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Initiating SGLT2 inhibitor therapy to improve renal outcomes for persons with diabetes eligible for an intensified glucose-lowering regimen: hypothetical intervention using parametric g-formula modeling

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ABSTRACT

Introduction Sodium–glucose cotransporter 2 (SGLT2) inhibitors are now recommended in guidelines for persons with type 2 diabetes mellitus (T2DM) and at risk of advanced kidney disease as part of the glucose-lowering regimen.

Research design and methods To explore the optimal threshold at which to initiate SGLT2 inhibitor therapy, we conducted an observational study analyzed under a counterfactual framework. This study used the electronic healthcare database in Japan, comprising data from approximately 20 million patients at approximately 160 medical institutions. Persons with T2DM with an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 in April 2014 were eligible. The primary end point was the composite of renal deterioration (>40% decline in eGFR) and the development of eGFR<30 mL/min/1.73 m^2. We estimated the risk of the composite end point occurring over 77 months in different scenarios, such as early or delayed intervention with SGLT2 inhibitors for uncontrolled diabetes at different hemoglobin A1c (HbA_{1c}) thresholds. The parametric g-formula was used to estimate the risk of the composite end point, adjusting for time-fixed and time-varying confounders.

Results We analyzed data from 36 237 persons (149 346 person-years observation), of whom 4679 started SGLT2 inhibitor therapy (9470 person-years observation). Overall, initiating SGLT2 inhibitor therapy was associated with a 77-month risk reduction in the end point by 1.3–3.7%. The largest risk reduction was observed within 3 months of initiation once the HbA_{1c} level exceeded 6.5% (risk reduction of 3.7% (95% CI 1.6% to 6.7%)) compared with a threshold of 7.0% or higher.

Conclusions Our analyses favored early intervention with SGLT2 inhibitors to reduce the renal end point, even for persons with moderately controlled HbA_{1c} levels. Our findings also suggest caution against clinical inertia in the care of diabetes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sodium–glucose cotransporter 2 (SGLT2) inhibitors are currently recommended in guidelines for persons with type 2 diabetes mellitus who are at risk of advanced kidney disease as part of the glucose-lowering regimen.

⇒ The optimal threshold for introducing SGLT2 inhibitors for patients with diabetes to maximize the renoprotective effect is unknown.

WHAT THIS STUDY ADDS

⇒ In this hypothetical intervention using retrospective observational data of 36 237 patients in Japan, early introduction of SGLT2 inhibitors at a hemoglobin A1c level ≥6.5% yielded the largest risk reduction of renal disease progression among 12 different strategies investigated.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Our analyses favored early intervention with SGLT2 inhibitors to reduce renal worsening and suggest caution against clinical inertia in the care of diabetes.

INTRODUCTION

The advent of sodium–glucose cotransporter 2 (SGLT2) inhibitors mirrors a major advance for persons with type 2 diabetes mellitus (T2DM) who are at risk of advanced kidney disease.[1 2] The renal benefit of SGLT2 inhibitors has been consistently shown in clinical trials and observational studies using real world data.[3–8] In clinical guidelines, SGLT2 inhibitors are now listed as the second-line therapy for persons with T2DM, and an estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2 is considered secondary prevention for diabetic kidney disease.[9]

In a recent placebo-controlled trial, dapagliflozin showed a favorable effect on kidney outcomes among patients with chronic kidney disease, regardless of the presence or absence of T2DM.[10] Another trial, EMPA-KIDNEY, is ongoing to examine whether empagliflozin prevents worsening of kidney disease among persons who have chronic kidney disease with or without T2DM.[11] These results indicate that, in the future, the SGLT2 inhibitor class could be used for persons with T2DM, regardless of glycemic control (or even for persons without diabetes); as of September 2021, dapagliflozin already had the authorized indication for non-diabetic persons with kidney disease.[12–14] Until the expanded indication is approved for other agents, persons with poorly controlled T2DM were most likely to be candidates for add-on SGLT2 inhibitor therapy. However, it is uncertain at what glycemic level SGLT2 inhibitors should be initiated to optimize renal outcomes for persons with T2DM or whether renal outcomes differ depending on the timing of SGLT2 inhibitor introduction. This topic is clinically relevant, given that glycemic control is one of the key components in preventing progression towards end-stage renal disease.[7]

This study aimed to explore the optimal threshold of hemoglobin A1c (HbA_{1c}) for intervention with SGLT2 inhibitor therapy for persons with T2DM under several hypothetical scenarios using observational data.

RESEARCH DESIGN AND METHODS

Data source

This study used the RWD database, an electronic healthcare database in Japan, the details of which are reported elsewhere.[6 15] This database collects the records of ~20 million patients from ~160 medical institutions in Japan. The stored information includes demographic data, diagnoses, prescriptions, and laboratory results from both outpatient and inpatient encounters. The data were automatically extracted from electronic health records at each medical institution. Patient records are maintained by assigning unique identifiers for each patient, which are valid only within the same institution. The diagnoses were recorded as *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision (ICD-10) codes, and the prescription records were kept in *Anatomical Therapeutic Chemical* codes.

The last available date of patient records varied across institutions, with a rapid decline in the number of records after September 2020; this was largely due to an administrative reason of the database holder, such as the COVID-19 pandemic.

Patient criteria

Eligible patients were prevalent users of diabetic medication with a diagnosis of diabetes in April 2014 (the index date), when the first SGLT2 inhibitor was available in Japan. We defined prevalent users as patients with at least one prescription record of a glucose-lowering agent (except for SGLT2 inhibitors) within 180 days of the index date. As disease coding practices in Japan were not sensitive enough to capture T2DM cases,[6] we used a broader case definition by ICD-10 codes including both E11 ('diabetes mellitus, type 2') and E14 ('diabetes, unspecified'), unless other specific types of diabetes were concurrently coded (eg, E10 representing type 1 diabetes). Other inclusion criteria were persons aged ≥20 years at the index date; persons whose laboratory data were available both within 90 days prior to the index date and after the index date; and eGFR >30 mL/min/1.73 m^2 at the index date. To identify prescriptions for diabetic medication, the *Anatomical Therapeutic Chemical* code A10 was used. No specific exclusion criteria were prepared.

Hypothetical intervention

We conducted several hypothetical interventions under a potential outcome framework, also known as the counterfactual framework (figure 1).[16 17] This framework requires three assumptions—positivity, conditional exchangeability, and consistency—for computation of the probability of an outcome occurring (Supplemental Methods in online supplemental file 1). These assumptions were statistically untestable,[17] and whether such assumptions would hold depends on the clinical context. For example, this study assumed that at each medical encounter, individuals who did and did not initiate SGLT2 inhibitors were exchangeable conditional on

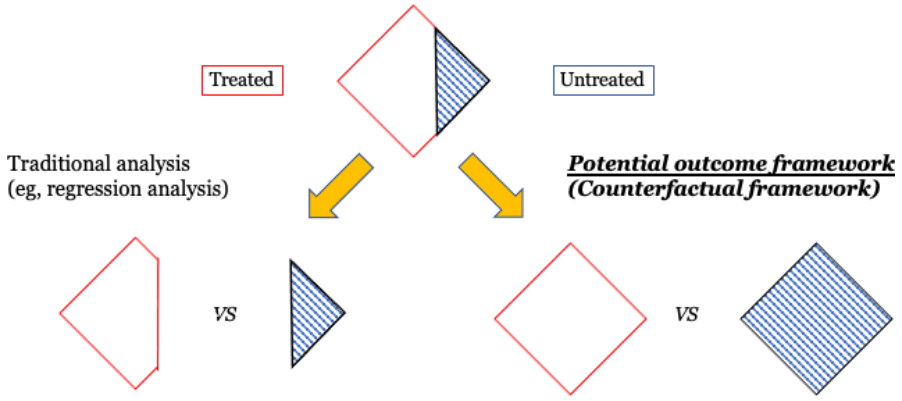

Figure 1 Illustrative scheme of the counterfactual framework.

the variables of age, sex, HbA_{1c}, and medication history other than SGLT2 inhibitors. Intuitively explained, if the outcomes differed between two exchangeable populations, the difference likely resulted from SGLT2 inhibitor use. As a per-protocol effect,[18] we assume that all persons who meet the criteria for initiating SGLT2 inhibitor therapy did start pharmacologic treatment and that SGLT2 inhibitors were sustained once they were started except for censoring. The estimated effect was analogous to that obtained from per-protocol analysis in a clinical trial.

Our de novo research question was 'If the timing of introducing SGLT2 inhibitors differed in people with T2DM, what would have been observed with respect to worsening renal risk?'. As such, we prepared the primary hypothetical intervention to introduce SGLT2 inhibitors for all persons once their HbA_{1c} level exceeded 7.0%. The probability of a hypothetical outcome occurring was compared with that of the natural course, a model-based simulation of observed data. The interval between HbA_{1c} measurement and SGLT2 inhibitor initiation was primarily set at 3 months, which was changed to 6 months, 9 months and 12 months in the sensitivity analysis. This mirrors the scenario of initiating SGLT2 inhibitors within 3 months (or 6 months, 9 months and 12 months) after HbA_{1c} exceeds ≥7.0%. In addition, the threshold of HbA_{1c} was changed to 6.5% and 7.5% in the sensitivity analyses; the same four intervals were tested.

Outcome

The outcome of interest was the incidence of sustained renal worsening, defined as either[1] a >40% decline in eGFR from the baseline value[19] or[2] eGFR <30 mL/min/1.73 m^2. For both measures, at least two measurements ≥30 days apart were required to define sustained deterioration. The value of eGFR was calculated with the following equation using the serum creatine value at the visit: eGFR (mL/min/1.73 m^2)=194 × creatine $^{-1.094}$ (mg/dl)×age$^{-0.287}$ (years) (×0.739 for women).

This formula was modified from the original Modification of Diet in Renal Disease equation, given the body composition of the Japanese population.[20]

Statistical analysis

Descriptive statistics were used to summarize patient characteristics. The crude annual eGFR slope was estimated by a mixed-effects linear model accounting for within-person clustering.

Under the potential outcome framework, the parametric g-formula was used to estimate the probability of outcome occurrence for each hypothetical intervention.[21–23] In daily clinical practice, patient conditions, namely, glycemic control and medications, can vary over time. The parametric g-formula is among the procedures accounting for such time-varying confounders.[24] We modeled age, sex and the grade of renal function at the index date as time-fixed covariates, whereas HbA_{1c} at each visit and exposure histories to other diabetic medications were accounted for as time-varying covariates. The estimates obtained using the parametric g-formula should be viewed as the population-level effect.

The observation started in April 2014, and all patients were assumed to be followed through September 2020 except for censoring due to death. Unlike traditional survival analysis, loss to follow-up is not treated as censoring in the parametric g-formula; data after loss to follow-up are modeled from the data of patients who remain in the cohort.[22] However, in the preliminary analysis, we noticed model instability when incorporating data after September 2020, when the patient population size rapidly declined. For this reason, we truncated patient data as of September 30, 2020. In this study, death was the competing event for the renal outcome; thus, data were censored at the time of death (if it occurred). The follow-up was monthly; if visit records were missing, the data, including medication and laboratory results, were carried forward from the last visit (until the next visit).

All statistical analyses were conducted using the R statistical environment (V.4.10). We also relied on the *gfoRmula* R package (V.0.32) for g-formula estimation.[25] Non-parametric bootstrapping with 200 samples was used to compute the 95% CI. The 95% CI did not cross a null effect; it was considered statistically significant.

Sensitivity analysis

Our study primarily included persons whose baseline eGFR was ≥30 mL/min/1.73 m^2. We added a sensitivity analysis that included persons with a baseline eGFR of ≥45 mL/min/1.73 m^2. This was because there was caution—though not contraindicated—against SGLT2 inhibitor use for persons with an eGFR of <45 mL/min/1.73 m^2 in the package insert of some SGLT2 inhibitors.[26 27] This means that persons whose eGFR was <45 mL/min/1.73 m^2 were less likely to receive SGLT2 inhibitor therapy, and this situation might correspond to the near violation of the positivity assumption. This was a post hoc analysis, reflecting the discussion among the authors.

Furthermore, four sensitivity analyses were added as recommended by the journal reviewers. First, the outcome was changed to the eGFR change (ie, a continuous variable) at the end of follow-up. Second, the inclusion criteria were expanded to persons whose baseline eGFR was ≥20 mL/min/1.73 m^2. These criteria were modified because SGLT2 inhibitors are not necessarily contraindicated to persons with an eGFR <30 mL/min/1.73 m^2 in Japan, and it is possible that such persons can use the SGLT2 inhibitors. The lower threshold of 20 mL/min/1.73 m^2 was determined by the authors to be compatible with the inclusion criteria of a previous randomized controlled trial[28] and the package insert of empagliflozin in Japan.[29] Third, the model was further adjusted by antihypertensive drug use and ACE inhibitor/angiotensin II receptor blocker use as time-varying confounders. Because blood pressure records for each person were lacking, this analysis was performed as a sensitivity analysis because of the concern for potential

model misspecification. Finally, we conducted benchmark analyses to illustrate how the g-formula worked in the case examples of dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, instead of SGLT2 inhibitors. A similar analytic framework to that of the primary analysis was adopted in these sensitivity analyses.

RESULTS

Characteristics of the cohort

A total of 36 237 persons were included in the analysis. The median age at the index date of April 2014 was 70 (IQR: 63–78) years, and men accounted for 62.7% (22 713/36 237) of the cohort. The baseline eGFR was 67.3 (median, IQR: 54.2–80.9) mL/min/1.73 m^2. The baseline data of quantitative urinary albumin-creatinine ratio was available in 11 165 persons, of which the median value was 20.6 (IQR: 8.6–73.0) mg/gCr. There were 4315 recorded deaths at a median of 27 months after the index date. Overall, the study cohort contributed 149 346 person-years of observation, with the longest observation being 77 months. The most commonly used glucose-lowering drug at the index date was DPP-4 inhibitors (55.5%), followed by biguanides (37.2%) and sulfonylureas (34.1%). The median HbA_{1c} value was 7.0%, with an IQR of 6.4%–7.7%. During the study period, 4679 persons (12.9%) started SGLT2 inhibitor treatment, and they contributed 9470 person-years of observation. Regarding the renal outcome, the crude overall decline in the eGFR was 0.80 (SE: 0.011) mL/min/1.73 m^2 annually, and one patient developed end-stage renal disease.

In the natural course scenario, 20.0% of persons experienced the renal composite end point, and this estimate was very close to the observed data (figure 2: upper left). This result means that the chance of our model misspecification was limited, although this is not guaranteed.[25]

Main analysis

In the hypothetical intervention involving initiation of SGLT2 inhibitors within 3 months of HbA_{1c} ≥7.0%, the 77-month risk of the composite end point was 17.2% of the study population, with a 3.1% lower risk relative to that of the natural course (table 1, figure 2). When initiation of SGLT2 inhibitors was deferred until 6 months, 9 months and 12 months, a beneficial effect of SGLT2 inhibitors was also observed, but the risk reduction was smaller than that observed with the 'within 3 months' strategy (table 1, figure 2: lower left).

In the sensitivity analyses using different thresholds of HbA_{1c} levels—6.5% and 7.5%—the most beneficial effects were observed in the 'within 3 months' intervention for people whose HbA_{1c} exceeded 6.5% (table 1, figure 2: right).

By stratifying the timing of intervention, we reaffirmed that the intervention, even at the lower HbA_{1c} threshold, could reduce renal worsening (figure 3).

Sensitivity analysis

In the analysis limited to persons with a baseline eGFR of ≥45 mL/min/1.73 m^2, data from 32 356 persons (138 540 person-years observation) were analyzed. Although the outcome occurrence was less frequent than that in the primary analysis, the results were essentially similar (online supplemental table 1). This sensitivity analysis also favored the earlier introduction of SGLT2 inhibitors for renoprotection among persons with T2DM.

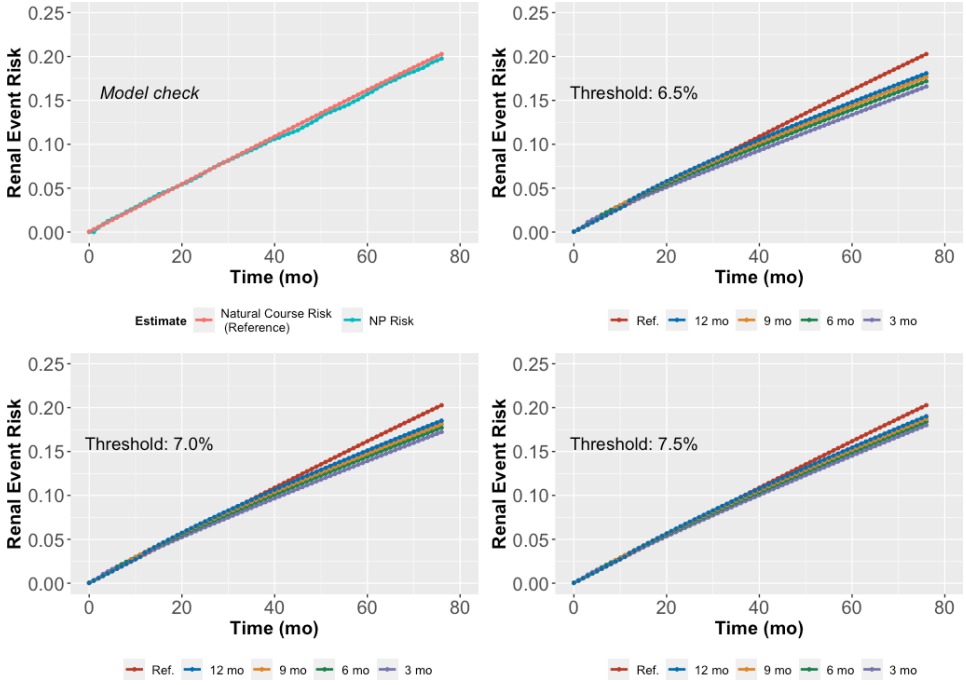

Figure 2 Renal outcome stratified by the threshold hemoglobin A1c (HbA_{1c}). mo, month(s); NP, non-parametric.

Table 1 Renal risk in different treatment strategies

Intervention	Crude risk (95% CI)	Risk difference (95% CI)	Risk ratio (95% CI)
Natural course	20.0 (19.8 to 21.1)%	(Reference)	(Reference)
A_{1c}≥7.0%, within 3 m	17.2 (14.8 to 20.2)%	−3.1 (−5.4 to −1.4)%	0.85 (0.73 to 0.97)
A_{1c}≥7.0%, within 6 m	17.7 (15.7 to 20.3)%	−2.5 (−4.6 to −1.2)%	0.87 (0.77 to 0.98)
A_{1c}≥7.0%, within 9 m	18.1 (16.3 to 20.4)%	−2.1 (−3.9 to −1.0)%	0.89 (0.80 to 0.99)
A_{1c}≥7.0%, within 12 m	18.5 (16.8 to 20.6)%	−1.8 (−3.3 to −0.93)%	0.91 (84 to 1.00)
A_{1c}≥6.5%, within 3 m	16.6 (13.7 to 20.0)%	−3.7 (−6.7 to −1.6)	0.82 (0.68 to 0.97)
A_{1c}≥6.5%, within 6 m	17.2 (14.6 to 20.2)%	−3.1 (−5.6 to −1.4)	0.85 (0.73 to 0.98)
A_{1c}≥6.5%, within 9 m	17.7 (15.6 to 20.3)%	−2.6 (−4.7 to −1.2)	0.87 (0.77 to 0.98)
A_{1c}≥6.5%, within 12 m	18.1 (16.2 to 20.4)%	−2.2 (−4.1 to −1.1)%	0.89 (0.80 to 0.99)
A_{1c}≥7.5%, within 3 m	18.0 (16.2 to 20.4)%	−2.3 (−4.0 to −1.1)%	0.88 (0.80 to 0.99)
A_{1c}≥7.5%, within 6 m	18.4 (16.8 to 20.5)%	−1.9 (−3.5 to −0.91)%	0.91 (0.83 to 0.99)
A_{1c}≥7.5%, within 9 m	18.7 (17.3 to 20.6)%	−1.6 (−2.9 to −0.80)%	0.92 (0.85 to 1.00)
A_{1c}≥7.5%, within 12 m	19.0 (17.7 to 20.7)%	−1.3 (−2.6 to −0.62)%	0.94 (0.87 to 1.00)
Never treated	20.3 (19.9 to 21.2)%	0.00 (−0.07 to 0.18)%	1.00 (1.00 to 1.01)

The 95% CI was calculated by bootstrapping, without p value output. A 95% CI of a rate that did not cross 0 or a ratio that did not cross 1 was regarded as statistically significant.
A_{1c}, hemoglobin A_{1c}.

Similarly, earlier introduction of SGLT2 inhibitors was associated with better renal outcomes in other sensitivity analyses in which[1] the outcome was the continuous eGFR value;[2] persons with a low eGFR were involved (data of 36 937 persons analyzed); and[3] an additional adjustment by antihypertensive drug and ACE inhibitor/angiotensin II receptor blocker use was conducted (online supplemental tables 2-4). In the analysis in which continuous eGFR change was the outcome, however, statistical significance was noted only for very early introduction of SGLT2 inhibitors (online supplemental table 2). Unlike SGLT2 inhibitors, there were no benefits observed in DPP-4 inhibitors and GLP-1 receptor agonists (online supplemental tables 5 and 6).

DISCUSSION

We estimated the 77-month risks of renal events among the T2DM population under different HbA_{1c}-guided strategies regarding the initiation of SGLT2 inhibitor therapy.

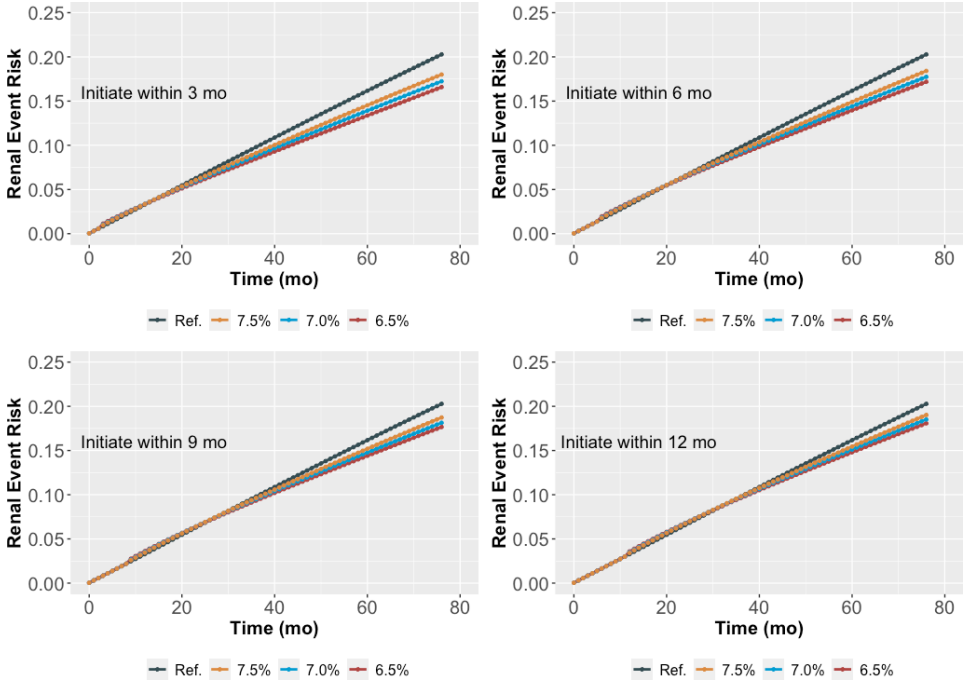

Figure 3 Renal outcome stratified by the lag time. mo, month(s).

Overall, the initiation of SGLT2 inhibitors was associated with a lowered risk of reaching the renal end point. For example, the strategy of starting SGLT2 inhibitors within 3 months of HbA_{1c} ≥7.0% could lower the risk by 3.1% at 77 months. The largest benefit was found with the strategy of initiating SGLT2 inhibitors within 3 months of HbA_{1c} ≥6.5% (risk reduction by 3.7%) compared with deferred initiation (vs within 6 months, within 9 months or within 12 months) or initiation at a higher HbA_{1c} threshold (vs 7.0% or 7.5%). The results were essentially similar in the sensitivity analysis that changed the inclusion criteria regarding baseline eGFR.

It is difficult to choose a single cut-off of HbA_{1c} to define 'uncontrolled' diabetes or when to start add-on therapy. In this study, the threshold of 7.0% was primarily selected to accord with the American Diabetes Association guidelines that recommend a target HbA_{1c}<7.0%.[30] As higher or lower target levels are also acceptable if taking into account individualized risk or preference, we also prepared two different thresholds: 6.5% and 7.5%. Somewhat unexpectedly, the largest benefit was observed with the strategy with a threshold of 6.5% for uncontrolled T2DM. This could be explained in two ways. First, tight glucose control was better for preventing renal worsening,[31] even for persons whose HbA_{1c} level exceeded 6.5%. The benefit of stricter glucose control is not clearly shown in T2DM, particularly with regard to renal protection. For example, earlier randomized trials of intensive glucose control often employed progression of albuminuria as a renal end point.[32 33] Future studies regarding intensive glucose control might support our explanation, but safety concerns for such trials remain.[34] An alternative explanation is that the number of persons receiving SGLT2 inhibitors was expected to increase as the thresholds for initiating therapy lowered. Thus, it is also possible that the largest benefit in the 6.5% threshold strategy was simply reflected by the largest sample size exposed to SGLT2 therapy, whose effect could be introduced via either glucose-lowering or non-glycemic pathways of SGLT2 inhibitors.[2]

We also found that the earlier introduction of SGLT2 inhibitors led to better renal outcome, irrespective of all the thresholds of HbA_{1c} examined (figure 2). The interpretation of this finding might be complicated because the period of exposure to SGLT2 inhibitors varied among different strategies; persons with early introduction (eg, within 3 months) were anticipated to receive SGLT2 inhibitor therapy longer than those with deferred introduction by the end of follow-up at 77 months (Supplemental Discussion in online supplemental file 1). It is intuitively difficult to understand whether—and to what extent, if any—these different exposure periods affected the estimated results among different strategies. With respect to this point, given the irreversible nature of the eGFR trajectory, we assumed that the estimated benefit of early initiation cannot be biased upward or overestimated (details in Supplemental Discussion in online supplemental file 1).

The parametric g-formula is a statistical method that can answer questions such as 'when to treat'.[24] Although this method is unfamiliar (or may be difficult to understand) to clinicians, it has recently been applied in clinical research to investigate when to initiate antiretroviral drugs[35] or to examine lifestyle modifications and the subsequent risk of stroke [36 37] in which the effect of a 'hypothetical' intervention was evaluated. The statistical advantage of the parametric g-formula is that it can account for time-varying confounders and treatment-confounder feedback, the complex situation where the confounder affects the treatment and the treatment affects the confounder; it is known that traditional regression methods may fail in the presence of treatment-confounder feedback.[38] In the care of diabetes, drug regimens and patient characteristics (eg, HbA_{1c}) change over time, and both interact with each other so that the presence of treatment-confounder feedback is likely in diabetes care. As such, we applied the parametric g-formula to explore when to best initiate SGLT2 inhibitors, a question that is difficult to answer with other study designs.

Since our results are premature to be translated directly into clinical practice at this moment, the implications of our study need discussion. First, it could provide a rationale for future research, including randomized controlled trials, to seek the optimal timing of SGLT2 inhibitor treatment to achieve its renal benefit. From a clinical perspective, we may quantify the negative effect of clinical inertia by comparing the scenarios between early versus deferred initiation or those between lower or higher thresholds to initiate intervention.[39 40] Our findings might also support the grade E recommendation of the American Diabetes Association that the medication regimen should be re-evaluated every 3–6 months.[28]

As the indication for SGLT2 inhibitors is expected to expand to non-diabetic persons at risk of renal disease, it may be interesting to explore whether our findings would be applicable to persons without diabetes. However, during the study period, SGLT2 inhibitors were only indicated for persons with T2DM, and thus, we did not have data on people without diabetes who used SGLT2 inhibitors. This research topic is the future agenda, when real-world data of non-diabetic persons are available.

Although the parametric g-formula is a sophisticated statistical approach, the model relies on several assumptions that cannot be tested. Moreover, whether findings obtained from this novel approach will change the clinical practice is yet to be certain. For transparency, we showed how the g-formula worked using DPP-4 inhibitors and GLP-1 receptor agonists as case examples (online supplemental tables 5 and 6). In the supplemental file, we have also provided the sample R codes.

There are several limitations in our study. First, there were unmeasured confounders, including dietary habits or duration of T2DM, in each person, which may have affected the results. Second, as we could not model the extent to which SGLT2 inhibitor therapy lowered HbA_{1c} with each strategy, we could not explore the relationship

between lowering HbA_{1c} levels and the downstream renal effect. Third, Asian populations are known to be more susceptible to diabetic renal disease, and thus, the generalizability of the findings to other populations is uncertain.[41] Fourth, we did not evaluate the harms of SGLT2 inhibitor therapy or its benefits other than kidney function protection. Potential adverse events associated with SGLT2 inhibitors include hypoglycemia, euglycemic diabetic ketoacidosis, genitourinary tract infection, volume depletion and bone fracture.[30] Although there were claims records for these conditions in our data set, we could not specify which events were due to SGLT2 inhibitor use. Furthermore, even if identification of such events was possible, events that did not require medical attention (eg, non-severe hypoglycemia) or instances when patients were treated by other facilities outside the RWD database could not be captured. Therefore, we could not fully evaluate whether our therapeutic strategy of SGLT2 inhibitor administration might increase drug-related adverse events. Finally, our estimates were population-level effects, meaning that it is uncertain whether the benefit of SGLT2 inhibitors was delivered equally, regardless of individualized risk.

In summary, using observational data of persons with T2DM with the parametric g-formula, we compared the effect of different strategies of SGLT2 inhibitor initiation on the renal end point using different HbA_{1c} thresholds and timings. Overall, our analysis favored the early introduction of SGLT2 inhibitors at a lower HbA_{1c} threshold to reduce renal worsening. Future studies may be warranted to assess whether this strategy could be implemented in clinical practice. Our findings also suggest caution against clinical inertia in the care of diabetes.

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Contributors MT and KK designed the study. MT conducted the data analyses and wrote the first draft of the manuscript. MO and NI provided critical comments from the viewpoint of a diabetologist, and the draft was substantially revised in response to their comments. All authors read the final version of the submitted manuscript.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee (#R2927). We used anonymized data, which were exempted from informed consent of each participant according to Japanese law.This study was conducted under the approval of our institutional review board (R2927).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data sharing is not allowed by the data provider. For inquiries regarding our data set, please contact the Real World Data Co., Ltd. (Kyoto, Japan).

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Supplemental Files

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Supplemental Methods

We here discuss the rationale for the three assumptions—consistency, positivity and conditional exchange ability, which were collectively referred to as identifiability conditions.

Consistency

The consistency assumption holds when the target intervention is well-defined. Our motivated intervention was HbA_{1c}-guided therapy, so we assumed this strategy was well-defined as long as the patients received HbA_{1c} testing regularly.

Positivity

The positivity assumption means that there is a positive probability—not zero or one—at each follow-up month to be assigned to SGLT2-inhibitor treatment based on the past observed covariate history. Our study population included the prevalent users of antidiabetic drugs without advanced kidney disease (i.e., no contraindication). Thus, we assumed that it was implausible that a patient who would never use SGLT2 inhibitor(s) or a patient who would absolutely use the one(s) was not involved in our cohort.

In a post-hoc sensitivity analysis, the different inclusion criteria were applied for the potential concern for the (near-)violation of this assumption.

Conditional exchangeability

Conditional exchangeability means that no unmeasured confounding variable exists. The duration of diabetes for each patient and the preference for SGLT2 inhibitors may be unmeasured confounding variables not available in our data set. However, we hypothesized that the lack of such information could be mitigated by including age, baseline eGFR, the trajectory of HbA_{1c}, and treatment history with antidiabetic drugs as measured covariates.

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Supplemental Table 1: Renal risk in different treatment strategy (only persons with eGFR ≥45 mL/min/1.73 m^2)

Intervention	Crude risk (95% CI)	Risk difference (95% CI)	Risk ratio (95% CI)
Natural Course	15.4 (15.0 to 16.0)%	(Reference)	(Reference)
A_{1c}≥7.0%, within 3 mo	11.9 (9.7 to 14.6)%	-3.5 (- 5.5 to -0.89)%	0.77 (0.64 to 0.94)
A_{1c}≥7.0%, within 6 mo	12.4 (10.3 to 14.8)%	-3.1 (-4.9 to -0.68)%	0.80 (0.68 to 0.96)
A_{1c}≥7.0%, within 9 mo	12.8 (10.9 to 15.0)%	-2.7 (- 4.3 to -0.50)%	0.83 (0.72 to 0.97)
A_{1c}≥7.0%, within 12 mo	13.2 (11.4 to 15.2)%	-2.3 (-3.8 to -0.28)%	0.85 (0.75 to 0.98)
A_{1c}≥6.5%, within 3 mo	11.3 (8.8 to 14.3) %	-4.1 (- 6.4 to -1.1)%	0.73 (0.58 to 0.93)
A_{1c}≥6.5%, within 6 mo	11.8 (9.6 to 14.6)%	-3.6 (-5.8 to -0.90)%	0.77 (0.63 to 0.94)
A_{1c}≥6.5%, within 9 mo	12.3 (10.2 to 14.8)%	-3.2 (-5.0 to -0.67)%	0.80 (0.67 to 0.96)
A_{1c}≥6.5%, within 12 mo	12.7 (10.8 to 15.0)%	-2.7 (-4.4 to -0.45)%	0.82 (0.71 to 0.97)
A_{1c}≥7.5%, within 3 mo	12.7 (10.9 to 14.9)%	-2.7 (-4.4 to -0.60)%	0.82 (0.72 to 0.96)
A_{1c}≥7.5%, within 6 mo	13.1 (11.4 to 15.1)%	-2.4 (-3.8 to -0.41)%	0.85 (0.75 to 0.97)
A_{1c}≥7.5%, within 9 mo	13.4 (11.9 to 15.2)%	-2.0 (-3.3 to -0.25)%	0.87 (0.78 to 0.98)
A_{1c}≥7.5%, within 12 mo	13.7 (12.3 to 15.4)%	-1.7 (-2.9 to -0.10)%	0.89 (0.80 to 0.99)
Never Treated	15.5 (15.0 to 16.1)%	0.095 (-0.067 to 0.23)%	1.01 (1.00 to 1.02)

A 95% CI was calculated by bootstrapping, without p-value output. A 95% CI of a rate that does not cross 0 or a ratio that does not cross 1 was regarded as statistically significance.

eGFR: estimated glomerular filtration rate, A_{1c}: hemoglobin A_{1c}, CI: confidence interval

Supplemental Table 2: **Change in eGFR in different treatment strategy**

Intervention	Change in eGFR (95% CI)
Natural Course	(Reference: 62.0 mL/min/1.73 m^2)
A_{1c}≥7.0%, within 3 mo	1.38 (-0.05 to 3.11) mL/min/1.73 m^2
A_{1c}≥7.0%, within 6 mo	1.27 (-0.12 to 2.90) mL/min/1.73 m^2
A_{1c}≥7.0%, within 9 mo	1.16 (-0.18 to 2.68) mL/min/1.73 m^2
A_{1c}≥7.0%, within 12 mo	1.07 (-0.22 to 2.46) mL/min/1.73 m^2
A_{1c}≥6.5%, within 3 mo	1.60 (0.02 to 3.62) mL/min/1.73 m^2
A_{1c}≥6.5%, within 6 mo	1.49 (-0.02 to 3.34) mL/min/1.73 m^2
A_{1c}≥6.5%, within 9 mo	1.38 (-0.11 to 3.15) mL/min/1.73 m^2
A_{1c}≥6.5%, within 12 mo	1.27 (-0.15 to 2.92) mL/min/1.73 m^2
A_{1c}≥7.5%, within 3 mo	1.06 (-0.15 to 2.42) mL/min/1.73 m^2
A_{1c}≥7.5%, within 6 mo	0.97 (-0.21 to 2.22) mL/min/1.73 m^2
A_{1c}≥7.5%, within 9 mo	0.88 (-0.24 to 2.04) mL/min/1.73 m^2
A_{1c}≥7.5%, within 12 mo	0.80 (-0.31 to 1.91) mL/min/1.73 m^2
Never Treated	-0.05 (-0.20 to 0.09) mL/min/1.73 m^2

A 95% CI was calculated by bootstrapping, without p-value output. A 95% CI that does not cross 0 was regarded as statistically significance.

eGFR: estimated glomerular filtration rate, A_{1c}: hemoglobin A_{1c}, CI: confidence interval

Supplemental Table 3: **Renal risk in different treatment strategy for persons with eGFR ≥20 mL/min/1.73 m^2**

Intervention	Crude risk (95% CI)	Risk difference (95% CI)	Risk ratio (95% CI)
Natural Course	21.9 (21.3 to 22.6)%	(Reference)	(Reference)
A_{1c}≥7.0%, within 3 mo	18.6 (16.0 to 20.8)%	- 3.4 (- 5.9 to -1.1)%	0.84 (0.73 to 0.95)
A_{1c}≥7.0%, within 6 mo	19.0 (16.8 to 21.0)%	-2.9 (-5.1 to -0.91)%	0.87 (0.76 to 0.96)
A_{1c}≥7.0%, within 9 mo	19.5 (17.5 to 21.3)%	-2.4 (-4.3 to -0.65)%	0.89 (0.80 to 0.97)
A_{1c}≥7.0%, within 12 mo	19.9 (18.1 to 21.6)%	-2.0 (-3.7 to -0.49)%	0.91 (0.83 to 0.98)
A_{1c}≥6.5%, within 3 mo	17.8 (14.9 to 20.6)%	-4.1 (-7.1 to -1.4)%	0.81 (0.68 to 0.93)
A_{1c}≥6.5%, within 6 mo	18.4 (15.9 to 20.7)%	-3.5 (-6.1 to -1.2)%	0.84 (0.72 to 0.95)
A_{1c}≥6.5%, within 9 mo	19.0 (17.3 to 21.3)%	-3.0 (-5.3 to -0.89)%	0.87 (0.76 to 0.86)
A_{1c}≥6.5%, within 12 mo	19.4 (17.3 to 21.1)%	-2.5 (-4.5 to -0.66)%	0.89 (0.79 to 0.97)
A_{1c}≥7.5%, within 3 mo	19.4 (17.3 to 21.1)%	-2.5 (-4.5 to -0.81)%	0.88 (0.79 to 0.96)
A_{1c}≥7.5%, within 6 mo	19.8 (18.0 to 21.4)%	-2.1 (-3.8 to -0.57)%	0.90 (0.85 to 0.98)
A_{1c}≥7.5%, within 9 mo	20.1 (18.6 to 21.6)%	-1.8 (-3.2 to -0.45)%	0.92 (0.85 to 0.98)
A_{1c}≥7.5%, within 12 mo	20.5 (19.1 to 21.9)%	-1.5 (-2.8 to -0.23)%	0.93 (0.87 to 0.99)
Never Treated	22.0 (21.4 to 22.7)%	0.08 (-0.03 to 0.19)%	1.00 (1.00 to 1.01)

A 95% CI was calculated by bootstrapping, without p-value output. A 95% CI of a rate that does not cross 0 or a ratio that does not cross 1 was regarded as statistically significance.

eGFR: estimated glomerular filtration rate, A_{1c}: hemoglobin A_{1c}, CI: confidence interval

Supplemental Table 4: Results from model further adjusted by antihypertensive medication and ACEi/ARB use

Intervention	Crude risk (95% CI)	Risk difference (95% CI)	Risk ratio (95% CI)
Natural Course	19.2 (18.7 to 20.1) %	(Reference)	(Reference)
A_{1c}≥7.0%, within 3 mo	16.1 (14.5 to 18.5) %	-3.1 (- 5.1 to -0.99) %	0.84 (0.75 to 0.95)
A_{1c}≥7.0%, within 6 mo	16.6 (15.2 to 18.5) %	-2.7 (-4.4 to -0.84) %	0.86 (0.78 to 0.96)
A_{1c}≥7.0%, within 9 mo	16.9 (15.7 to 18.6) %	-2.3 (- 3.8 to -0.74) %	0.88 (0.81 to 0.96)
A_{1c}≥7.0%, within 12 mo	17.3 (16.2 to 18.9) %	-2.0 (-3.3 to 0.54) %	0.90 (0.84 to 0.97)
A_{1c}≥6.5%, within 3 mo	15.6 (13.6 to 18.2) %	-3.7 (- 6.0 to -1.2) %	0.81 (0.70 to 0.93)
A_{1c}≥6.5%, within 6 mo	16.0 (14.4 to 18.4) %	-3.2 (-5.2 to -1.1) %	0.83 (0.74 to 0.95)
A_{1c}≥6.5%, within 9 mo	16.5 (15.1 to 18.4) %	-2.8 (-4.5 to -0.88) %	0.86 (0.77 to 0.95)
A_{1c}≥6.5%, within 12 mo	16.8 (15.2 to 18.5) %	-2.4 (-3.9 to -0.76 %	0.88 (0.80 to 0.96)
A_{1c}≥7.5%, within 3 mo	16.9 (15.6 to 18.6) %	-2.3 (-3.9 to -0.75) %	0.88 (0.81 to 0.96)
A_{1c}≥7.5%, within 6 mo	17.2 (16.1 to 18.7) %	-2.0 (-3.4 to -0.65) %	0.89 (0.83 to 0.97)
A_{1c}≥7.5%, within 9 mo	17.5 (16.5 to 18.9) %	-1.7 (-2.9 to -0.49) %	0.91 (0.85 to 0.97)
A_{1c}≥7.5%, within 12 mo	17.8 (16.8 to 19.2) %	-1.5 (-2.5 to -0.30) %	0.92 (0.87 to 0.98)
Never Treated	19.3 (18.8 to 20.2) %	0.055 (-0.030 to 0.18) %	1.01 (1.00 to 1.01)

A 95% CI was calculated by bootstrapping, without p-value output. A 95% CI of a rate that does not cross 0 or a ratio that does not cross 1 was regarded as statistically significance.

ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blocker, eGFR: estimated glomerular filtration rate, A_{1c}: hemoglobin A_{1c}, CI: confidence interval

Supplemental Table 5: Dipeptidyl peptidase 4 inhibitor[1]

Intervention	Risk difference (95% confidence interval)
Natural Course	(Reference)
A_{1c}≥7.0%, within 3 mo	1.17 (-0.67 to 3.36)%
A_{1c}≥7.0%, within 6 mo	1.69 (0.14 to 3.53)%
A_{1c}≥7.0%, within 9 mo	2.12 (0.64 to 3.63)%
A_{1c}≥7.0%, within 12 mo	2.43 (1.06 to 3.87)%
A_{1c}≥6.5%, within 3 mo	0.84 (-1.53 to 3.52)%
A_{1c}≥6.5%, within 6 mo	1.50 (-0.41 to 3.75)%
A_{1c}≥6.5%, within 9 mo	2.04 (0.31 to 4.01)%
A_{1c}≥6.5%, within 12 mo	2.45 (0.78 to 4.11)%
A_{1c}≥7.5%, within 3 mo	1.29 (0.04 to 2.90)%
A_{1c}≥7.5%, within 6 mo	1.67 (0.47 to 2.90)%
A_{1c}≥7.5%, within 9 mo	1.95 (0.84 to 3.08)%
A_{1c}≥7.5%, within 12 mo	2.14 (1.11 to 3.17)%

1: Data from 24,245 persons were used for the computation.

Supplemental Table 6: Glucagon-like peptide-1[1]

Intervention	Risk difference (95% confidence interval)
Natural Course	(Reference)
A_{1c}≥7.0%, within 3 mo	-0.11 (-3.01 to 3.86) %
A_{1c}≥7.0%, within 6 mo	0.008 (-2.62 to 3.38) %
A_{1c}≥7.0%, within 9 mo	0.10 (-2.30 to 3.00)%
A_{1c}≥7.0%, within 12 mo	0.18 (-2.07 to 2.92) %
A_{1c}≥6.5%, within 3 mo	-0.23 (-3.63 to 4.57) %
A_{1c}≥6.5%, within 6 mo	-0.08 (-3.18 to 4.07) %
A_{1c}≥6.5%, within 9 mo	0.02 (-2.77 to 3.51) %
A_{1c}≥6.5%, within 12 mo	0.13 (-2.45 to 3.18)%
A_{1c}≥7.5%, within 3 mo	-0.007 (-2.25 to 2.95) %
A_{1c}≥7.5%, within 6 mo	0.84 (-1.98 to 2.56) %
A_{1c}≥7.5%, within 9 mo	0.15 (-1.78 to 2.42) %
A_{1c}≥7.5%, within 12 mo	0.21 (-1.60 to 2.19)%

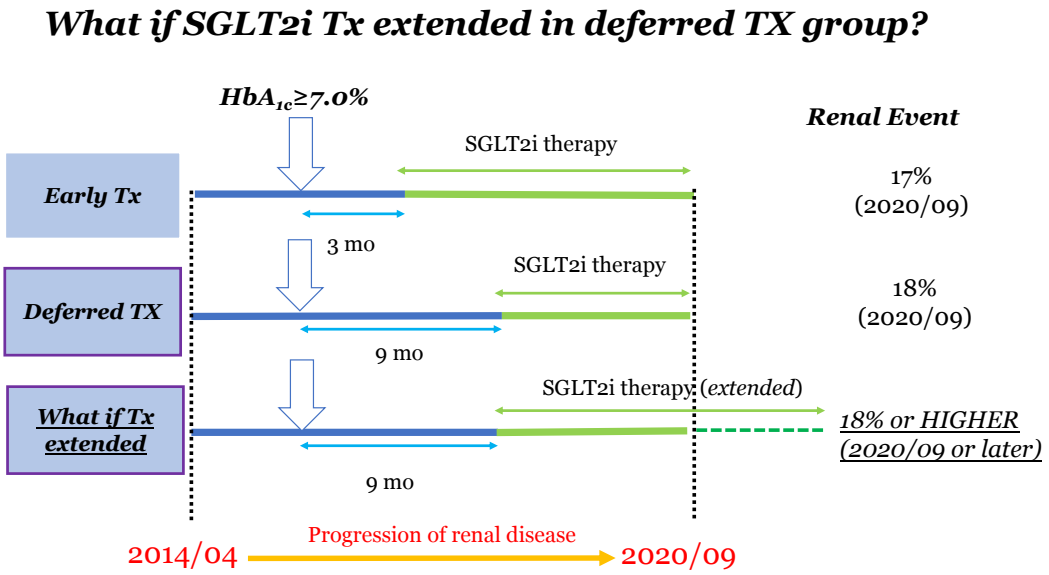
1: Data from 1261 persons were used for the computation.

Supplemental Discussion

Our study favored the early introduction of SGLT2 inhibitors. This result could be influenced the duration of exposure to SGLT2 inhibitors as the end of follow up was fixed in September, 2020 for all persons. In the illustrative example below, the early treatment population initiating SGLT2 inhibitors therapy had 6-month longer duration under drug exposure (the upper vs the middle). Thus, it naturally comes to the mind whether or not the lower incidence of the composite renal event in earlier initiation population was resulted from the different SGLT2 inhibitors exposure time.

To explain this influence, imagine the situation where had the duration of SGLT2 inhibitors be extended in deferred treatment population (the middle and the lower). In the lower hypothetical group, the renal event would have occurred in 18% (as identical to the middle) in September, 2020. Given the irreversible nature of eGFR trajectory (ie, declining over time), the incidence of the renal outcome in the lower group could have been expected as 18%—or even higher—even if the SGLT2 therapy extended.

That is, we assume that the renal benefit in earlier treatment was largely explained by the early introduction of SGLT2 inhibitors, rather than the longer duration of drug exposure within the fixed observation period.



SGLT2i: Sodium–glucose cotransporter 2 inhibitors, Tx: treatment/therapy

Sample programing code

```
library(gfoRmula) #version 0.3.2
library(parallel) #for speed up

##############################################################################################
A: time-varying treatment (eg, SGLT2 inhibitors use)
L1, L2: time-varying covariates (can be increased in number as needed). In this
example, L1 is continuous (eg, HbA1c) and L2 is binary.
L3: baseline covariate (can be increased in number as needed)
Y: binary outcome
t0: time index.
id: unique identifier for each individua
##############################################################################################

id <-'id'
time_points <- max(my_data$t0) + 1
time_name <-'t0'
covnames <- c('L1','L2','A')
outcome_name <-'Y'
outcome_type<- 'survival'
compevent_name <-'D'
covtypes <- c('normal', 'binary', 'binary')
histories <- c(lagged, lagavg)
histvars <- list(c('A','L1', 'L2'), c('A','L1', 'L2'))
covparams <- list(covmodels = c(L1 ~ lag1_A + lag_cumavg1_A + lag1_L1  +
                                  lag_cumavg1_L1 + lag1_L2  + lag_cumavg1_L2 + L3 + t0,
                            L2 ~ lag1_A + lag_cumavg1_A + lag1_L1 + lag_cumavg1_L1 +
                              lag1_L2 + lag_cumavg1_L2 + L3 + t0,
                            A ~ lag1_A + lag_cumavg1_A + lag1_L1 + lag_cumavg1_L1 +
                              lag1_L2 + lag_cumavg1_L2 + L3 + t0))


ymodel <- Y ~ A + L1 + L2 + lag1_A + lag_cumavg1_A + lag1_L1 + lag_cumavg1_L1 +
  lag1_L2 + lag_cumavg1_L2 + L3 + t0

dyn_int <- function(newdf, pool, intvar, intvals, time_name, t){
  threshold <- intvals[[1]]
  m <- intvals[[2]]
  if (t == 0){
    newdf[L1 >= threshold, `:=` (cond_met_ever = 1, cond_tracker = t)]
    newdf[L1 < threshold, cond_met_ever := 0]
  } else {
    newdf[cond_met_ever == 0 & L1 >= threshold, `:=`
         (cond_met_ever = 1, cond_tracker = t)]
  }

  if (t > 0){
    newdf[pool[get(time_name) == (t - 1), get(intvar) == 1], (intvar) := 1]
  }

  newdf[cond_met_ever == 0, (intvar) := 0]

  if (t >= m){ newdf[cond_tracker <= (t - m), (intvar) := 1]
  }
}

histories <- c(lagged, lagavg)
intvars<- list('A', 'A', 'A', 'A', 'A', 'A', 'A', 'A', 'A', 'A', 'A', 'A', 'A', 'A', 'A')
int_descript<- c('Thres_7.0_3', 'Thres_7.0_6', 'Thres_7.0_9', 'Thres_7.0_12',
                 'Thres_6.5_3', 'Thres_6.5_6', 'Thres_6.5_9', 'Thres_6.5_12',
                 'Thres_7.5_3', 'Thres_7.5_6', 'Thres_7.5_9', 'Thres_7.5_12',
                 'Never Treat')
interventions<- list(list(c(dyn_int, 7.0, 3)), list(c(dyn_int, 7.0, 6)),
list(c(dyn_int, 7.0, 9)), list(c(dyn_int, 7.0, 12)),
```

```
                    list(c(dyn_int, 6.5, 3)), list(c(dyn_int, 6.5, 6)), list(c(dyn_int,
6.5, 9)), list(c(dyn_int, 6.5, 12)),
                    list(c(dyn_int, 7.5, 3)), list(c(dyn_int, 7.5, 6)), list(c(dyn_int,
7.5, 9)), list(c(dyn_int, 7.5, 12)),
                    list(c(static, rep(0, time_points))))

nsimul <- 10000

gform<- gformula(obs_data = my_data, id = id,
                 time_points = time_points,
                 time_name = time_name, covnames = covnames,
                 outcome_name = outcome_name,
                 outcome_type = outcome_type,
                 compevent_name = compevent_name,
                 covtypes = covtypes,
                 covparams = covparams, ymodel = ymodel,
                 intvars = intvars,
                 interventions = interventions,
                 int_descript = int_descript,
                 histories = histories, histvars = histvars,
                 basecovs = c('age', 'sex', 'Grade'), nsimul = nsimul,
                 parallel = TRUE, ncores = parallel::detectCores()-1,
                 ref_int = 0,
                 nsamples = 200,
                 seed = 611)

print(gform)
```

Reference

1. McGrath S, Lin V, Zhang Z, Petito LC, Logan RW, Hernán MA, Young JG. gfoRmula: An R Package for Estimating the Effects of Sustained Treatment Strategies via the Parametric g-formula. *Patterns (N Y)*;1:100008.