

Longitudinal Model-Based Meta-Analysis in Type 2 Diabetes: Assessment of link between fasting plasma glucose and HbA1c according to antidiabetic drug class

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Status and Problem

The key glycemic efficacy end-points that are being evaluated in anti-diabetic clinical trials are fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c). The effect of anti-diabetic therapy on HbA1c, the primary efficacy endpoint in registration trial, is delayed by several weeks due to the formation and elimination kinetics of this surrogate end-point.

The link between FPG and HbA1c has previously been described using empirical correlations at steady state and semi-mechanistic modeling for few anti-diabetic compounds. In particular, the correlation between HbA1c and FPG has been established in several studies (1)(2). Although these correlations or models have been calculated or developed on large populations of subjects, they have generally not been assessed and compared across different types of treatments. To that end, a model based meta-analysis was performed to assess the link between FPG and HbA1c over a large set of anti-diabetic drug classes. In particular, this model-based framework could be used to predict effect on HbA1c using early data collected for FPG.

Pharmacometric Approach

Analysed data: A database of aggregated longitudinal data from publicly available summary results for T2DM randomized clinical trials (3) was assembled according to the following criteria:

- Monotherapy treatment arms with at least 12 weeks duration
- Documented HbA1c with FPG data
- Drug classes including more than 5 trials, and exclusion of insulin

Final database made of a total of 1150 trial arms coming from 426 trials (7 drug class), divided into a development dataset and a validation dataset (100 studies randomly selected).

Modeling methodology:

- ID: trial arm
- Dependent variable: mean change (from study baseline) HbA1c (fig.1)
- Exploratory variable: mean change FPG (1)(2)
- Residual error normalized by the number N of HbA1c measurements per trial arm
- Non Linear Mixed effect methodology using Monolix 4.3.3

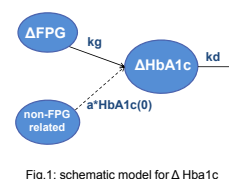


Fig.1: schematic model for ΔHbA1c

Results

1) Final model:

Describes the longitudinal evolution of ΔHbA1c in terms of ΔFPG:

$$\frac{d\Delta HbA1c}{dt} = k_g \cdot \Delta FPG - k_d \cdot \Delta HbA1c + (a + a_{soc} \cdot e^{-k \cdot t}) \cdot HbA1c(0)$$

- Drug impacts on transfert rates described by a baseline HbA1c dependent term, composed of a constant term (a) and a transient standard of care term (asoc)
- Covariates integrated on a: drug class, % male in the trial arm, and presence (β_{wo}) + duration of washout (dw_{02})
- Covariates integrated on k_d : drug class (SGLT2 and TZD), and baseline HbA1c

$$a_i = a_{pop} + b_{wo} \cdot e^{-h \cdot dw_{02}} \cdot \beta_{wo} + \beta_{drug.class} + \beta_{male} \cdot (male - male_{median}) + \eta_i$$

$$k_{d,i} = k_{d,pop} \cdot \exp(\beta_{SGLT2} + \beta_{TZD} + \beta_{HbA1c_{BL}} \cdot (HbA1c_{BL} - HbA1c_{BL,median}) + \eta_i)$$

2) Model qualification:

The model was qualified using GOF plots, VPC and other classical diagnosis criteria (fig.2,3).

- Good parameters estimations were obtained, with r.s.e. $\leq 30\%$.
- Results were globally quite satisfying until 100 weeks.

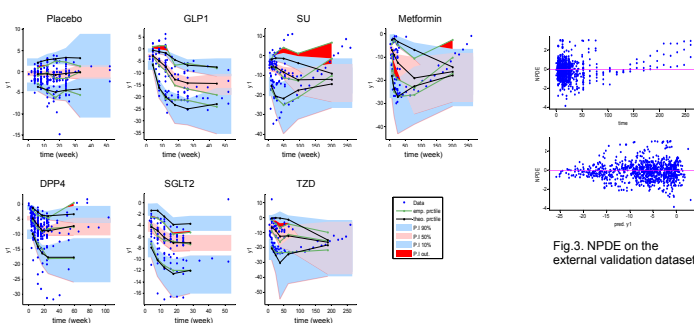


Fig.2. VPC on the external validation dataset, per drug class ($y_1 = \Delta HbA1c \cdot \sqrt{N}$ (%))

3) Prediction of long term HbA1c based on short term FPG

- The final model was applied to the subset of the validation database studies with both week 4 and week 8 FPG assessments. ΔHbA1c was predicted up to 28 weeks based on 8 weeks ΔFPG data, assuming ΔFPG stability between 8 and 28 weeks. Individual predictions were obtained using individual parameters estimated only on 8 weeks data (fig.4).

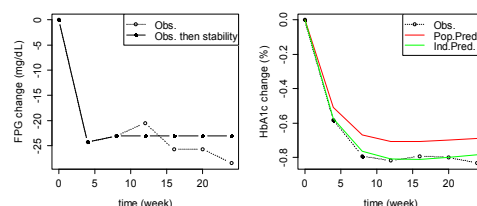


Fig.4. For one trial arm (MB102-032_4), ΔFPG profile and comparison of observed and predicted ΔHbA1c.

- Predictions intervals match quite well with observations (fig.5).
- The mean absolute error is of 0.22% for pop. predictions and of 0.18% for indiv. predictions between 24 and 28 weeks.
- Globally good predictions are obtained, except for metformin for which errors are higher (fig.6).

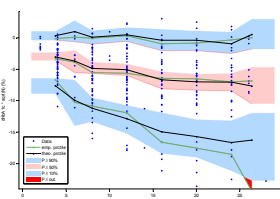


Fig.5. VPC obtained from 8 weeks ΔFPG data on the external validation database until 28 weeks.

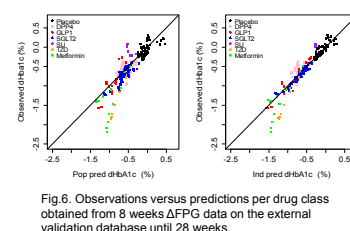


Fig.6. Observations versus predictions per drug class obtained from 8 weeks ΔFPG data on the external validation database until 28 weeks.

- Using ΔFPG values up to 4 weeks and the same methodology, ΔHbA1c predictions were in general of less quality, but were still quite good for GLP1 agonists.

Conclusions & Critical Impact

- A link between FPG and HbA1c over a large set of anti-diabetic drug classes was successfully assessed.
 - A drug class impact was identified on this link.
 - Model was globally well qualified until 100 weeks.
- Long term HbA1c was successfully predicted based on FPG measurement at 8 weeks. Good predictions were also obtained with FPG measured at 4 weeks for GLP1 drug class.

By predicting long term HbA1c response given shorter terms glycemia, this work will help phase 2 decision making and designing phase 3 in T2DM.

Acknowledgments & References

Thanks to M.Dubar, B.Goebel, T.Kiabunde, D.Rueppel and H.C. Schneider, from SANOFI R&D, for their contributions in this work.

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