach.

$$D = \sum (y_i - \mu_i)^2 / \phi$$

To account for excessive zeros, the zero-inflated negative binomial (ZINB) model was developed [3,4,5]. In this model, each observation is generated to be zero with a probability of $q$, and to be from a negative binomial distribution mean $\alpha(x)\mu_i$ with probability of $1-q$.

$$P(y_i = 0) = q$$

$$P(y_i > 0) = \alpha(x)\mu_i$$

$$\mu_i = \alpha(x)$$

Generally, the baseline adjustment generally improves the statistical power.

- NBSP and NBWD were 95% for the total hypoglycemia events, but was slightly higher than 5% for nocturnal hypoglycemia events.

Methods

- Let $Y_1, Y_2, \ldots, Y_T$ be a set of count data. The data with negative binomial distribution is defined by $P(Y = y) = \frac{\Gamma(y + k)}{\Gamma(y + k + 1)\mu^y}e^{-\mu}$, where $\mu = \alpha(x)$ is in a shape parameter. The variance of $Y$ is $Var(Y) = \mu + \phi \mu^2$. The negative binomial regression works through the negative binomial distribution with a link function to connect the mean parameter $\mu$ and the independent variable $X_i$. Typically, a log link function is used for negative binomial regression such that $\log(\mu_i) = X_i' \beta$.

- We let $NBSP$ denote the negative binomial regression with $\phi$ estimated using Pearson Chi-square statistic:

$$z^2 = \sum (y_i - \hat{\mu}_i)^2 / \hat{\phi}$$

$$NBSP$$

Summary of results from the example

- Insulin B significantly reduced the nocturnal hypoglycemia events compared to insulin A when adjusting for baseline value. The result was not significant when adjusting for baseline value.
- The Type I error rate was too strong on model assumption.
- Nocturnal hypoglycemia events are hypoglycemia events occurring during the night and can be dangerous due to the lack of awareness. We increased the dispersion parameter $\phi$ of the post baseline hypoglycemia event rate from 2.02 to 2.09 in Case A to 2.16 in Case B in order to evaluate the model performance when data is extremely over-dispersed.

Table 1 shows the mean and standard deviation of negative binomial distributions for baseline and postbaseline for treatment Group 0 and Group 1. Case A was close to monotonic negative hypoglycemia event rates for Type 1 Diabetes (T1D) patients. Nocturnal hypoglycemia events are hypoglycemia events occurring during the night and can be dangerous due to the lack of awareness. We increased the dispersion parameter $\phi$ of the post baseline hypoglycemia event rate from 2.02 to 2.09 in Case A to 2.16 in Case B in order to evaluate the model performance when data is extremely over-dispersed.

Table 2. The comparison of hypoglycemia events between insulin A and insulin B using various models (relative rate, standard error, 95% confidence interval and p-value).

Application

We applied various analysis methods with and without adjustment for baseline values for a Phase 2 clinical study (Table 2).

- Comparing insulin B with insulin A for patients with Type 2 Diabetes.
- No Type 1 Diabetes patients.
- 4 weeks of lead-in period (prior to randomization) at baseline.
- 12 weeks of treatment period.
- A hypoglycemia event was defined as a blood glucose value < 70 mg/dl.

We also assessed Type-I error by repeatedly randomly splitting subjects into 2 treatment groups for 3,000 times (Figure 3).

References