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Yuchen Zhang Date

Estimating Optimal Inpatient Treatment for Type 2 Diabetes

By

Yuchen Zhang

Master of Science in Public Health

Biostatistics and Bioinformatics

Limin Peng, PhD

(Thesis Advisor)

Francisco J. Pasquel, MD, MPH

(Reader)

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Yuchen Zhang

B.S.

China Agricultural University

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Thesis Advisor: Limin Peng, PhD

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An abstract of
A thesis submitted to the Faculty of the
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Abstract

Estimating Optimal Inpatient Treatment for Type 2 Diabetes

By Yuchen Zhang

Background: Hyperglycemia contributes to a significant increase in morbidity, mortality, and healthcare costs in the hospital. The basal insulin regimen is recommended as the mainstay of diabetes therapy in the inpatient setting; however, it simultaneously amplifies the risk of hypoglycemia and other complications. While non-insulin agents could effectively improve glycemic control with a low risk of hypoglycemia, they may only fit for the patients diagnosed with mild and moderate hyperglycemia. It is not clear how determine the most appropriate treatment regime for Type 2 Diabetes patients with different characteristics to achieve optimal glycemic outcomes.

Methods: We explored the optimal treatment regime for targeted patients with Type 2 Diabetes by utilizing cutting-edge Dynamic Treatment Regime (DTR) methodology. We applied Q-Learning, inverse probability weighted estimator (IPWE), and augmented inverse probability weighted estimator (AIPWE), to determine the optimal treatment decision rules and estimate the expected outcomes. Model selection was conducted to decide the outcome regression models and propensity score models involved in these statistical procedures. The utility/value function for optimal treatment regime was defined either by the continuous outcome of mean blood glucose (BG) from day 2 to day 7 or the binary outcome of achieving BG target (i.e.,70-180 mg/dL) without hypoglycemia (<70 mg/dL).

Results: Using different DTR methods, we identified data driven treatment decision rules that utilized linear scores of admission BG and creatinine level to achieve optimal expected mean BG from day 2 to day 7, and treatment decision rules to achieve optimal chance of reaching BG target without hypoglycemia that utilized linear scores of admission BG and age. Based on the 10-fold cross-validation, the predicted mean BG by the optimal treatment regime derived from Q-learning, IPWE, and AIPWE are respectively 156.75 mg/dL, 155.79 mg/dL, and 161.63 mg/dL, which are all lower than the observed actual mean BG level, 163.1 mg/dL.

Conclusions: Our treatment rules suggest treating Type 2 diabetes patients who are older, with higher admission BG, or higher creatinine concentration with basal insulin over oral agents. Our results are consistent with current clinical practice but provide more specific data-driven guidance.

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1. Introduction

1.1 Type 2 diabetes (T2D)

Diabetes has affected more than 34 million people of all ages in the United States.[1] It is often accompanied by multiple complications, such as cardiovascular and cerebrovascular diseases, vision problems, kidney diseases, and limb amputations, etc. These complications will significantly increase the morbidity and mortality of patients with diabetes. Epidemiological studies conducted in the past four decades have shown that the prevalence of diabetes in the United States is significantly increasing, and many adults have undiagnosed diabetes, impaired fasting glucose, and impaired glucose tolerance.[2] We can prevent diabetes by changing patients' lifestyles, such as controlling diet, controlling weight, and avoiding obesity.[3] Although we have a new understanding of the pathophysiology of this disease with the development of medicine, and many new drugs are being developed, there is no cure for the disease. Therefore, for different patients with diabetes, the management methods should be tailored to improve type 2 patients with diabetes' blood sugar status to achieve a good treatment effect.

1.2 Therapy for Type 2 diabetes

Although diabetes can be prevented through diet control and lifestyle adjustments, for patients who already have diabetes, we need some appropriate treatments to manage diabetes. At present, the main diabetes management methods are basal insulin and non-insulin antidiabetic drugs. Basal insulin is often used for patients with more intensive conditions, while oral antidiabetic drugs are usually considered as more suitable for patients with mild to moderate disease.

1.2.1 Basal Insulin

Clinical guidelines recommend using insulin as the primary treatment for patients with diabetes in hospitals. Insulin treatment includes many formulations, such as intermediate-acting insulin, long-acting insulin, and ultra-long-acting insulin. Insulin treatment has many benefits: it lowers glucose levels quickly and has sound effects; it can also effectively prevent or delay complications. Human insulin formulations and analogs have limited side effects; however, excessive dosage can lead to hypoglycemia, and severe hypoglycemia may even be life-threatening. Besides, Van den Berghe et al. [4] illustrated that preventing even moderate hyperglycemia with insulin during intensive care could preserve the central and peripheral nervous systems, shorten the intensive care dependency, and possibly provide better long-term rehabilitation. With respect to the insulin management for patients with diabetes in the hospital, Pasquel et al. stated that for the patients with mild diabetes, it is recommended to use low-dose basal insulin or OAD; for the patients with moderate diabetes might be treated with basal insulin with or without correction; for the patients with severe hyperglycemia, basal-bolus regimen is recommended.[5]

1.2.2 Oral Antidiabetic Drugs (OADs)

In addition to insulin, oral antidiabetic drugs (OADs) are also a common diabetes treatment. OADs are often used in combination with insulin in the hospital. This treatment has many benefits: first, it can reduce the amount of insulin to varying degrees, and at the same time, it can avoid hyperinsulinemia caused by overuse of insulin therapy. Most importantly, combination therapy may significantly reduce the incidence of hypoglycemia. However, oral hypoglycemic drugs also have certain limitations. The use of these drugs during the patient's hospitalization may cause delays in efficacy and fail to achieve the expected

effectiveness, which does not guarantee the need for blood glucose control and dose adjustment for acutely ill patients. Hence, the American Diabetes Association (2004 and 2009) and the Endocrine Society's 2012 practice guidelines [6] for diabetes management recommended not to use oral hypoglycemic drugs and non-insulin injections during hospitalization, taking into account safety and effectiveness.

We will introduce several kinds of oral hypoglycemic drugs, most of which are widely used in modern diabetes management, and some of them are still in the research stage. All have sound effects on blood sugar control and reduce the incidence of hypoglycemia.

Metformin

Metformin is the primary treatment for type 2 diabetes in outpatients. Besides, metformin is the most commonly used oral drug among hospitalized patients in the United States and other countries.[7] The main site of action of metformin is the liver, which can reduce excessive sugar release in the liver of patients with type 2 diabetes. Metformin does not cause weight gain and is usually the first choice for the treatment of type 2 diabetes. But for patients with kidney or liver disease and heart failure, metformin cannot be used. Metformin is not recommended for patients at risk for lactic acidosis, such as those with anaerobic metabolism, impaired metformin clearance, or impaired lactic acid clearance.[8] In hospital, the patient's lactate concentration should be measured in time, if it increases significantly, the use of metformin should be discontinued.[9]

Sulfonylureas

Sulfonylureas have become one of the primary sources of non-insulin-dependent oral treatments. According to the data of inpatients from 659 emergency hospitals in the United

States, about one-fifth of patients received sulfonylurea treatment during the hospitalization period. In other countries and regions, the hospitalization use rate of sulfonylureas is higher.[10] Sulfonylureas mainly reduce blood glucose concentration by stimulating insulin secretion. There is little clinical evidence for the pancreatic effects of the drug. Therefore, the results of sulfonylurea drugs are limited to patients who retain β-cell function, and the best outcomes are only observed in the early stages of the disease. Treatment with sulfonylureas usually starts relatively late.

Thiazolidinediones

There is meager literature on the use of thiazolidinediones (TZDs) in hospitalized patients. It is estimated that 7-11% of patients treated with hypoglycemic drugs in hospitals will receive TZD treatment, and the drug is more commonly used in India.[11] TZD is the first drug to solve insulin resistance. Also, such drugs may be effective in treating non-diabetic insulin resistance patients. In recent years, domestic and foreign scholars' research on the anti-diabetic mechanism of TZDs has mainly focused on insulin sensitization and β-cell protection. The insulin-sensitizing effect of TZDs is related to increasing adiponectin and reducing adipocytes' volume. Studies have shown that pioglitazone has an insulin-sensitizing impact partly because it can inhibit cytokine signal transduction inhibitor-3. This effect is related to the phosphorylation of signal transducer and adiponectin's increased production.[12] The onset of action for TZDs is slow and thus they are not routinely used in the hospital.

GLP-1 Receptor Agonist

Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are two incretin hormones that influence nutrient absorption in the gastrointestinal tract.

Glucagon-like peptide 1 (GLP-1) is a kind of gut-derived incretin hormone that could stimulate insulin and inhibit glucagon secretion, lower appetite, food intake, and prohibit gastric emptying. In a recent study for non-ICU patients with type 2 diabetes, treatment with exenatide plus basal insulin caused a greater blood glucose level within the target range of 3.9-10.0 mmol/L compared with exenatide alone or basal-bolus insulin.[13] More research is needed with these drugs to determine whether they can control the blood glucose level efficiently without causing hypoglycemia in the hospital setting.

Dipeptidyl-Peptidase-4 Inhibitors

Several RCTs and observational studies have shown that DPP-4-I alone or in combination with basal insulin is secure and efficacious for treating type 2 diabetes. The first compound was launched in 2006 and now includes more than 11 different combinations.[14] Its efficacy is similar to SU, but it usually does not cause hypoglycemia or weight gain. Besides, it has more than no side effects and has not shown an increase in cardiovascular and cerebrovascular risk in a large number of clinical trials recently. A randomized controlled trial showed that the combination of DPP-4 inhibitor with basal insulin was as effective as basal bolus in hospitalized patients with diabetes [15] Treatment with basal insulin requires lowering the daily insulin dose and reducing the injection dose. This item is a safe, effective, and convenient alternative to the standard basal-bolus insulin treatment program, especially in hospitals and areas with insufficient staff and resources. The results obtained from Umpierrez et al. indicate that treatment with sitagliptin alone or basal insulin is secure and adequate for managing hyperglycemia in general medicine and surgery patients with Type 2 diabetes.[16] Vellanki et al. proved that for patients with T2D, daily linagliptin is a

safe and effective alternative to multi-dose insulin therapy, which results in similar glucose control with lower hypoglycemia.[17]

SGLT-2 Inhibitors

SGLT-2 inhibitors are a class of oral hypoglycemic agents that can block the cotransporter of SGLT-2 glucose collecting in the proximal renal tubules.[18] This can prevent the kidney from reabsorption of glucose, thereby lowering blood sugar levels. Recently, inhibitors of renal sodium-glucose cotransporters have been developed to reduce plasma glucose concentration. These oral hypoglycemic drugs can improve blood sugar control, avoid hypoglycemia, and promoting weight loss.

2. Background

Many clinical trials and observational studies on hospitalized patients have shown that hyperglycemia can bring various undesirable results, such as increased hospitalization time, other complications, and even death.[19] Hence, blood glucose control for hospitalized patients is critical, which can significantly shorten hospitalization length and reduce the occurrence of related complications, thereby bringing better treatment to patients. For patients with diabetes, the current leading treatment methods are insulin injection and oral hypoglycemic drugs. Recent practice guidelines recommend using basal-bolus insulin therapy because it has a better effect on blood sugar control. However, despite these recommendations, the patient's blood sugar control sometimes fails to achieve the desired results and even brings the risk of hypoglycemia. Severe hypoglycemia symptoms can cause shock and death. Thus, we also need to explore other treatment methods to achieve better treatment results. Oral hypoglycemic drugs are another newer type of treatment than insulin injections. By taking different kinds of oral hypoglycemic drugs, the blood sugar

level can be controlled to a certain extent. It can also effectively prevent the incidence of diabetes complications and reduce the possibility of hypoglycemia. The coordinated use of oral hypoglycemic drugs and insulin can improve blood sugar control to a certain extent and reduce the risk of complications and hypoglycemia at the same time.

Different diabetes treatment methods are suitable for patients with T2D. Insulin injection therapy is ideal for patients with severe diabetes. It can control blood glucose levels and maintain the patient's blood glucose levels in a relatively stable state, but insulin injections will risk hypoglycemia. Although insulin is sufficient, some studies have shown that the basal-bolus regimen amplifies hypoglycemia risk and may lead to overtreatment, particularly for those with mild to moderate hyperglycemia. Taking oral hypoglycemic drugs is another diabetes management approach in the hospital but less well studied. Many observational studies and clinical trials have shown that it can significantly reduce the risk of complications and hypoglycemia.[20,21] However, oral hypoglycemic drugs are only suitable for patients with mild or moderate diabetes because compared to insulin therapy, oral hypoglycemic drugs have a slower and milder effect. Insulin and oral hypoglycemic drugs can also be used in conjunction. When conducting the appropriate proportion of the different treatments, this treatment method can control blood sugar and reduce the risk of related complications and hypoglycemia. Umpierrez et al. recommend that glucose management protocols should avoid hypoglycemia in the hospital.[22]

For chronic diseases, we need a series of treatment decisions, and we need to make different decisions based on patients' characteristics at different time points. A dynamic treatment

regime consists of many continuous decision rules, each related to a critical decision point in the disease or disorder process. Each rule corresponds to the patient's characteristic information, including each individual's baseline and evolving characteristics. Hence, we can choose the most feasible treatment method according to the patient's characteristics at the time and before. Then, A dynamic treatment regime regulates how doctors choose treatment methods based on patient information. An optimal dynamic treatment regime can be specified when a specific treatment method is selected for the entire diseased population. It can lead to the optimal outcome on average, so this specific population's therapeutic effect can be optimal. We can further develop precision medicine through a dynamic treatment regime and provide more practical and quantitative theoretic support for researchers' treatment decisions. Laber et al. pointed out that dynamic treatment regime is of growing interest across the clinical sciences since these regimes provide a way to optimize and determine sequential personalized clinical decision making.[23] Chakraborty et al. suggested that the regimes are useful for managing chronic disorders. The Value of a DTR is the expected outcome when the DTR is used to commit treatments to a population of interest.[24] Murphy et al. indicated that a dynamic treatment regime is a list of decision rules for how the treatment level will be tailored through time to an individual's changing status.[25] Heckman et al. considered semiparametric identification structural dynamic discrete choice models and models for dynamic treatment effects.[26]

Hyperglycemia contributes to a significant increase in morbidity, mortality, and healthcare costs in the hospital. The basal insulin regimen is recommended as the mainstay of diabetes therapy in the inpatient setting; however, it simultaneously amplifies the risk of hypoglycemia and other complications. While the non-insulin agents could effectively

improve glycemic control with a low risk of hypoglycemia, they are only fit for the patients diagnosed with mild and moderate hyperglycemia. Thus, we need to determine the optimal treatment regime for patients with different characteristics to get a more efficient type 2 diabetes management method. This thesis project aimed to conduct different methods to assign treatment to patients with Type II Diabetes according to patient characteristics and clinical history. The methods include Q-Learning, inverse probability weighted estimator (IPWE), and augmented inverse probability weighted estimator (AIPWE). We conduct model selection to decide the outcome regression models and propensity score. Based on the selected models, we can determine the treatment decision rules to achieve the best expected cited outcomes. We perform cross-validation to assess the predictive performance of the optimal treatment decision rules derived from different methods.

3. Methods

Suppose we examine n subjects sampled from the target population, we only focus on two treatment options: control and experimental group, and let A, taking values 0 or 1, denote the received treatment. Let X be a vector of subject characteristics as the covariates, and let Y be the outcome of interest. Assume larger values of Y are better. Based on the assumption that the observed data (Y_i, A_i, X_i), $i = 1, \ldots, n$, are independent and identically distributed across i, we aimed to determine the optimal inpatient diabetes treatment regime based on these data.[27]

In this context, a treatment regime is a function f that maps values of X to {0,1}, so that a patient with covariate value $X = x$ would receive therapy 1 if $f(x) = 1$ and therapy 0 if $f(x) = 0$. To establish the optimal treatment regime, we define here potential outcomes $Y^*(0)$ and $Y^*(1)$, representing the outcomes that would receive. We assume that $Y = Y^*(1)A + Y^*$

(0) (1−A) so that the observed outcome is the potential outcome that would be seen under treatment received. We also assume *{Y* (0), Y * (1)}* independent of *A* conditional on *X*, which means there are no unmeasured confounders here. Thus, for *a = 0, 1*, *E {Y* (a)}* represents the overall population mean when all patients in the population to receive treatment *a*.[27]

3.1 Data Sources

We analyzed deidentified data from patients receiving diabetes therapy in the inpatient setting at Emory University affiliated hospitals. To determine the best treatment regimen in the hospital we focused on basal-bolus treatment and non-insulin drugs. We defined the basal-bolus treatment as receiving basal insulin and/or detemir/glargine insulin at least 1 day. We defined non-insulin treatment as receiving any medication (Metformin, Sulfonylurea, DPP4-inhibitor, TZD, GLP1-agonist, SGLT2) for at least 2 days. The demographic characteristics of the cohort are shown in the demographic table in the next section. When conducting descriptive statistics, Pearson's Chi-squared test and Kruskal-Wallis rank sum test were used to compare the demographic characteristics among different treatment groups, in corresponding with categorical variables and continuous variables.

3.2 Statistical Methods

3.2.1 Q – Learning

Q-Learning is an approach to estimate the optimal regime and expected value based on a posited regression model for $\mathrm{Q}_1(\mathrm{h}_1, \mathrm{a}_1) = \mathrm{E}(\mathrm{Y}|\mathrm{H}_1 = \mathrm{h}_1, \mathrm{A}_1 = \mathrm{a}_1)$ The assumption of this approach is that the outcome regression model is correctly specified.[27] The outcome

regression estimator of the optimal treatment regime, $\hat{d}_{Q,1}^{opt}(h_1)$, is characterized by the estimated rule

$$\hat{d}_{Q,1}^{opt}(h_1) = \text{argmax}_{a_1 \in A_1} Q_1(h_1, a_1; \widehat{\beta_1}),$$

where $Q_1(h_1, a_1; \beta_1)$ is a model for $Q_1(h_1, a_1) = E(Y|H_1 = h_1, A_1 = a_1)$ and $\widehat{\beta_1}$ is a suitably obtained estimator of β_1. The value $V(d^{opt})$ can be determined by the sample average

$$\widehat{V}_Q(d^{opt}) = n^{-1} \sum_{i=1}^{n} \max_{a_1 \in A_1} Q_1(H_{1i}, a_1; \widehat{\beta_1}).$$

3.2.2 Value Search Estimator Based on AIPWE

In general, with respect to a class of regimes D_η, with elements $d_\eta = \{d_1(h_1; \eta_1)\}$, we can estimate an optimal restricted regime d_η^{opt} in D_η, where d_η^{opt} is characterized by the rule

$$d_1(h_1; \eta_1^{opt}),\ \eta_1^{opt} = \text{argmax}_{\eta_1} V(d_\eta),$$

so that

$$d_\eta^{opt} = \{d_1(h_1; \eta_1^{opt})\}$$

That is an optimal restricted regime in D_η that achieved the maximum value among all regimes in D_η, which is attained when $\eta_1 = \eta_1^{opt}$. Thus, exploring an optimal regime in D_η is equivalent to estimating η_1^{opt} defined above.

Given an estimator for the value of a fixed regime d, $V(d)$, let's say, our goal is to estimate $V(d_\eta)$ by $\widehat{V}(d_\eta)$ for any fixed $\eta = \eta_1$, treat $\widehat{V}(d_\eta)$ as a function of η_1, and then maximize $\widehat{V}(d_\eta)$ in η_1; that is, estimate η_1^{opt} by

$$\widehat{\eta_1}^{opt} = \text{argmax}_{\eta_1} \widehat{V}(d_\eta).$$

The estimator for the rule $d_1(h_1; \eta_1^{opt})$ characterizing an optimal regime in D_η is then

$$d_1(h_1; \widehat{\eta_1}^{opt}),$$

and the estimator $\widehat{d_\eta^{opt}}$ for an optimal regime d_η^{opt} in D_η is

$$\widehat{d_\eta^{opt}} = \{d_1(h_1; \widehat{\eta_1}^{opt})\}.$$

We define $\widehat{d_\eta^{opt}}$ as a value search estimator, because this approach involves searching over the parameter space of $\eta = \eta_1$ for $\widehat{\eta_1}^{opt}$ maximizing an estimator of the value $\widehat{V}(d_\eta)$.

For binary treatment A_1 defined as $\{0, 1\}$, the augmented inverse probability weighted estimator for the value of regime $d_1(H_1; \eta_1)$ with fixed $\eta = \eta_1$ is

$$\widehat{V}_{AIPW}(d_\eta) = n^{-1} \sum_{i=1}^{n} \{ \frac{C_{d_\eta,i} Y_i}{\pi_{d_\eta,1}(H_{1i};\, \eta_1, \widehat{\gamma_1})} - \frac{C_{d_\eta,i} - \pi_{d_\eta,1}(H_{1i};\, \eta_1, \widehat{\gamma_1})}{\pi_{d_\eta,1}(H_{1i};\, \eta_1, \widehat{\gamma_1})} Q_{d_\eta,1}(H_{1i};\, \eta_1, \widehat{\beta_1}) \},$$

where $C_{d_\eta} = I\{A_1 = d_1(H_1; \eta_1)\}$, is the indicator of whether or not the treatment option actually received is in consistent with the option dictated by d. The propensity for receiving treatment consistent with regime d given an individual's history is $\pi_{d,1}(H_1) = P(C_d = 1|H_1)$.We can deduce that,

$$\pi_{d,1}(H_1) = \pi_1(H_1) I\{d_1(H_1) = 1\} + \{1 - \pi_1(H_1)\} I\{d_1(H_1) = 0\}.$$

which can be estimated by positing a model $\pi_1(H_1; \gamma_1)$ for $\pi_1(H_1) = P(A_1 = 1|H_1)$. Thus

$$\pi_{d,1}(H_1; \gamma_1) = \pi_1(H_1; \gamma_1) I\{d_1(H_1) = 1\} + \{1 - \pi_1(H_1; \gamma_1)\} I\{d_1(H_1) = 0\},$$

and $\widehat{\gamma_1}$ is a suitable estimator for γ_1.

Finally,

$$Q_{d_\eta,1}(H_1;\, \eta_1, \beta_1) = \sum_{a_1 \in A_1} Q_1(H_1,\, a_1; \beta_1) I\{d_1(H_1; \eta_1) = a_1\},$$

where $Q_1(H_1,\, a_1; \beta_1)$ is a model for $Q_1(h_1,\, a_1) = E(Y|H_1 = h_1,\, A_1 = a_1)$ and $\widehat{\beta_1}$ is a suitable estimator for β_1.

3.2.3 Value Search Estimator Based on IPWE

The simple inverse probability weighted estimator is the special case where $Q_{d_\eta,1}(h_1,\, a_1) \equiv 0$:

$$\widehat{V}_{IPW}(d_\eta) = n^{-1}\sum_{i=1}^{n} \frac{C_{d_\eta,i}Y_i}{\pi_{d_\eta,1}(H_{1i};\, \eta_1, \widehat{\gamma_1})},$$

and the optimal treatment regime is $\widehat{d_{\eta,IPW}^{opt}} = \{d_1(h_1;\, \widehat{\eta_{1,IPW}^{opt}})\}$ is defined in terms of $\widehat{\eta_{1,IPW}^{opt}}$

$$\widehat{\eta_{1,IPW}^{opt}} = \text{argmax}_{\eta_1} n^{-1}\sum_{i=1}^{n} \frac{C_{d_\eta,i}Y_i}{\pi_{d_\eta,1}(H_{1i};\, \eta_1, \widehat{\gamma_1})}$$

The optimal treatment regime, $\widehat{d_{\eta,AIPW}^{opt}} = \{d_1(h_1; \widehat{\eta_{1,AIPW}^{opt}})\}$, is that which maximizes the value, and thus

$$\widehat{\eta_{1,AIPW}^{opt}} = \text{argmax}_{\eta_1} n^{-1}\sum_{i=1}^{n} \{\frac{C_{d_\eta,i}Y_i}{\pi_{d_\eta,1}(H_{1i};\, \eta_1, \widehat{\gamma_1})}$$

$$- \frac{C_{d_\eta,i} - \pi_{d_\eta,1}(H_{1i};\, \eta_1, \widehat{\gamma_1})}{\pi_{d_\eta,1}(H_{1i};\, \eta_1, \widehat{\gamma_1})} Q_{d_\eta,1}(H_{1i};\, \eta_1, \widehat{\beta_1})\}.$$

We used the R package *DynTxRegime* to determine the optimal treatment decision rules and the expected values. This package includes the methods to estimate dynamic treatment regime through Q-Learning, Inverse Probability Weighted Estimators (IPWE), and Augmented Inverse Probability Weighted Estimators (AIPWE). To perform the Q-Learning method, we used the *qLearn* function. To perform the Inverse Probability Weighted Estimators (IPWE) method, we used the *optimalSeq* function; to perform the Augmented Inverse Probability Weighted Estimators (AIPWE) method, we used the *optimalSeq* function. Concerning the Q-Learning method, using *buildModelObj* function to construct the main effects and interaction term of the outcome regression model, the

parameter iteration is 0. For the Inverse Probability Weighted Estimators (IPWE) method, using *buildModelObj* function to construct the propensity score regression model, the value of domains is between -10 and 10, the starting values are zero, the iteration size is 1000. For the Augmented Inverse Probability Weighted Estimators (AIPWE) method, using *buildModelObj* function to construct the main effects and interaction term of the outcome regression model and the propensity score regression model, the value of domains is between -10 and 10, the starting values are zero, the iteration size is 1000. All methods mentioned above were implemented to the continuous outcome and binary outcome.

3.2.4 Methods for Model Selection

Best Subset Selection

Suppose we use a set of variables to predict the outcome of interest and hope to successfully select a subset of those variables that can accurately predict the outcome. Once we have determined the type of model, one method is to fit all possible combinations of variables and select the best variables based on some criteria, such as AIC, BIC, etc. This is called best subset selection. This method is computationally demanding. For p potential predictors, we need to fit a 2^p model. Besides, we can use cross-validation to evaluate its performance.

Forward Selection

In forward selection, the first variable that enters the constructed model is the variable that has the greatest correlation with the dependent variable. The variables selected to enter the model will be evaluated according to certain criteria. The most common is Mallows' Cp or Akaike's information criteria. If the previously selected variable meets the criteria, the

forward selection is continued. When there are no other variables that meet the input conditions, the process will terminate.

Backward Selection

Stepwise backward selection (or backward elimination) is a variable selection method that starts with a model that contains all variables to be considered and then deletes the least effective variables in sequence according to some criteria, such as AIC, BIC, etc. The process will terminate until a pre-specified stopping rule is reached or until there are no variables in the model.

We used the R package *glmulti* to determine the best fitted models. This package could conduct model selection automatically based on generalized linear models and related function. From a list of independent variables, it can select the best fitted model based on some specific criteria from all possible unique models including the explanatory variables and their pairwise interactions. Besides, we could apply marginality rule to our models so that when the interaction term in involved in the model, its corresponding main effects would also appear in the model. This option could help us build the models that fit for the dynamic treatment regime function. One advantage of this package is that it can explore the candidate set with a genetic algorithm (GA), through which can improve the speed a lot when looking for the best models.

Table 2. Dependent & Independent Variables for Model Selection

Variable	Measure	Notation
Dependent Variables		
MEAN_BG	Mean BG from Day 2 to Day 7	MBG
Target_BG_Average_nohypo	Mean hospital BG 70-180 mg/dL with no hypoglycemia (<70 mg/dL), excluding the day of admission	ACTAR
Independent Variables		
GENDER	Male or Female	GEND
SPECIAL_TYPE	Medical or surgical	TYPE
RACE	African American & Other / Caucasian	RACE
treat	1: Patients received non-insulin [a] but no basal [b]; 0: Patients received basal without receiving non-insulin and patients received both basal and	TRT
AGE_AT_ENCOUNTER[c1]	Age at encounter	AGE
BMI[c2]	BMI, kg/m^2	BMI
Admit_BG[c3]	BG at admission	ABG
CHARLSON_SCORE[c4]	Charlson score	CHS
CREAT_FIRST_VALUE[c5]	First creatinine value: mg/dL	CRL

a: Any patient who received any medication (metformin, sulfonylurea, DPP4-inhibitor, TZD, GLP1-agonist, SGLT2) at least 2 days

b: Any patient received basal insulin AND/OR detemir/glargine insulin at least 1 day

c: These continuous independent variables (c1-c5) are normalized when conduct model selection.

3.2.5 Methods for Cross-Validation Analysis

The cross-validation method could evaluate the performance of different methods. Usually, the cross-validation process randomly divides the data into a set of similarly sized data. Leave out one group and use the remaining (a -1) groups to estimate the interest parameters. Then, the estimated value is used to classify or predict the observations in the missing set. For example, ten-fold cross-validation (a = 10) randomly divides the data into ten similar

size parts. Use 9/10 of the data for ten times to estimate, and each time apply the estimated value to the omitted 1/10 of the data.

For comparison between methods, we calculate the value function based on the cross-validation analysis. We perform the analysis on 10-fold cross-validation. The procedure is as follows: 1. Shuffle the dataset randomly; 2, Split the dataset into 10 groups; 3. For each unique group, take the group as the test dataset, take the remaining groups as a training dataset, fit an optimal treatment regime based on the train dataset and apply it to the test dataset, calculate the expected value function; 4. Calculate the average of all the values (remove the outliers) and conduct comparison among three methods.

4. Results

4.1 Data Summary

Table 1. Demographic table

	Basal & Combination of Basal and non-insulin (N=3577)	Non-insulin (N=348)	Total (N=3925)	p value
Age	61.8 (14.9)	65.7 (12.5)	62.2 (14.7)	< 0.001
Gender (Male%)	1652 (46.2%)	166 (47.7%)	1818 (46.3%)	0.588
Medical or surgical, N (%)				< 0.001
Medical	3244 (90.7%)	296 (85.1%)	3540 (90.2%)	
Surgical	333 (9.3%)	52 (14.9%)	385 (9.8%)	
First creatinine level, mg/dL	2.0 (2.1)	1.3 (1.3)	1.9 (2.0)	< 0.001
Race, N (%)				0.311
White	980 (28.0%)	111 (32.4%)	1091 (28.4%)	
Black	2444 (69.7%)	224 (65.3%)	2668 (69.3%)	
Other	81 (2.3%)	8 (2.3%)	89 (2.3%)	
LOS	5.5 (4.8)	5.8 (4.6)	5.5 (4.8)	0.010
BMI	33.1 (9.6)	31.9 (8.1)	33.0 (9.5)	0.051
Charlson Score	4.5 (2.5)	3.9 (2.4)	4.5 (2.5)	< 0.001
Achieving BG target without hypoglycemia, N (%)	965 (27.0%)	182 (52.3%)	1147 (29.2%)	< 0.001
Mean of BG (Day2-7)	164.7 (51.4)	146.7 (44.5)	163.1 (51.1)	< 0.001

In our study, 3925 patients diagnosed with diabetes in Emory University Hospital were included. We categorized all treatments into two groups, one is basal and the combination of basal and non-insulin treatment, the other is only non-insulin treatment. The non-insulin treatment group patients made up 8.9% (348) of all patients. The mean age of patients included in the study was 62.2 years (SD = 14.7) with 46.3% male (1818). Of the entire study population, 3540 (90.2%) patients underwent medical supplies and 385 (9.8%)

underwent surgical supplies. The first creatinine level for patients who underwent the basal treatment and the combination of basal and non-insulin treatment was 2.0 mg/dL (SD = 2.1) greater than those of non-insulin treatment was 1.3 mg/dL (SD = 1.3, $p < 0.01$). The BMI for patients who underwent the basal treatment and the combination of basal and non-insulin treatment was 33.1 (SD = 9.6) greater than those of non-insulin treatment was 31.9 (SD = 8.1, $p < 0.01$). The Charlson score for patients who underwent the basal treatment and the combination of basal and non-insulin treatment was 4.5 (SD = 2.5) greater than those of non-insulin treatment was 3.9 (SD = 2.4, $p < 0.01$). The mean of BG for the total cohort is 163.1 mg/dL (SD = 51.1), the BG for patients who underwent the basal treatment and the combination of basal and non-insulin treatment is greater than that for those of non-insulin treatment ($p < 0.01$). The proportion for patients who Achieving BG target without hypoglycemia was 27.0% less than those of non-insulin treatment was 52.3% ($p < 0.01$).

4.2 Model selection

4.2.1. Continuous Outcome Regression Model

Through the R package *glmulti*, the best-fitted model and parameter estimates are shown below. The interaction term with treatment involving creatinine level and admission BG could be used to build the decision rules when the outcome is the continuous variable mean of BG.

Outcome Regression Model:

$$\begin{aligned} MBG = {} & \beta_0 + \beta_1 \cdot GEND + \beta_2 \cdot TYPE + \beta_3 \cdot RACE + \beta_4 \cdot TRT + \beta_5 \cdot AGE + \beta_6 \cdot CRL + \beta_7 \\ & \cdot BMI + \beta_8 \cdot ABG + \beta_9 \cdot CHS + \beta_{10} \cdot (TRT \cdot GEND) + \beta_{11} \cdot (BMI \cdot AGE) \\ & + \beta_{12} \cdot (ABG \cdot CRL) + \beta_{13} \cdot (ABG \cdot BMI) + \beta_{14} \cdot (CHS \cdot CRL) + \beta_{15} \cdot (GEND \\ & \cdot CRL) + \beta_{16} \cdot (GEND \cdot ABG) + \beta_{17} \cdot (TYPE \cdot CHS) + \beta_{18} \cdot (RACE \cdot CRL) \\ & + \beta_{19} \cdot (RACE \cdot CHS) + \beta_{20} \cdot (TRT \cdot CRL) + \beta_{21} \cdot (TRT \cdot ABG) \end{aligned}$$

Table 3. Coefficients of the continuous outcome regression model

	Estimate	Std. Error	t value	Pr (>| t |)
(Intercept)	162.04	1.17	138.90	<0.001
GEND	2.26	1.59	1.42	0.16
TYPE	0.91	2.53	0.36	0.72
EACE	1.12	1.69	0.67	0.51
TRT	-8.13	4.08	-1.99	0.05
AGE	-4.56	0.80	-5.71	<0.001
CRL	-6.57	1.24	-5.30	<0.001
BMI	4.33	0.78	5.59	<0.001
ABG	15.86	1.03	15.40	<0.001
CHS	-1.74	0.97	-1.79	0.07
GEND x TRT	9.12	5.35	1.71	0.09
BMI x AGE	2.11	0.80	2.65	0.008
ABG x CRL	-1.51	0.83	-1.81	0.07
ABG x BMI	4.01	0.74	5.41	<0.001
CRL x CHS	1.60	0.81	1.97	0.049
GEND x CRL	2.61	1.53	1.71	0.09
GEND x ABG	4.18	1.53	2.74	0.006
TYPE x CHS	-3.69	2.56	-1.44	0.149
RACE x CRL	-5.95	2.33	-2.55	0.01
RACE x CHS	5.07	1.66	3.06	0.002
TRT x CRL	6.59	4.11	1.60	0.11
TRT x ABG	10.19	3.37	3.02	0.003

* Multiple R-squared 0.19, Adjusted R-squared 0.19.

4.2.2 Binary Outcome Regression Model

Through the R package *glmulti*, the best-fitted model and parameter estimates are shown below. The interaction term with treatment involving age and admission BG could be used to build the decision rules when the outcome is the binary variable.

Binary Outcome Regression Model

$$logit(ACTAR) = \beta_0 + \beta_1 \cdot TYPE + \beta_2 \cdot TRT + \beta_3 \cdot AGE + \beta_4 \cdot CRL + \beta_5 \cdot BMI + \beta_6 \cdot ABG + \beta_7 \cdot CHS + \beta_8 \cdot (CRL \cdot AGE) + \beta_9 \cdot (BMI \cdot AGE) + \beta_{10} \cdot (ABG \cdot BMI) + \beta_{11} \cdot (TYPE \cdot ABG) + \beta_{12} \cdot (TRT \cdot AGE) + \beta_{13} \cdot (TRT \cdot ABG)$$

Table 4. Coefficients of the binary outcome regression model

	Estimate	Std. Error	z value	Pr (>| z |)
(Intercept)	-1.23	0.05	-24.57	<0.001
TYPE	-0.67	0.20	-3.31	<0.001
TRT	0.49	0.19	2.57	0.01
AGE	0.05	0.05	1.15	0.25
CRL	-0.02	0.04	-0.49	0.62
BMI	-0.12	0.05	-2.34	0.02
ABG	-1.16	0.06	-19.24	<0.001
CHS	-0.09	0.04	-2.09	0.04
AGE x CRL	-0.08	0.04	-1.90	0.06
AGE x BMI	-0.09	0.05	-1.99	0.05
BMI x ABG	-0.21	0.06	-3.41	<0.001
TYPE x ABG	-0.71	0.26	-2.71	<0.001
TRT x AGE	-0.24	0.16	-1.47	0.14
TRT x ABG	-0.67	0.25	-2.65	<0.001

4.2.3 Propensity Score Regression Model

Through the R package *glmulti*, set BIC as the selection criteria, and applied the marginality rule. The best-fitted model and parameter estimates are shown below.

Propensity Score Regression Model

$$logit(TRT) = \beta_0 + \beta_1 \cdot GEND + \beta_2 \cdot TYPE + \beta_3 \cdot AGE + \beta_4 \cdot CRL + \beta_5 \cdot BMI + \beta_6 \cdot ABG + \beta_7 \cdot CHS + \beta_8 \cdot (BMI \cdot AGE) + \beta_9 \cdot (BMI \cdot CRL) + \beta_{10} \cdot (ABG \cdot CRL) + \beta_{11} \cdot (CHS \cdot CRL) + \beta_{12} \cdot (GEND \cdot CRL) + \beta_{13} \cdot (GEND \cdot ABG) + \beta_{14} \cdot (TYPE \cdot CHS)$$

Table 5. Coefficients of the propensity score regression model

	Estimate	Std. Error	z value	Pr (>| z |)
(Intercept)	-2.85	0.13	-22.32	<0.001
GEND	0.16	0.16	1.02	0.31
TYPE	0.12	0.25	0.48	0.63
AGE	0.21	0.07	3.11	0.002
CRL	-1.01	0.24	-4.18	<0.001
BMI	-0.32	0.09	-3.61	<0.001
ABG	-0.45	0.10	-4.32	<0.001
CHS	-0.24	0.08	-2.93	0.003
AGE x BMI	-0.17	0.07	-2.66	0.008
CRL x BMI	-0.49	0.17	-2.91	0.004
CRL x ABG	0.24	0.13	1.87	0.06
CRL x CHS	-0.26	0.16	-1.62	0.11
GEND x CRL	0.55	0.26	2.09	0.04
GEND x ABG	-0.28	0.15	-1.89	0.06
TYPE x CHS	-0.97	0.26	-3.75	<0.001

4.3. Optimal Treatment Decision Rules

4.3.1. Continuous Outcome

As the dynamic treatment regime method's framework is defined, the intersection part from treatment and other covariates in the outcome regression model would produce the basic construction of the decision rules. Combined with the outcome regression models we got from the previous section, we can find out the form of a decision rule for the continuous outcome (MBG) is $\beta_0 + \beta_1 \cdot \text{ABG} + \beta_2 \cdot \text{CRL} > 0$ and that for the binary outcome (ACTAR) is $\beta_0 + \beta_1 \cdot \text{ABG} + \beta_2 \cdot \text{AGE} > 0$, which means we could determine the optimal treatment regimen for patients based on their admission BG and creatinine level when the outcome of interest is mean of BG from day 2 to day 7. Also, we could determine the optimal

treatment regimen for patients based on their admission BG and age when the outcome of interest is whether or not achieving the target BG (70-180 mg/dL) with no hypoglycemia (<70 mg/dL).

Table 6. Decision rules and expected values for different methods for continuous outcome. The decision rules take the form that when $\beta_0 + \beta_1 \cdot \text{ABG} + \beta_2 \cdot \text{CRL} > 0$ we choose non-insulin treatment as the optimal treatment.

	β_0	β_1	β_2	$E\{Y^*(g_\eta^{opt})\}$
Q-Learning	8.08	-10.11	-6.33	156.79
IPWE	6.24	-5.62	-1.91	143.83
AIPWE	3.25	-7.64	-2.63	156.60

The specific decision rules determined by Q-Learning, IPWE, and AIPWE for the continuous variable outcome are shown in Table 6. From the tables, we also could gain the average expected mean of BG from day 2 to day 7 ($E\{Y^*(g_\eta^{opt})\}$) for the total cohort when all of the them received the optimal treatment regime. By the Q-Learning methodology, the decision rule is $8.08 - 10.11 \times \text{ABG} - 6.33 \times \text{CRL} > 0$, which means we can determine the treatment regime for patients with different admission BG and creatinine level, the average expected mean of BG from day 2 to day 7 that all of the cohort could achieve is 156.79mg/dL. By the IPWE methodology, the decision rule is $6.24 - 5.62 \times \text{ABG} - 1.91 \times \text{CRL} > 0$, the average expected mean of BG from day 2 to day 7 that all of the cohort could achieve is 143.83 mg/dL. By the AIPWE methodology, the decision rule is $3.25 - 7.64 \times \text{ABG} - 2.63 \times \text{CRL} > 0$, the average expected mean of BG from day 2 to day 7 that all of the cohort could achieve is 156.60mg/dL. From the results, IPWE performs the best among the three methods since the smaller the mean of BG, the better results we get.

4.3.2 Binary Outcome

Table 7. Decision rules and expected values for different methods for binary outcome. The decision rules take the form that when $\beta_0 + \beta_1 \cdot \text{ABG} + \beta_2 \cdot \text{AGE} > 0$ we choose non-insulin treatment as the optimal treatment.

	β_0	β_1	β_2	$E\{Y^*(g_\eta^{opt})\}$
Q-Learning	0.49	-0.67	-0.24	0.41
IPWE	-0.02	-0.46	-0.01	0.39
AIPWE	-0.30	-0.50	-0.90	0.36

The specific decision rules determined by Q-Learning, IPWE, and AIPWE for the binary variable outcome are shown in Table 7. From the tables, we also could gain the average expected proportion ($E\{Y^*(g_\eta^{opt})\}$) of the total cohort who achieved the target BG (70-180 mg/dL) with no hypoglycemia (<70 mg/dL), when all of the cohort received the optimal treatment regime. By the Q-Learning methodology, the decision rule is $0.49 - 0.67 \times \text{ABG} - 0.24 \times \text{AGE} > 0$, which means we can determine the treatment regime for patients with different admission BG and age, the average expected proportion who achieved the target BG with no hypoglycemia that the cohort could achieve is 41%, when all of the cohort received the optimal treatment regime. By the IPWE methodology, the decision rule is $-0.02 - 0.46 \times \text{ABG} - 0.01 \times \text{AGE} > 0$, the average expected proportion who achieved the target BG with no hypoglycemia that the cohort could achieve is 39%, when all of the cohort received the optimal treatment regime. By the AIPWE methodology, the decision rule is $-0.30 - 0.50 \times \text{ABG} - 0.90\text{AGE} > 0$, the average expected proportion who achieved the target BG with no hypoglycemia that the cohort could achieve is 36%, when all of the cohort received the optimal treatment regime. From the results, Q-Learning

performs the best among the three methods since the greater the proportion of patients who achieved the target BG (70-180 mg/dL) with no hypoglycemia, the better results we get.

4.4. Cross-Validation Analysis Results

4.4.1. Continuous Outcome

The results are shown below as in Table 8. Based on the 10-fold cross-validation, the expected values for mean of BG are 156.75 mg/dL for Q-learning, 155.79 mg/dL for IPWE and 161.63 mg/dL for AIPWE. Compared with the actual mean BG level for the cohort 163.1 mg/dL, all the three methods would have improved the outcome, and Q-Learning and IPWE performs better than AIPWE.

Table 8. Cross-Validation analysis for the outcome as mean of BG. The analysis is based on10-fold cross-validation, using the specific group in the table as the test dataset, and the remaining groups as the training dataset.

Group No.	Q-Learning	IPWE	AIPWE
1	154.03	115.58	164.34
2	153.82	140.76	158.94[2]
3	159.00	135.97	155.40
4	157.50	141.71	156.80
5	156.03	142.71	165.04
6	157.66	134.96	152.49
7	157.69	174.88	165.97
8	156.70	152.38	154.57
9	156.13	129.86[1]	183.33
10	157.68	289.10	158.38
Average	156.75	155.79	161.63

1. 1 outlier was removed for the IPWE method based on group 9 as the test data.

2. 1 outlier was removed for the AIPWE method based on group 2 as the test data.

4.4.2 Binary Outcome

We also conduct the cross-validation analysis as the outcome of interest is whether or not achieving target BG without hypoglycemia. The results are shown in Table 9. Based on the 10-fold cross-validation, the expected values for the proportion of patients who achieved target BG without hypoglycemia are 40.6% for Q-learning, 41.5% for IPWE and 34.1% for AIPWE. Compared with the actual proportion of patients who achieved target BG without hypoglycemia for the cohort 29.2%, all the three methods have improved the outcome, and Q-Learning and IPWE performs better than AIPWE.

Table 9. Cross-Validation analysis for the outcome as whether or not achieved target BG without hypoglycemia. The value function is for the proportion of individuals who achieved target BG without hypoglycemia. The analysis is based on10-fold cross-validation, using the specific group in the table as the test dataset, and the remaining groups as the training dataset.

	Q-Learning	IPWE	AIPWE
1	0.404	0.430	0.397
2	0.412	0.714	0.313
3	0.399	0.754	0.346
4	0.426	0.561	0.305
5	0.404	0.367	0.385
6	0.405	0.259	0.336[1]
7	0.416	0.228	0.345
8	0.414	0.322	0.290
9	0.400	0.182	0.345
10	0.380	0.332	0.353
Average	0.406	0.415	0.341

1. 1 outlier was removed for the AIPWE method based on group 6 as the test data.

4.5. Comparison on Optimal Treatment and Actual Treatment

4.5.1. Continuous Outcome

In this section, we compared the optimal treatment regime gained from Q-Learning, IPWE and AIPWE, with the actual treatments that the patients received in their diabetes management. As the outcome is mean BG, the results for the three methods are shown in Table 10. Based on Q-Learning, for the patients who received insulin treatment, 36.26% of them can adopt insulin as the optimal treatment, and 63.74% should adopt non-insulin as the optimal treatment; for the patients who received non-insulin treatment, 12.93% of them can adopt insulin as the optimal treatment, and 87.07% should adopt non-insulin as the optimal treatment. Based on IPWE, for the patients who received insulin treatment, 16.77% of them can adopt insulin as the optimal treatment, and 83.23% should adopt non-insulin as the optimal treatment; for the patients who received non-insulin treatment, 6.32% of them can adopt insulin as the optimal treatment, and 93.68% should adopt non-insulin as the optimal treatment. Based on AIPWE, for the patients who received insulin treatment, 48.59% of them can adopt insulin as the optimal treatment, and 51.41% should adopt non-insulin as the optimal treatment; for the patients who received non-insulin treatment, 21.55% of them can adopt insulin as the optimal treatment, and 78.45% should adopt non-insulin as the optimal treatment. The main discrepancy between the actual treatment and the data-driven optimal treatment decision is that many patients who received insulin treatment should have received non-insulin according to the optimal treatment regime identified by the applied DTR methods.

Table 10. Comparison on Optimal Treatment and Actual Treatment as the Outcome is Mean BG from day 2 to day 7.

Method				Optimal Treatment		Total
				Insulin	Non-Insulin	
Q-Learning	Actual Treatment	Insulin	Count	1297	2280	3577
			%	36.26%	63.74%	100%
		Non-Insulin	Count	45	303	348
			%	12.93%	87.07%	100%
	Total		Count	1342	2583	3925
			%	34.19%	65.81%	100%
IPWE	Actual Treatment	Insulin	Count	600	2977	3577
			%	16.77%	83.23%	100%
		Non-Insulin	Count	22	326	348
			%	6.32%	93.68%	100%
	Total		Count	622	3303	3925
			%	15.85%	84.15%	100%
AIPWE	Actual Treatment	Insulin	Count	1738	1839	3577
			%	48.59%	51.41%	100%
		Non-Insulin	Count	75	273	348
			%	21.55%	78.45%	100%
	Total		Count	1813	2112	3925
			%	46.19%	53.81%	100%

4.5.2 Binary Outcome

As the outcome is whether or not achieving target BG without hypoglycemia, the results for the three methods are shown in Table 11. Based on Q-Learning, for the patients who received insulin treatment, 23.90% of them can adopt insulin as the optimal treatment, and 76.10% should adopt non-insulin as the optimal treatment; for the patients who received non-insulin treatment, 10.06% of them can adopt insulin as the optimal treatment, and 89.94% should adopt non-insulin as the optimal treatment. Based on IPWE, for the patients who received insulin treatment, 60.11% of them can adopt insulin as the optimal treatment, and 39.89% should adopt non-insulin as the optimal treatment; for the patients who received non-insulin treatment, 43.10% of them can adopt insulin as the optimal treatment,

and 56.90% should adopt non-insulin as the optimal treatment. Based on AIPWE, for the patients who received insulin treatment, 61.59% of them can adopt insulin as the optimal treatment, and 38.41% should adopt non-insulin as the optimal treatment; for the patients who received non-insulin treatment, 65.23% of them can adopt insulin as the optimal treatment, and 34.77% should adopt non-insulin as the optimal treatment. Similarly, to the findings based on the mean BG outcome, the data drive optimal treatment rule suggests a large proportion of patients who actually received insulin treatment should be treated with non-insulin treatment.

Table 11. Comparison on Optimal Treatment and Actual Treatment as Whether or Not Achieving Target BG without Hypoglycemia.

Method				Optimal Treatment		Total
				Insulin	Non-Insulin	
Q-Learning	Actual Treatment	Insulin	Count	855	2722	3577
			%	23.90%	76.10%	100%
		Non-Insulin	Count	35	313	348
			%	10.06%	89.94%	100%
	Total		Count	890	3035	3925
			%	22.68%	77.32%	100%
IPWE	Actual Treatment	Insulin	Count	2150	1427	3577
			%	60.11%	39.89%	100%
		Non-Insulin	Count	150	198	348
			%	43.10%	56.90%	100%
	Total		Count	2300	1625	3925
			%	58.60%	41.40%	100%
AIPWE	Actual Treatment	Insulin	Count	2203	1374	3577
			%	61.59%	38.41%	100%
		Non-Insulin	Count	227	121	348
			%	65.23%	34.77%	100%
	Total		Count	2430	1495	3925
			%	61.91%	38.09%	100%

5. Discussion

Hyperglycemia contributes to a significant increase in morbidity, mortality, and healthcare costs in the hospital. The basal insulin regimen is recommended as the mainstay of diabetes therapy in the inpatient setting; however, it simultaneously amplifies the risk of hypoglycemia and other complications. While the non-insulin agents could be effective in improving glycemic control with low risk of hypoglycemia, they are only fit for the patients diagnosed with mild and moderate hyperglycemia. Thus, it is important for us to determine the optimal treatment regime for patients with different characteristics to get a more efficient way of Type 2 Diabetes management.

The thesis project aimed at conducting different methods to help determine which treatment is optimal to the patients with Type 2 Diabetes. The methods including Q-Learning, inverse probability weighted estimator (IPWE) and augmented inverse probability weighted estimator (AIPWE). The best regression models and propensity score models can be posited by model selection approaches. The intersection part of the outcome regression models could produce the forms of decision rules. Combined with the outcome regression models we got from the previous section, we can find out the form of a decision rule for the continuous outcome that mean of BG from day 2 to day 7 is $\beta_0 + \beta_1 \cdot \text{ABG} + \beta_2 \cdot \text{CRL} > 0$ and that for the binary outcome that whether or not achieving the target BG (70-180 mg/dL) with no hypoglycemia (<70 mg/dL) is $\beta_0 + \beta_1 \cdot \text{ABG} + \beta_2 \cdot \text{AGE} > 0$, which means we could determine the optimal treatment regimen for patients based on their admission BG and creatinine level when the outcome of interest is mean of BG from day 2 to day 7. Also, we could determine the optimal treatment regimen

for patients based on their admission BG and age when the outcome of interest is whether or not achieving the target BG (70-180 mg/dL) with no hypoglycemia (<70 mg/dL). The parameters for the covariates in the decision rules are negative in three methods. This means, for patients with higher admission BG and higher creatinine level, the preferred treatment (in terms of achieving lower mean BG) is more likely to be insulin treatment. When the treatment goal is to achieve target BG without hypoglycemia, age and admission BG may be the key factors to decide between insulin vs non-insulin treatment. In this case, insulin treatment may be preferred for older patients with higher admission BG. These decision rules are reasonable because if the patients have more severe diabetes, their blood glucose levels are higher when they enter the hospital, so it is more suitable for intensive treatment such as basal insulin, as only non-insulin treatment may not be enough to control their BG level. Saydah et.al states that as age increasing, the prevalence of diabetes increased from the youngest group to the oldest group.[28] From the decision rules, the parameter for creatinine level is negative, which means as creatinine increasing, patients need to choose insulin treatment as preference. We still need more research on the related associations between creatinine level and type 2 diabetes.

Based on the 10-fold cross-validation, the expected values for mean of BG are 156.75 mg/dL for Q-learning, 155.79 mg/dL for IPWE and 161.63 mg/dL for AIPWE. Compared with the actual mean of BG level for the cohort 163.1 mg/dL, all the three methods have improved the outcome, and Q-Learning and IPWE performs better than AIPWE. Based on the 10-fold cross-validation, the expected values for the proportion of patients who achieved target BG without hypoglycemia are 40.6% for Q-learning, 41.5% for IPWE and 34.1% for AIPWE. Compared with the actual proportion of patients who achieved target

BG without hypoglycemia for the cohort 29.2%, all the three methods have improved the outcome, and Q-Learning and IPWE performs better than AIPWE. In order to figure out the conditions that patients received the related treatments, we compared the optimal treatment regime gained from Q-Learning, IPWE and AIPWE, with the actual treatments that the patients received in their diabetes management. As the outcome is mean of BG, a large proportion of patients who received insulin treatment actually should receive non-insulin treatment as the optimal treatment regime among three methods. As the outcome is the binary outcome, a large proportion of patients who received insulin treatment actually should receive non-insulin treatment as the optimal treatment regime in Q-Learning method.

The study has potential limitations. Firstly, the mean age of our total cohort is 62.2. Thus, our results mainly focus on older adults; we need to implement our methods to more general population later. Secondly, we use the mean of BG from day 2 to day 7 as our continuous outcome. However, many aspects of this outcome can be affected, and some confounding explanatory variables may exist. Thus, we need to explore more related covariables in our future work. Our study explored two treatments: basal and the combination of basal and non-insulin, and only non-insulin treatment; in future investigations, it might be possible to examine multiple treatments and improve the methods we implemented.

In this paper, we successfully posited an outcome regression model and treatment propensity score model. Using the R package *DynTxRegime*, we built treatment decision

rules for diabetes patients, which may help achieve the most desirable outcome: lower mean of BG and higher proportion of patients that achieving target BG without hypoglycemia. Based on the decision rules, we can determine optimal treatment regimens (involving basal insulin and/or non-insulin drugs) for each individual based on their age, serum creatinine level, and blood glucose concentration. We believe this may help improve diabetes management for many patients with diabetes in the future.

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