Bayesian Borrowing in the DINAMO Pediatric Study using Informative Priors Derived from Model-based Extrapolation

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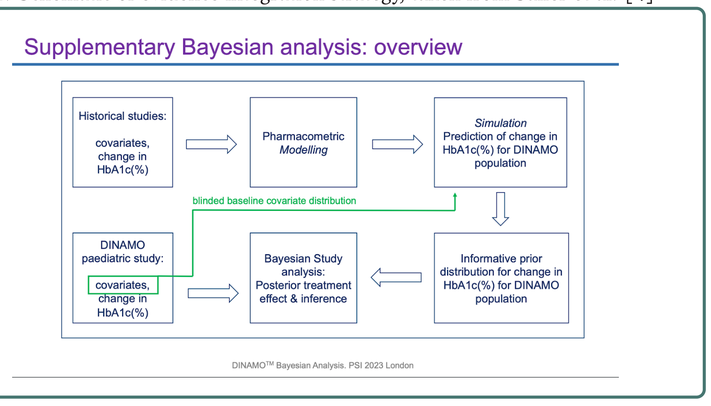
Background and Overview

- The DINAMO study was designed to evaluate the efficacy and safety of empagliflozin and linagliptin in pediatric patients with type 2 diabetes mellitus (T2DM) [8].
- Following FDA guidance for pediatric extrapolation, we leveraged previously developed PK and ER models for empagliflozin and linagliptin, built primarily on adult data, to predict treatment effects in the pediatric population.
- A Bayesian analysis was developed using a robust mixture prior [1, 2, 3]. Prior variances and a prior weight for the informative component in the mixture were pre-specified according to a previously published justification [4, 5].
- Justification for the prior mean of pediatric outcomes based on PK and ER models is explored herein and involves extrapolation from the adult population using relevant covariate adjustments (e.g., weight, eGFR, age, race, and sex).

Figure 1: Schematic of evidence integration strategy, taken from Sailer et al. [4]

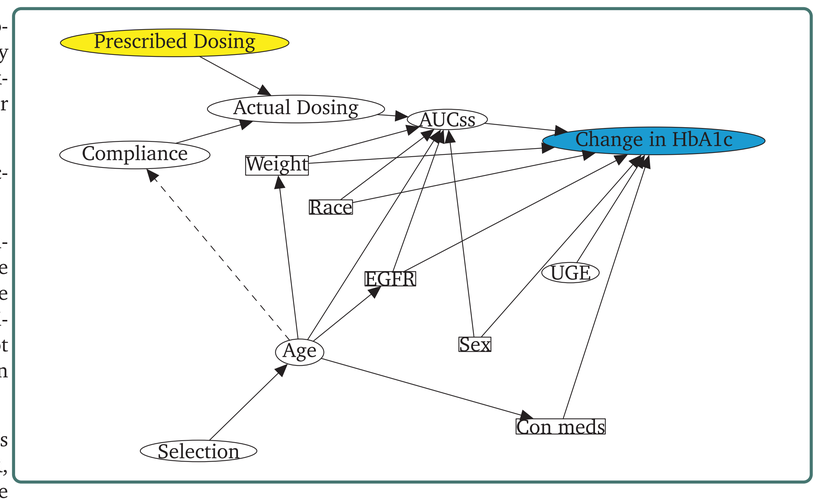


Methods

- PK models were estimated on adult and limited pediatric data with relevant covariate adjustments (e.g., weight, eGFR, age, race, and sex).
- The ER model for empagliflozin was based solely on adult data, whereas the model for linagliptin leveraged adult and adolescent data.
- Both ER models included relevant covariate adjustments (e.g., weight, eGFR, race, sex, and concomitant medication).
- The covariate adjustments were assumed to be sufficient to allow for pediatric extrapolation given our confidence in describing differences in exposure after allometrically scaling by weight and having observed comparable responses for short-term markers of efficacy (urinary glucose excretion for empagliflozin, and DPP-4 inhibition for linagliptin) in pediatric patients with T2DM relative to adults.
- The covariate adjustment strategy was also retrospectively evaluated via causal selection graphs as a formal justification for transportability between populations [6].
- Pediatric predictions adjusted for variables are represented in rectangles, while uncolored ellipses indicate variables that were likely to influence the outcome but were not adjusted for in the model. Age is a special case, since it was adjusted for in the pharmacokinetic simulations but not in the pharmacodynamic simulations. Prior evidence suggested that (conditional on eGFR) urine glucose excretion (UGE) does not depend on age, providing support for the lack of direct effect of age on change in HbA1c (**Figure 2**).
- The adjustment sets computed from this analysis imply that valid extrapolation is possible either by direct adjustment for age or by adjustment for body weight, eGFR, and concomitant medications (as long as the effects of age are mediated by these latter three variables, as implied by **Figure 2**).

Figure 2: A causal selection graph for pediatric predictions.

This selection graph was developed retrospectively as one element of formal justification for the transportability between adult and pediatric populations. Per the criteria of Pearl and Bareinboim [6], such a selection graph may be formally analyzed to identify conditions for conditional exchangeability of evidence, i.e. conditions under which similarity is expected between adults and pediatrics.



Results

Figure 3: Accuracy of placebo-corrected HbA1c predictions for empagliflozin.

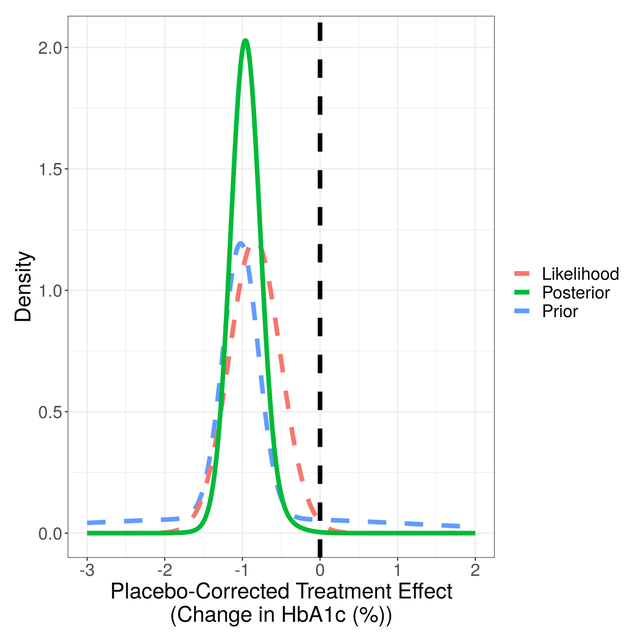


Figure 4: The density of the **prior** for the placebo-corrected treatment effect for the two normal components and the mixture.

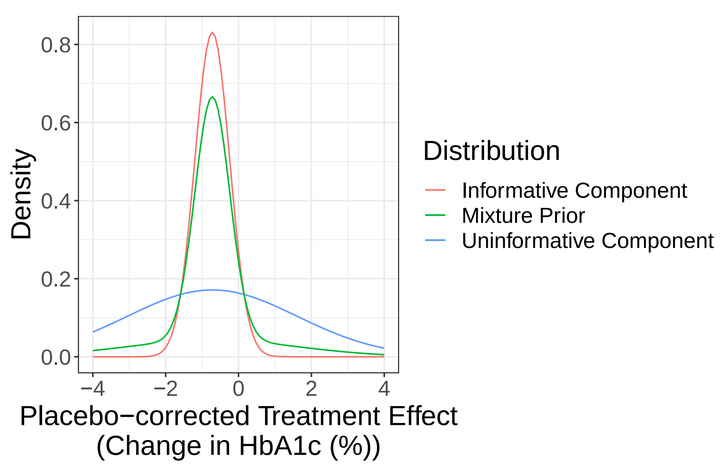


Figure 5: Accuracy of placebo-corrected HbA1c predictions for linagliptin.

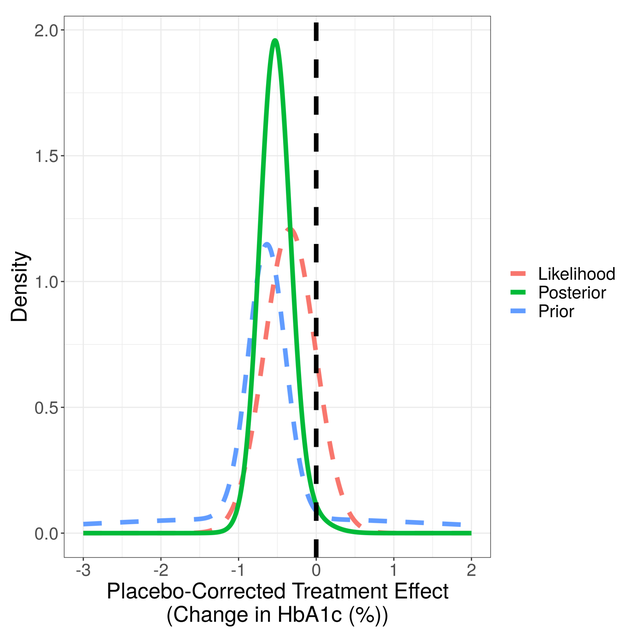
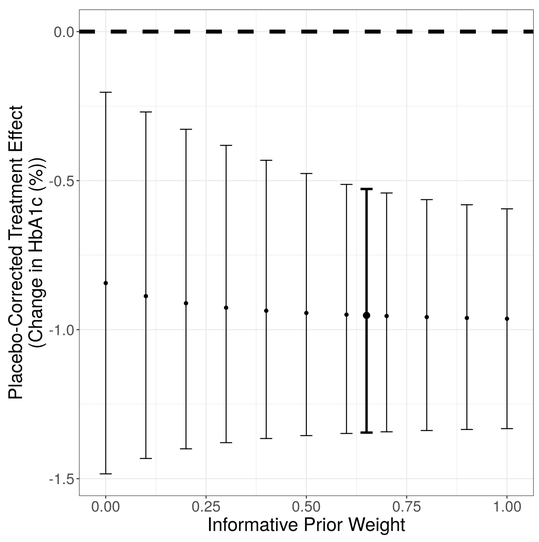


Figure 6: Placebo-corrected treatment effect versus informative prior weight for empagliflozin.

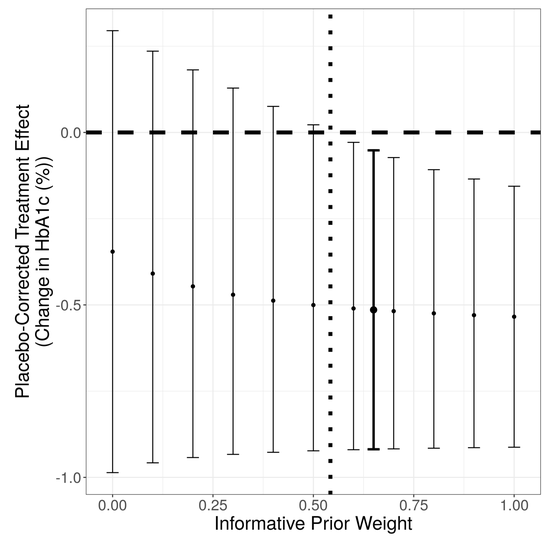
The 95% credible intervals are represented by the ends of line segments. The horizontal dashed line corresponds to the null effect. The bold interval corresponds to the pre-specified informative weight of 0.65.



- Near the center of the distribution, the mixture follows the informative component, and in the tails of the distribution, the mixture follows (with an offset) the uninformative component. The mixture is also very non-normal which is visually noticeable for the non-quadratic shape. This visualization communicates how in each region (prior-data agreement or disagreement) of the estimated treatment effect, the gradient of the prior follows the appropriate distribution, and the effect of the other distribution is negligible (**Figure 4**).
- After adjusting for relevant covariates, the predicted treatment effect for empagliflozin (-1.02 %) was close to the observed treatment effect in DINAMO (-0.84 %) (**Figure 3**).
- For empagliflozin, the prior and likelihood distributions substantially overlap, so the posterior has lower variance than using just the likelihood (i.e., a frequentist analysis) (**Figure 6**).
- In the linagliptin analysis, the ER model predicted a greater treatment effect (-0.64 %) than was observed in DINAMO (-0.34 %) (**Figure 5**).
- The linagliptin conclusions depended on the pre-specified informativeness of the mixture prior. The tipping point sensitivity analyses showed that the informative prior weight where the posterior probability of the placebo-corrected treatment effect being less than zero was 97.5% was a weight of 0.54 (**Figure 7**).
- Due to the information gain, the estimated credible intervals of the treatment effect in the Bayesian borrowing analysis were narrower than that for the traditional analysis using only DINAMO data.

Figure 7: Placebo-corrected treatment effect versus informative prior weight for linagliptin.

The 95% credible intervals are represented by the ends of line segments. The horizontal dashed line corresponds to the null effect and the dotted line corresponds to the tipping point threshold. The bold interval corresponds to the pre-specified informative weight of 0.65.



Conclusion

- Bayesian borrowing is an increasingly popular technique for evidence integration [7].
- Bayesian borrowing can be informed by prior beliefs about conditional exchangeability (the idea that certain observations are comparable after making known covariate adjustment) while also providing a fail-safe if those exchangeability assumptions become inconsistent with the data.
- The acceptance of the results also relies upon the pre-specification of the prior weight and the assessment of subsequent sensitivity analyses [7][9].
- Collaboration between pharmacometricians, statisticians, and stakeholders about the proposed methodology early on, prior to model development, can increase confidence and support successful implementation of Bayesian borrowing.

QR code

References

[1] Best, N., et al. Assessing efficacy in important subgroups in confirmatory trials: An example using Bayesian dynamic borrowing. Pharm. Stat. 20 (2021):551–562. [2] Schmidli, H., et al. Beyond Randomized Clinical Trials: Use of External Controls. Clin. Pharmacol. Ther. 107 (2020):806–816. [3] Weber, S., et al. Applying Meta-Analytic-Predictive Priors with the RBayesian Evidence Synthesis Tools. J. Stat. Softw. 100 (2021): 1–32 [4] Sailer, O., et al. Pharmacometrics-enhanced Bayesian borrowing for paediatric extrapolation - A case study of the DINAMO trial. PSI London (2023). [5] Fayette, L., et al. Pharmacometrics enhanced Bayesian borrowing approach to improve clinical trial efficiency: Case of empagliflozin in type 2 diabetes. CPT Pharmacometrics Syst Pharmacol (2023). [6] Pearl, J., et al. External Validity: From Do-Calculus to Transportability Across Populations. SSO Schweiz. Monatsschr. Zahnheilkd. 29 (2014):579–595. [7] FDA. BLA 125370/s-064 and BLA 761043/s-007 Multidisciplinary review and evaluation of Benlysta® (belimumab) for intravenous infusion in children 5 to 17 Years of age with SLE. Technical report (2018). [8] Laffel, L. et al. Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO). Lancet Diabetes Endocrinol 11 (2023):169–181. [9] Neuenschwander, B., et al. Predictively consistent prior effective sample sizes. Biometrics 76 (2020):578–587.

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