A MATHEMATICAL MODELING APPROACH FOR OPTIMAL TIMING OF INSULIN INITIATION IN TYPE 2 DIABETIC PATIENTS

(TİP 2 DİYABETLİ HASTALARIN INSÜLİNE BAŞLAMASININ OPTİMAL ZAMANI İÇİN MATEMATİKSEL BİR MODELLEME YAKLAŞIMI)

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The aim of this thesis is to optimize the current treatment process, including the initiation of insulin therapy which is a controversial issue for patients with type 2 diabetes who should manage each stage of the disease well.

Thanks to the topic of my study, I understood how optimization techniques should be implemented in a real-life problem and how these methods can be effective in health care environment.

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TABLE OF CONTENTS

LIST OF SYMBOLS

AADE	**:** American Association of Diabetes Educators
ADA	**:** American Diabetes Association
ASCVD	**:** Atherosclerotic Cardiovascular Disease
BMI	**:** Body-Mass Index
CBE	**:** Clinical Breast Exam
CKD	**:** Chronic Kidney Disease
CRC	**:** Colorectal Cancer
CVD	**:** Cardiovascular Disease
DM	**:** Diabetes Mellitus
DPP-4i	**:** Dipeptidyl Peptidase-4 Inhibitor
DSMES	**:** Diabetes Self-Management Education and Support
ESLD	**:** End-Stage Liver Disease
GLP-1 RA	**:** Glucagon-like Peptide-1 Receptor Agonist
HbA1c	**:** Glycosylated hemoglobin level in blood
HF	**:** Heart Failure
HIV	**:** Human Immunodeficiency Virus
IFR	**:** Increasing Failure Rate
IG	**:** Insulin Glargine
IHD	**:** Ischemic Heart Disease
MDP	**:** Markov Decision Process
MET	**:** Metformin
OGA	**:** Oral Glucose Agent
POMDP	**:** Partially Observable Markov Decision Process
QALY	**:** Quality-adjusted Life Year
SGLT 2i	**:** Sodium-glucose Cotransporter 2 Inhibitor
SMBG	**:** Self-monitored Blood Glucose
SU	**:** Sulfonylurea
TZD	**:** Thiazolidinedione
T2DM	**:** Type 2 Diabetes Mellitus
USA	**:** the United States of America
WHO	**:** World Health Organization

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Diabetes is a chronic disease that is rapidly spreading worldwide. This prevalence increases the health expenditures for this disease in a serious way. In the treatment of patients with type 2 diabetes, the most common type of the disease, doctors have many intervention methods. Taking the right action at the most appropriate time among these many types of interventions will make a great contribution to the patient's health as well as the cost of treatment. Therefore, in this study, it is aimed to draw a road map by using a mathematical approach for the uncertainty in deciding the optimal time to start insulin therapy for type 2 diabetic patients. To this end, a finite-horizon Markov Decision Process model is developed by including disease stages within patients' health states and drug use history. The model is operated by using existing data in the literature and the results are discussed. In addition, different sensitivity analysis on different input demonstrate the effect of value changes on the model.

ÖZET

Diyabet hastalığı, tüm dünyada hızla yayılmakta olan kronik bir hastalıktır. Hastalığın bu kadar yaygınlaşması, bu hastalık için yapılan harcamaları da ciddi bir şekilde arttırmaktadır. En sık görülen diyabet türü olan tip 2 diyabetli hastaların tedavisinde doktorlar, birçok ilaçlı müdahale yöntemine sahiptir. Bu tür müdahalelerde doğru aksiyonu en uygun zamanda almak, hastanın sağlığına ve tedavi maliyetlerine büyük katkı sağlayacaktır. Bu nedenle, bu çalışmada insülin tedavisine başlamanın en uygun zamanı için matematiksel bir yaklaşım sergilenerek belirsizliklere dair bir yol haritası çizmek hedeflenmektedir. Bu hedef doğrultusunda, hastalık aşamaları, hastanın sağlık durumunu ve ilaç kullanım geçmişini kapsayacak şekilde bir sonlu-ufuk Markov Karar Süreci modeli geliştirilmektedir. Model, literatürdeki veriler kullanılarak çalıştırılıp, sonuçlar tartışılmaktadır. Ek olarak, farklı veriler üzerindeki farklı duyarlılık analizleri, değer değişikliklerinin model üzerindeki etkisini göstermektedir.

1. INTRODUCTION

In most countries, health services cover a significant percentage of the Gross National Product. By the aging of people, healthcare costs have been increasing over the last couple of decades in all around the world. Therefore, governments apply many strategies to find a way to minimize the cost of health spending. They are investing an ever-increasing amount of money in researches to be able to cover this healthcare expenditure. For this purpose, many researchers investigate the efficiency of operations, treatments or disease diagnoses in the health sector.

Among the health problems in hospitals, most patients have chronic diseases, including not only a chronic condition, but also combinations of these conditions. According to Buttorff et al. (2017), as of 2014, 60 percent of American adults had at least one chronic condition, and 42 percent had more than one chronic condition. The study of Buttorff et al. (2017) also notes that 90% of all health care spending is made for patients with chronic illnesses and in 2014, diabetes mellitus ranked fourth among these diseases with a prevalence of 10.4% of the total population in the United States.

Diabetes Mellitus (DM) is one of the most critical chronic diseases of the century because it triggers other health problems due to the uncontrolled blood glucose level. E.R.F. Collaboration et al. (2010) elaborated on this by providing that patients with diabetes have a two to three times more the risk of cardiovascular heart diseases (CVDs) or strokes and pertaining to reduced blood flow, neuropathy increases the risk of foot ulcer, infection and inevitable necessity of limb amputation.

Blindness is another result of diabetes mellitus so-called diabetic retinopathy. V.L.E. Group et al. (2013) reported that diabetic retinopathy occurs slowly over time by damaging the small vessels in the retina and measured that 2.6% of global blindness is

because of diabetes. In addition to all these adverse effects of diabetes, it also has a significant impact on kidney impairment or failure (National Institutes of Health et al., 2014).

Globally, diabetes becomes increasingly important due to its impacts, its prevalence and its role both economically and socially in patients' lives. World Health Organization (WHO) estimated that 422 million adults (over 18 years of age) have diabetes in 2014, escalating from 108 million in 1980. According to the organization, global widespread of the disease has also risen from 4.7% to 8.5% by 2014. The report underlines that diabetes is no longer a disease of rich nations, the prevalence of diabetes is remarkably increasing also in middle- and low-income countries (WHO, 2016).

There is another factor for the worldwide importance of diabetes, which is the cost of the disease. Cost of diabetes has a huge toll on third-party payers, such as government and private insurances. ADA (2018) notes that diabetes imposes a substantial burden on society in the form of higher medical costs, lost productivity, premature mortality, and intangible costs in the form of reduced quality of life. The article estimated that overall cost burden of diagnosed diabetes in the US in 2017 as $327 billion, containing $237 billion in direct medical costs and $90 billion in reduced productivity. The report also analyzed the cost of diabetes for the categories and measured that people with diagnosed diabetes incur average medical expenditures of ~$16,750 per year, of which ~$9,600 is attributed to diabetes.

Diabetes has also social impacts on patients. These impacts apply not only to diabetes but also to chronic conditions in general. Basu et al. (2016) explains this as chronic conditions like diabetes last for a long time and cause functional limitations when therapy begins. It is because these kinds of illnesses require ongoing monitoring or treatment. Therefore, management of diabetes plays an essential role in patients' social lives.

To better understand and manage the disease, diabetes is divided into clusters as Type 1, Type 2 and Gestational Diabetes Mellitus. Of overall diagnosed diabetes patients,

approximately 90% have type 2 diabetes mellitus (T2DM) which makes it the most prevalent form of diabetes. For this reason, T2DM management is important as a priority.

According to the latest guideline Davies et al. (2018); physicians have a consensus on some of the key issues to be followed in the management of the T2DM. Treatment begins when a patient's HbA1c level is detected to be higher than the target value. The guideline notes by referencing Riddle et al. (2018) that a reasonable HbA1c target for most non-pregnant adults with enough life expectancy to see microvascular benefits (generally ~10 years) is around 53mmol/mol (7%) or less.

The latest guideline Davies et al. (2018) orders the steps of T2DM management as follows.

First, the aim of the management is to avoid diabetes complications such as organ amputation and to optimize the quality of life. In the first step of the treatment, the key characteristics of the patients should be determined. These key features include clinical characteristics, i.e., HbA1c, age, weight; existing lifestyle, whether patients have comorbidities, i.e., atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), and heart failure (HF); whether patients are motivated or have a psychological depression and cultural and socioeconomic context of the patients.

In addition to the evaluation of basic characteristics, there are some factors that affect the choice of treatment. The assessment of these factors should take place in the second step. In this step, the goal of HbA1c should be personalized; the impact of weight, hypoglycemia, patient drug availability and drug cost should be considered; the side effect profile of medication should be identified; complexity of regimen, i.e., frequency, mode of administration should be taken into consideration; and finally the best regimen to optimize adherence and persistence to treatment should be chosen.

The third step consists of a shared decision-making management plan which prioritizes the delivery of patient-centered care. The plan aims to have trained and well-informed

patients (family/caregivers), taking care of patient preferences, providing good patient guidance including motivational interviewing, goal setting and shared decision making, strengthening patients, and offering ongoing diabetes self-management education and support (DSMES) programs.

In the fourth step, doctors should agree with patients on a management plan to determine a target with features called SMART (Specific, Measurable, Achievable, Realistic, Time limited).

Once the management plan has been determined and approved by shared decision making, the fifth step is to implement the plan. One important point of this implementation is that patients who do not achieve their goals should come to control at least every 3 months if the progress is being succeeded.

The sixth step provides continuous monitoring and support with emotional well-being, checking tolerability of medication, monitoring glycemic status, biofeedback including self-monitored blood glucose (SMBG), weight, step count, HbA1c, blood pressure, lipids.

After completing all these six steps, the management plan should be reviewed in the seventh step by mutual agreement if changes are necessary. Time is an important issue to refrain from clinical inertia in this last step. Decision cycle should be undertaken regularly at least once/twice a year.

1.1 Motivation

The World Health Organization (WHO) describes Diabetes Mellitus (DM) as a chronic disease that occurs when the pancreas responsible to produce insulin in the body is not functional or the insulin produced in the body cannot be used efficiently (WHO, 2018). In accordance with the facts in ADA (2015) and Davies et al. (2018), the key points related to T2DM can be demonstrated as first; insulin is not used adequately in patients with T2DM. This improper use in patients' body is called insulin resistance. Insulin

resistance is thought to be associated with obesity, hypertension, and excess fat level in the blood. The organ of pancreas secretes extra insulin to compensate for this. However, over time, the pancreas cannot work with adequate functionality and cannot secrete enough insulin to maintain blood glucose at normal level. As a result, the body becomes needing blood glucose lowering supports from the outside and treatment starts at this point. Treatment provides better glycemic control which means having improved HbA1c level to patients. Wagner et al. (2001) gives an idea about the impact of having better HbA1c on health care costs and utilization. The article established that better glycemic control provides an average of $685-950 per patient for health care expenditure to organizations or insurance companies.

T2DM is gradually treated with lifestyle changes, oral medications (pills), and insulin. The newest guide Davies et al. (2018) offers a wide range of treatment steps and states that insulin is very efficient for T2DM patients and should be preferred during the last stage of treatment.

To be more specific, in addition to lifestyle changes in the first step of treatment, patients are followed with metformin for start of medication. If metformin does not work to reduce the HbA1c level to or below the target value, treatment will continue with additional drugs (GLP-1 RA, SGLT2i, DDP-4i, SU, TZD, and basal insulin) called dual therapy after 3 months. ADA (2017) states that each new type of noninsulin oral glucose agents (OGA) added to initial therapy generally diminishes HbA1c level by ~ 0.9% to 1.1%. If dual treatment does not respond well enough for improved HbA1c, treatment is switched to triple-drug combination after another 3 months follow-up. Insulin is often prescribed as the final stage of reaching the targeted level of blood glucose after the unsuccessful triple therapy in T2DM.

Several important clinical trials have shown that insulin therapy reduces microvascular complications ((U.K.P.D.S Group, 1998) and (Ohkubo et al., 1995)). Another clinical study also suggests that early insulin therapy decreases the risk of macrovascular adverse events in type 2 diabetes (Holman et al., 2008). One more important result of U.K.P.D.S Group (1998) is also that the decrement in the risk of long-term

complications in type 2 diabetes is more related to better glycemic control instead of a specific glucose-lowering agent. This has caused the difficult task of choosing the right prescription from many possible glucose-lowering interventions. On the other hand, Nathan (2002) suggests that insulin therapy should be the best cost-effective alternative among all available interventions.

Although there is a certain acceptation for the advantages and need of insulin therapy, controversy still exists on when to initiate insulin first. Swinnen et al. (2009) says that it is evident there is a need for the clarification of insulin initiation time for type 2 diabetic patients. Halperin et al. (2008) specifies that treatment for uncontrolled HbA1c particularly after dual therapy is not unequivocal. Some patients are more suitable to treat in accordance with the guideline, while others are suitable for early insulin therapy.

To add a little note here to give an idea about what patients use before having started to use insulin, Mast et al. (2016) establishes that before initiating insulin therapy, patients with constantly HbA1c $\geq$ 7.0% use only metformin, only SU (sulfonylurea), metformin and SU together, another combination of oral glucose-lowering agents with 11.1%, 18.5%, 54.8%, 3.8%, respectively and patients with fluctuating around 7.0% use these drugs with 22.9%, 10.0%, 40.9%, and 5.7%, respectively.

Hanefeld et al. (2016) supplies a broad range of study of researches indicating the benefits of early insulin initiation and defends that conventional treatment results in an unfortunate delay in achieving good glycemic control. The article approaches the discussion with early initiation of insulin glargine, which is one of the most prevalent types of basal insulin prescribed by physicians. It reports that the decrease in HbA1c for the patients who started early insulin glargine was significantly greater for those with diabetes duration of <5 years, lower HbA1c at baseline, lower body-mass index (BMI) at baseline and notes that hypoglycemia risk was very tolerable. The studies described in the article and more help to support the idea that optimal timing at the onset of insulin is controversial.

Traditional approaches to lower HbA1c level might be stepwise to introduce insulin as mentioned. If insulin treatment is effective, it should be asked why it is expected to not to be used until the final stage, because each failure in treatment delays successful intervention and increases the risk of adverse events and complications, as well as uncontrolled hyperglycemia problems. AADE (2017) reports all cause of reluctance in the use of insulin and groups the reasons in three types of barriers as follow. Patient barriers are 1) the perception that insulin is a treatment of last resort; 2) perception that the use of insulin is evidence of a personal failure to appropriately self-manage diabetes; 3) concerns about long-term complications and side effects, especially hypoglycemia; 4) cost; 5) inconvenience and interference with social and work activities and relationships; 6) fear of needles, self-injecting, and the pain of insulin injections; 7) weight gain; 8) loss of independence; 9) depression; 10) the perception of insulin as a threat or punishment; 11) the failure to see health benefits of insulin therapy; 12) lack of social support; and concerns about social stigma and discrimination. Clinician barriers are 1) lack of experience and knowledge of available insulins; 2) inadequate guidance about when to intensify insulin therapy; 3) the perception that patients will resist or be unable to cope insulin initiation or intensification; 4) inadequate monitoring to identify patients who will benefit from insulin progression; 5) concerns about hypoglycemia and weight gain; and 6) general clinical inertia and delayed initiation until insulin is “absolutely necessary”. System barriers to insulin initiation and intensification include lack of resources for patient education, inadequate time to provide patient education and address dose adjustments, and lack of staff to provide diabetes education and training.

Apparently, insulin initiation in clinics is still not straightforward today. The purpose of this paper is to assist patients and/or health care providers in determining the best time for insulin onset. For this purpose, the Markov Decision Process (MDP) was used to take the correct measure (wait, add new drug or initiate insulin therapy) according to the health states of patients in the progression of T2DM treatment.

The remainder of this study is organized as follows. Section 2 provides the relevant articles on the topic and method. Section 3 includes the theory of MDP technique and the application of MDP to chronic disease treatment processes. Section 4 contains the

design of numerical implementation and results as well as the results of sensitivity analysis. A summary of the work in the article and future research directions are given in the last two sections.

2. LITERATURE REVIEW

In this part of the report, the studies done by using Markov Chain and Markov Decision Processes (MDPs) will be presented in an expressive way and shown in a table at the end.

Lefevre (1981) worked with the continuous-time MDP to deal with an epidemic problem in a population with N habitants. The author developed this model by defining states as the number of people infected and the others in the population are accepted open to being infected. Transition probabilities are assigned by calculating the rate of transmission of the epidemic from some external sources, the rate of infection from those infected to the susceptible people in the population, and the rate of those recovered from the epidemic disease. There are two parameter levels in the system to decide: (1) the amount of the population that needs to be quarantined, and (2) the amount of medical treatment to infected people. The objective is to minimize the total expected discounted cost which includes social expenditure, quarantine cost, and medical treatment cost.

Hu et al. (1996) attempted to find the best dosage policy by taking drug concentrations into account for anesthetized patients. The problem arose from the fact that the imbalance in the dose caused some adverse events for the patients. They modeled the problem by using Partially Observable Markov Decision Process (POMDP).

Ahn & Hornberg (1996) created a model in which patients' preferences were considered in health conditions that were effective in selecting the quality of the kidney suitable for transplantation. Instead of solving the problem clearly as an MDP, the authors limited their research to threshold policies, thus reducing the problem to the problem of finding the optimal threshold level.

Launois et al. (1996) aimed to find out the best regimen used docetaxel, paclitaxel or vinorelbine drugs for metastatic breast cancer in terms of cost-utility or cost-effectiveness analysis. Since there was no concrete comparative work on docetaxel, paclitaxel or vinorelbine interventions, this paper was designed offering a model to figure out the effects of the 3 interventions on the utility of sources and cost. By the help of stochastic decision tree, A Markov process model, based on 53 disease states, was thus constructed to evaluate the socioeconomics of the 3 treatment regimens.

Magni et al. (2000) suggested an MDP approach to the problem of the prophylactic surgery in mild hereditary spherocytosis a disease that causes the chronic destruction of red blood cells. The article compares the proposed model with an existing static approach for the same problem.

Hauskrecht & Fraser (2000) developed a POMDP model to medical therapy planning for patients with Ischemic Heart Disease (IHD). The authors consider the diagnosis and treatment of a disease related to each other in a health service environment. It is, therefore, always good to design a model that describes an integrated decision process that relates diagnosis and treatment of a disease to its relevant characteristics.

To design such a model, the stochastic decision tree and the Markov Decision Process (MDP) are the most commonly used decision tools in the literature. However, the stochastic decision trees are not enough to structure a model when the problem is complex. The standard and widely known MDP model - perfectly observable MDP - allows us to demonstrate the dynamics and stochastic structure of the basic process and captures the uncertainty about the outcome of the treatment. However, it does not capture the processes in which disease states are not certainly known. Hence, a Partially Observable Markov Decision Process (POMDP), which represents two sources of uncertainty in the problem, is proposed.

Ivy (2002) designed a POMDP model to assist clinicians in selecting one of two decision alternatives, clinical breast exams (CBE) and mammograms in breast cancer screening or examination. The author aims to minimize the total expected cost over a patient's lifetime by taking into consideration the patient's breast cancer health states.

Alagoz et al. (2004)'s study is based on the increase of living donors for liver transplantations in the USA. Thus, the problem of optimal timing for liver transplantation was considered as the focus of the paper. A Markov Decision Process (MDP) model was designed by identifying the maximization of patient's total reward as objective and defining the states of the process as patient health. In the end, the study seeks a policy that explains the health states of living donor liver transplantation and the point where waiting is the most appropriate action.

Faissol et al. (2006) developed an MDP model for diseases (showing particularly for the case of Hepatitis C) to determine the optimal test (treatment) time for people who did not know they were ill.

Alagoz et al. (2007) created another MDP model for liver allocation for patients in need of transplantation. In this study, the authors also consider the impact of the waiting list on the model, including patient health and, therefore, organ arrival. In the end, they suggest an optimal control-limit policy as a solution.

Alagoz et al. (2007) designed an extensional MDP model, but this time the model assists to the patients with end-stage-liver disease (ESLD) in deciding which liver to choose when they have livers available for transplant from a deceased person and a living donor at the same time.

Sandikci et al. (2008) estimated the price of privacy as the number of life days lost because of the privacy concerns (lack of publicity) in waiting lists within the models developed for the liver allocation system in the USA by using MDP in which the state of the process is described by patient health, quality of the offered liver, and a measure of the rank of the patient in the waiting list.

Shechter et al. (2008) investigated the best time to start HIV treatment with the MDP method that aim to maximize the expected lifetime or quality-adjusted lifetime of a patient, considering the negative consequences of delaying HIV treatment.

Alterovitz et al. (2008) formulated an MDP model for motion planning of steerable needles of imaging procedures in clinics to reach the inaccessible points of conventional stiff needles by considering the uncertainty encountered during motion plan optimization. The authors describe the causes of uncertainty in needle movement as patient differences and difficulty in predicting needle / tissue interaction. They also expect their model to be useful for clinical operations in several ways.

Maillart et al. (2008) sought an answer to questions about the relative value and frequency of mammogram screening for premenopausal and post-menopausal women. The authors modeled the problem with POMDP that includes the causes of conflicting age-based dynamics of both the disease and the accuracy of the test results.

Kreke et al. (2008) designed an MDP model resulting in an optimal control-limit policy to eliminate unnecessary residence time in hospital and to make the length of staying time most efficient for patients with pneumonia-related sepsis.

Wen-Lu et al. (2008) worked on an elderly diabetic patient population from Shanghai, China to assess the tendency and the factors that change over time and impact the secondary failure in efficacy of sulphonylurea by using Markov process modeling.

Denton et al. (2009) investigated the optimal time to begin statin therapy for patients with type 2 diabetes, considering the uncertainty of time-dependent change in the patient's cholesterol level to reduce cholesterol levels and minimize the risk of heart attack or stroke. The states in the model were formed by considering cholesterol levels and occurrence of heart attack, stroke or any reason of mortality. The probabilities of occurrence of adverse events were estimated by using three different risk models. The decision epoch for deciding whether the statin treatment should be implemented is

determined as one year. The overall objective of this work was also to maximize quality-adjusted life years (QALYs).

Kurt et al. (2012) took their study, Denton et al. (2009), of optimal time for statin initiation further. In their study, the authors implement an MDP by estimating the model for infinite decision horizons. Mason et al. (2012) conducted a study progressing their previous work which investigates the optimal time for statin initiation for type 2 diabetic patients by examining the effect of statin adherence on this optimal timing using MDP again. Mason et al. (2014) presented an MDP model which searches the optimal time of blood pressure and cholesterol medications for type 2 diabetes. The authors' model involves the use of multiple medications for simultaneous control of multiple risk factors.

Chhatwal et al. (2010) developed a finite-horizon discrete-time MDP for the problem that addresses the breast biopsy practices in clinics. The study says that biopsy tests are mostly done by radiologists when the mammogram results are not clear, and this creates an additional burden on health expenditures. Therefore, the authors worked on an MDP model to help physicians perform better in determining the optimal time of biopsy testing for a woman, based on mammography characteristics and demographic factors.

Alagoz et al. (2010) aimed to provide fundamentals of MDPs under uncertainty and a path for use in healthcare operations. This was demonstrated by the help of the context of the timing of liver transplantation in a patient who has a living donor available. Moreover, the study suggested that MDPs can be used for all reasonable timing strategies that have simple-detailed and very-well defined sequential decisions. It also indicated the homology between MDP and standard Markov process.

Ayvaci et al. (2012) contributed a decision analysis about the diagnosis of breast cancer to select the best intervention among routine follow-up mammography, short-term follow-up mammography and biopsy based on a patient's health state, in other words, risk assessment following mammography screening. The paper studied the tradeoff between choosing biopsy and delaying biopsy, formulating an MDP with the objective

of maximization the patients' QALYs while considering the effect of budget constraints on the optimal decision.

Erenay et al. (2014) designed a POMDP model to improve the screening policy for colorectal cancer (CRC) prevention and surveillance in the USA. The model provides an individualized CRC screening by incorporating age, gender, and risk of having CRC factors into a contemporary structure.

Lobo et al. (2015) worked on a decision analysis process to investigate prostate cancer treatment decisions in the post-prostatectomy setting. The study includes a comparison of genomic classifier estimates of prostate cancer progress to contribute use of radiotherapy and hormonal treatments. A Markov state transition model was used in the paper for evaluation of the cancer progression of each simulated individual by taking into consideration everyone has their own progression in formed by a genomic classifier. The objective of the overall study is to maximize quality-adjusted life years (QALYs) of patients and the consequences of multi-year cancer progression.

Suen et al. (2018) studied on drug sensitivity testing. Drug sensitivity testing is an expensive but definitive test for patients with drug resistance tuberculosis. The writers created a POMDP model that saves a big amount of money for India to develop a new drug sensitivity testing policy which gives the optimal time for testing.

To our knowledge, our study is the first that determines the optimal time to start insulin. There are studies in the literature that suggest early onset, but this is the first study to place this on the mathematical plane with MDP. Among the previous studies, the studies closest to our study have investigated the optimal time of statin therapy and include cholesterol and high-density lipoprotein levels, and cardiovascular events as the risk factors for health states. In our study, we investigate the optimal time to start insulin for patients with type 2 diabetes without any other chronic disease such CVD, CKD or HF. On the other hand, our health states consider the patients' drug history, HbA1c levels, and BMI levels. We anticipate our findings help eliminate the uncertainty about the optimal time to start insulin by being expanded in the future studies.

Table 2.1 Literature comparison table

Disease/Work Group	Author(s)	Method(s)
Epidemic disease	Lefèvre	MDP
Anasthetized patients	Hu et al.	POMDP
Kidney transplantation	Ahn and Hornberger	Markov Chain
Metastatic breast cancer	Launois et al.	Markov Decision Tree
Hereditary spherocytosis	Magni et al.	MDP
Ischemic heart disease	Hauskrecht and Fraser	POMDP
Breast cancer	Ivy	POMDP
Liver transplantation	Alagoz et al.	MDP
Hepatitis C	Faissol et al.	MDP
Liver transplantation	Alagoz et al.	MDP
Liver transplantation	Alagoz et al.	MDP
Liver transplantation	Sandikci et al.	MDP
AIDS	Shechter et al.	MDP
Steerable needles in imaging	Alterovitz et al.	MDP
Mammogram screening	Maillart et al.	POMDP
Pneumonia-related sepsis	Kreke et al.	MDP
Diabetes	Wen-Lu et al.	Markov Chain
Diabetes	Denton et al.	MDP
Diabetes	Kurt et al.	MDP
Diabetes	Mason et al.	MDP
Diabetes	Mason et al.	MDP
Breast biopsy	Chhatwal et al.	MDP
Liver transplantation	Alagoz et al.	MDP
Breast cancer	Ayvaci et al.	MDP
Colorectal cancer	Erenay et al.	POMDP
Prostate cancer	Lobo et al.	Markov Chain
Drug resistance in tuberculosis	Suen et al.	POMDP

3. MODELING AN MDP FOR A CHRONIC DISEASE TREATMENT

In this part of the section, we will provide a tutorial, in general, about how to create an MDP model to solve a problem in the course of the treatment for a chronic disease. Denton & Steimle (2016) shed light on the formulation of our structure in their article.

MDPs have been becoming increasingly needed tools in making medical decisions to overcome the problems that arise in chronic disease treatment processes. The treatment process is represented by the wide definition of the disease, which expresses the severity of the disease, the patient's clinical condition and the medical history. Since there are uncertainties in the progress of the treatment which differs from patient to patient, MDPs are exposed to the curse of dimensionality, which means the explosion in the size of the state space due to history dependence of the disease to be able to cover all possible situations that can occur for a patient. However, these models also offer a structure that minimizes the problem to avoid computing difficulties by using the Markov feature, indicating that the next result in the progression of the disease is solely relevant to the current state and the action implemented.

Denton & Steimle (2016) formulates a good MDP modeling approach that can be used to analyze and resolve a possible problem in the course of chronic disease treatment. The terms that should be defined in the model are specified as *decision epochs*, *time horizon*, *state space*, *action space*, *transition probabilities*, and *rewards*.

Decision epochs: Decisions in treatment for a chronic disease are taken at the decision epochs. The length of time between each epoch is determined by the clinician. According to the guideline, for type 2 diabetes, it is more appropriate to make the decision to start a new drug treatment every 6 months or once a year (Denton &Steimle, 2016)**.**

Time horizon: Time horizon for an MDP model can be both finite and infinite. For finite-horizon models, the number of decision epochs can be counted, whereas the infinite-horizon models are continuous processes. Researchers favor the use of infinite models when one decision period is relatively too short to the length of the time horizon which decisions are taken for the whole model. Infinite models are also associated with two different characters. First one is that they reach an absorbing state with 100%, while the other is that the models are not variable, they are stationary, indicating that the parameters do not vary over time.

State space: The state space of the model demonstrates the information that may be helpful to a clinician when deciding on a patient. A state vector characteristically consists of the combination of patient's clinical conditions which gives an idea about the stiffness of the disease or the probability of developing a disease, the patient's demographic information like age and race, and relevant medical history such as medication or adverse events history. Most MDPs use the discretization technique to decrease the size of state space to achieve more understandable and feasible solutions. Better structured models include larger state spaces to reflect all aspects of the patient's health. However, this also increases the size of computation to solve the model, and at the same time creates more sampling errors into the estimation of transition probabilities. Shechter (2013) discusses the balance between more discretization and sampling error in the article for finer discrete models. In many models of chronic disease using the MDP tool, it is always close to the cut to mention the presence of an absorbing state representing the main complications and / or death. However, in some embodiments, the absorbing states may be more than one absorbing state when the model can be derived from different health states or when the rewards for the respective absorbing states change. In addition to all this, patient data is always essential for the estimation of transition probabilities between states.

Action space: Treatment options are important for choosing the action space. If the best treatment option is available, MDPs use two different actions, initiating or waiting for the treatment. Problems with this type of two action options are called optimal stopping-time problems due to the decision taker seeks the best time to quit the process and get

into the absorbing after-treatment state. For some situations, there may be many treatment alternatives available at each decision epoch. In this kind of cases, the size of the action space increases exponentially. For example, for a treatment process with more than one drug that can be used in any combination and not known which combination is the best, the action space alters with the formula $2^{(usable\ number\ of\ drugs)}$ at each decision epoch.

Transition probabilities: The definition of this term helps to show the disease progression before and after the treatment. It may require building a natural history model that explains how the disease advances without treatment. However, in order to estimate the impacts of the treatment, it might be more appropriate to use longitudinal data by observing measurements of risk factors with and without the treatment process, since most data are recorded when patients are diagnosed with the disease and started treatment. This situation is not concerned when the best therapy is available, which means the problem is an optimal stopping-time problem. It is because the effects of the treatment do not impact the decision due to the patient will pass to an absorbing state with probability 1.

Rewards: One important element here is the definition of the decision taker's perspective. The decision maker can deal with the problem from the perspective of the patient, the third-party payer (insurance companies) or from the societal perspective which combines these two views. The treatment process includes both benefits and costs for the reward function. The benefit can be defined as a potentially longer life for the patient. The term used in literature for the benefit is QALY (quality-adjusted life year), which indicates a one-year measure of quality of life, combined with discomfort from medical interventions. 1 QALY represents a patient who has perfect health. The decrease in quality of life is shown as a decrease from 1 to zero in QALY score. The costs of the treatment, such as financial costs (medication, hospitalization) and side effects of medication, can be expressed as the causes of a reduction in the quality of life of a patient. For the models with societal perspective, willingness to pay factor is used as a monetary value of QALY minus costs of medical interventions. Values that have

mostly been used in the literature for 1 QALY are $50000 and $100000; however, the exact value is often controversial (Denton & Steimle, 2016).

In MDP models, patient data play a vital role in predicting transition possibilities and rewards. The results of the solution of MDP models are generally very significant in terms of cost-effectiveness after collecting the correct data from the literature or longitudinal data.

The elements used in deciding which method to choose for MDP solutions are the size of the state-action pair space and whether the time horizon is finite or infinite. Although there are different approximation algorithms in the literature to bypass the curse of dimensionality problem for MDP models, *policy iteration*, *value iteration* and *linear programming* are mainly applied to solve infinite-horizon problems and *backward induction* is often used for finite-horizon problems.

Because chronic diseases are progressive illnesses, there is a property used for computational advantage while working on MDP problems. This property, called *Increasing Failure Rate (IFR),* indicates that chronic diseases will worsen over time. Based on this statement, the IFR, together with some other conditions, provides the *optimal control-limit policy* for certain optimal stopping-time problems. This policy measures a threshold to take one action before this value and another action after that value. In the case of problems with such a policy feature, the effort shown to solve the MDP is reduced because the process of calculating a value function for each state-action pair will be eliminated. Thus, a control-limit policy facilitates the way to the solution in this way.

Once the model has been solved, it is important to validate the solution for chronic diseases. There are some common techniques used in the literature for this purpose. Below, you can find the brief descriptions of these methodologies.

Expert Opinion: It is the easiest and simplest verification method. One who solves the MDP seeks the opinion of an expert in the field. This expert can be a health care

researcher or clinician. It is not a scientifically powerful way, because it is subjective. However, its ease of use makes it sometimes preferable.

Independent Study: It is done by comparing the existing solution with another solution. This approach is helpful when a gold standard model exists to compare with.

Retrospective validation: This validation technique is applied when past results of a patient group are used for the relevant disease. One of the important points here is to change the patient cohort used. Otherwise, it may cause optimism deviation.

Prospective validation: Prospective validation is accepted as the gold standard of validation. This is because that the technical process in prospective validation is long-term and it predicts some outcomes and compares them with actual results. However, the use of this method is rarely encountered in the literature.

4. MODEL

4.1 Model Formulation and Assumptions

To find an optimal time for insulin initiation, we use a finite-horizon discounted MDP model where optimal action is determined at every decision epoch based on a patient's health state. First, we prefer to specify and to minimize the general insulin initiation problem because all possible situations of diabetes patients to be put into the model will cause the realization of the curse of dimensionality. In order to avoid this, we make several assumptions related to the patient profile and the problem itself.

While identifying patients in our model, the current guideline for the management of type 2 diabetes, Davies et al. (2018), is considered. Here, a glucose-lowering medication roadmap is determined with respect to the patient type (with or without other chronic diseases) or the patient's primary need in the treatment process. According to the guideline, we determine our patient profile in which we apply our model as patients with type 2 diabetes who have no other chronic diseases and that it is a priority to stop weight gain or encourage weight loss so that we refrain from the curse of dimensionality. Figure 4.1.1 shows the medication stages of patients with type 2 diabetes, including the stage used in our model.

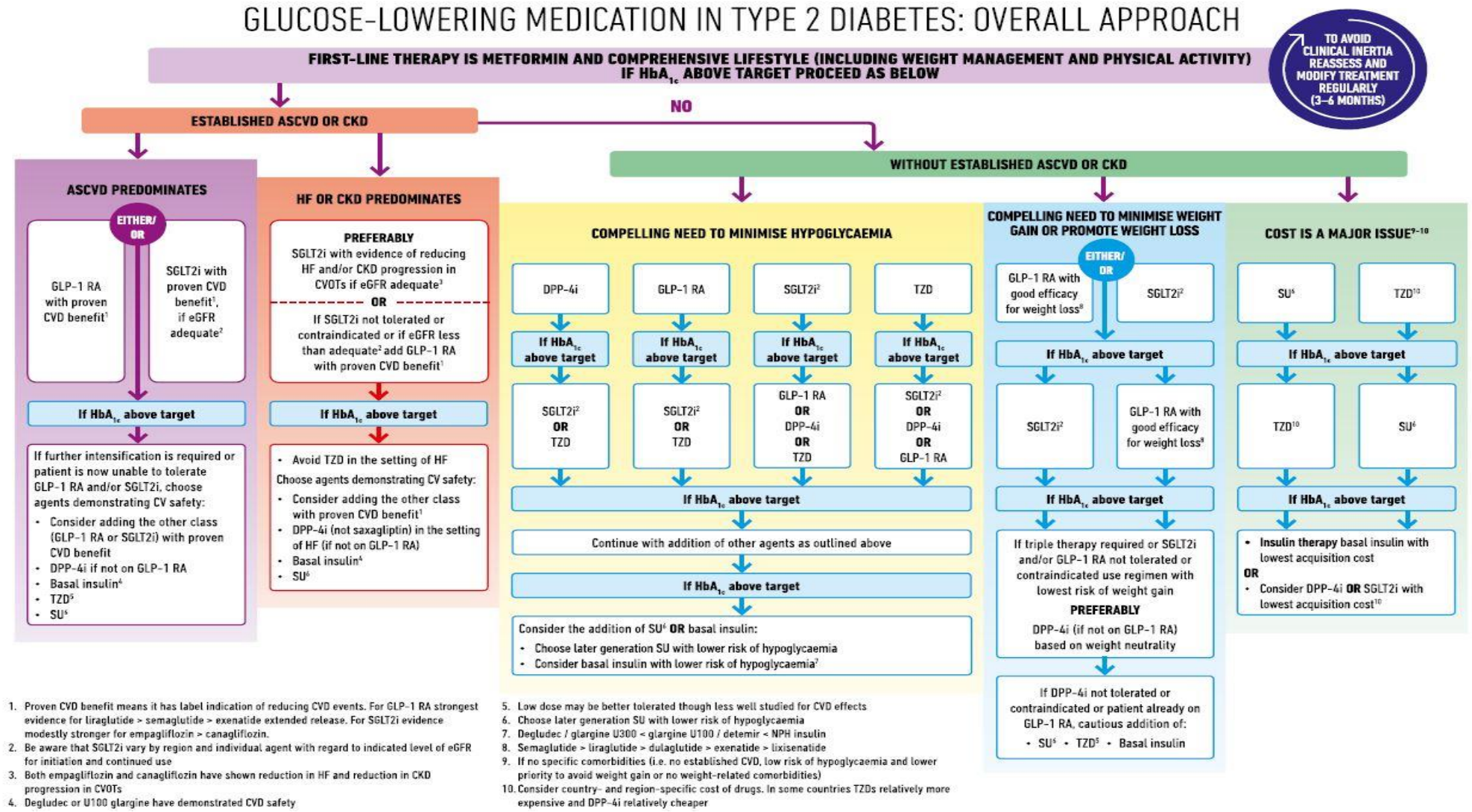

Figure 4.1.1 Schematic representation of glucose-lowering medication

Time horizon and decision epoch: In the model, t denotes the decision epochs or periods, t = 0,1, 2…T < ∞, and our time horizon, T, is 40 and our cycle time is six months. Thus, we evaluate the model for 20 years between 40 and 60 years of age.

State space: As seen in the figure 4.1.1, there are three important criteria for the treatment of diabetes with the priority of weight-control: 1) whether the HbA1c level is below 7%, which is accepted as the standard of being diabetic 2) Therapy type, which refers to the drug combination used in the patient's current medication stage. This could be one of the follows: only metformin, metformin + GLP1 RA, metformin + SGLT 2i, metformin + SGLT 2i + DPP 4i 3) whether the patient's weight is under control.

Since glucose level (HbA1c) and weight (BMI) are directly affected by the drug combination used as a result of the action taken in decision making, these three criteria are interrelated to each other and placed in our model to define a patient's health state.

To add a small note about BMI here, BMI is an indicator of height and weight ratio. We assume that all patients' current height and weight may change over time. However, in our model, since we assume the patient profile we are interested in starting from the age of 40 and there is a low chance of a change in the patient's height after this age, it is decided whether the BMI is under control or not by controlling the weight of the patient. For brief information about BMI, we show the weights of the patients according to their heights in figure 4.1.2 below.

BMI Table (Metric)

	Underweight			Normal						Overweight					Obese					
BMI	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**
Height (cm)	**Body Weight (Kg)**																			
145	34	36	38	40	42	44	46	48	50	53	55	57	59	61	63	65	67	69	71	74
150	36	38	41	43	45	47	50	52	54	56	59	61	63	65	68	70	72	74	77	79
155	38	41	43	46	48	50	53	55	58	60	62	65	67	70	72	74	77	79	82	84
160	41	44	46	49	51	54	56	59	61	64	67	69	72	74	77	79	82	84	87	90
165	44	46	49	52	54	57	60	63	65	68	71	74	76	79	82	84	87	90	93	95
170	46	49	52	55	58	61	64	66	69	72	75	78	81	84	87	90	92	95	98	101
175	49	52	55	58	61	64	67	70	74	77	80	83	86	89	92	95	98	101	104	107
180	52	55	58	62	65	68	71	75	78	81	84	87	91	94	97	100	104	107	110	113
185	55	58	62	65	68	72	75	79	82	86	89	92	96	99	103	106	110	113	116	120
190	58	61	65	69	72	76	79	83	87	90	94	97	101	105	108	112	116	119	123	126
195	61	65	68	72	76	80	84	87	91	95	99	103	106	110	114	118	122	125	129	133
200	64	68	72	76	80	84	88	92	96	100	104	108	112	116	120	124	128	132	136	140

Figure 4.1.2 Calculated BMI Chart

S represents the state space, S = {1, … ,17} and s_t denotes the health state of a patient in time period t where $s_t \in$ S, and s_t = {h, k, b} where h stands for the HbA1c condition, k represents the therapy type, considering the number of drugs used in the combination, and b symbolizes the BMI condition of a patient at time t and 17th state represents the health state of insulin initiation. Instead of indicating the insulin therapy state with {h, k, b}, an average threshold value is assumed alone, as in the case of optimal stopping time problems.

By implication of conditions for HbA1c and BMI, it is meant that these two types of values are under control or not under control. So, in our model, h and b can take one of two different values which we code as h_c and b_c for controlled situations and h_u and b_u for uncontrolled situations.

We do not include the state of death in our model because, as we will discuss later, we looked for all numerical information in the literature, thus, it was difficult to find the death data of the patients from the literature, and we also considered that such a decision which targets to timing of insulin initiation works for the patients who survive.

The notifications and their definitions are as described in Table 4.1.1.

Table 4.1.1 The elements of a health state and their explanations

Notification	Definition
h	
h_c	Controlled HbA1c level
h_u	Uncontrolled HbA1c level
k	
1	Metformin
2a	Met + GLP1 RA
2b	Met + SGLT 2i
3	Met + SGLT 2i + DPP 4i
b	
b_c	Controlled BMI
b_u	Uncontrolled BMI

The drug combinations are sequentially placed in patients' health states according to the number of drugs, considering the weight loss priority as indicated in the guideline and blue painted area of Figure 4.1.1. One point to note here is that GLP1 RA and SGLT 2i together can be used with metformin, but this triple drug therapy is not a highly preferred combination according to Kalra et al. (2018) due to the fact that there is not enough numerical analysis about the use of these drugs together. Based on this information, the possible use of this triple drug combination is neglected in our model.

We assume first that patients are at least on monotherapy, which is the treatment with metformin, at the beginning of decision-time horizon for each health state. If the patient does not respond to metformin treatment, he or she will switch to dual therapy using one of the drugs GLP1 RA and SGLT 2i. In the dual drug therapy stage, if the patient uses GLP 1 RA and metformin and does not take the expected response, the patient may prefer SGLT 2i instead of GLP 1 RA. However, if the patient uses SGLT 2i and metformin dual therapy, either (s)he can switch to a triple drug therapy using DPP 4i or, (s)he can change SGLT 2i to GLP1 RA and remain in the dual therapy with metformin. There is an important point to note here that GLP1 RA and DPP 4i cannot be used together in a drug combination. Therefore, a combination of drugs containing GLP1 RA can only be dual therapy. On the other hand, if the triple therapy, metformin and SGLT 2i and DPP 4i, does not get

successful, we assume that the patient does not consider any other alternative drug combination and begins to use the insulin therapy directly.

Below figure represents the model framework which demonstrates the stages of the treatment process in our model.

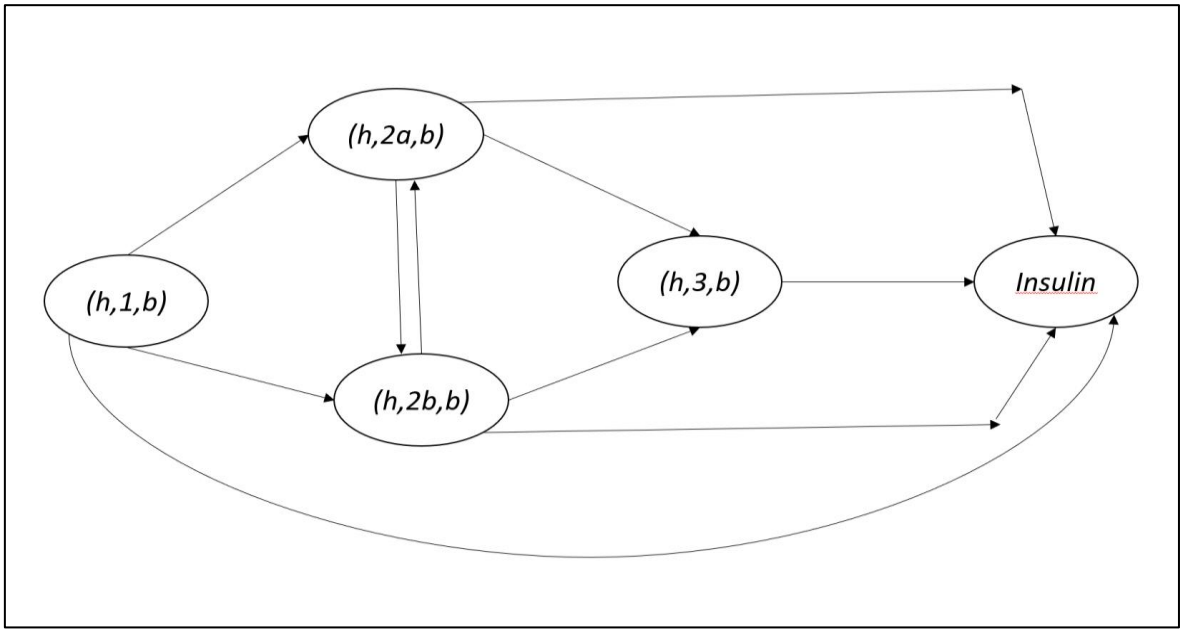

Figure 4.1.3 Model framework for all possible actions

Thus, the possible metabolic states of patients with type 2 diabetes, having no other chronic disease or risks and prioritizing weight loss, form 16 different health states. The number 16 is derived from the product of 2 HbA1c states (in control, out of control), 4 therapy type states (met, met + GLP1 RA, met + SGLT 2i, met + SGLT 2i+ DPP 4i) and 2 BMI states (in control, out of control) (i.e. 2x4x2=16).

Table 4.1.2 below shows all health states in state space S except the insulin initiation.

Table 4.1.2 All possible health states in our model except insulin therapy

1	2	3	4	5	6	7	8
(h_c,1,b_c)	(h_c,2a,b_c)	(h_c,2b,b_c)	(h_c,3,b_c)	(h_c,1,b_u)	(h_c,2a,b_u)	(h_c,2b,b_u)	(h_c,3,b_u)
9	10	11	12	13	14	15	16
(h_u,1,b_c)	(h_u,2a,b_c)	(h_u,2b,b_c)	(h_u,3,b_c)	(h_u,1,b_u)	(h_u,2a,b_u)	(h_u,2b,b_u)	(h_u,3,b_u)

In addition, one assumption here is related to the progression of therapies in the treatment process, which is that when patients switch to an advanced or an alternative therapy, they cannot return to receive the same therapy they used before. Although this is clinically possible, this assumption is made because we avoid the curse of dimensionality since we do not have patients' treatment progression data. For example, we assume that a patient who has received metformin monotherapy and switched to metformin + SGLT 2i dual therapy cannot use metformin monotherapy again. This is an important assumption for our model because it considers the insulin therapy irreversible.

Action space: The possible actions to be taken at period t, where $a_t \in A_t$, are considered as,

$$a_t = \left\{ \begin{array}{c} W: Wait \\ A: Add\ new\ drug \\ I: Initiate\ insulin \end{array} \right\}$$

The action of add new drug is also given in view of the transition between dual therapies. This not only means adding a new drug, but also a change in therapy since we eventually add a new drug in this case as well.

Transition probabilities: State transition probabilities are demonstrated as $P_t^{s,s'}(a)$. It shows the probability that a patient will be in state $s' \in$ S at decision epoch $t+1$ given that (s)he is in state $s \in$ S at decision epoch t and action a is taken. For example, $P_t^{2,3}(A)$ denotes the probability that a patient in state 2 (h_c,*2a*,b_c) at period t will be in state 3 (h_c,*2b*,b_c) in period $t+1$ when the chosen action at t is A (add new drug). The transition probability matrix in period t when action a is taken is shown as $P_t(a)$.

We need to mention here some important assumptions about the transitions. We assume in our model that $P_t^{s,s'}(a)$ where s=1,2,3,4,9,10,11,12 and s'=5,6,7,8,13,14,15,16 for any action a at any given period t has a probability of 0. The main feature of these transitions is that they are transitions from where the BMI is under control, b_c, to those that are not under control, b_u. In our model, we ignore uncontrolled BMI situations due to external factors and focus only on the drug effect. Since none of the drug combinations except insulin has weight gain effect, based on many studies in the literature and guideline, the

transition from b_c to b_u is impossible with only therapy impact, thus, these values are set to zero.

On the other hand, for the remaining health state transitions that include the transitions from b_u to b_c, only one criterion is taken into consideration, that is whether or not the drug therapies used leads to the desired weight loss, thus, these transition probabilities vary depending on the therapy type.

The other assumption is that when examining the health state transitions in respect of HbA1c level, *h*, two different approaches are shown in the model. The first is how successful the therapy is in terms of patients' continuity to the therapy when the patient's HbA1c is in control. This indicates the probability of treatment failure due to the related drug combination effect. The second approach is that with which success rate patients can achieve the desired standard HbA1c level of 7% or less when the patient's HbA1c is not in control.

Rewards: $R_t(s, a)$ represents the expected reward between time period t and $t + 1$ when the patient is in state $s \in$ S and action a is taken. In our model, we identify our point of view as the societal (physician indirectly) perspective. Thus, the reward is a function of an individual's QALY's monetary value at the respected state and the associated costs of that state.

Value function: $V_t(s)$ denotes the value function and represents the expected remaining reward when the patient is in state s in period t.

Discount factor: λ is the discount factor in our model where $0 < \lambda < 1$. We use a 97% annual discount factor (λ=0.97) which is considered coherent with standard practice in the health policy literature based on the study of (Brouwer & Exel, 2004).

As described in Section 3.1, Bellman's equations below help us to find the optimal solution. Also, since we have a finite state space and action set, any policy that satisfies Bellman's equations is an optimal policy for our model.

$$V_T(s) = 0\,, \forall s \in S, \tag{1}$$

$$V_t(s) = \max\{R_t(s,W) + \sum_{i=0}^{16} P_t^{si}(W)\lambda V_{t+1}(i), \qquad R_t(s,A) + \sum_{i=0}^{16} P_t^{si}(A)\lambda V_{t+1}(i), \;\; R_t(s,I), \forall t < T \tag{2}$$

where i represents an individual's health state in the next decision period $t+1$.

4.2 Numerical Findings

As we specified before, we assume the time horizon is between the ages 40 and 60. Since our cycle time is 6 months, T is 40 where $t = 0$ corresponds to age 40. In this stage of the study, we estimate the transition probabilities and find rewards and costs. We use a function of monetary value of QALYs and costs as rewards. All necessary figures are taken from the literature. Below you can find the detailed explanation for each of the estimated parameters.

4.2.1 Transition Probabilities

The transition probability matrices for each action are formed by scanning the medical publications. We use the most appropriate and reasonable values for the 6 months decision period due to the scarce of sources specifically for our model in the literature. The assumptions that are considered when estimating these values were mentioned in Section 4.1.

When the information is placed on the transition probability matrices, either they are taken directly, or some calculations and assumptions are made based on the articles.

Kwon et al. (2018) give us the probability of treatment failure of metformin monotherapy. The treatment failure in the transition probability matrices means that even if the patient has started a specific oral medication, he or she cannot control the HbA1c level in 6 months and does not continue the therapy because of loss of glucose control. This transition is represented as transferring from h_c (controlled) to h_u (uncontrolled) in a health state of a patient.

Brown et al. (2004) have the information about the probability of decreasing HbA1c level to 7% or below by using metformin. This is supplied by calculating the average likelihood of having HbA1c >7% after metformin monotherapy onset within a mean period of 6 months in the article.

Baptista et al. (2007) focus on the effect of metformin in weight loss. It provides us the transition probability of uncontrolled BMI by losing not enough weight with metformin. The probability is assigned by dividing the number of patients with increasing BMI or influencing their BMI below the average by the total number of patients. Although the paper has studied schizophrenia patients, we ignore this situation and take the impact of metformin in weight loss due to very limited number of works in the literature about weight change with type 2 diabetes and oral antidiabetics used.

We assume about the treatment failure transition probability for metformin + GLP1 RA dual therapy based on Ratner et al. (2006) and take the percentage of loss of glucose control among causes of quitting the therapy as the probability of switching from h_c to h_u in HbA1c. On the other hand, the probability of achieving the target HbA1c level of 7% for this drug combination is directly taken from the 30-week trial value of the same paper. In contrast to studies on weight loss, many studies have been conducted and values have been found for different drug combinations used for type 2 diabetes related to the probability of reducing HbA1c to or less than 7 percent in the literature. However, the values of the articles and below are used in our study.

Blonde et al. (2006) report that in the result part of their article, at the end of 82 weeks, 81 percent of patients with type 2 diabetes experience weight loss by using metformin and

GLP1 RA combination. This value is the transition probability to the controlled state of BMI by assuming that the 6-month value, due to data deprivation, is close to it and, thus, ignoring the difference that can occur in time.

Charokopou et al. (2015) directly provide the information of the probability of discontinuation, treatment failure, to metformin + SGLT 2i dual therapy.

Bailey et al. (2013) include the likelihoods of reducing HbA1c level to 7% or below by combining metformin and different doses of SGLT 2i. For the probability value used in the model for this parameter of patient health state, we take the average of three different combinations made for 24 weeks.

Prato et al. (2015) have the statistics of a cohort with 400 patients using metformin and SGLT 2i combination. The probability of whether this dual therapy results in the desired weight loss is calculated by dividing the number of patients with having weight loss and remaining in the control group at the end of the 26-week period by the total number of patients.

Matthaei et al. (2015) give the probability of HbA1c falling to 7% or below for the triple therapy with metformin + SGLT 2i + DPP 4i directly as a result of the study. However, the probability of treatment failure is determined by the numerical information of discontinuation in the efficacy section of the paper, assuming lack of glucose control as the only cause of withdrawal of patients from the therapy. It reports that 4 patients were rescued or discontinued for loss of glycemic control over 153 patients. Thus, we find the likelihood of treatment failure by dividing 4 over 153.

All these explanations are summarized in the illustrative table below to make them clearer.

Table 4.2.1.1 Illustrative table of the inputs used in our model

Therapy	Transition		Probability	Signification	Reference	Year
	HbA1c	BMI				
MONOTHERAPY (ONLY METFORMIN)	$h_c \rightarrow h_c$		0.954	Treatment success or not	Kwon et al.	2018
	$h_c \rightarrow h_u$		0.046			
	$h_u \rightarrow h_c$		0.2526	HbA1c gets ≤7% or not	Brown et al.	2004
	$h_u \rightarrow h_u$		0.7474			
		$b_c \rightarrow b_c$	1	Absolute control or not	Guideline	2018
		$b_c \rightarrow b_u$	0			
		$b_u \rightarrow b_c$	0.9167	Desired weight loss or not	Baptista et al.	2007
		$b_u \rightarrow b_u$	0.0833			
DUAL THERAPY (MET + GLP1 RA)	$h_c \rightarrow h_c$		0.97	Treatment success or not	Ratner et al.	2006
	$h_c \rightarrow h_u$		0.03			
	$h_u \rightarrow h_c$		0.46	HbA1c gets ≤7% or not	Ratner et al.	2006
	$h_u \rightarrow h_u$		0.54			
		$b_c \rightarrow b_c$	1	Absolute control or not	Guideline	2018
		$b_c \rightarrow b_u$	0			
		$b_u \rightarrow b_c$	0.81	Desired weight loss or not	Blonde et al.	2006
		$b_u \rightarrow b_u$	0.19			
DUAL THERAPY (MET + SGLT 2i)	$h_c \rightarrow h_c$		0.919	Treatment success or not	Charokopou et al.	2015
	$h_c \rightarrow h_u$		0.081			
	$h_u \rightarrow h_c$		0.35	HbA1c gets ≤7% or not	Bailey et al.	2015
	$h_u \rightarrow h_u$		0.65			
		$b_c \rightarrow b_c$	1	Absolute control or not	Guideline	2018
		$b_c \rightarrow b_u$	0			
		$b_u \rightarrow b_c$	0.885	Desired weight loss or not	Del Prato et al.	2015
		$b_u \rightarrow b_u$	0.115			
TRIPLE THERAPY (MET + SGLT 2i + DPP 4i)	$h_c \rightarrow h_c$		0.974	Treatment success or not	Matthaei et al.	2015
	$h_c \rightarrow h_u$		0.026			
	$h_u \rightarrow h_c$		0.353	HbA1c gets ≤7% or not	Matthaei et al.	2015
	$h_u \rightarrow h_u$		0.647			
		$b_c \rightarrow b_c$	1	Weight loss is neglected	Guideline	2018
		$b_c \rightarrow b_u$	0			
		$b_u \rightarrow b_c$	0	Weight loss is neglected	Guideline	2018
		$b_u \rightarrow b_u$	1			

In addition, by considering the conditional probability, for the cases in which both HbA1c and BMI values have a chance to alter, a new single transition probability is obtained by multiplying the single transition probabilities of these two parameters of a patient's health state. This calculation is valid for each state transition probability. However, for some cases, BMI value, *b*, has no chance to change. This provides us with ease of calculation. As it is mentioned that the weight gain effect of the antidiabetics other than insulin is not observed, they either reduce or neutralize the weight. Due to this assumption, BMI has a transition probability of 1 for remaining in the same state of BMI when it is in control, which means transitions that include from b_c to b_c. Thus, the product of the multiplication with 1 gives the same result with the probability of HbA1c changes when BMI is in state of b_c for all therapies.

Moreover, this assumption gives us the transition probability values for the states where BMI is not under control, b_u, only within the triple therapy as well. This is because, as we know from the guideline, triple therapy attempts to neutralize a patient's weight, so it does not help to lose weight. This means that if a patient on the triple therapy is in a state where the *b* value is b_u, the patient will continue to be on the same *b* value, b_u, with a probability of 1. Thus, as in the state transitions that include from b_c to b_c, the product of the multiplication in this case also gives the same result with the transition probability of HbA1c changes.

The sequential tables below show transition probability matrices for all actions used in the model.

Table 4.2.1.2 Estimated transition probability matrix of wait action

P_t (W)		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
S	s_t	(h_c,1,b_c)	(h_c,2a,b_c)	(h_c,2b,b_c)	(h_c,3,b_c)	(h_c,1,b_u)	(h_c,2a,b_u)	(h_c,2b,b_u)	(h_c,3,b_u)	(h_u,1,b_c)	(h_u,2a,b_c)	(h_u,2b,b_c)	(h_u,3,b_c)	(h_u,1,b_u)	(h_u,2a,b_u)	(h_u,2b,b_u)	(h_u,3,b_u)	insulin
1	(h_c,1,b_c)	0.9540	0	0	0	0	0	0	0	0.0460	0	0	0	0	0	0	0	0
2	(h_c,2a,b_c)	0	0.9700	0	0	0	0	0	0	0	0.0300	0	0	0	0	0	0	0
3	(h_c,2b,b_c)	0	0	0.9190	0	0	0	0	0	0	0	0.0810	0	0	0	0	0	0
4	(h_c,3,b_c)	0	0	0	0.9740	0	0	0	0	0	0	0	0.0260	0	0	0	0	0
5	(h_c,1,b_u)	0.8745	0	0	0	0.0795	0	0	0	0.0422	0	0	0	0.0038	0	0	0	0
6	(h_c,2a,b_u)	0	0.7857	0	0	0	0.1843	0	0	0	0.0243	0	0	0	0.0057	0	0	0
7	(h_c,2b,b_u)	0	0	0.8133	0	0	0	0.1057	0	0	0	0.0717	0	0	0	0.0093	0	0
8	(h_c,3,b_u)	0	0	0	0	0	0	0	0.9740	0	0	0	0	0	0	0	0.0260	0
9	(h_u,1,b_c)	0.2526	0	0	0	0	0	0	0	0.7474	0	0	0	0	0	0	0	0
10	(h_u,2a,b_c)	0	0.4600	0	0	0	0	0	0	0	0.5400	0	0	0	0	0	0	0
11	(h_u,2b,b_c)	0	0	0.3500	0	0	0	0	0	0	0	0.6500	0	0	0	0	0	0
12	(h_u,3,b_c)	0	0	0	0.3530	0	0	0	0	0	0	0	0.6470	0	0	0	0	0
13	(h_u,1,b_u)	0.2316	0	0	0	0.0210	0	0	0	0.6851	0	0	0	0.0623	0	0	0	0
14	(h_u,2a,b_u)	0	0.3726	0	0	0	0.0874	0	0	0	0.4374	0	0	0	0.1026	0	0	0
15	(h_u,2b,b_u)	0	0	0.3098	0	0	0	0.0403	0	0	0	0.5753	0	0	0	0.0748	0	0
16	(h_u,3,b_u)	0	0	0	0	0	0	0	0.3530	0	0	0	0	0	0	0	0.6470	0
17	insulin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Table 4.2.1.3 Estimated transition probability matrix of add new drug action

Pt (A)		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
S	s_t	(h_c,1, b_c)	(h_c,2a, b_c)	(h_c,2b, b_c)	(h_c,3, b_c)	(h_c,1, b_u)	(h_c,2a, b_u)	(h_c,2b, b_u)	(h_c,3, b_u)	(h_u,1, b_c)	(h_u,2a, b_c)	(h_u,2b, b_c)	(h_u,3, b_c)	(h_u,1, b_u)	(h_u,2a, b_u)	(h_u,2b, b_u)	(h_u,3, b_u)	insulin
1	(h_c,1,b_c)	0	0.4850	0.4595	0	0	0	0	0	0	0.0150	0.0405	0	0	0	0	0	0
2	(h_c,2a,b_c)	0	0	0.9190	0	0	0	0	0	0	0	0.0810	0	0	0	0	0	0
3	(h_c,2b,b_c)	0	0.4850	0	0.4870	0	0	0	0	0	0.0150	0	0.0130	0	0	0	0	0
4	(h_c,3,b_c)	0	0	0	0.9740	0	0	0	0	0	0	0	0.0260	0	0	0	0	0
5	(h_c,1,b_u)	0	0.3929	0.4067	0	0	0.0922	0.0528	0	0	0.0122	0.0358	0	0	0.0029	0.0047	0	0
6	(h_c,2a,b_u)	0	0	0.8133	0	0	0	0.1057	0	0	0	0.0717	0	0	0	0.0093	0	0
7	(h_c,2b,b_u)	0	0.3929	0	0.0000	0	0.0922	0	0.4870	0	0.0122	0	0.0000	0	0.0029	0	0.0130	0
8	(h_c,3,b_u)	0	0	0	0	0	0	0	0.9740	0	0	0	0	0	0	0	0.0260	0
9	(h_u,1,b_c)	0	0.2300	0.1750	0	0	0	0	0	0	0.2700	0.3250	0	0	0	0	0	0
10	(h_u,2a,b_c)	0	0	0.3500	0	0	0	0	0	0	0	0.6500	0	0	0	0	0	0
11	(h_u,2b,b_c)	0	0.2300	0	0.1765	0	0	0	0	0	0.2700	0	0.3235	0	0	0	0	0
12	(h_u,3,b_c)	0	0	0	0.3530	0	0	0	0	0	0	0	0.6470	0	0	0	0	0
13	(h_u,1,b_u)	0	0.1863	0.1549	0	0	0.0437	0.0201	0	0	0.2187	0.2876	0	0	0.0513	0.0374	0	0
14	(h_u,2a,b_u)	0	0	0.3098	0	0	0	0.0403	0	0	0	0.5753	0	0	0	0.0748	0	0
15	(h_u,2b,b_u)	0	0.1863	0	0.0000	0	0.0437	0	0.1765	0	0.2187	0	0.0000	0	0.0513	0	0.3235	0
16	(hu,3,b_u)	0	0	0	0	0	0	0	0.3530	0	0	0	0	0	0	0	0.6470	0
17	insulin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

For add new drug action, the probabilities of transferring to possible states (if there are two possible states) are taken from the wait action matrix as half of the probabilities of the states in which the current state can go. The numbers in red color indicate the transition probabilities of all states with triple therapy. They are in red because they are infeasible states that have no effect on the action result and so they are not accurately placed. We give a very small number for their rewards in our reward vector to get the result of starting insulin therapy.

Table 4.2.1.4 Estimated transition probability matrix of insulin initiation action

Pt (I)		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
S	s_t	(h_c,1, b_c)	(h_c,2a, b_c)	(h_c,2b, b_c)	(h_c,3, b_c)	(h_c,1, b_u)	(h_c,2a, b_u)	(h_c,2b, b_u)	(h_c,3, b_u)	(h_u,1, b_c)	(h_u,2a, b_c)	(h_u,2b, b_c)	(h_u,3, b_c)	(h_u,1, b_u)	(h_u,2a, b_u)	(h_u,2b, b_u)	(h_u,3, b_u)	insulin
1	(h_c,1,b_c)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
2	(h_c,2a,b_c)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
3	(h_c,2b,b_c)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
4	(h_c,3,b_c)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
5	(h_c,1,b_u)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
6	(h_c,2a,b_u)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
7	(h_c,2b,b_u)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
8	(h_c,3,b_u)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
9	(h_u,1,b_c)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
10	(h_u,2a,b_c)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
11	(h_u,2b,b_c)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
12	(h_u,3,b_c)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
13	(h_u,1,b_u)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
14	(h_u,2a,b_u)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
15	(h_u,2b,b_u)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
16	(hu,3,b_u)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
17	insulin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

4.2.2 Quality Adjusted Life Years (QALYs)

Because there is uncertainty in a patient's health state, the aim of our MDP model is to find the optimal policy which shows the optimal decisions at each 6-months decision epoch and state by using the available information. The optimal decision is the decision with estimated monetary value of QALYs minus costs averaged over all possible future states. Thus, a future reward is related to the monetary value of a QALY and the utility(disutility) of a patient's health state.

The rewards for each state depend only on the current state of a patient and action taken. We suppose that there is no specific burden on taking an action in our model. We use annual QALY's monetary value of $ 50000, which we initially assigned to a patient in excellent health.

When calculating the QALYs, we assume at the beginning that we have a starter utility that belongs to patients with type 2 diabetes. This utility only includes the decrement of weight gain describing a patient with controlled HbA1c level. We subtract disutility and add QALYs gained by the medication therapy used to find expected future rewards. Therefore, other than BMI and HbA1c level, the selected therapies are also important because of their direct impact on a patient's quality of future life years.

Matza et al. (2007) provide the information about the starter utilities of type 2 diabetic patients with basic health states. The study measures the utilities in the view of weight gain, treatment-related adverse events and fear of hypoglycemia. We assume that our patients are not exposed to an adverse event. Therefore, based on this article, we suppose that a patient with 3% lower weight and no adverse event has a controlled BMI state. Thus, the utility of 0.80 in the article represents the starter utility of the states with a value of b_c for BMI. Unlike this situation, a patient with 3% higher weight and no adverse event has the starter utility of 0.68 which is used for uncontrolled BMI with a value of b_u in a patient's health state.

Hunt et al. (2015) report that controlling HbA1c levels of most of a studied group of patients with type 2 diabetes, whose HbA1c levels are not under control, provides an average of 0.16 utility on a patient's quality of a future life year. Based on that, if a patient loses control of the HbA1c level, we can accept that the patient experiences a loss of 0.16 utility. This value is subtracted from the starter utility if the level of HbA1c is h_u in a patient's health state. Conversely, if it is h_c, nothing is added or subtracted because the already established starter utilities in the article are evaluated with the consideration of type 2 diabetics who are in control of their glucose levels.

For insulin initiation, we ignore the situations in which patients must start insulin immediately such as severe hyperglycemia attacks. Since using oral glucose-lowering agents will affect a patient's quality of future life years, our model requires a new starter utility value for the insulin initiation. Boye et al. (2011) measure the utilities by considering antidiabetics that can be used up to the onset of insulin for type 2 diabetic patients. Based on this article, we assume the starter utility value of insulin initiation health state as 0.813. This is an average calculated value. The fact that antidiabetics have both negative and positive effects on QALY makes this value different from 0.80 and 0.68. And, the fact that it is higher tells us that the overall positive effect is at the forefront.

The table below explains the information provided above.

Table 4.2.2.1 Estimated QALY values without considering the medication effects

Information	Health State	Starter Utility	Reference	Year
Mean utility of controlled HbA1c	(h_c,*,b_c)	0.8	Matza et al.	2007
	(h_c,*,b_u)	0.68	Matza et al.	2007
Mean utility of uncontrolled HbA1c	(h_u,*,b_c)	0.64 (0.8-0.16)	Hunt et al.	2015
	(h_u,*,b_u)	0.52 (0.68-0.16)	Hunt et al.	2015
Mean utility of antidiabetics uses before insulin	insulin initiation	0.813	Boye et al.	2011

While the use of oral antidiabetics has a positive effect on QALY by inducing weight loss and decreasing HbA1c, the risk of hypoglycemia and the injectability, if the drug is injectable, cause a decrease in QALY. Chakravarty et al. (2018) calculate the QALY gain of 1kg weight loss and 1% HbA1c decrease. In the model, we multiply these values by the

weight loss and HbA1c decrease resulting from each therapy for 6 months and add the product of the multiplication to the starter utilities to find the specific impacts of the therapies on their rewards. However, insulin causes weight gain, thus, the weight effect of insulin on QALY is negative.

The effects of therapies on weight and HbA1c are taken from as follows: Ratner et al. (2006) have the values which belong to the dual therapy of metformin+GLP1 RA, Bailey et al. (2013) have the values of metformin + SGLT 2i, Baptista et al. (2007) have the values of metformin mono therapy, Matthaei et al. (2015) have the values of metformin + SGLT 2i + DPP 4i triple therapy and Buse et al. (2009) have the values of insulin glargine with metformin therapy. If a note needs to be added here, since the study of Metformin + SGLT 2i dual therapy is performed using three different doses of SGLT 2i, the mean value of the data for 24 weeks is found to determine the values we need.

The following table summarizes the data and gives the results used in our model.

Table 4.2.2.2 QALY figures for utility effects of each therapy

	Decrease in HbA1c (%)	Weight Loss	Reference	Year	QALY GAIN per 1% HbA1c decrease	QALY GAIN per 1 kg weight decrease	Reference	Year	Total Gain in QALY
Monotherapy (Met)	0.71	1.40	Baptista et al.	2007	0,022	0,0149	Chakravarty et al.	2018	0.0365
Dual therapy (Met+GLP1 RA)	0.70	2.30	Ratner et al.	2006					0.0497
Dual therapy 2 (Met+SGLT2i)	0.713	2.51	Bailey et al.	2013					0.0531
Triple therapy (Met + SGLT 2i+DPP 4i)	0.51	0.53	Matthaei et al.	2015					0.0191
Insulin Therapy (Met + IG)	1.70	-2.50	Buse et al.	2009					0.0001

On the other hand, Zhang et al. (2014) have the disutility of hypoglycemia and injectable medications. These are the values that have a negative effect on QALY of a patient. The information in the article belongs to each single antidiabetic other than SGLT 2i. Therefore, to find the disutility for the therapies involving these antidiabetics in

combination, we sum up their single values for each therapy type and disutility category. Besides that, we complete the missing disutility of SGLT 2i by using the probability of severe hypoglycemia of dapagliflozin, which is a type of SGLT 2i, and metformin combination from the study of (Charokopou et al., 2015).

The table below shows the disutility and overall gain or loss in QALY for each therapy.

Table 4.2.2.3 QALY figures for disutility effects of each therapy

	Disutility of hypoglycemia	Disutility of injectable medication	Reference	Year	Total Loss in QALY	Overall Total Change in QALY
Monotherapy (Met)	-0.0002	0	Zhang et al.	2014	-0.0002	0.0363
Dual therapy (Met+GLP1 RA)	-0.0007	-0.0032	Zhang et al.	2014	-0.0039	0.0458
Dual therapy 2 (Met+SGLT2i)	-0.0004	0	Charokopou et al.	2015	-0.0004	0.0527
Triple therapy (Met + SGLT 2i+DPP 4i)	-0.0006	0	Zhang et al.	2014	-0.0006	0.0185
Insulin Therapy (Met + IG)	-0.0143	-0.0032	Zhang et al.	2014	-0.0175	-0.0174

4.2.3 Costs

Each state has an associated cost. All the cost information is obtained from the literature and determined by taking half of the values in the articles, considering that the model has a 6-months decision period, and adjusted to 2019 USD with 3% annual inflation rate.

On the other hand, costs are grouped in three main categories: 1) total medical cost (inpatient, outpatient, emergency room visits, urgent care visits, calls to physicians) 2) total drug (medication) cost 3) total cost of weight increase which may occur as an effect of the therapies.

Costs are taken from the studies as follows: D. P. P. Group (2012) have 10 years follow-up medical cost information of metformin therapy, Pharm et al. (2018) search and supply the medical costs of GLP1 RA and insulin dual therapies with metformin, Chakravarty et al. (2018) have the difference medical cost between metformin + SGLT 2i and metformin + GLP1 RA, the drug costs of dual and triple therapies and also the cost per 1 kg weight

increase which is important when calculating total insulin glargine therapy cost because in contrast to what we know for other therapies, we learn from Buse et al. (2009) that insulin therapy has a weight gain effect of about 2.5 kgs, and finally (Kwon et al., 2018) provide the drug costs of metformin and insulin glargine therapies. Since there is no available cost-effectiveness study in the literature for Met + SGLT 2i + DPP 4i at the time of this study, a sensitivity analysis will be made for the medical cost of triple therapy. Considering the other medical costs, the average of triple therapy medical cost is assumed to be $ 2000 in our base model application. One under this value ($ 1000) and one even lower value ($ 500) will be included for the operation of the sensitivity analysis of our model.

The table below shows the costs used in our model and includes their references.

Table 4.2.3.1 Associated costs with each therapy in 2019 $

	Total medical cost (2019 $)	**Reference**	**Total drug cost (2019 $)**	**Reference**	**Cost of weight increase due to medication (2019 $)**	**Reference**	**TOTAL COST**
Monotherapy (Met)	1242.14	Group (2012)	13.51	Kwon et al. (2018)	0	Guideline (2018)	1255.65
Dual therapy (Met + GLP1 RA)	1768.58	Pharm et al. (2018)	3991.60	Chakravarty (2018)	0	Guideline (2018)	5760.17
Dual therapy 2 (Met + SGLT2i)	1565.69	Chakravarty (2018)	2617.57	Chakravarty (2018)	0	Guideline (2018)	4183.26
Triple therapy (Met + SGLT 2i + DPP 4i)	2000.00	Assumption	5032.58	Chakravarty (2018)	0	Guideline (2018)	7032.58
Insulin Therapy (Met + IG)	2351.55	Pharm et al. (2018)	2065.31	Kwon et al. (2018)	925.24	Chakravarty (2018)	5342.10

4.2.4 Rewards

All in all, to find future rewards of a patient's health states, we add the total changes in QALY to the starter utilities of the related states and multiply the results by $ 25000 which, we assume, is the QALY's 6-month monetary value. Then, we subtract the costs of each medication therapy from the results of the multiplications and find the willingness-to-pay factor for each health state and action pair. Here is a note to add for the calculation of

rewards in action *A,* which is that since we add a new drug in this action, the costs subtracted are the costs of therapies that can be used in the next stage. If it is possible to choose one of two different therapies at the next stage, half of the costs of these therapies are deducted in our model.

Below table represents the rewards of each state-action pair in period $t = 0$.

Table 4.2.4.1 Undiscounted rewards for each state-action pair

S	s_t	$R_t(s_t,W)$	$R_t(s_t,A)$	$R_t(s_t,I)$
1	(h_c,1,b_c)	19651.35	15935.28	14549.15
2	(h_c,2a,b_c)	15384.08	16960.99	14549.15
3	(h_c,2b,b_c)	17133.86	14915.75	14549.15
4	(h_c,3,b_c)	13430.34	-100000.00	14549.15
5	(h_c,1,b_u)	16651.35	12935.28	14549.15
6	(h_c,2a,b_u)	12384.08	13960.99	14549.15
7	(h_c,2b,b_u)	14133.86	11915.75	14549.15
8	(h_c,3,b_u)	10430.34	-100000.00	14549.15
9	(h_u,1,b_c)	15651.35	11935.28	14549.15
10	(h_u,2a,b_c)	11384.08	12960.99	14549.15
11	(h_u,2b,b_c)	13133.86	10915.75	14549.15
12	(h_u,3,b_c)	9430.34	-100000.00	14549.15
13	(h_u,1,b_u)	12651.35	8935.28	14549.15
14	(h_u,2a,b_u)	8384.08	9960.99	14549.15
15	(h_u,2b,b_u)	10133.86	7915.75	14549.15
16	(h_u,3,b_u)	6430.34	-100000.00	14549.15
17	insulin	14549.15	14549.15	14549.15

For the triple therapy, a very small number for rewards is given in order not to get the action of add new drug because we already assume for our model that if it does not make sense to continue with triple therapy during a decision period, the patient should start insulin therapy. Otherwise, he or she should wait for another decision period.

Subsequent to calculating the rewards, the goal is to determine the action at each state which has the maximum expected future reward. Expected future rewards are calculated by

starting with the multiplication of the rewards and the transition probabilities in each respective health state. This multiplication helps us to decide on the action at $t = 0$. After deciding on the action at each state at the beginning of the decision horizon which we assume between 40 and 60 years of age, our objective function has a discount factor of 0.97 to reflect the discounted value of rewards for future years of life and therapy costs.

To find the optimal policy, the optimal treatment action can be computed efficiently at each state by using backward induction for our finite-horizon MDP model. The optimal action is decided by selecting between the expected discounted future rewards of 1) the patient waiting until the next decision epoch 2) the patient adding a new drug for another 6 months and 3) the patient initiating insulin therapy.

5. RESULTS

5.1 Base Case

After all the inputs used in the solution are decided, the results are obtained as follows from the MATLAB R2018b computer program to get rid of computational complexity of the solution.

The table below shows the results taken from the $ 2000 assumption of the average medical cost for the triple therapy. In the table, the set of S in the y axis indicates our health states, while the horizontal x axis represents a 20-year decision horizon, each of which is a 6-month decision period. Moreover, the internal values demonstrate the actions at each decision epoch as follows: *W*) wait at the current therapy, *A*) add a new drug and change the current therapy *I*) initiate insulin.

Table 5.1.1 The optimal policy for the base case

T		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	(h_u,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
14	(h_u,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	Insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
T		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	(h_u,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
14	(h_u,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*	*I*	*I*	*I*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	Insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*

Moreover, the value function for the first 4 and last 4 decision periods is measured as in Table 5.1.2. We choose these decision periods randomly as an example for the values that the value function takes. The numbers are given by rounding to the nearest exact value.

Table 5.1.2 Value function outcomes for different decision periods

T		**1**	**2**	**3**	**4**		**38**	**39**	**40**	**41**
S	***s_t***									
1	(h_c,1,b_c)	448790	442990	437010	430840		56730	38530	19650	0
2	(h_c,2a,b_c)	386210	381220	376070	370770		49120	33380	16960	0
3	(h_c,2b,b_c)	386380	381390	376250	370940		49290	33550	17130	0
4	(h_c,3,b_c)	341560	337120	332550	327840		42350	28660	14550	0
5	(h_c,1,b_u)	445530	439730	433740	427580		53470	35300	16650	0
6	(h_c,2a,b_u)	382830	377840	372700	367390		45790	30110	14550	0
7	(h_c,2b,b_u)	383010	378010	372870	367570		45960	30290	14550	0
8	(h_c,3,b_u)	341560	337120	332550	327840		42350	28660	14550	0
9	(h_u,1,b_c)	436280	430480	424490	418330		48160	31810	15650	0
10	(h_u,2a,b_c)	377280	372290	367150	361840		42420	28660	14550	0
11	(h_u,2b,b_c)	377450	372460	367320	362010		42600	28660	14550	0
12	(h_u,3,b_c)	341560	337120	332550	327840		42350	28660	14550	0
13	(h_u,1,b_u)	433020	427210	421230	415060		44900	28680	14550	0
14	(h_u,2a,b_u)	373980	368990	363850	358540		42350	28660	14550	0
15	(h_u,2b,b_u)	374160	369160	364020	358710		42350	28660	14550	0
16	(h_u,3,b_u)	341560	337120	332550	327840		42350	28660	14550	0
17	insulin	341560	337120	332550	327840		42350	28660	14550	0

When we look at Table 5.1.1, the actions that should be taken in each decision period for most health states are constant for a long time as they started at 40 years of age. In the table, the cells stained with blue show the decision periods in which the actions change. The changes only evolve to action of starting insulin therapy. After the change, there is no transition from this therapy to another therapy as previously assumed for the model. This is the case because when a cost analysis is performed, it appears that the cost of insulin therapy ($ 5342,10) is higher than the costs of uncontrolled HbA1c ($ 4000) and BMI ($ 3000). Thus, this postpones the onset of insulin in our model, which considers the reason for choosing actions with lower cost. The corresponding cost of uncontrolled HbA1c and BMI are determined from the defects of these values on QALY. That is to say:

uncontrolled HbA1c has a decrease of 0.16 on QALY, which corresponds to a cost of $ 4000 ($ 25000 * 0.16) while uncontrolled BMI causes to a decrease of 0.12 (0.80-0.68) and this is reflected in a cost of $ 3000 ($ 25000 * 0.12).

On the other hand, for any health state involving monotherapy with metformin alone, initiating insulin to patients is not recommended. It is recommended to continue the same treatment because of the low cost of the therapy. This is a predictable outcome and has been an output of our model. In fact, it is presumed that metformin mono therapy does not work in the first place, and this is considered the starting point, but the result is the opposite. Reaching a more realistic result is possible if real data is used. The reason here is the opposite of starting insulin therapy. While the cost of insulin therapy is higher than the uncontrolled costs of HbA1c and BMI, the cost of metformin therapy ($ 1255.65) is even less than half of these two costs separately. Thus, the model remains in the same therapy for a long time, preferring to cover the cost of therapy for metformin.

For dual therapies, where any of the HbA1c or BMI is uncontrolled, transitions to insulin can be recommended at final decision periods. Furthermore, in health states where both HbA1c and BMI cannot be controlled, it is advised that the patient should be started on insulin from the age of 58 years according to our model.

For health states involving triple therapy, continuing therapy (i.e. taking action *W*) is never meaningful because of high drug costs and the presumed medical cost of $ 2000 (for action *A,* since adding a new drug after triple therapy already means initiating insulin, we ignore the possible results of action *A*).

Another conclusion that can be drawn is again related to dual therapies. Since the cost of metformin+GLP1 RA is high compared to metformin + SGLT 2, our model recommends changing this therapy by choosing action *A* (i.e. adding a new drug) to metformin + SGLT 2 in health states involving metformin+GLP1 RA. However, it can be said according to our model that in health states where both HbA1c and BMI are uncontrolled, this difference disappears after the age of 58 and a direct transition to insulin can be made.

5.1 Sensitivity Analysis

In this part of the section, we can further customize our perspective and observe the effects of parameter changes on the results of our model. One sensitivity analysis is carried out by assigning the medical cost value of $ 1000 and $ 500 for the triple therapy due to the failure to obtain a cost from the literature and in order to see what the cost that can change the outcome of action *I* could be in all health states of this type of treatment.

The table below shows that a cost of $ 1000 does not change our result from the cost of $ 2000.

Table 5.2.1 Optimal policy results of $1000 medical cost for triple therapy

T		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
S	s_t																				
1	$(h_c,1,b_c)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	$(h_c,2a,b_c)$	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	$(h_c,2b,b_c)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	$(h_c,3,b_c)$	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	$(h_c,1,b_u)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	$(h_c,2a,b_u)$	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
7	$(h_c,2b,b_u)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
8	$(h_c,3,b_u)$	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	$(h_u,1,b_c)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	$(h_u,2a,b_c)$	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
11	$(h_u,2b,b_c)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
12	$(h_u,3,b_c)$	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	$(h_u,1,b_u)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
14	$(h_u,2a,b_u)$	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
15	$(h_u,2b,b_u)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
16	$(h_u,3,b_u)$	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	Insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
T		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
S	s_t																				
1	$(h_c,1,b_c)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	$(h_c,2a,b_c)$	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	$(h_c,2b,b_c)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	$(h_c,3,b_c)$	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	$(h_c,1,b_u)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	$(h_c,2a,b_u)$	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*
7	$(h_c,2b,b_u)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
8	$(h_c,3,b_u)$	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	$(h_u,1,b_c)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	$(h_u,2a,b_c)$	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*
11	$(h_u,2b,b_c)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*
12	$(h_u,3,b_c)$	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	$(h_u,1,b_u)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
14	$(h_u,2a,b_u)$	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*	*I*	*I*	*I*
15	$(h_u,2b,b_u)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*
16	$(h_u,3,b_u)$	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	Insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*

On the other hand, a $500 cost assignment results in a change. Although $500 is a small cost when we consider other costs, a triple therapy medical cost value of around $ 500 concludes that a patient with controlled HbA1c and BMI values can continue triple therapy as shown in the table below. Moreover, in other states, no changes are observed for this value as well. The areas painted in green represent the health states that have completely different action(s) compared to the base case.

Table 5.2.2 Optimal policy results of $500 medical cost for triple therapy

T		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	(h_u,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
14	(h_u,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	Insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
T		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	(h_u,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*

11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
14	(h_u,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*	*I*	*I*	*I*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	Insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*

In another sensitivity analysis, the disutility of uncontrolled HbA1c is examined. Our model shows sensitivity after a disutility of 0.07 for this parameter. This means that if the QALY loss due to uncontrolled HbA1c is 0.07 or less, whether the HbA1c is under control does not change the result at any future decision point. After 0.07, for health states in which HbA1c is uncontrolled, insulin onset is recommended earlier gradually as the value increases. We showed the results in the base case for 0.16. Now, you can see the outcomes for 0.25 in the table below.

Table 5.2.3 Optimal policy result for 0.25 disutility of uncontrolled HbA1c

T		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	(h_u,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
14	(h_u,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
T		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*

2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
10	(h_u,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*	*I*	*I*	*I*	*I*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*	*I*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*
14	(h_u,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*

Furthermore, changes according to 0.50, which can be considered a much higher value for the disutility caused by uncontrolled HbA1c, are observed as follows by another sensitivity analysis. As shown here, since the cost of uncontrolled HbA1c will be very high, direct insulin onset is recommended for health states where this value is not in control. However, for low-cost monotherapy, it is still possible to observe the wait action until the end of the decision horizon.

Table 5.2.4 Optimal policy result for 0.50 disutility of uncontrolled HbA1c

T		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	(h_u,2a,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
11	(h_u,2b,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*

14	(h_u,2a,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
15	(h_u,2b,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
T		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
10	(h_u,2a,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
11	(h_u,2b,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
14	(h_u,2a,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
15	(h_u,2b,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*

Another analysis is conducted on the discount factor λ. The decrease in this parameter makes it possible to determine that insulin initiation should be taken earlier. If HbA1c and BMI are uncontrolled and an individual is on dual therapy, the model recommends starting insulin earlier gradually up to 0.81 with minor changes in other health states. However, at 0.80, direct insulin initiation is recommended for the entire time horizon to a patient in the same metabolic conditions. This explains that the discount factor should have a value between 0.80 and 0.81 or less to make a patient who is not in control of HbA1c and BMI start insulin directly after 40 years of age by bypassing dual therapies.

A significant change in this analysis is also observed if a patient with uncontrolled HbA1c and BMI is taking monotherapy. As the discount factor decreases, we can see the result of insulin initiation for this health state as well. The below tables represent these changes.

Table 5.2.5 Action results of each decision epoch for 0.81 discount factor

T		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	(h_u,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
14	(h_u,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
T		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	(h_u,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*	*I*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*
14	(h_u,2a,b_u)	*A*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*

Table 5.2.6 Action results of each decision epoch for 0.80 discount factor

T		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	(h_u,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
14	(h_u,2a,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
15	(h_u,2b,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
T		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	(h_u,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*	*I*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*
14	(h_u,2a,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
15	(h_u,2b,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*

One more sensitivity analysis is also performed by changing the amount of money corresponding to the cost-effectiveness ratio. The cost-effectiveness ratio per year is $ 100000 instead of $ 50000 this time. In the application of the model with such monetary value, the initiation of insulin is observed in more decision periods, while another important change occurs in the states with monotherapy compared with the base case. In monotherapy, we also see insulin initiation actions because the higher cost-effectiveness ratio can tolerate the difference from the cheap therapy of metformin by the QALY difference between respective health states and insulin initiation state.

The results appear as in the table below.

Table 5.2.7 Changes in optimal policy for QALY's monetary value of $ 100000

T		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
S	s_t																				
1	$(h_c,1,b_c)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	$(h_c,2a,b_c)$	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	$(h_c,2b,b_c)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	$(h_c,3,b_c)$	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	$(h_c,1,b_u)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	$(h_c,2a,b_u)$	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
7	$(h_c,2b,b_u)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
8	$(h_c,3,b_u)$	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	$(h_u,1,b_c)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	$(h_u,2a,b_c)$	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
11	$(h_u,2b,b_c)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
12	$(h_u,3,b_c)$	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	$(h_u,1,b_u)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
14	$(h_u,2a,b_u)$	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
15	$(h_u,2b,b_u)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
16	$(h_u,3,b_u)$	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
T		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
S	s_t																				
1	$(h_c,1,b_c)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	$(h_c,2a,b_c)$	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	$(h_c,2b,b_c)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	$(h_c,3,b_c)$	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	$(h_c,1,b_u)$	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*

6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*
10	(h_u,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*	*I*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*
14	(h_u,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*

We also apply such an analysis for an annual monetary value of $ 200000 for 1 QALY. The results turned out to be much more interesting and to include many more wait actions. When we look at dual therapy results, we can conclude that if both of HbA1c and BMI or only HbA1c are uncontrolled, either of GLP1 RA or SGLT 2i can be used for this QALY monetary value without having to choose between them. Such a conclusion for triple therapy is obtained because the higher cost-effectiveness ratio for QALY tolerates the difference in cost between therapies. However, for dual therapies, the result stems from the transition probabilities between therapies. For example, when we look at the health state of (*hu,2a,bc*), this health state has lower QALY and higher cost compare to the insulin initiation state. The result is supposed to be insulin initiation action, but it is still wait action. Therefore, the difference in transition possibilities appears to be the cause.

Table 5.2.8 represents the outcomes.

Table 5.2.8 Changes in optimal policy for the cost-effectiveness ratio of $ 200000

T		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*

7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	(h_u,2a,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
14	(h_u,2a,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
T		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*
10	(h_u,2a,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
14	(h_u,2a,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*

Another analysis is also established to see what happens if we change the starter utility of insulin initiation. As expected, as the value moves away from our base case value of 0.813, the transition to insulin decreases in the negative direction of 0,813 and increases in the positive direction of 0,813 in the optimal policy. The model does not recommend taking insulin initiation action, especially when the starter utility of insulin onset has values less than 0.68. When we give a value (0.70) between the other two starter utilities (0.68 and 0.80), the results change as in Table 5.2.9.

Table 5.2.9 Optimal policy for the starter utility of 0.70 for insulin initiation

T		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	(h_u,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
12	(h_u,3,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
14	(h_u,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
T		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
10	(h_u,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
12	(h_u,3,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
14	(h_u,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*

One another analysis is based on the cost of metformin, which is always reflected in the results as wait action because it has a much lower cost than other costs in our model. When deciding on the assigned value, a cost of $ 4,000 is preferred to be equivalent to the uncontrolled costs of HbA1c and BMI and close to other therapy costs. With such a cost, more health states involving monotherapy take add new drug action, as shown in Table 5.2.10.

Table 5.2.10 Results for metformin mono therapy cost of $ 4000

T		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
10	(h_u,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
14	(h_u,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
T		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
S	s_t																				
1	(h_c,1,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
2	(h_c,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
5	(h_c,1,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
6	(h_c,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*	*I*
10	(h_u,2a,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*

12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*	*I*	*I*	*I*	*I*
14	(h_u,2a,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*	*I*	*I*	*I*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*

Finally, if we set our perspective from the patient's perspective by resetting the cost values, the results below occur. No painted areas are specified here, because the results refer to another perspective independent of the base case. According to these results, the following can be said in general. Monotherapy and triple therapy are not recommended for any health state, but rather staying in dual therapy is recommended. In some health states, in the second half of the decision horizon, some changes between dual therapies are recommended, while direct insulin transitions are also observed. Non-monotonicity in a few health states appears in the result because we only focus on the QALY values in this perspective and there are very small differences in QALY, which is also multiplied by the transition probabilities of less than 1. This can be neglected for the stability of the treatment process.

Table 5.2.11 Optimal policy result from patient perspective

T		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
S	s_t																				
1	(h_c,1,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
2	(h_c,2a,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
5	(h_c,1,$_{bu}$)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
6	(h_c,2a,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
10	(h_u,2a,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*
14	(h_u,2a,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
15	(h_u,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*

17	insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
T		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
S	s_t																				
1	(h_c,1,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*W*
2	(h_c,2a,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*A*	*A*	*W*
3	(h_c,2b,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
4	(h_c,3,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*
5	(h_c,1,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*
6	(h_c,2a,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*A*	*A*	*A*	*A*	*I*	*I*
7	(h_c,2b,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*
8	(h_c,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
9	(h_u,1,b_c)	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
10	(h_u,2a,b_c)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*	*I*
11	(h_u,2b,b_c)	*W*	*W*	*W*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*A*	*W*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
12	(h_u,3,b_c)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
13	(h_u,1,b_u)	*A*	*A*	*A*	*A*	*A*	*A*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
14	(h_u,2,b_u)	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
15	(h_u,2.2,b_u)	*W*	*W*	*W*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
16	(h_u,3,b_u)	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*	*I*
17	Insulin	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*	*W*

6. SUMMARY OF RESULTS

Our study provides a mathematical approach to the controversy about when insulin therapy should be initiated in patients with type 2 diabetes. We made several assumptions at the beginning of the study. However, the most important of these is that we set it for a specific patient profile because observing other health problems such as CVD, heart failure and chronic kidney disease increases the risk factors of patients and makes their metabolic states more complex.

On the other hand, we get some conclusions from our model.

First, we can assert that controlling the weight is almost as important as the patient's blood sugar control for the group of type 2 diabetic patients in our study, and that also it leads to gain a good quality of future life for a patient.

Second, the effect of cost and QALY gains on initiation of insulin, which varies according to the type of therapy, demonstrates the importance of the type of therapy used.

Furthermore, the importance of the current metabolic state of a patient (i.e., which HbA1c and BMI values are under control) is recognized. The uncontrolled HbA1c and BMI values together negates the type of dual therapy used after a certain age (58 years) and makes it important to start insulin directly. The use of GLP1 RA is not preferred because it is injectable and more expensive than SGLT 2i. Unlike the other types of therapy, insulin therapy causes a reduction in a patient's QALY in total from year to year because of its weight gain effect.

Additionally, some sensitivity analysis was used to test the model by changing the values in the table below.

Table 6.1 Summary of tests done in the sensitivity analysis

Parameter	Value Used in the Base Case	Value Changed to for Sensitivity Analysis
Medical cost of triple therapy	$ 2000	$ 1000
		$ 500
Disutility of uncontrolled HbA1c	0.16	0.07
		0.25
		0.5
The discount factor	0.97	0.81
		0.8
Annual cost-effectiveness ratio	$ 50000	$ 100000
		$ 200000
The starter utility of insulin therapy	0.813	0.7
Cost of metformin mono therapy	$ 1255.65	$ 4000
Perspective	Physician	Patient

Because we did not have the necessary data, first sensitivity analysis was applied to the medical cost of triple therapy to see how much triple treatment cost changed the result. It was found that the result has changed at a cost of $ 500.

In order to see the effect of non-control of HbA1c level which is an important parameter in our health states, the results were evaluated for lower and higher values than the value we considered. It was found that a disutility up to 0.07 does not actually make a difference with the absence of it. Early insulin initiation is recommended for a larger value of 0.25, while direct insulin initiation has been detected in dual and triple therapies for a high value of 0.50.

By testing the discount factor, it was observed that if the value is between 0.81 and 0.80, it may be advisable to eliminate the difference between dual therapies and start insulin directly after 40 years of age.

It was observed that doubling the putative cost-effectiveness ratio resulted in initiating insulin treatment earlier, and when it was quadrupled, the individual should stay on the dual therapy if (s)he uses a dual therapy and more wait action would make sense in general.

The results were seen when the larger, compared to other starter utilities (0.68 and 0.80), insulin initiation starter utility (0.813) had an occasional value. While the results of the base case already represent the value for greater than 0.80, it was tested by assigning a value of 0.70 as it would be difficult to start insulin if it was less than 0.68.

The fact that monotherapy with much lower cost than other costs resulted in continuous wait action led us to see how the result changes if we accept this value close to other values. As a result, it was suggested action A, which can be considered more logical, for the health state of mono therapy when the two parameters (HbA1c and BMI) are not under control.

For the last sensitivity analysis, the changes in the optimal policy were observed when the perspective is changed to the patient perspective by resetting the cost of all types of therapies. In this way, it was determined how the perspective can make big differences in optimal policy.

7. CONCLUSION

7.1 Thesis Contribution

In our model, we use the Markov decision process to determine the optimal time for insulin onset for type 2 diabetic patients. We found that the patient's metabolic states and the type of therapy currently used has a direct effect on insulin initiation time. We have also investigated and demonstrated the sensitivity of this optimal time to start insulin to annual therapy costs (or the reward for future years of life). In conclusion, based on our study, we can clearly state that the patient's profile (whether there are any other chronic disorders), the metabolic states (whether weight and blood sugar levels are under control), and the medication the patient is currently using play an important role in making a decision about starting insulin. On the other hand, based on our numerical experiments, for the groups of patients with type 2 diabetes we identified, we can recommend that patients should remain in metformin + SGLT 2i therapy until the age of 60 when any of HbA1c and BMI values are not under control, and if both of them are not under control, they would pass insulin by the age of 58. As a result of our study, we provide a mathematical perspective in addition to the effects of therapy in guideline on insulin therapy which often has a controversy over the early or late onset, and on the cost values of the types of therapy used before insulin initiation.

7.2 Limitations and Future Works

To the best of our knowledge, a mathematical approach for initiating insulin has not been studied in the literature before, thus, it has not been possible to work with the relevant

longitudinal data in the short period of writing this thesis. Actual data will make the transition probability matrices more accurate, especially BMI-related probabilities.

Due to the shortage of access to an already held data, it was necessary to ignore some of the situations and reveal a general conclusion. Since the data are provided from the literature and the data for each sex are not clear, the probabilities of transition matrices and QALY inputs and cost values are considered as an average value without considering gender and age differences.

In addition, in our study, we assumed that patients always go forward in the treatment process (i.e. for example, if they switch from monotherapy to dual therapy, they cannot switch to monotherapy again, or that there will be no return to oral antidiabetics after starting insulin therapy) but these assumptions can be experienced in clinics, as our expert doctors say. Furthermore, our model considers a single patient type according to guideline (chronic disease-free, hypoglycemia risk and cost is not a priority, weight gain is minimized, and weight loss is encouraged) but it does not include other patient profiles. For a future study, an inclusive new model, based on carefully maintained data and considering the fact that most patients with type 2 diabetes also have other chronic diseases, will make the clinical applications of our model that we presented in this study for the sake of a beginning more practical and meaningful.

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BIOGRAPHICAL SKETCH

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