

Introduction

Within the area of type 2 diabetes, the choice of the most appropriate model to predict glycated hemoglobin (HbA1c) is crucial. Five different models have already been developed to describe HbA1c-formation using different biomarkers, such as mean plasma glucose (MPG), fasting plasma glucose (FPG), fasting plasma insulin (FPI) or a combination of those. The standard pharmacometric approach of model selection ignores model uncertainty, potentially leading to impaired predictive performance, which may partially be solved by the model averaging approach (MA) ⁶. Models' performance can be compared using model averaging (MA) with different weighting methods. In this study, an Akaike Information Criterion- (AIC), a Cross-validation- (CV) ⁸ and a Bootstrap- (BS) ⁷ weighting methods were used to perform model comparison.

Aim

Investigate and compare several published models for type 2 diabetes using the MA approach with different weighting methods and to assess potential models' contribution to the HbA1c prediction for the reduced trial duration on a population and individual level.

Discussion and Conclusion

On the population level, ADOPT was selected as the best model with trial duration up to 6 weeks, when IGRH showed the best performance with the trial duration of 4 weeks. Consistent result with marginal difference in weights has been shown with all three MA methods. However, the BS method had the additional advantage of clearly indicating that a 4-week trial duration is too short to give precise estimates. On the individual level, more investigations have to be done to define specific patient populations that benefit from certain models.

Methods

Models

Model	Main Biomarker apart from HbA1c
ADOPT ¹	MPG
IGRH ²	MPG
FHH ³	FPG
LILLY ⁴	FPG-FPI
FFH ⁵	FPG-FPI

Model averaging

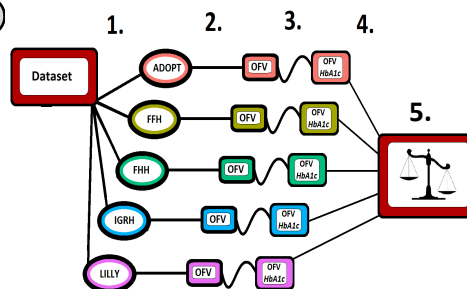
Each model was given a weight (w_m , eq. 1) between 0 and 1. The total weight of all models were then summed up to 1. I_m was the obtained model OFV (eq. 2). On the population level, $I_{m,min}$ was the lowest OFV between the models (eq. 2). ΔI_m was corrected by the number of individuals (500). On the individual level, $I_{m,min}$ was the lowest OFV between models for every individual.

$$w_m = \frac{e^{-\frac{\Delta I_m}{2}}}{\sum_{m'=1}^M e^{-\frac{\Delta I_{m'}}{2}}} \quad (\text{eq. 1})$$

$$\Delta I_m = I_m - I_{m,min} \quad (\text{eq. 2})$$

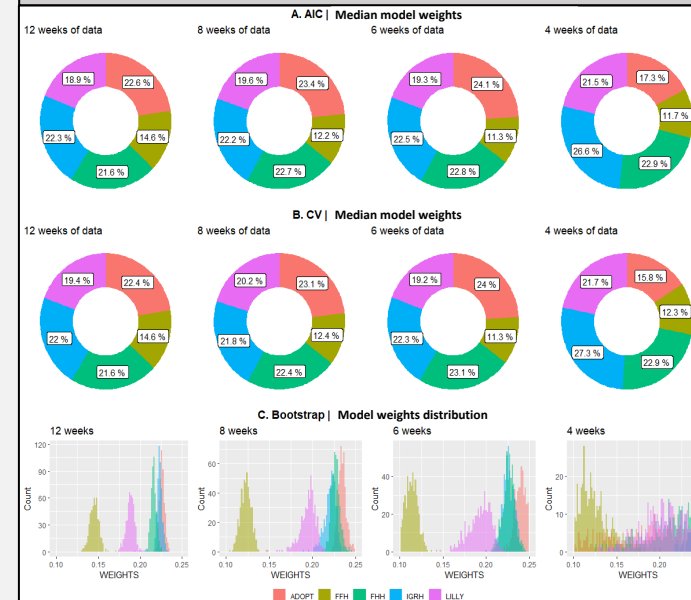
Weighting methods

1. Model fit
2. Estimation step
3. **Keep only HbA1c-data. Update the model with estimated parameters and fit the model (MAXEVAL=0). Obtain the OFV_{HbA1c}.**
4. **AIC:** Calculate AIC-corrected OFV_{HbA1c}
 $\text{AIC} = \text{OFV}_{\text{HbA1c}} + (2 \times k)$
 $k = \text{number of estimated parameters}$
CV: Summarise the obtained OFV_{HbA1c} (4 in total) for each model
BS: Analyse each model by every bootstrap dataset (500 in total)
5. Weight and compare the models' performance

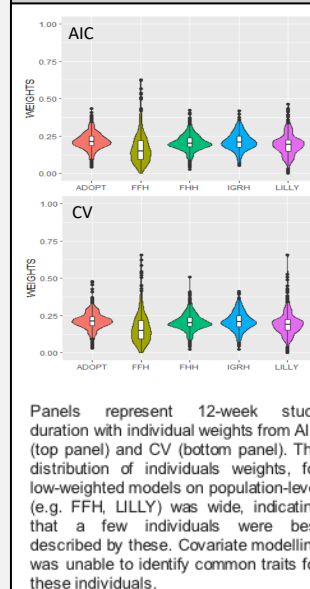


Results

Population level



Individual level



References:

1. Möller, J.B. et al., 2013, CPT PSP, 2. Lledo-García, R. et al., 2013, JPKPD, 3. Hamrén B. et al., 2008, Clin Pharmacol Ther, 4. Gaitonde P. et al., 2018, Clin Pharmacol Ther, 5. Choy S. et al, 2016, CPT PSP, 6. Buatois et. al., 2018, AAPS J., 7. Aoki Y. et.al, 2017, JPKPD, 8. Erik Salomonsson. Model-averaging using a cross-validation weighting method. Unpublished MS-thesis. 2019. Uppsala University.