Quantifying drug effects in phase 2a anti-diabetic studies: Power of four HbA1c models

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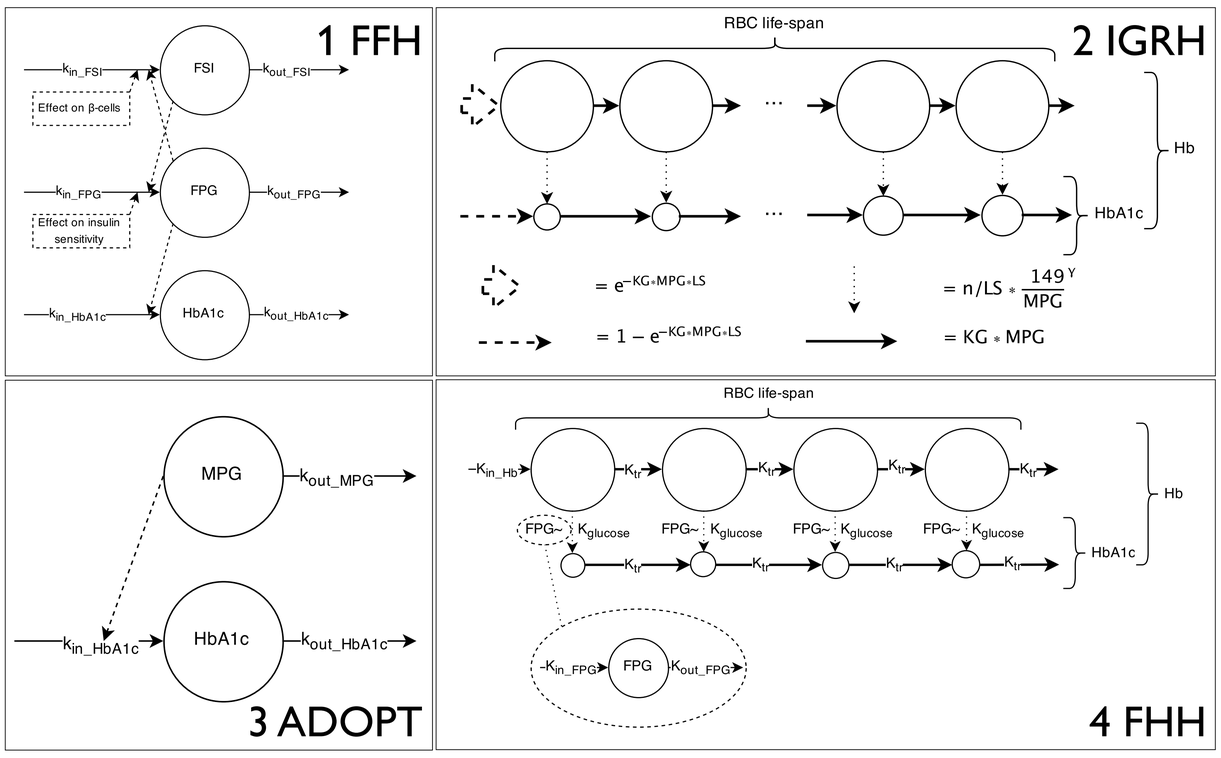
Introduction

Several dynamic models for HbA1c have been proposed for analysis of anti-diabetic study data: : FPG-FSI-HbA1c (FFH)[1], ADOPT[2], Integrated Glucose-RBC-HbA1c (IGRH)[3] and FPG-HbA1c-Hb (FHH)[4]. HbA1c formation is in these models driven by fasting plasma glucose (FPG) or mean plasma glucose (MPG), with or without incorporating fasting serum insulin (FSI).

HbA1c models



(1) The FFH model, adapted from de Winter[1] (2) The IGRH model, adapted from Lledó-García[3] (3) The ADOPT model, adapted from Møller[2] (4) The FHH model, adapted from Hamrén[4].

Methods

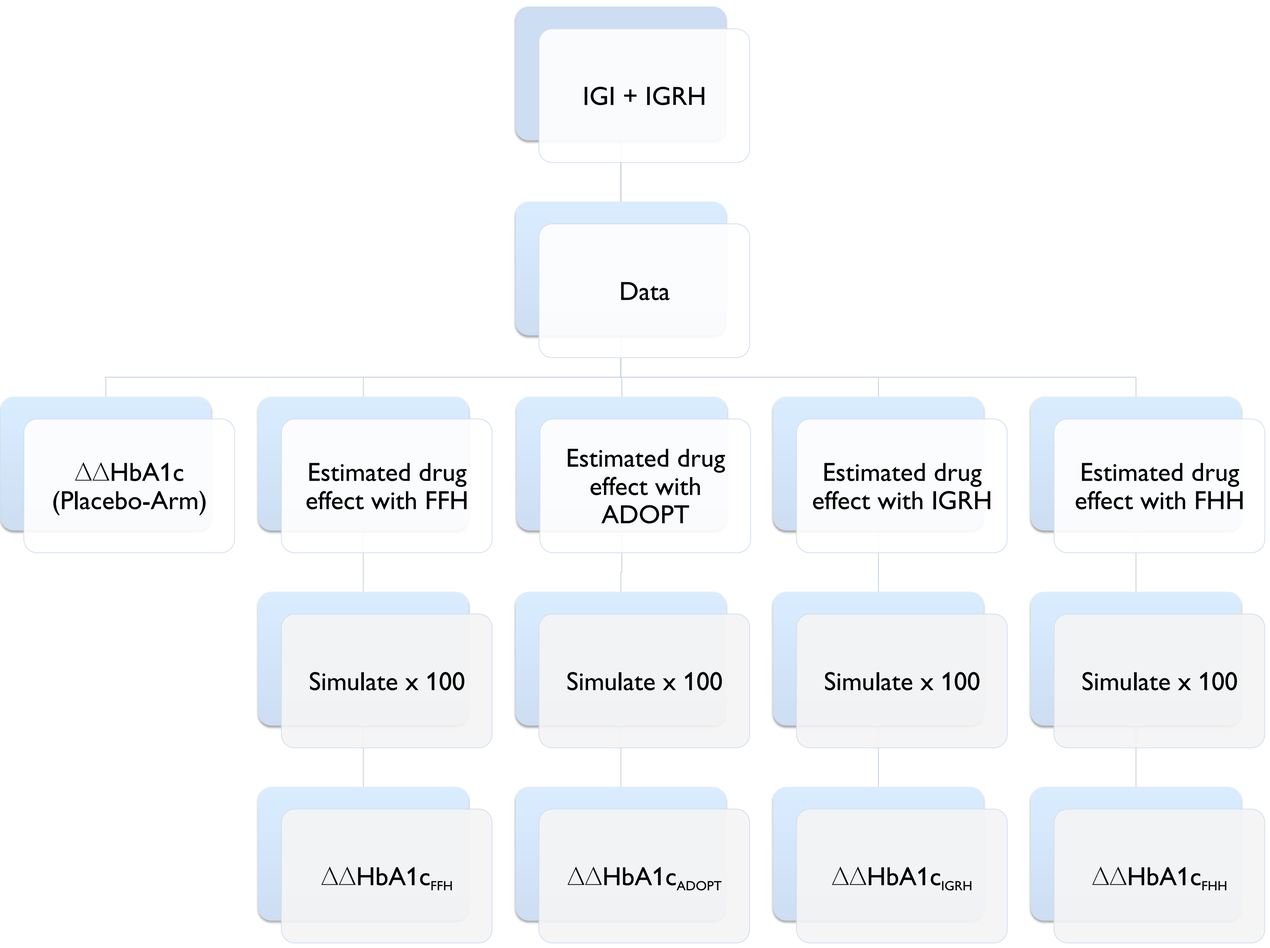


Figure 1. A schematic picture of the study setup.

A 26-week parallel study design with 4 arms (3+placebo) was simulated. Glucose (MPG and FPG) and insulin (FSI) was simulated using the IGI model[5] for 5 hypothetical antidiabetic drug effects: endogenous glucose production (EGP), basal insulin secretion (Basal insulin), incretin response (Incretin), insulin dependent glucose elimination (CLGI) or insulin independent glucose elimination (CLG). MPG was used in the IGRH model to simulate HbA1c. One thousand individuals/arm were simulated and analyzed with each of the four models above. The power to detect a drug effect was assessed comparing the difference in individual objective function value (△iOFV) with and without drug effect using 12-week data.

Conclusions

The choice of model does not affect the power of the study greatly, hence the model should be selected based on what data is available. The FFH model displayed the highest power, except for a drug effect on incretin response. This is probably due to additional information given by the FSI measurements. The relative merit of the models depends on which mechanism of action the studied drug.

Objectives

To compare the four models and their abilities to detect drug effects with respect to power with the aim to aid drug developers in the choice of model.

Results

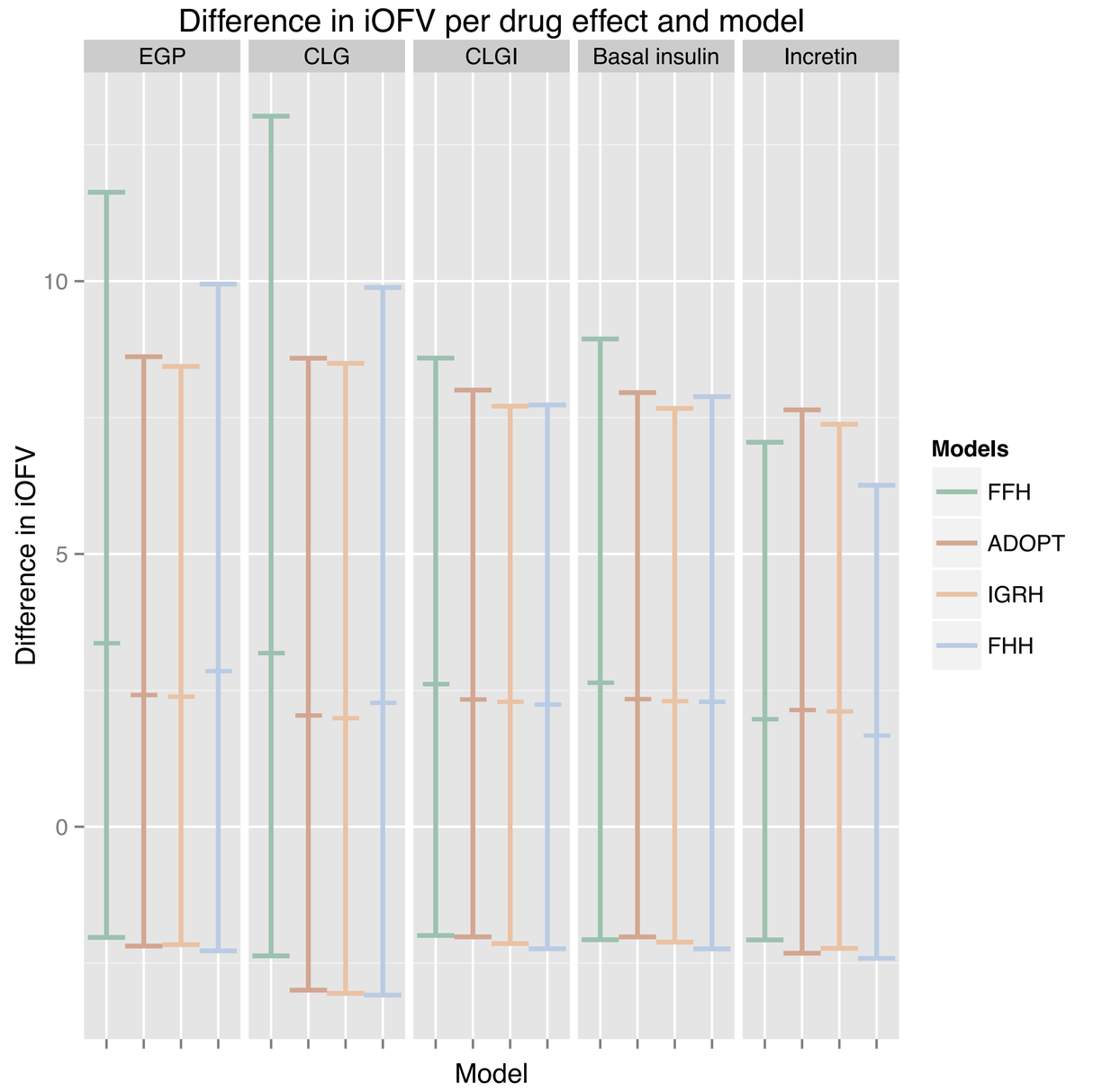


Figure 2. Median △iOFV with 5th and 95th percentiles by model and drug effect.

FPG, rather than MPG, driving HbA1c predictions gives equal or higher △iOFV for all drug effects except incretin. The FFH model (using FSI in addition to FPG) displays higher △iOFV than FHH. The MPG driven models perform similar in the investigated setting.

Discussion

Comparing the results for FHH and FFH, insulin seems to increase power. The MPG driven models differ in how mechanistic they are. The ADOPT model is quick and stable to run but requires observations of HbA1c. The IGRH model is more mechanistic, incorporating the life-span of red blood cells and can be used with only MPG observations for predictions of HbA1c.

References

[1] Winter W de et al. J Pharmacokinet Pharmacodyn. 2006.
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[3] Lledó-García R et al. J Pharmacokinet Pharmacodyn. 2013.
[4] Hamrén B et al. Clin Pharmacol Ther. 2008.
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