I. Background and Objectives:

In recent years, a number of “so-called” cardiovascular outcomes trials (CVOT) have been published for a number of drug classes in type 2 diabetes. Evidence of benefit on hard outcomes for two classes, GLP1s and SGLT2s, is interesting because it cannot be explained entirely by effects on the traditional physiological parameters like HbA1c, SBP, and body weight that are the key determinants in widely used risk prediction equations such as the UKPDS Outcomes Model. As many diabetes models are based on these risk prediction equations, they are poorly fitted to predict the outcomes of these trials.

The purpose of this challenge is to examine the predictive accuracy of diabetes models on hard endpoints in two recent CVOTs and to examine whether recalibration can be used to better replicate CVOT results.

II. Simulation Overview:

You are asked to use your model to simulate the results of two recent CVOTs involving SGLT2s, EMPA-REG and the CANVAS Program (including 4 scenarios):

1. Replicate the EMPA-REG trial to the extent possible and simulate 3-year outcomes, separately by treatment arm (pooled 10mg and 25mg doses)
2. Calibrate, if your model allows, the model parameters to the outcomes in the placebo arm to the EMPA-REG trial and re-run for both study arms (document your methods)
3. Replicate the CANVAS Program to the extent possible and simulate 4-year outcomes, separately by treatment arm
4. Replicate the CANVAS Program to the extent possible and use the recalibrated model (constructed in Step 2) to simulate 4-year outcomes, separately by treatment arm

Key study publications are listed at end of this document. You may use any additional documents describing these studies that are in the public domain, but please do not use any non-public information. An Excel document, with 6 worksheets is provided to help you work through and document the parameterization of your model to match these simulations.

III. The Challenge Simulations:

1. Replicate and simulate the empagliflozin and placebo arms of EMPA-REG
   A. Read the EMPA-REG studies
   B. Familiarize yourself with the accompanying Excel document (all worksheets) and:
      i. Describe the health states in your model on the worksheet “Health States” and the degree of match with EMPA-REG and CANVAS Program outcomes on the “Best Health State Match” worksheet
      ii. Describe the baseline patient characteristics required for your model on the worksheet “Baseline Patient Characteristics”
   C. Load your model using the embedded EMPA-REG studies (see appendix), other publicly available data, and assumptions and document it in the Excel worksheet (“Input
Characteristics” and “Efficacy”). The empagliflozin and the placebo arms should be simulated separately.

i. Baseline patient characteristics should reflect the EMPA-REG study population. Many of the baseline patient characteristics from EMPA-REG are reproduced in the Excel workbook on Worksheet “Input Characteristics” for the pooled trial population. Use values pooling the placebo and empagliflozin study arms, where possible if you source data elsewhere. If other parameters are required, use the best available data and document data sources and assumptions in the Excel workbook.

ii. Initial biomarker changes and parameter drifts should be modelled so as to best match the EMPA-REG trial and the specifics of your model. If anti-hypertensive and anti-dyslipidemia agent treatment patterns are a key feature in your model, consider modelling the (relatively limited) data available on treatment evolution in EMPA-REG.

D. Run the simulations of the empagliflozin and the placebo arms for a period of 3 years (median in EMPA-REG was 3.1 years), if your model allows. Otherwise run the simulations for the closest period (and considering interpolating values to get figures relevant for 3-year study follow-up).

E. Extract the outcomes for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, hospitalization for heart failure (HHF), hospitalization for angina, microalbuminuria, macroalbuminuria, end-stage renal disease (ESRD), major atherosclerotic cardiac events (MACE), coronary revascularization, transient ischemic attack (TIA) and enter in “EMPA-REG Outcomes” in the accompanying workbook.

F. If you have multiple sets of risk prediction equations (i.e., UKPDS 68 and UKPDS 82), please repeat the experiment and report the results using each of the different alternatives.

2. If your model permits risk adjustment for the key outcomes in EMPA-REG (whether via relative risk reductions, direct multipliers, direct manipulation of the risk equations, or other means), please recalibrate your model as follows:

A. Recalibrate model to predict the results for the placebo arm of EMPA-REG as closely as possible (do not adjust for empagliflozin arm) and re-run simulations

i. Use the simulated results from the placebo arm in Step 1 to recalibrate the model to better fit the results of EMPA-REG using whatever options your model includes and appropriate techniques. Document the technique used to calibrate the model, as well as actual parameter values.

ii. Use same settings as in Step 1, except please use recalibrated parameters (Note: in this simulation, the empagliflozin arm will be modelled using placebo-recalibrated risks)

iii. Run the simulations for the same follow-up period as in Step 1, separately for each treatment arm

iv. Extract the outcomes for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, hospitalization for heart failure (HHF), hospitalization for angina, microalbuminuria, macroalbuminuria, ESRD, MACE, coronary revascularization, TIA and enter in “EMPA-REG Outcomes” in the
accompanying workbook. This gives a measure of how much of the observed empagliflozin treatment effects can be explained by changes in known risk factors and how much is unexplained (see embedded PDF “Kuo et al” for an illustration).

B. Recalibrate model to predict the results for just the empagliflozin arm of EMPA-REG as closely as possible and re-run simulations

i. Use the simulated results from the empagliflozin arm in Step 1 to recalibrate the model to better fit the results of EMPA-REG using whatever options your model includes and appropriate techniques. Document the technique used to calibrate the model, as well as actual parameter values.

ii. Use same settings as in Step 1, except the placebo arm will be modelled using the placebo-recalibrated risks and the empagliflozin arm will be modelled using the empagliflozin-recalibrated risks

iii. Run the simulations for the same follow-up period as in Step 1, separately for each treatment arm

iv. Extract the outcomes for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, hospitalization for heart failure (HHF), hospitalization for angina, microalbuminuria, macroalbuminuria, ESRD, MACE, coronary revascularization, TIA and enter in “EMPA-REG Outcomes” in the accompanying workbook. This gives a measure of how well the results of the trial (with many interdependent outcomes) can be replicated within the limitations of our models (with many moving parts). It also sets up the next challenge, where the recalibrations will be assessed in a different trial setting.

C. If you have multiple sets of risk prediction equations, calibrate and simulate only your “preferred” set. Indicate which set that was in the Excel workbook (Alternatively, please repeat the experiment and report the results using each of the different alternatives).

3. Replicate and simulate the canagliflozin and placebo arms of the CANVAS Program (using the uncalibrated model)

A. Read the CANVAS Program studies

B. Load your model using the embedded CANVAS Program papers, other publicly available data, and assumptions and document it in the Excel worksheet (“Input Characteristics” and “Efficacy”)

i. Baseline patient characteristics should reflect the CANVAS Program study population. Many of the baseline patient characteristics from the CANVAS Program are reproduced in the Excel workbook on Worksheet “Inputs Characteristics”. Use values pooling the placebo and canagliflozin study arms, where possible. If other parameters are required, use the best available data and document data sources and assumptions in the Excel workbook.

ii. Initial biomarker changes and parameter drifts should be modelled so as to best match the CANVAS Program and the specifics of your model. Consider modelling anti-hypertensive and anti-dyslipidemia agent treatment patterns in EMPA-REG if this is a key feature of your model.

C. Run the simulations for a period of 4 years (mean follow-up in CANVAS Program was 3.6 years), if your model allows. Otherwise run the simulations for the closest period (and considering interpolating values to get figures relevant for 3.6-years but indicate that you have done that).
D. Extract the outcomes for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, HHF, amputations, and MACE and enter in “CANVAS Outcomes” in the accompanying workbook.

E. If you have multiple risk prediction equations, please repeat the experiment and report the results using each of the different alternatives.

4. Replicate and simulate the canagliflozin and placebo arms of the CANVAS Program using the model version that was recalibrated based on EMPA-REG results in Step 2 (to the extent you are able)

A. Estimate outcomes using just the placebo-recalibrated risks for both treatment arms (allows for estimation of how much of the observed empagliflozin treatment effects can be explained by changes in known risk factors and how much is unexplained (see embedded PDF “Kuo et al” for an illustration))
   i. Use same settings as in Step 3, except use the same recalibrated parameters from Step 2 for placebo arm
   ii. Run the simulations for the same follow-up period as in Step 3
   iii. Extract the outcomes for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, HHF, amputations, and MACE and enter in “Outcomes” in the accompanying workbook

B. Estimate outcomes using just the placebo-recalibrated risks for both treatment arms but applying direct HRs from CANVAS for the canagliflozin treatment arm (“CANVAS HRs” in the accompanying workbook). Because the hard outcomes are likely to be in part mediated by the corresponding changes in risk factors, this analysis provides an estimate of the magnitude of possible double-counting)
   i. Use same settings as in Step 3, except use the same recalibrated parameters from Step 2 for placebo arm
   ii. Run the simulations for the same follow-up period as in Step 3, applying HRs for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, HHF, amputations, and MACE for the canagliflozin arm (see (“CANVAS HRs” in the accompanying workbook
   iii. Extract the outcomes for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, HHF, amputations, and MACE and enter in “Outcomes” in the accompanying workbook

C. Using just the placebo-recalibrated risks for the placebo arm and the empagliflozin recalibrated risks for the canagliflozin arm (allows evaluation of how well recalibration translates across trials within a drug class, where patient recruitment differs)
   i. Use same settings as in Step 3, except use the recalibrated parameters from Step 2 for the placebo and empagliflozin arms separately for placebo and canagliflozin, respectively
   ii. Run the simulations for the same follow-up period as in Step 3
   iii. Extract the outcomes for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, HHF, amputations, and MACE and enter in “CANVAS Outcomes” in the accompanying workbook
D. If you have multiple sets of risk prediction equations, calibrate and simulate only your “preferred” set. Indicate which set was used in the Excel workbook (Alternatively, please repeat the experiment and report the results using each of the different alternatives)

IV. Prepare an Overview/Discussion of your Key Findings

1. Prepare a brief document in Word (or some easily readable and widely accessible) format. Cover topics like:

   A. What was most difficult in parameterizing and running these scenarios?
   B. How did the unadjusted model perform? Absolute event risks? Relative treatment differences? LYS? QALYs?
   C. Was recalibration feasible? Useful? What was the impact on performance?
   D. If you have multiple sets of risk prediction equations:
      i. How did the results compare between risk equations? Did any capture the treatment effects without recalibration particularly well? Why?
      ii. Were any more/less amenable to recalibration?
      iii. Any general comments?

2. What did you learn from this challenge? Do you believe you can model these data credibly? Suggest possible ideas for improving model performance in predicting risks in T2DM with existing risk equations? Do you believe new risk prediction equations are warranted or can existing risk prediction equations be used (and possibly updated) into the future?

3. How to further model the cardiovascular risk
   A. How to predict after the study duration?
   B. How long to apply study effects?
   C. When to switch to next line of therapy?
   D. What will be the next line of therapy?

V. Prior to the meeting:

1. Submit the Excel results worksheet (“MH CHALLENGE 9 – Cardiovascular Outcomes Challenge_GROUP”) to mthood2016@gmail.com by September 21, 2018.

   Note: Please replace “GROUP” in file name to your group name before submitting.

2. Do not forget to submit the documentation (Section IV) including possible ideas for improving model performance in predicting risks in T2DM with existing risk equations and how to further model the cardiovascular risk
Appendix Relevant papers:

EMPA-REG


2. Supplementary Appendix This appendix has been provided by the authors to give readers additional information about their work. Supplement to: Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. DOI: 10.1056/NEJMoa1504720


4. Supplementary Appendix This appendix has been provided by the authors to give readers additional information about their work. Supplement to: Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323-34. DOI: 10.1056/NEJMoa1515920


CANVAS Program


Kuo et al (2018)