A Model-based Meta-analysis Comparison of the Effects of Linagliptin and Sitagliptin on HbA1c Levels in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Objectives: Linagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor developed for treatment of Type 2 diabetes mellitus. Sitagliptin is another available DPP-4 inhibitor and serves as a relevant comparator. Our objective was to estimate the magnitude of the HbA1c lowering effects of linagliptin and sitagliptin, based on a comprehensive analysis of available clinical trial data. Specifically, we sought to provide the comparison by means of a longitudinal dose-response meta-analysis based on indirect comparisons. Given appropriate covariate adjustment to account for differences in study designs and patient population, one may infer the efficacies of linagliptin and sitagliptin relative to placebo when administered to comparable patients under comparable conditions.

Methods: An analysis data set was assembled based on a systematic review of available clinical trials for sitagliptin and summary statistics computed from Boehringer Ingelheim internal data sources for linagliptin. A Bayesian hierarchical model was developed to describe HbA1c levels as a function of dose, time, and selected covariates. Covariates related to demographics and study design were evaluated and incorporated in the model where appropriate. Standard model diagnostics were applied to ensure adequate model convergence and model fit. Population simulations based on the selected model were used to evaluate the average effects of linagliptin and sitagliptin in a reference population over 24 weeks of treatment.

Results: The final model described HbA1c levels for placebo treated individuals as a nonlinear function of time. Drug effects were incorporated as multiplicative adjustments to the placebo time course, and additional multiplicative covariate adjustments were made for baseline HbA1c, washout duration and race. Population simulations assuming a study design with no washout and a mean baseline HbA1c of 8% resulted in expected HbA1c differences from placebo at 24 weeks of −0.810 percentage points for linagliptin 5 mg (90% credible interval from −0.881 to −0.740) and −0.807 percentage points for sitagliptin 100 mg (90% credible interval from −0.878 to −0.737).

Conclusion: Consistent with the common mechanism of action, this model-based meta-analysis showed that the new DPP-4 inhibitor linagliptin (5 mg qd) results in a comparable efficacy as seen with the DPP-4 inhibitor sitagliptin (100 mg qd).

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INTRODUCTION

- Linagliptin and sitagliptin are dipeptidyl peptidase-4 inhibitors developed for the treatment of type 2 diabetes mellitus (T2DM)
- At present, no head-to-head trial has been conducted to support a direct comparison between linagliptin and sitagliptin
- Each drug has been compared separately to placebo in randomised trials, but naïve comparison of placebo-adjusted results is confounded by differences in trial designs and enrolled populations

OBJECTIVE

- To estimate the longitudinal treatment effects of linagliptin and sitagliptin for the control of glycated haemoglobin (HbA1c), based on a comprehensive assessment of available data, while accounting for differences in study designs and enrolled populations

METHODS

Data

- A database of aggregated data from the literature was assembled according to prospective search and acceptance criteria, using methodology that has been described previously[1] (Table 1)
- Where available, data were extracted at the level of racial subsets of treatment arms; otherwise, data were extracted at the level of treatment arms. In this poster, we refer to both arms and arm subsets simply as 'groups'

Table 1: *Size of the literature database. Sample means were counted at each time point for each group*

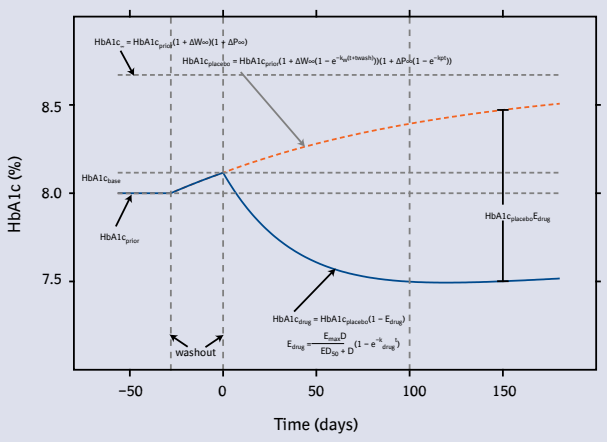
Drug	Trials, n	Groups, n	Sample means, n	Patients, n
Linagliptin	10	29	139	3797
Placebo	21	39	158	2770
Sitagliptin	15	39	145	4667
Total	**25**	**107**	**442**	**11,234**

Base Model

- The conditional expectation for the mean HbA1c on the i^{th} occasion in the j^{th} group and k^{th} study is modelled as follows (a schematic representation of the base model is shown in Figure 1):

$$\widehat{\text{HbA1c}}_{ijk} = \text{HbA1c}_{\text{prior},jk} \times (1 + \Delta W_{\infty,jk}(1 - e^{-k_W(t_{ijk} + t_{\text{wash},jk})})) \quad \text{(washout effect)}$$
$$\times (1 + \Delta P_{\infty,jk}(1 - e^{-k_P t_{ijk}})) \quad \text{(placebo effect)}$$
$$\times \left(1 - \frac{E_{\max,\text{drug}jk} D_{jk}}{ED_{50,\text{drug}jk} + D_{jk}} (1 - e^{-k_{\text{drug}} t_{ijk}})\right) \text{(drug effect)}$$

Figure 1: *Schematic representation of the base model*



Covariates

- The following variables were considered as potential covariates on ΔW_∞, ΔP_∞, and E_{max}: race, age, body mass index, gender, background medications (per protocol medications only), duration of T2DM, and fraction of patients who underwent washout of prior medications
- In general, covariate effects were implemented using conventional parametric forms
- In order to model the effects of race for records representing mixed-race treatment arms, an aggregate conditional expectation was computed using a weighted average:

$$\widehat{\text{HbA1c}}_{ijk} = \sum_{r \in (\text{white, black, Asian, other})} F^r_{ijk} \widehat{\text{HbA1c}}^r_{ijk}$$

where $\widehat{\text{HbA1c}}^r_{ijk}$ is the race-specific conditional expectation for race r and F^r_{ijk} is the fraction of the arm identifying with race r

Reparameterisation and Random Effects

- To improve convergence properties, random effects associated with washout and placebo effects were implemented using a reparameterisation of the model in terms of fractional effects at reference time 24 weeks, denoted ΔW^* and ΔP^*, rather than directly modelling variation in ΔW_∞ and ΔP_∞
- For the same reason, baseline random effects were implemented in terms of $\text{HbA1c}_{\text{base}}$ (Figure 1) rather than in terms of $\text{HbA1c}_{\text{prior}}$
- Following the approach of Ahn et al.[2], both inter-group variances and residual variances were weighted by sample size in order to fully account for longitudinal correlations
- Inter-study random effects were also evaluated for baseline, washout, and placebo parameters (the specification is not provided due to space constraints)

METHODS

- Following the approach of Ahn et al.[2], the equations below fully account for longitudinal correlations:

$$\log(1 + \Delta W^*_{jk}) \sim N(\log(1 + \Delta W^*_{\text{study},k}), \omega^2_{\Delta W}/n_{1jk})$$
$$\log(1 + \Delta P^*_{jk}) \sim N(\log(1 + \Delta P^*_{\text{study},k}), \omega^2_{\Delta P}/n_{1jk})$$
$$\log(\text{HbA1c}_{\text{base},jk}) \sim N(\log(\text{HbA1c}_{\text{base-study},k}), \omega^2_{\text{HbA1c}_{\text{base}}}/n_{1jk})$$
$$\text{HbA1c}_{ijk} \sim N\left(\widehat{\text{HbA1c}}_{ijk}, \frac{\sigma^2}{n_{ijk}}\right)$$

Computation

- OpenBUGS, version 3.2.1 was used to fit the model
- Four Marchov Chain Monte Carlo (MCMC) chains were simulated, each consisting of 100,000 initial samples, of which the first 50,000 were discarded for 'burn-in'
- Every 50th sample of those remaining was kept for inference, resulting in a total of 4 * 50,000 / 50 = 4000 samples
- Convergence diagnostics included MCMC history plots, Gelman-Rubin diagnostics, and univariate density plots of the posterior

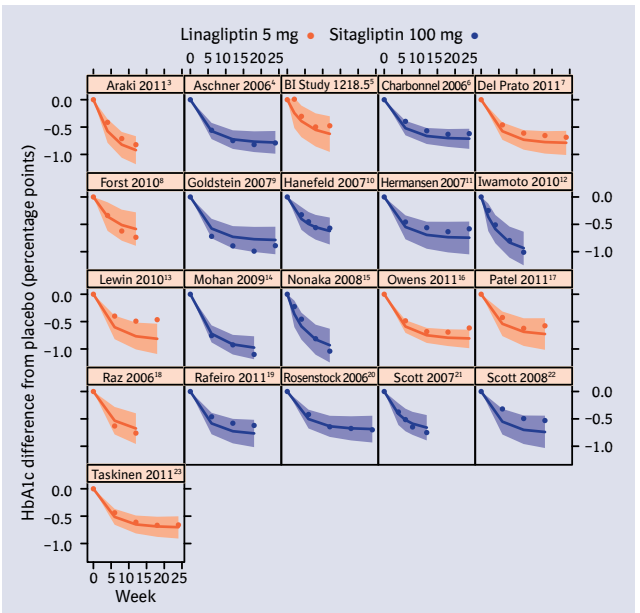
Simulation and Inference

- Treatment effects were estimated by posterior population simulation, i.e., for a given covariate distribution, a population (n=1000) was simulated and an average treatment effect was computed for each posterior sample, resulting in a posterior distribution for the average treatment effect

RESULTS

- The final model included race as a covariate on baseline, drug E_{max} parameters, and ΔP. Attempts to include other covariate effects resulted in poor convergence diagnostics, so these covariates were excluded from the final model. All excluded covariates were examined for potential association with model random effects and no clear associations were observed
- Convergence diagnostics for the final model were consistent with adequate mixing and convergence to a well-defined posterior
- Posterior predictive checks for both unadjusted means (not shown) and placebo-adjusted means (Figure 2) suggest that the model adequately characterises the observed data, with no systematic over- or under-prediction
- Treatment effect estimates based on population simulations suggest nearly identical treatment effects for linagliptin and sitagliptin within each racial group as well as (by consequence) in racially mixed populations. A reference simulation in a population with an HbA1c baseline of 8.0%, consisting of 61.5% white, 1.5% black, and 37.0% Asian patients, showed (placebo-adjusted) treatment effects of 0.81% (90% credible interval: 0.74, 0.88) for linagliptin 5 mg and 0.81% (90% credible interval: 0.74, 0.89) for sitagliptin 100 mg (Figure 3)

Figure 2: *Difference from placebo values (percentage points) of the 21 studies with relevant treatment arms (i.e., studies with linagliptin 5 mg or sitagliptin 100 mg, and placebo arms) over time: comparison of observed and predicted HbA1c difference from placebo. Filled dots represent observed data and shaded regions show the unconditional 90% prediction intervals, and the central line represents the median prediction*

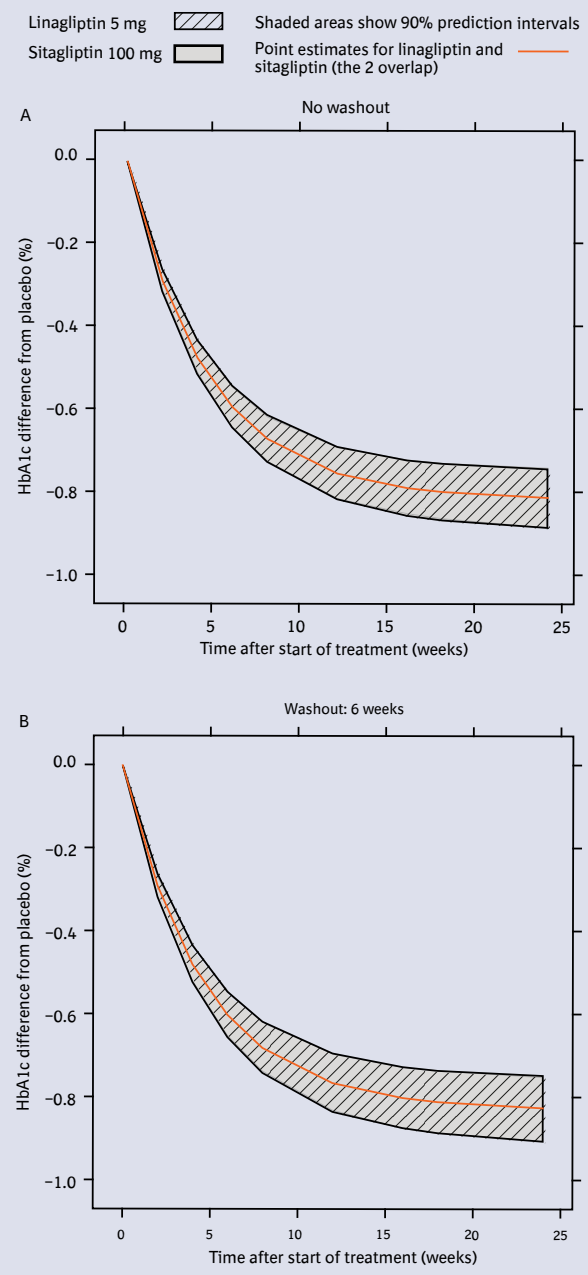


CONCLUSIONS

- The proposed model permits a valid synthesis of the totality of available relevant data for comparing the treatment effects of linagliptin and sitagliptin
- The model adjusts for important differences in trial designs and enrolled populations, including treatment duration, washout duration, baseline HbA1c, and race
- Based on simulation from the fitted model, the treatment effects of linagliptin and sitagliptin appear to be practically indistinguishable when the 2 drugs are administered to comparable populations of patients under comparable experimental conditions
- Both drugs reduced mean HbA1c by approximately 0.8% following 24 weeks of treatment in patients with T2DM and a baseline HbA1c of 8.0%

RESULTS

Figure 3: *A. Estimated drug effects on HbA1c for reference population, with no pre-treatment washout, over 24 weeks (difference from placebo); B. Estimated drug effects on HbA1c for reference population, with a 4-week washout and a 2-week placebo run-in period, over 24 weeks (difference from placebo). Reference population of 1000 patients, HbA1c baseline: 8.0%, racial composition: 61.5% white, 1.5% black, 37.0% Asian*



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