ABSTRACT

MASON, JENNIFER E. Optimal Timing of Statin Initiation for Patients with Type 2 Diabetes. (Under the direction of Dr. Brian Denton).

HMG Co-A reductase inhibitors (statins) are an important part of the treatment plan for patients with type 2 diabetes. However, the optimal time to initiate treatment is influenced by many factors. We investigate two such factors in this thesis: (1) the decision maker's criteria for optimal treatment initiation and (2) the patient's long-term adherence to treatment.

Statins are effective in reducing cholesterol, a primary risk factor for cardiovascular disease in patients with diabetes. However, patients who are prescribed statins often stop taking the drug altogether or take less than the prescribed amount. This imperfect adherence can lessen the drug's benefit. We propose a Markov decision process (MDP) model to optimize the treatment decision for hypercholesterolemia in patients with type 2 diabetes while considering issues of adherence to statins. Our model incorporates a discrete time Markov process for adherence states of the patients. We found that in the long run approximately 25% of patients remain highly adherent, taking 80 to 100% of their medication. We also found, based on the optimization model, that patients with imperfect adherence should start statins 5 to 7 years later than their perfectly adherent counterparts. Although adherence levels greatly affect the optimal start time for statins, we found that starting statins later in life did not significantly increase the expected quality adjusted life years for patients with imperfect adherence. We conclude that it is more important for patients to improve their adherence than to adjust the timing of initiation to help compensate for imperfect adherence.

We also consider three different decision making criteria with our model: society, patient, and third-party payer. Decision makers with these different perspectives have different objectives in mind. We have assumed that the patient is concerned with his or her quality of life, the third-party payer is concerned with minimizing expected costs, and society is concerned with maximizing expected rewards minus costs. These decision maker objectives are reflected in different reward functions in our MDP model. We find that it is optimal for patients to initiate statins early in the decision horizon under the patient perspective while the earliest optimal start times under the society and third-party payer

perspectives are generally 4 and 15 years later, respectively.

Finally, we formulate an inverse optimization model to estimate the implied societal willingness to pay. We use our MDP model and U.S. guidelines for initiating statins to estimate the implied reward for a year of quality life. Our estimates indicate a societal willingness to pay between \$120,000 and \$160,000 per quality adjusted life year.

Optimal Timing of Statin Initiation for Patients with Type 2 Diabetes

by
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BIOGRAPHY

Jennifer Elizabeth Mason was born on January 30, 1985, to Ford and Martha Mason in Columbia, SC. Her love of mathematics and puzzles was likely fostered by her older brother, Jonathan. Jennifer received her Bachelor of Science in Mathematics from the University of South Carolina Honors College in 2007. She then made the big move north to pursue the study of Operations Research at North Carolina State University. After the completion of her Masters degree, Jennifer will continue her studies at N.C. State by pursuing a PhD in Industrial and Systems Engineering.

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LIST OF ABBREVIATIONS

ATP III: Adult Treatment Panel III

CDC: Centers for Disease Control

CHD: Coronary Heart Disease

DEMS: Diabetes Electronic Management System

HDL: High-Density Lipoprotein

IFR: Increasing Failure Rate

LDL: Low-Density Lipoprotein

Mayo EMR: Mayo Electronic Medical Records

MDP: Markov Decision Process

NCEP: National Cholesterol Education Program

NHI: National Health Informatics

PDHR: Post Decision Horizon Reward

QALY: Quality Adjusted Life Year

RCT: Randomized Control Trial

TC: Total Cholesterol

UKPDS: United Kingdom Prospective Diabetes Study

Chapter 1

Introduction

The Centers for Disease Control (CDC) estimates show that 23.6 million people in the United States, or approximately 8% of the population, have diabetes [1]. Between 90 and 95 percent of all diagnosed diabetic patients have type 2 diabetes. People who have type 2 diabetes are not able to produce enough insulin or their cells are resistent to insulin. In addition to having trouble managing their blood glucose, patients with diabetes often have high cholesterol, high blood pressure, and poor circulation. Due to these risk factors, these patients are at a higher risk for poor health outcomes such as heart attack, stroke, limb amputation, and renal failure. Diabetes affects more than just the health of the diagnosed patient. In 2002, medical expenditures and loss in productivity due to diabetes was reported to be $132 billion [2]. It is important to study the progression of type 2 diabetes because the number of people that have this disease is growing very quickly in the U.S. and other countries. Prevalence rates of type 2 diabetes more than doubled between 1990 and 2005 [3].

It has been shown that patients with diabetes are at much higher risk for adverse events related to cardiovascular disease such as heart attack or stroke than their counterparts without diabetes [4] [5]. There are a number of controllable risk factors including total cholesterol (TC), blood pressure, and HbA1c (the latter is a surrogate measure of long run average blood sugar). In recent years TC has become a focus of attention. TC can often be reduced through diet and exercise; however, in practice patients are often unable to adhere to such lifestyle changes long term or these changes are insufficient for reaching metabolic goals. HMG Co-A reductase inhibitors (statins) are an important part of a medication treatment plan for reducing TC [6].

While there are rational guidelines that make recommendations for when a patient should begin statin treatment [7] [6], the guidelines do not consider a patient's adherence to the medication. Patients often do not take all of their medication as prescribed by their doctors. A patient that does not take all of her statin doses may not realize the full benefit of the cholesterol-lowering drug. Our results show that the percentage decrease in TC is significantly reduced when patients are less than fully adherent. By measuring the percentage of days a patient takes her medication estimated from pharmacy refills, we are able to determine a measure of adherence and monitor their adherence behavior over time. We find that only 25% of patients remain highly adherent in the long term. We use these adherence findings to determine the optimal times for patients to initiate statins.

Although multiple statistical models exist to predict the probability of a patient having a coronary heart disease (CHD) event or stroke in the future [8] [9] [10], methods for using this information to determine a patient's treatment plan are needed. We propose a Markov decision process (MDP) model to determine the optimal time for patients to start statins based on their TC and high-density lipoprotein (HDL, also known as "good cholesterol") using one of these statistical models. Also built into our model is a Markov model of the patient's adherence to the medication, once statins are initiated.

We compare the results of our model as found from three different perspectives: society, patient, and third-party payer. The patient perspective focuses on maximizing the patient's expected quality of life over her lifetime. The goal with the third-party payer perspective is to minimize expected costs related to treatment and hospitalizations. The society perspective combines the goals of the other two perspectives by maximizing the monetary reward for quality adjusted life years minus the costs of treatment and hospitalizations. We find that the earliest optimal start times are for the patient perspective with the earliest optimal start times generally occurring 4 and 15 years later for the society and third-party payer perspectives, respectively.

One of the parameters in our model, the monetary reward for a patient's year of life, is highly debated. We formulate and solve an inverse optimization problem to estimate the implied societal willingness to pay based on U.S. guidelines for statin initiation. We present a linear programming formulation to find this reward value by minimizing the difference between the total rewards accumulated with the policy generated by the MDP model and the policy that follows a set of U.S. guidelines for statin initiation. We find that this reward value ranges from approximately \$120,000 to \$160,000, and increases with respect to age. We also find differences in the estimates with respect to gender.

The remainder of this thesis is organized as follows. Chapter 2 presents a brief literature review of the medical decision making literature. Chapter 3 describes the MDP model formulation including the adherence Markov model. We also present results from numerical experiments using the MDP model and identify a number of interesting insights about optimal policies for statin treatment in the presence of imperfect adherence. In Chapter 4, we define the three decision-maker perspectives in detail and report the results associated with these perspectives. In Chapter 5, we present a linear program to estimate the implied willingness to pay based on current U.S. guidelines for statin treatment. Finally, Chapter 6 highlights the main findings, limitations, and opportunities for future work.

Chapter 2

Literature Review

2.1 Introduction

Richard Bellman coined the term Dynamic Programming to describe the process of solving multi-stage decision problems. Bellman's classic paper [11] describes the initial theory of dynamic programming. MDPs extend dynamic programming to decision making in the presence of uncertainty. Martin Puterman's book *Markov Decision Processes: Discrete Stochastic Dynamic Programming* [12] thoroughly describes the theory and some applications of MDPs, including methods for solving stochastic MDPs such as our model. In this literature review we focus on the medical decision making literature and methods for understanding adherence to treatment.

2.2 Medical Decision Making

Markov models are not new to medical decision making. In 1993, Sonnenberg and Beck [13] highlighted that many clinical problems could be modeled using Markov processes. Recent years have seen an increase in research in this area, as well as extensions to treatment optimization based on MDPs. More recently, Schaefer et al. [14] reviewed many examples of MDPs that have been presented in the medical literature to solve problems related to kidney transplantation, breast cancer screening, and treatment of many diseases. The sequential nature of medical decision making and the uncertainty of a patient's health status and benefit from treatment suggest that MDP models are very appropriate. Following are some notable examples that have some similarity to our MDP model.

Shechter et al. [15] use an MDP model to find the optimal time to initiate HIV therapy while maximizing the patients quality of life. At monthly decision epochs, the decision is made to initiate therapy or wait until the next month to decide. The health states are based on CD4 count and the reward function is expected lifetime in months. They assume a stationary infinite horizon model and prove that if it is optimal to initiate treatment at a given CD4 count, it is also optimal to initiate treatment for patients with higher CD4 counts.

Alagoz et al. [16] [17] [18] have written several papers on different versions of their MDP models for the optimal timing of liver transplantation. The simplest model finds the optimal timing for a patient to have a transplant from a living donor. The patients transition probabilistically through health states defined by a scoring system for end-stage liver disease. With the donor assumed to be available at any time, the MDP maximizes the patient's quality adjusted lifetime – striking a balance between having the transplant before the patient becomes too sick and waiting long enough due to the limited amount of time a patient can live after a transplant. Alagoz et al. also explore the more complicated problem of optimal timing of a liver transplant when both living-donor and cadaveric organs are considered. For these various contexts they are able to identify a number of structural properties of the optimal policy. For example, they proved that if the probability transition matrix has the increasing failure rate (IFR) property, the total discounted expected reward is nonincreasing in h (the patient's health state): $V(s) \geq V(s+1)$ where $s = 1, ..., H$ where greater values of s represent worse health states. They also proved that if the transition probability P is an IFR matrix and P and the post transplant expected future rewards $r(h, T)$ satisfy certain other conditions outlined in the paper, then there exists an optimal control-limit policy.

Our MDP model is similar to the HIV and liver transplantation MDPs since the patient's health is defined by a finite set of states based on risk factors, and there is a single action that can be taken with all three models (treat HIV, transplant liver, and initiate statins). Our model is different from the MDPs for HIV therapy and liver transplantation models in several ways. First and most obviously because it models a decision problem for a different disease. With diabetes there are different risk factors to consider compared to HIV and liver disease. Our model considers multiple adverse events (CHD and stroke). Our model also differs in that it incorporates the influence of patient adherence to treatment.

2.3 Adherence

Studying the behavior, effects, and causes of adherence to medications is an increasing focus of medical research. Medical adherence is often studied through retrospective studies of medical records. Different methods exist for determining a patient's adherence to a treatment.

Shalev et al. [19] investigate the effect of statin therapy in a diverse cohort of patients treated for dyslipidemia. Clinical trials are limited studies because they do not include individuals with multiple comorbid conditions taking many medications. Patients were divided into primary and secondary prevention cohorts. Using proportion of days covered based on pharmacy claims data for measurement of adherence, Shalev et al. demonstrate a strong association between adherence to statin treatment and improved survival of patients. As would be expected, higher continuity of treatment is associated with longer survival for patients with and without a history of CHD.

Pladevall et al. [20] use claims data to study the relationship between adherence to metformin, statins, and ACE inhibitors and clinical outcomes of diabetes patients (e.g., HbA1c, LDL levels, and blood pressure). Patients were followed over 3 years. A continuous measure of medication gaps (CMG) was used as a measure of nonadherence. This measure reports the proportion of days the patient has not filled their prescription over the observation. Patients with CMG greater than 20% were defined to be nonadherent in this study. Findings showed statistically significant associations between nonadherence and increases in HbA1c and LDL levels.

Another study of medical and pharmacy claims (over 3 years) analyzed the burden of medication among patients with hypertension. Robertson et al. [21] track the persistence of medication and patients medication possession ratio of lipid lowering drugs. They reported that patients with greater burden of medication had longer persistence and were more likely to be adherent, concluding that medication burden should not deter doctors from prescribing medications.

Nichol et al. [22] use a California Medicaid cohort to find the percentage of days covered as a measure of adherence to anti-hypertensive and lipid-lowering medications.

Annual transition probabilities were calculated for year one through year six after initiation of treatment. The study found that about 40% of the population to be nonadherent after the first year of statin initiation with race, insurance coverage, and type of lipid-lowering medication being important factors in transitioning to the nonadherent states. We also use the method of reviewing medical and pharmacy claims to understand the behavior and effects of patients' statin treatment behavior.

Our adherence model differs from the above models in one main way. To our knowledge our model is the first to directly associate adherence level (of statins) to the associated risk factor (TC). This association allows our MDP model to directly consider the influence of patient adherence to the optimal time to initiate statin treatment.

2.4 Decision Maker Perspectives

There are multiple parties involved in making healthcare decisions: patients, families, doctors, and third-party payers (i.e. insurance companies). Previous work has been done with consideration of different decision maker perspectives. Ross et al. [23] formulate a Monte-Carlo simulation based on a Markov model to test different screening strategies for prostate cancer. Their analysis compares screening strategies in terms of health outcomes (effect on the patient) and resources used (effect on the healthcare system). They report the nondominated strategies as the best and make further comparisons among these policies. Those that were dominated were both less effective and used more resources than the other strategies.

Ivy [24] presents a partially observable MDP to develop a tool for determining the most cost-effective way to screen for and treat breast cancer while taking into account the patient's and the payer's objectives (maximizing discounted expected utility and minimizing discounted expected costs over the patient's lifetime, respectively). The tool also allows for a combination of these objectives. As in Ross's model, Ivy uses her model to develop efficient frontiers to balance differing objectives and preferences.

Unlike the papers by Ross and Ivy, we use our model to determine the optimal timing of initiating treatment using different perspectives. Since we do not test multiple screening policies, we do not develop efficient frontiers to balance preferences. We combine the patient and third-party payer perspectives into the society perspective.

2.5 Inverse Optimization

Lee et al. [25] use a computer simulation to model the treatment costs and effects on QALYs of a population with end-stage renal disease. Incremental cost-effectiveness ratios of current practice to the next least costly option and no dialysis were calculated. While Lee et al. use these cost-effectiveness ratios to estimate the monetary reward for a patient's quality year of life, we formulate a linear program to determine this value. Our inverse optimization problem determines the implied societal willingness to pay based on U.S. guidelines for statin initiation.

Chapter 3

Patient Adherence to Treatment

3.1 Introduction

Medical adherence, the extent to which a patient continues an agreed-upon mode of treatment, can influence a treatment's effectiveness. Outcomes from randomized controlled trials (RCTs) are estimates based on interventions, and patients are often pre-selected for their ability to adhere to the treatment regimens. Therefore reported findings can be misleading about the true effect of treatment. For example, statin treatment has been shown in RCTs to be effective in secondary prevention of MI [26] [27] [28]. Despite this benefit, observational studies have shown that many patients do not remain adherent to statins even after a myocardial infarction [29].

Due to diabetes patients' increased risk of heart attack, stroke, and other complications such as blindness and kidney failure, medical care plans require a number of treatments to control risk factors (blood sugar, blood pressure, blood lipids, depression). The medical regimens and guidelines for self-management of diabetes are numerous and complex [30] [31]. They have the potential to greatly influence an individual's health, however, they are highly dependent on a patient's ability to adhere [32] [33] [34] [35]. Because of this, it is particularly important to understand the effects of varying levels of adherence on a diabetes patient's risk for adverse events.

A number of studies have observed imperfect patient adherence [36] [37] [26] (even in some randomized trials [38]). We develop an MDP model to determine the influence of adherence to statin treatment on intermediate outcomes (lipid levels) and long term outcomes (cardiovascular events) in a large cohort of patients with type 2 diabetes. We report the development of an adherence model that considers the implications of patients taking less than the prescribed dosage of statins on their total cholesterol levels. We further use the United Kingdom Prospective Diabetes Study (UKPDS) model [39] [40] [9] to estimate this effect on the patient's risk of cardiovascular events. This model is a proportional-hazard rate model developed from a large study of type 2 diabetes patients in the U.K. The variables included in the model are the age, sex, ethnicity, smoking status, HbA1c, systolic blood pressure, and lipid ratio (TC/HDL) of the patient. Combining this within an MDP model [41] we study the influence of imperfect adherence on the optimal start time of statins over the course of a patient's lifetime and evaluate the effect of adherence on expected quality adjusted life years (QALYs) for diabetic patients. QALYs are a commonly used measure of disease and treatment burden to the patient in the health policy and operations research literature [42]. Both the quality and quantity of a patient's lifetime are captured with this measure. We estimate the total incremental benefit possible from improved adherence. We also estimate the influence of optimal timing of treatment initiation assuming imperfect adherence. For instance, we investigate whether the adverse effects of stochastic adherence on QALYs can be mitigated by changing the timing of initiation.

3.2 Methods

The optimal statin timing problem can be formulated as a discrete time, finite horizon, discounted MDP in which patients transition through health states corresponding to varying risks of future complications, their history of complications, and death from other causes unrelated to diabetes [41]. Metabolic risk factors that influence the risk of complications include blood pressure, cholesterol, and HbA1c. A patient's HbA1c is measured with a simple blood test and is primarily used to identify average blood sugar levels over time. In our model, blood pressure and HbA1c values are age dependent, and TC and HDL evolve probabilistically over time according to a Markov process as patients age. HDL is known as the "good" cholesterol and LDL is known as the "bad" cholesterol. These two, together with triglycerides, make up TC. These continuous attributes are represented as a discrete set of states defined by clinically relevant thresholds (low (L), medium (M), and high (H), and very high (V)). At each of a set of annual decision epochs (yearly time periods where decisions must be made) the patient is observed to be in one of many health states which can be grouped into two categories: *living states* and *absorbing states.* Living states define the patient's current metabolic risk factors and the history of nonfatal cardiovascular events such as myocardial infarction (hereafter referred to as CHD event) and stroke. Absorbing states include death from cardiovascular complications and other causes. In each epoch a decision maker (e.g. patient and/or physician) selects one of two possible decisions: *initiating statin treatment* and *deferring the decision until the next epoch.* If the decision maker (e.g., the patient) delays the decision, then she faces the same decision in the next epoch, provided she does not enter an absorbing state. Once a patient has initiated statins, the living states also include the patient's level of adherence. Following is a brief description of the MDP model:

Time Horizon: The decision to initiate statins is revisited periodically within a finite horizon with N (yearly) decision epochs, with nonstationary transition probabilities.

Table 3.1: Ranges for TC and HDL.

	L	M	H	V
TC	< 160	160 - 200	200 - 240	> 240
HDL	< 40	40 - 50	50 - 60	> 60

States: As described above, there are two categories of states: *living states* and *absorbing states.* We let L represent the set of all living states and S represent the set of all absorbing states. Living states define the patient's risk state. We denote total cholesterol states by the set $L_{TC} = \{L, M, H, V\}$ and HDL states by the set $L_{HDL} = \{L, M, H, V\}$ as seen in Table 3.1. Also included in this state definition is the number of nonfatal CHD and stroke events. In our model, the patient may incur up to 5 of each event. In order to have a finite state space, we use 5 as a reasonable upper bound on the number of strokes or CHD events a patient may incur over the decision horizon. The sets of event states are $L_{CHD} = \{0, 1, \ldots, 5\}$ and $L_{STR} = \{0, 1, \ldots, 5\}$. Thus, $L = L_{TC} \times L_{HDL} \times L_{CHD} \times L_S$. There are a total of 576 living states in our model. Patients transition to absorbing states $S = \{D_{CHD}, D_S, D_O\}$ when they have a fatal CHD event (D_{CHD}), fatal stroke event (D_S), or death from other causes (D_O) not related to cardiovascular disease. Including these absorbing states, there are a total of 579 states in our model. The treatment status of the patient is defined by a binary indicator $m \in M = \{0, 1\}$, where 0 and 1 refer to *not using* and *using* statins, respectively. Patients that initiate statins transition probabilistically through a set of adherence states. Upon initiation, the patient's adherence level becomes part of the living state definition. Letting y represent the percentage of the year a patient takes her medication, the adherence state A is defined to be

$$A = \begin{cases} \text{NON} & \text{if } y \leq 10\%, \\ \text{LOW} & \text{if } 10\% < y \leq 40\%, \\ \text{MED} & \text{if } 40\% < y \leq 80\%, \\ \text{HIGH} & \text{if } y > 80\% \end{cases} \tag{3.1}$$

We consider patients to be nonadherent if they take their medication 0 - 10% of the time. In our model we assume that the patient's adherence state is independent of their health state. In other words, a history of CHD or stroke does not make them more adherent (a reasonable assumption given poor adherence is observed in patients even after a cardiovascular event [29]). For patients that initiate treatment, we define their living state as $L' = L \times A$. We use ℓ to index the sets L and L' for untreated and treated patients respectively.

As in other studies, we defined patients to be adherent if they took their medication at least 80% of the time [26] [43]. Once a patient initiates statin treatment, they probabilistically enter one of the four adherence states and continue to move probabilistically between the adherence states every year after initiation. Figure 3.1 illustrates the adherence Markov process. The MDP model considers all of the future rewards gained when deciding whether or not to start statins, and the adherence process reveals the actual health impact and cost of statin treatment in future years.

Adherence states are assumed to be associated with the cost of statin treatment. We assume that a patient who is adhering to statins at a certain level will pay an amount consistent with the midpoint of the adherence range. For example, a patient that is adhering in the 40 - 80% range will have annual statin medication cost estimated at 60% of the annual full dose cost.

Each adherence level corresponds to an associated change in TC. We assume no significant change in the patient's HDL (see Appendix A for more details). Although some RCTs have indicated moderate increases in HDL, we did not observe this in our data set.

Decisions: Initiating treatment is assumed to be a one-time irreversible decision. This is consistent with clinical practice in which the intention is for patients to remain on statins

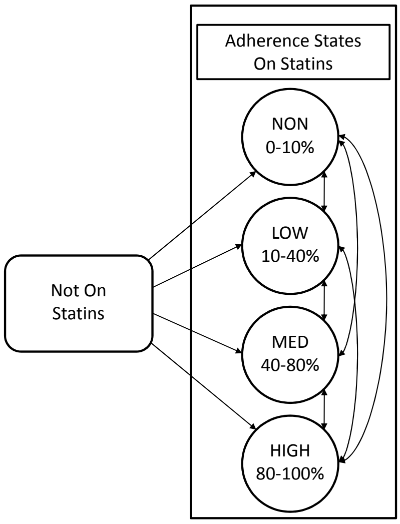

Figure 3.1: Diagram of the adherence states and transitions.

permanently, provided they are tolerated (in a small number of cases statins must be discontinued due to liver problems or myalgia). Statins have been observed to cause a proportional decrease in cholesterol based on results of clinical control trials [44], [45]. Thus, statins reduce the probability of transitioning to absorbing states by decreasing the probability of fatal CHD events and strokes. Once statin treatment is initiated, the patient continues on treatment until she transitions to an absorbing state $\ell \in S$, which terminates the process. The possible decisions that can be made depend on the current value of m:

$$a_{(\ell,m)} = \begin{cases} \{I, W\} & \text{if } m = 0 \text{ and } \ell \in L \\ \{W\} & \text{if } m = 1 \text{ and } \ell \in L \end{cases} \tag{3.2}$$

where I denotes initiating treatment and W deferring the decision until the next epoch (if $m = 0$), or continuing treatment (if $m = 1$). We assume that patients who have had a stroke or CHD event start statins immediately after the event occurred, as this is also consistent with clinical practice.

Transition Probabilities: Our model employs four categories of probabilities: transition probabilities among health states, transition probabilities among adherence states, probabilities of CHD or stroke events, and probability of death from other causes. At epoch $t \in T$, death from other causes occurs with probability $p_t(D)$. Otherwise, if the patient is in state $(\ell, m) \in L \times M$, a nonfatal stroke or CHD event occurs with probability $\pi_t^S(\ell, m)$ and $\pi_t^C(\ell, m)$, respectively, which depend on the patient's age, health state, and other risk factors such as race and gender. Fatal stroke and CHD events occur with probability $\overline{\pi_t^S}(\ell, m)$ and $\overline{\pi_t^C}(\ell, m)$, respectively. Given that the patient is in health state $\ell \in L$, the probability of being in state ℓ' in the epoch following is denoted by $q_t(\ell'|\ell)$. Given that the patient is in state (ℓ, m) at epoch t, the probability of moving into one of the absorbing states $s \in S$ at epoch $t+1$ is denoted by $p_t(s, m|\ell, m)$, where

$$p_t(s, m|\ell, m) = \begin{cases} p_t(D) & \text{if } s = \text{death from other causes} \\ \overline{\pi_t^C}(\ell, m) & \text{if } s = \text{fatal CHD event} \\ \overline{\pi_t^S}(\ell, m) & \text{if } s = \text{fatal stroke} \end{cases} \tag{3.3}$$

for $(\ell, m) \in L \times M$, and $p_t(s, m|s, m) = 1$ for all $t \in T$ and $m \in M$. We define $p_t^d(\ell', m'|\ell, m)$ to be the probability of being in state (ℓ', m') at epoch $t+1$, given action $\alpha \in a_{(\ell,m)}$ is taken in state (ℓ, m) at epoch t. This can be written as:

$$p_t^W(\ell', m'|\ell, m) = \begin{cases} \big[1 - \sum\limits_{s \in S} p_t(s, m|\ell, m)\big] q_t(\ell'|\ell) & \text{if } m = m' \text{ and } \ell, \ell' \in L \text{ and } s \in S, \\ p_t(s, m|\ell, m) & \text{if } m = m' \text{ and } \ell \in L,\ \ell' = s \in S, \\ 1 & \text{if } \ell = \ell' = s \in S, \\ 0 & \text{otherwise.} \end{cases} \tag{3.4}$$

$$p_t^I(\ell', m'|\ell, m) = \begin{cases} \big[1 - \sum\limits_{s \in S} p_t(s, 1|\ell, 1)\big] q_t(\ell'|\ell) & \text{if } m = 0,\ m' = 1 \text{ and } \ell, \ell' \in L \text{ and } s \in S, \\ p_t(s, 1|\ell, 1) & \text{if } m = 0,\ m' = 1,\ \ell \in L \text{ and } \ell' = s \in S, \\ 0 & \text{otherwise.} \end{cases} \tag{3.5}$$

Transition probabilities $q_t(\ell'|\ell)$ are estimated from the Mayo Clinic data set [41], the probabilities $p_t(D)$ are based on the US CDC tables, and the probabilities $\pi_t^C(\ell, m)$, $\pi_t^S(\ell, m)$, $\overline{\pi_t^S}(\ell, m)$, and $\overline{\pi_t^C}(\ell, m)$ are based on the UKPDS risk engine model.

Rewards: $r(\ell, m)$ is the dollar reward for QALYs minus treatment costs accrued in state (ℓ, m) as described in the following equation:

$$r(\ell,m)=\begin{cases} R(\ell,m)-C^{O} & -\left(CF^{S}(\ell)+CF^{CHD}(\ell)\right)-mC^{ST}(\ell) \\ & -\left(C^{S}(\ell)+C^{CHD}(\ell)\right), \text{ for } t=1,\dots,T-1 \\ R(\ell,m)-C^{O} & -\left(CF^{S}(\ell)+CF^{CHD}(\ell)\right)-mC^{ST}(\ell) \\ & -\left(C^{S}(\ell)+C^{CHD}(\ell)\right)+E[PDHR|\ell], \text{ for } t=T \end{cases} \tag{3.6}$$

where $R(\ell,m)=R_0(1-d^{S}(\ell))(1-d^{CHD}(\ell))(1-d^{ST}(m))$ is the reward for one QALY. R_0 is the reward for a quality year of life. When a patient has an event or initiates statins, her quality of life is decreased. The decrement factors d^S, d^{CHD}, and d^{ST} represent the decrease in quality of life from a stroke, a CHD event, or statins initiation, respectively. The costs C^O, C^{ST}, C^S and C^{CHD}, and CF^S and CF^{CHD} represent cost of other healthcare for diabetes patients, cost of statin treatment, cost of initial hospitalization for stroke and CHD events, and cost of follow-up treatment for stroke and CHD events, respectively.

The last term in (3.6), $E\left[PDHR|\ell\right]$, is the expected post decision horizon reward (PDHR) [41]. This expected PDHR is an end of horizon approximation that estimates the rewards for a patient living past the decision horizon (we assume the decision to start statins is made between age 40 and 80). The PDHR depends on the state and treatment status of the patient in the last year of the decision horizon and the number of years into the post decision horizon the patient lives. This approximation of rewards is needed because of the limited samples in the dataset for patients over age 80.

For a patient in state (ℓ,m) in epoch t, let $v_t(\ell,m)$ denote the patient's maximum total expected discounted rewards prior to her first event or death. The following recursion defines the optimal action in each state:

$$v_t(\ell,m)=\max_{\alpha\in a_{(\ell,m)}}\left\{r(\ell,m)+\lambda\sum_{\forall(k',m')\in L\times M,S\times M} p_t^d(k',m'|\ell,m)v_{t+1}(k',m')\right\} \tag{3.7}$$

where k' indexes states in L or S, and $\lambda\in[0,1)$ is the discount factor per stage, which is commonly set to 97% in health economic evaluations (see chapter 7 of [46] for a discussion of this). If $m=1$ only action W is permitted by definition. To simplify (3.7) we define $\mu_t(\ell)$ as the patient's *expected post-treatment reward* if treatment is initiated in state $\ell\in L$ at epoch $t\in T$. These rewards are determined recursively by a separate Markov reward chain. By dropping the superscripts in transition probabilities and letting $v_t(\ell)$ denote $v_t(\ell,0)$,

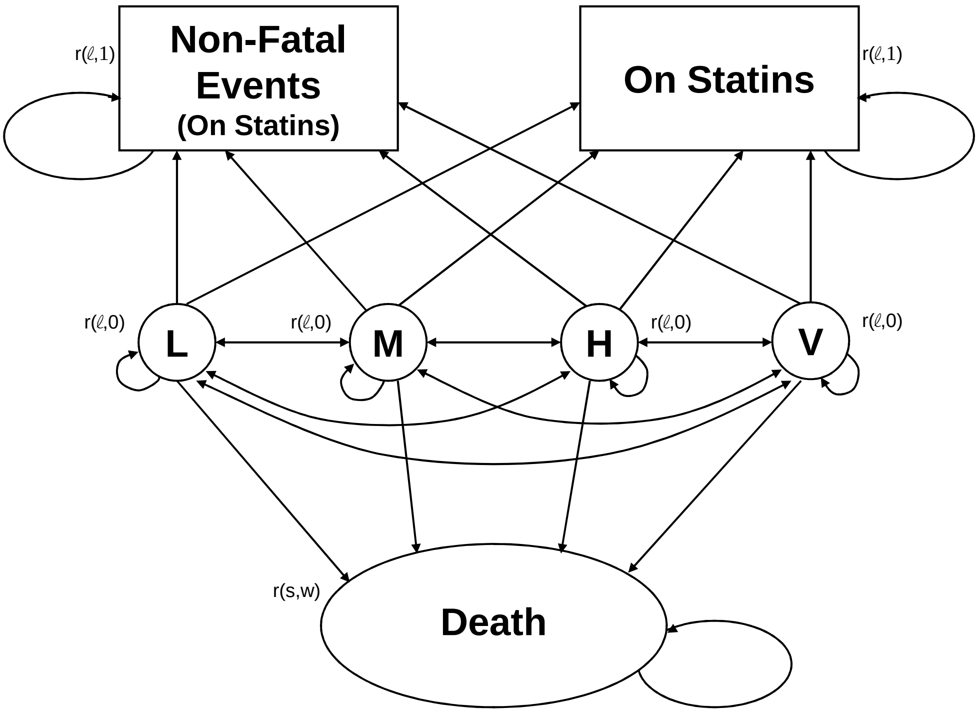

Figure 3.2: Simplified state transition diagram showing the relationship among death and off and on statins states.

(3.7) simplifies to:

$$v_t(\ell) = \max\left\{r(\ell,0) + \lambda \sum_{k' \in L,S} p_t(k',0|\ell,0)v_{t+1}(k'), \mu_t(\ell)\right\} \ \forall\ \ell \in L,\, t \in T, \tag{3.8}$$

By (3.8), if treatment is initiated in health state $\ell \in L$ at epoch $t \in T$, the patient receives the post-treatment reward $\mu_t(\ell)$ and leaves the decision process.

In words, the decision problem reduces to selecting between two options: (a) continuing the decision process or (b) selecting a one-time reward defined by expected future dollar rewards for QALYs minus costs until death. [12] gives a detailed description of solution methods and structural properties of MDPs such as this. In our model the imperfect nature of adherence decreases the post treatment reward $\mu_t(\ell)$. Thus adherence affects expected rewards associated with statin treatment and possibly the optimal decision.

A simplified state transition diagram can be found in Figure 3.2. Patients start in one of the living states (L, M, H, or V in this simplified description of the model). Before initiation of statins, patients probabilistically move between the living states and receive a yearly reward of $r(\ell, 0)$. Patients who initiate statins while in these living states subsequently transition to one of the two medication states representing treatment with statin medication, depending on whether the initiation of treatment is by choice before an event or by default as a result of an event. Upon entering one of these statins states the patient receives the one-time reward of $r(\ell, 1)$, the reward for all future years of life. The three absorbing states are represented by the death state at the bottom of the diagram.

3.3 Data and Study Population

Descriptions and values of the model parameters can be found in Table 3.2. All costs in the table are for one year.

Table 3.2: Description of model parameters including cost inputs and utility decrements for the reward function of the MDP model.

Parameter Type	Parameter	Value	Source
Cost Inputs	Initial hospitalization for stroke (C^S)	\$13,204	[47]
	Initial hospitalization for CHD (C^{CHD})	\$18,590	[47]
	Follow-up for stroke (CF^S)	\$1,664	[48]
	Follow-up for CHD (CF^{CHD})	\$2,576	[49] [48]
	Statin Treatment (C^{ST})	\$234	[50]
	Reward for a year of quality life (R_0)	\$100,000	[51]
	Discount Factor (λ)	0.97	[46]
Utility Decrements	CHD decrement (d^{CHD})	0.07	[52] [53]
	Stroke decrement (d^S)	0.21	[52] [54] [55]
	Statins decrement (d^{ST})	0.003	[56] [57] [58]

Other values drawn from the literature were the transition probabilities to absorbing states. The CDC mortality tables [59] were used to estimate the probability of death from other causes. The UKPDS model [40] [9] [60] was used to compute probabilities of incurring a CHD event or stroke.

The transition probabilities among health states were computed from an observational data set based on medical records from the Mayo Electronic Medical Records (Mayo EMR) and Diabetes Electronic Management System (DEMS) for a large cohort of patients receiving treatment for type 2 diabetes at Mayo Clinic, Rochester, MN. The DEMS dataset included 663 patients with cholesterol, HbA1c, blood pressure, and other laboratory values. A spline fit is used to interpolate missing laboratory values for cholesterol values to obtain an estimate of quarterly levels for these risk factors [41] [61].

Data from the National Health Informatics (NHI) database was used to compute adherence transition probabilities as described in Appendix B. NHI is a research-oriented database that is maintained by Ingenix and that is employed across United Health Group for longitudinal studies. It houses claims, membership, provider, and laboratory data for over 25 million current members and includes records going back to 1994. This data is subject to, and is protected by the Health Insurance Portability and Accountability Act (HIPAA). The eligible population for our study consists of members currently or previously enrolled in United Healthcare commercial medical and pharmacy benefit plans. We used pharmacy claims and lab data to measure the adherence transition probabilities and effects on total cholesterol. A complete list of model inputs can be found in Table 3.3.

Table 3.3: Summary of sources for model inputs.

Model Input	Source
Probability among Health States	Mayo EMR & DEMS
Adherence Transition Probabilities	NHI
Probability of Death from other Causes	CDC Mortality Tables
Probability of Stroke and CHD Events	UKPDS Models
Cost and Utility Values	Secondary Sources (see Table 3.2)

A cohort of 54,036 patients diagnosed with type 2 diabetes was identified by employing HEDIS criteria to administrative claims data in the NHI database. HEDIS requirements for claim encounter data include two face-to-face encounters with different dates of service in an outpatient setting or non-acute inpatient setting, or one face-to-face encounter in an acute inpatient setting or emergency department setting [62]. ICD-9 diagnosis codes were used to discern type 2 diabetes, and CPT procedure codes were used to discern the type of setting in face-to-face encounters.

To be included in the cohort, we imposed a requirement that a member must have been continuously enrolled in medical and pharmacy plans for a minimum length of five years, with at least one year of enrollment before the first encounter date, and at least four years of enrollment after the first encounter date. Although it's not possible to know a patient's medical history with certainty from claims data alone, the requirement of continuous enrollment lends support to the assumption that diabetes-related medical events during the five-year period would appear in the claims database. The NHI cohort contains 24,630 females and 29,406 males. Dates of first encounters range from January 1995 to June 2004. It is for this portion of patients for which we measure adherence and examine its effect on cholesterol levels.

We use the natural history model described in [41] as the basis for transition probabilities among living and absorbing states. We use the NHI cohort to evaluate the adherence portion of our model. Using pharmacy claims, we identified a subset of 12,658 members of the NHI cohort that initiated statin medication. To be included in this subset, we require that members have a minimum one-year period with no statin prescriptions, and a minimum four-year period of pharmacy enrollment after the first statin prescription is filled. A timeline was established for each individual, with the date of the first prescription marking the beginning of year one. We use possession of medication as a proxy for adherence [63]. The formula used is percent of days covered: the ratio of the sum of days supply to 365. We carry over any excess supply into the numerator of the quantity for the subsequent year. Raw adherence measurements range from zero to 100%.

3.4 Results

We used the NHI cohort data to count the number of transitions among the states from year to year and formed three transition matrices: years one to two, two to three, and three to four. The absolute differences among the three transition matrices are small, which suggests that the transition probabilities among adherence states are stationary. An estimate of the one-step transition matrix was constructed by computing the average number of people that transition among the states from year to year. We calculated the one-step transition matrices separately for men and women, though the differences were not significant. The initial probability vector for year one is $p = (0.091, 0.165, 0.257, 0.487)$, and the one-step transition matrix is given by the following:

$$P = \begin{array}{c} \\ NON \\ LOW \\ MED \\ HIGH \end{array} \begin{array}{c} \begin{array}{cccc} NON & LOW & MED & HIGH \end{array} \\ \begin{pmatrix} 0.787 & 0.106 & 0.082 & 0.025 \\ 0.498 & 0.205 & 0.213 & 0.084 \\ 0.199 & 0.154 & 0.390 & 0.257 \\ 0.028 & 0.046 & 0.189 & 0.737 \end{pmatrix} \end{array}$$

This transition matrix corresponds to the diagram of Figure 3.1. The remainder of this section is organized as follows. First we discuss interesting insights that can be drawn from the adherence Markov process alone. Next, we discuss results from the MDP model for optimal treatment policies in the presence of adherence.

3.4.1 Effect of Adherence on Total Cholesterol

Statins are effective in reaching lipid level goals by lowering total cholesterol; however, the effects of adherence on cholesterol levels is less studied. In this section we examine these effects by employing the available laboratory results for those members of the diabetes cohort who initiated statin medication. The mean of all laboratory readings for the year prior to statin initiation is used for year $t = 0$. To observe the effects of year-to-year changes in adherence, the mean of all readings in the last six month period is used for year $t = 1$.

Table 3.4: Percent changes in TC from pre-initiation to year one post-initiation based on adherence level.

Adherence States		Percent Change in TC
NON	$\leq 10\%$	-5.217%
LOW	10 - 40%	-8.214%
MED	40 - 80%	-18.081%
HIGH	$> 80\%$	-25.246%

The percent change in total cholesterol from pre-initiation ($t = 0$) to post-initiation ($t = 1$) of statins was calculated using these laboratory values. Each adherence level also corresponds to a mean percent change in total cholesterol as exhibited in Table 3.4. Analysis of our laboratory values showed statin treatment had no significant change in HDL. Randomized control trials report noticeable changes in HDL [45], but our analysis based

Table 3.5: Steady state distribution.

Steady State Distribution			
π_{NON}	π_{LOW}	π_{MED}	π_{HIGH}
0.4577	0.1101	0.1786	0.2536

on our observational data does not support this. More details on these calculations can be found in Appendix A.

3.4.2 Long Term Adherence

Using the adherence transition probability matrix, we computed the steady state distribution of the adherence states in Table 3.5. This shows that once a population starts statins, in the future approximately 25% of the patients will be in the HIGH adherence state. We also see that over 45% of the population is on average in the NON adherence state. With such poor long-term adherence, most patients will not obtain the full benefit of statin treatment. Table 3.6 shows it takes around 20 years for the distribution to reach the steady state but only 10 years for the percentage of highly adherent patients to reach 27%. We also calculate the mean first passage time to the nonadherence state in Appendix C.

3.4.3 Numerical Experiments

We use our MDP model to calculate the optimal start times for statins for both male and female patients based on the parameter estimates in Table 3.2. We first compare the optimal policy for statin initiation for stochastic and perfect adherers based on gender and living state for patients that have not had an event. We consider patients with perfect adherence as this case is consistent with the context of an RCT where patients are monitored closely. Next we calculate the expected QALYs over the patient's lifetime to gain insight into the influence of imperfect adherence. The difference between these results provides insight into the potential benefits of adherence improvement, such as might be achieved through patient educational interventions.

In Table 3.7 we present earliest optimal start times for females by total cholesterol and HDL levels. The differences in start times between patients assumed to have perfect ($A = HIGH$) and stochastic adherence (A evolves according to the Markov process in

Table 3.6: Adherence distribution over time.

$p \cdot P^n$	
n	Distribution of Adherence
1	{0.2186, 0.1055, 0.2349, 0.4411}
2	{0.2836, 0.1012, 0.2154, 0.3998}
3	{0.3277, 0.1024, 0.2044, 0.3656}
4	{0.3598, 0.1040, 0.1975, 0.3387}
5	{0.3837, 0.1055, 0.1927, 0.3181}
6	{0.4018, 0.1066, 0.1892, 0.3024}
7	{0.4154, 0.1075, 0.1866, 0.2905}
8	{0.4257, 0.1082, 0.1846, 0.2815}
9	{0.4335, 0.1087, 0.1832, 0.2746}
10	{0.4394, 0.1091, 0.1820, 0.2694}
11	{0.4439, 0.1094, 0.1812, 0.2655}
12	{0.4473, 0.1096, 0.1805, 0.2625}
13	{0.4499, 0.1098, 0.1801, 0.2603}
14	{0.4519, 0.1099, 0.1797, 0.2586}
15	{0.4533, 0.1100, 0.1794, 0.2573}
16	{0.4545, 0.1101, 0.1792, 0.2563}
17	{0.4553, 0.1101, 0.1790, 0.2555}
18	{0.4559, 0.1102, 0.1789, 0.2550}
19	{0.4564, 0.1102, 0.1788, 0.2546}
20	{0.4568, 0.1102, 0.1787, 0.2542}

Section 3.2) range from 0 to 11 years, depending on the patient's state. We see that it is optimal for patients with lower risk for CHD events and strokes to initiate treatment later in life. The earliest optimal start time for males for both perfect and stochastic adherence was age 40, no matter the state. Two model parameters explain why we see very early optimal start times, irrespective of the state and associated risk levels. In our model, statins cost $234 per year and the decrement to quality of life is 0.003, which is consistent with other studies [56] [57] [58]. This cost of yearly treatment is for a generic statin and is therefore a lower bound on the cost of branded statins. The monetary and quality of life decrements for having a CHD event or a stroke are much greater. With almost no downside for initiating statins and the benefit of helping to prevent very costly events, it is not surprising that the results show these early optimal start times.

In order to gain insight into the different start times for females, we compare the expected QALYs from age 40 when assuming patients start statins optimally given perfect or stochastic adherence. Although it is optimal for males in all states to initiate treatment at age 40, the effects of less than perfect adherence can be seen by comparing the expected QALYs. In Figures 3.3 and 3.4 we also see the expected QALYs for a patient starting statins when it is optimal for a perfectly adherent patient to start statins with a 24% increase in TC and an 8% decrease in HDL as reported in RCTs [44]. The QALYs associated with the RCT start times are the greatest.

3.4.4 Effects of Discounting

A larger difference in the expected future QALYs would be seen between patients who start statins optimally with perfect or stochastic adherence if we did not use λ to discount expected future costs and rewards for QALYs. We observe that discounting greatly diminishes the value of rewards in the distant future. We choose to discount all rewards and costs at a fixed rate of 3%. This is consistent with standard practice in the health policy literature [64]. A discussion of the impact of discounting on the results of our model can be found in Appendix D.

Table 3.7: Optimal start times for females based on TC/HDL with an annual statin cost of $C^{ST} = \$234$ and a decrement to quality of life for statins of $d^{ST} = 0.003$.

Optimal Start times for Patients with Stochastic Adherence															
V/L	H/L	M/L	L/L	V/M	H/M	M/M	L/M	V/H	H/H	M/H	L/H	V/V	H/V	M/V	L/V
40	40	40	40	40	40	40	42	40	40	42	46	40	40	45	51
Optimal Start times for Patients with Perfect Adherence															
V/L	H/L	M/L	L/L	V/M	H/M	M/M	L/M	V/H	H/H	M/H	L/H	V/V	H/V	M/V	L/V
40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40

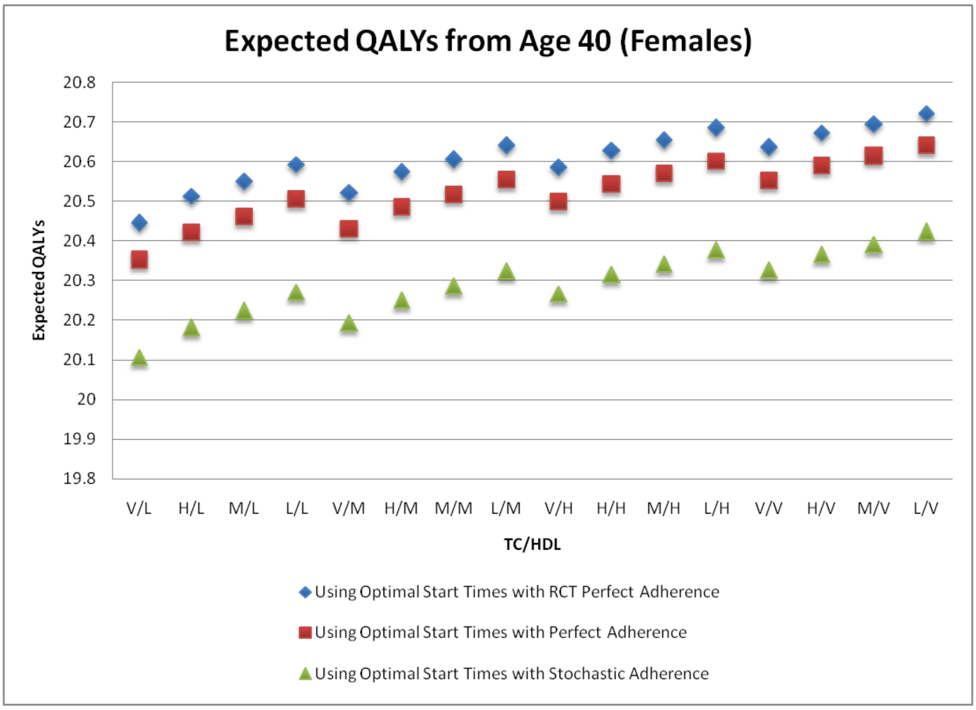

Figure 3.3: Expected QALYs from age 40 for females with $d^{ST} = 0.003$ and $C^{ST} = \$234$.

3.4.5 Sensitivity Analysis

Our model has many parameters that are not known to be one specific value, and some parameters are hard to estimate. For this reason we performed sensitivity analysis. In this section we present sensitivity analysis results for males; results for females are found in Appendix E.

The cost parameter we used for statins was \$234. This price for a year of statin treatment represents an estimate for the cost of generic medication [65]. We also considered the impact of higher costs consistent with branded statins ($c^{ST} = 713, 1435$). Table 3.8 shows the optimal start times for statin treatment based on the given costs of statins, holding all other parameters to their original values. For higher costs of statins, it is optimal to start statins later for patients in the lower risk categories. It is logical to delay the decision to start statins when there is a higher cost for that decision and the risk to the patient is not very high.

We also considered a large range of different values for the reward for QALYs.

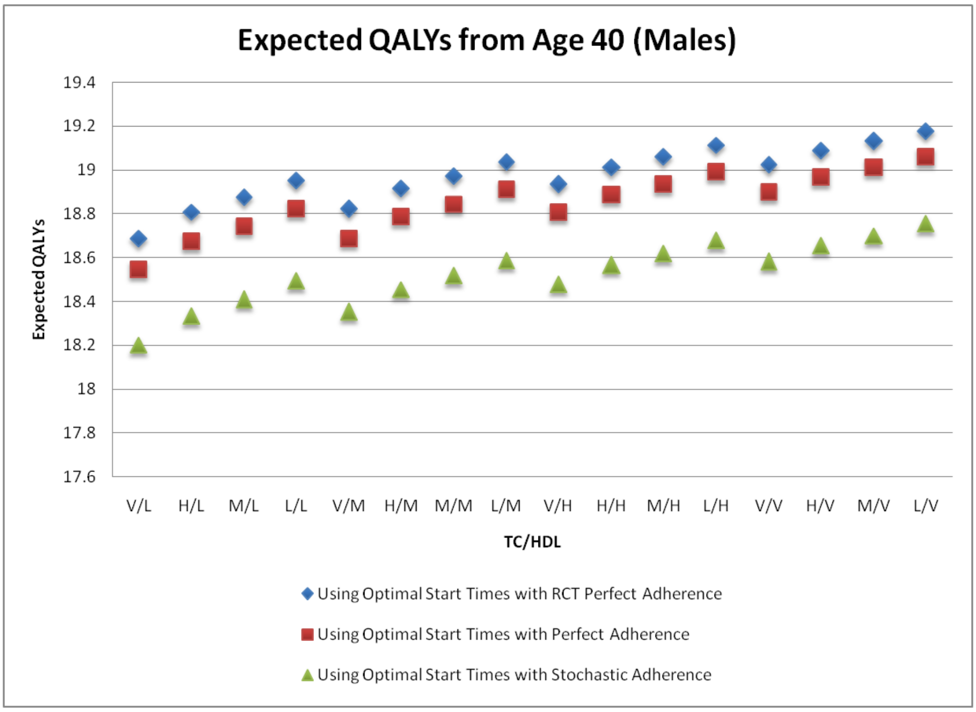

Figure 3.4: Expected QALYs from age 40 for males with $d^{ST} = 0.003$ and $C^{ST} = \$234$.

While we initially used $R_0 = \$100,000$, which is common in the health policy literature, there is debate about the appropriate dollar value that should be used [51]. We explore a large range of reward values for males in Table 3.9. This allows us to understand the effect this important parameter has on the model outcomes. Over the range \$50,000 to \$250,000 we see very little difference in optimal start times, likely because the beginning of the decision horizon is age 40. However, there is a more noticeable difference in start times for $R_0 = \$25,000$.

Table 3.8: Optimal start times for males based on TC/HDL with sensitivity analysis for the cost of statins, assuming all other parameters are as defined in Table 3.2.

C^{ST}	V/L	H/L	M/L	L/L	V/M	H/M	M/M	L/M	V/H	H/H	M/H	L/H	V/V	H/V	M/V	L/V
$234	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
$713	40	40	40	40	40	40	40	40	40	40	40	42	40	40	42	45
$1435	40	40	40	40	40	40	41	45	40	42	45	51	40	45	49	55

Table 3.9: Optimal start times for males based on TC/HDL with sensitivity analysis for the reward for life years, assuming all other parameters are as defined in Table 3.2.

R_0	V/L	H/L	M/L	L/L	V/M	H/M	M/M	L/M	V/H	H/H	M/H	L/H	V/V	H/V	M/V	L/V
$25,000	40	40	40	40	40	40	40	44	40	40	44	47	40	43	47	55
$50,000	40	40	40	40	40	40	40	40	40	40	40	41	40	40	40	43
$75,000	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	41
$100,000	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
$125,000	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
$150,000	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
$175,000	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
$200,000	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
$225,000	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
$250,000	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40

Another parameter for which we investigate sensitivity is the decrement for statins, d^{ST}. This parameter is hard to estimate in practice and may vary considerably from one patient to another. To understand how this parameter affects the model, we use a higher statin decrement of 0.01. This is the upper bound on the range reported by Pignone et al. [58]. In Tables 3.10 and 3.11, we see noticeable variation in the earliest optimal start times by states depending on the assumed adherence levels and effects. Note that we likely would have seen similar variation with the original statin decrement of 0.003 if the model allowed patients to initiate statins before age 40.

Patients with perfect adherence receive the greatest possible reduction in their TC. In contrast, patients with unknown adherence levels move through the adherence states probabilistically. They do not receive the full reduction in TC, but they do incur the financial and quality of life costs when taking the medication. Therefore it is logical that the patients with stochastic adherence delay statin initiation until later in life when their risk of CHD event or stroke is greatest.

We also compare the incremental benefit of improved adherence versus changing the timing of initiation to control for imperfect adherence. Figures 3.5 and 3.6 show the expected QALYs from age 40 depending on the different adherence levels and assumed effects from statin initiation. The additional piece of information captured in these two figures that was not found in the previous two figures of expected QALYs is the expected QALYs for a patient that has stochastic adherence but initates statins at the time when patients with perfect adherence would optimally initiate treatment. We see very little difference in the expected QALYs between the two results for patients with stochastic adherence. This leads us to conclude that the optimal timing of initiation of the medication is not sufficient to compensate for poor adherence. Rather, it is necessary to improve long-term adherence (e.g. through multiple regular interventions).

Table 3.10: Earliest optimal start times for females with $d^{ST} = 0.01$, assuming all other parameters are as defined in Table 3.2. Note: * represents that it is never optimal for the patient to start statins.

Adherence	V/L	H/L	M/L	L/L	V/M	H/M	M/M	L/M	V/H	H/H	M/H	L/H	V/V	H/V	M/V	L/V
Stochastic	46	48	51	55	50	52	56	61	54	57	60	65	56	61	65	*
Perfect	40	40	40	44	40	41	44	47	40	45	47	51	45	48	51	55
Perfect, RCT Effects	40	40	40	40	40	40	41	45	40	42	45	48	40	45	48	51

Table 3.11: Earliest optimal start times for males with $d^{ST} = 0.01$, assuming all other parameters are as defined in Table 3.2.

Adherence	V/L	H/L	M/L	L/L	V/M	H/M	M/M	L/M	V/H	H/H	M/H	L/H	V/V	H/V	M/V	L/V
Stochastic	40	40	40	45	40	41	45	49	40	45	49	55	45	51	54	58
Perfect	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	43
Perfect, RCT Effects	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40

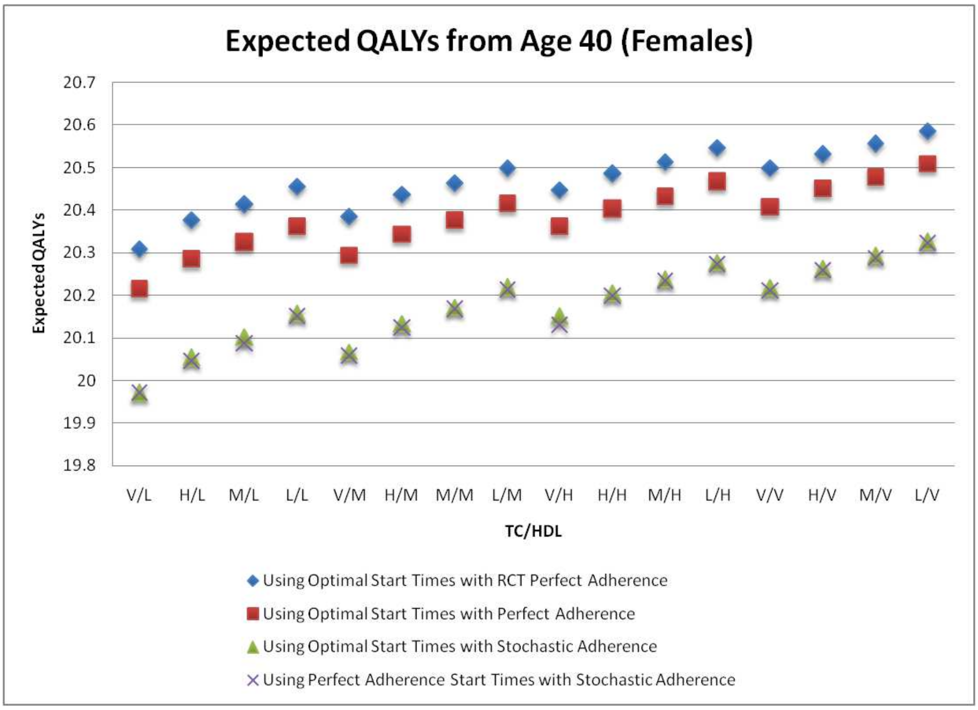

Figure 3.5: Expected QALYs from age 40 for females with $d^{ST} = 0.01$.

3.5 Discussion

Our model's main objectives are to determine the effect of stochastic adherence on optimal statin initiation policies and the total effect on expected QALYs over the patient's lifetime. While the optimal starting times were different depending on stochastic or perfect adherence, we saw that the effect of these different start times on expected QALYs was relatively small. We observe that improving adherence has a much greater effect on expected QALYs than changing the timing of statin initiation. We also observed that patients who take less than their prescribed dosage of medication received a smaller percentage change in TC, and we found that in the long term only 25% of patients remain highly adherent. These results support the need for patient intervention programs for improving adherence to statin treatment.

We also found through sensitivity analysis that some of the model parameters produced large changes in the results. While changing the monetary reward for QALYs did not greatly affect the optimal start times (for the range we considered), we saw fairly large

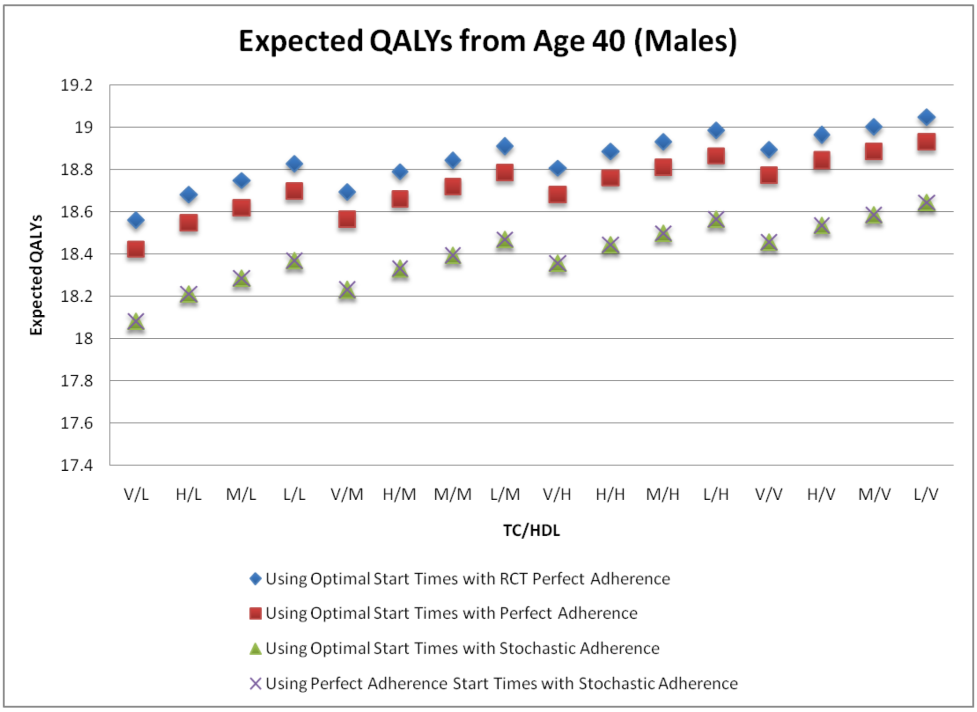

Figure 3.6: Expected QALYs from age 40 for males with $d^{ST} = 0.01$.

changes in the optimal start times when changing the statins decrement from $d^{ST} = 0.003$ to $d^{ST} = 0.01$. These differences are important since patients will have a range of different side effects and burden of taking the medication.

Chapter 4

Decision Maker Perspectives

4.1 Introduction

We now consider the problem of optimal timing of initiation of statin treatment over the lifetime of a patient with type 2 diabetes, considering society, patient, and third-party payer perspectives. We assume the patient makes treatment plans such that they maximize expected QALYs, the third-party payer (e.g. an insurer or HMO) seeks treatment policies that minimize expected costs, and society takes both of these viewpoints into account through a weighted sum of the patient and third-party payer criteria. In Chapter 3, we considered what we refer to as the society perspective. We analyze how changing perspectives (reward functions) affects the range of optimal start times of statin initiation. The MDP model with stochastic adherence (and other initial parameters) outlined in Chapter 3 is used here for each of the three perspectives.

4.2 Criteria

Under the assumption that optimal start times may differ depending on the perspective being considered, we present three different reward functions to use with the model. The society perspective aims to capture all effects of a patient starting statins: expected costs and non-monetary effects on the patient. The patient perspective only considers QALYs. Finally, the third-party payer perspective ignores the effects on the patient's QALYs and only considers the expected costs.

4.2.1 Society

The objective for the societal perspective model is to maximize the dollar reward for patient QALYs minus costs of treatment and health services. As described in Chapter 3, the reward function is as follows:

$$r(\ell, m) = \begin{cases} R(\ell, m) - C^O & -\left(CF^S(\ell) + CF^{CHD}(\ell)\right) - mC^{ST}(\ell) \\ & -\left(C^S(\ell) + C^{CHD}(\ell)\right), \text{ for } t = 1, \ldots, T-1 \\ R(\ell, m) - C^O & -\left(CF^S(\ell) + CF^{CHD}(\ell)\right) - mC^{ST}(\ell) \\ & -\left(C^S(\ell) + C^{CHD}(\ell)\right) + E[PDHR|\ell], \text{ for } t = T \end{cases} \tag{4.1}$$

where $R(\ell, m) = R_0(1 - d^S(\ell))(1 - d^{CHD}(\ell))(1 - d^{ST}(m))$ is the reward for one QALY.

Let us now consider the reward function for the societal perspective in a different form. We will display the case for $t = 1, \ldots, T-1$ as the case for $t = T$ is similar.

$$r(\ell, m) = R_0 D(\ell, m) - K_0 C(\ell, m) \tag{4.2}$$

As before, R_0 is the dollar reward per QALY. We let $D(\ell, m)$ be the overall disutility factor for a given living state and treatment status. We define K_0 to be the cost coefficient. For the society perspective, $K_0 = 1$. This notation will be useful when defining the patient and third-party payer perspectives. $C(\ell, m)$ is defined to be the sum of all treatment and health services costs.

4.2.2 Patient

For the patient perspective model, we do not consider costs. The objective is to maximize QALYs. The patient perspective reward function is the same as that of the societal perspective with $R_0 = 1$ and $K_0 = 0$. By setting these coefficients to 1 and 0, we eliminate dollars as the unit of measure from the reward. The reward value function is as follows:

$$r(\ell, m) = \begin{cases} D(\ell, m), \text{ for } t = 1, \ldots, T-1 \\ D(\ell, m) + E[PDHR|\ell], \text{ for } t = T \end{cases} \tag{4.3}$$

As with the societal perspective, when a patient is in the final epoch of the decision horizon (i.e., age 79), there is an expected post decision horizon reward ($E[PDHR|\ell]$) for future years of life. In this case $E[PDHR|\ell]$ is an estimate of future expected QALYs.

4.2.3 Third-Party Payer

For the third-party payer perspective model, we assume the objective is to minimize expected discounted costs of treatment and health services. No disutilities are considered in this model since the patient's quality of life is not considered at all. The reward value function for this perspective is the societal reward with $R_0 = 0$ and $K_0 = -1$. The reward function is as follows:

$$r(\ell, m) = \begin{cases} C(\ell, m), \text{ for } t = 1, \ldots, T-1 \\ C(\ell, m) + E[PDHR|\ell], \text{ for } t = T \end{cases} \tag{4.4}$$

Again, $E[PDHR|\ell]$ represents the expected costs that the third-party payer will incur on the patient's behalf after the end of the decision horizon.

4.3 Comparison of Perspectives

In this section we present results illustrating the influence of the reward function criteria on the optimal treatment policy. For the purpose of this analysis, we use a statin decrement of $d^{ST} = 0.01$. Figures 4.1 and 4.2 show all of the ages for which it is optimal for females and males, respectively, to initiate statin treatment according to the three different perspectives. The x axis represents the patient's metabolic state according to their TC and HDL levels, and the y axis represents the age of the patient. For any portion of the bar line that is colored in for a given perspective, it is optimal for a patient at that age in that state to begin statins, according to the perspective. For a diabetic patient that has not already initiated statin treatment, for every age of the decision horizon we can see whether or not it is optimal to initiate statins according to each perspective. For example, in Figure 4.1 we see it is optimal for female patients with very high TC and low HDL to initiate statins between ages 41 and 79, according to the patient perspective. According to the society perspective, it is optimal for these patients to initiate treatment from age 46 to age 75. Finally, according to the third-party payer perspective we see it is optimal for these patients to initiate treatment from age 56 to age 78.

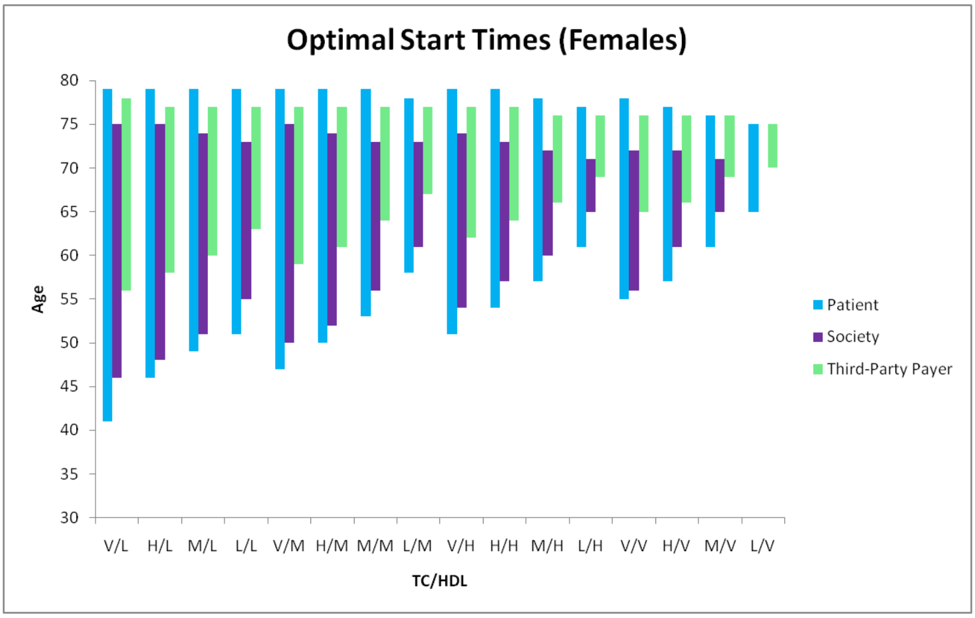

Figure 4.1: Ages for which it is optimal for females to start statins according to the three different perspectives, with $d^{ST} = 0.01$, $C^{ST} = \$234$, and $R_0 = \$100,000$.

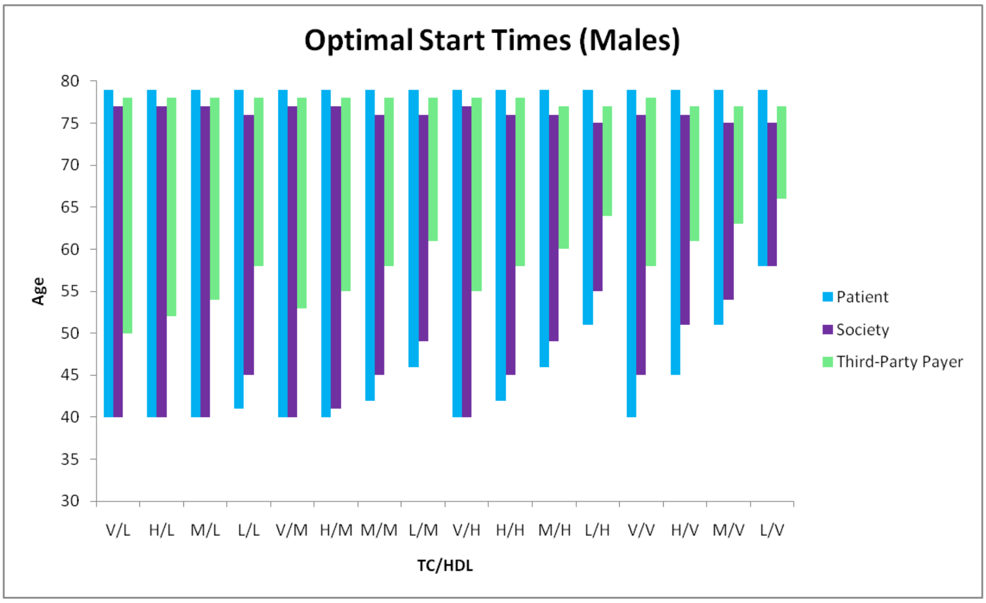

Figure 4.2: Ages for which it is optimal for males to start statins according to the three different perspectives, with $d^{ST} = 0.01$, $C^{ST} = \$234$, and $R_0 = \$100,000$.

4.4 Discussion

There is a general decrease in patient risk for cardiovascular events towards the right of the x axis. These patients have lower TC and higher HDL. Patients with high TC and low HDL are at the greatest risk for adverse events. Thus, we see earlier optimal start times for statins among the high risk patients.

The optimal start times greatly depend on the sex of the patient, with the earliest optimal start times for women as many as 7 years later than those for men when considering any of the perspectives. This is consistent with the fact that being male increases risk for cardiovascular events.

The start times are sensitive to the choice of reward function. For men there is generally a three or four year gap between the patient perspective and the society perspective for the earliest optimal start times when both earliest start times are not age 40. The same trend is seen for the female patients. There is a much larger difference in the range of optimal start times between the society and third-party payer perspectives. While these two perspectives both consider costs, the reward functions are structured in different ways. The reward for the society perspective model decreases in two major ways when an event occurs: the utility decrement to the reward for a year of life and the cost of the treatment. While the reward also decreases in these two ways when statins are initiated, the statins utility decrement and cost for statins are small compared with those for cardiovascular events. Therefore, in the society perspective model there is more incentive (built into the objective function) to delay cardiovascular events by initiating statins than in the third-party payer perspective model. Thus we see as many as ten years in delay for the earliest optimal start times for the third-party perspective over that of the society perspective. For similar reasons, the society perspective optimal start time range ends younger than the other two perspectives. The reduced risk gained by starting statins so late in life is not great enough to make it optimal to start statins at these ages.

Although the decision horizon extends up to age 80 (with the last age possible to start statins being age 79), none of the perspectives recommend starting that late in life. For both the society and third-party payer perspectives the latest optimal start times range from age 74 to 77 for males and 70 to 77 for females. This observation is likely due to the fact that death from other causes increases over time. There are competing factors in a patient's life as they age. Initiating statins late in life may not bring enough value to the patient given the cost. This observation also helps to validate our end of horizon approximation.

Chapter 5

Implied Societal Willingness to Pay

5.1 Introduction

There is much debate about the appropriate dollar amount to be used for one QALY. The most commonly used value of $50,000 in the health policy literature [51] dates back to the 1980s and has not been updated for inflation or other factors. We propose a new model for estimating the implied monetary reward per QALY based on US guidelines for statin treatment initiation.

Other methods for determining this monetary value have been used in the past. Braithwaite et al. [66] quantify the incremental costs and benefits of modern health care (post 1950s) and unsubsidized health insurance to determine if the long-used $50,000 per QALY is an appropriate cost-effectiveness parameter. Their results showed that the appropriate amount per QALY should be between $183,000 and $264,000. They found that $50,000 was a gross underestimate.

Lee et al. [25] use a computer simulation to model the treatment costs and effects on QALYs of a population with end-stage renal disease. Incremental cost-effectiveness ratios of current practice to the next least costly option and no dialysis were calculated. The average ratio was found to be $129,090 per QALY. However, there was a large range of reported values: $65,496 to $488,360. The higher ratios were calculated with older patients and patients that had more comorbid conditions.

In contrast to these two methods for estimating the monetary value per QALY (referred to as R_0 in our MDP model), we present a different approach. We use a novel formulation for approximating this reward based on our MDP model and U.S. guidelines. Also, our estimate is based on cardiovascular disease which is the most common cause of death. In contrast, end-stage renal disease is less common and using this disease may not be the best way to estimate the R_0 that is used in policy research for treatments of all types of diseases.

5.2 Guidelines

We solve an inverse optimization problem to compute the implied societal willingness to pay based on the Adult Treatment Panel III (ATP III) guidelines for statin initiation [6]. The ATP III clinical guidelines were produced by the National Cholesterol Education Program (NCEP). NCEP outlines goals for managing cholesterol and guidelines for achieving these goals in the U.S. population. ATP III continues to promote the goals of ATP I and ATP II (earlier guidelines for primary prevention of CHD in persons with high LDL and concentrated management of LDL in patients with established CHD, respectively). ATP III has the additional goal of focusing on primary prevention of CHD in patients with multiple risk factors including diabetes. The report makes recommendations for when to begin initiation of statins based on other risk factors including age, gender, LDL levels, and probability of a CHD event in the next ten years.

5.3 Methodology

We formulate our inverse optimization model as a linear program with constraints to represent our MDP (constraints 5.2, 5.3, and 5.4) for finding the optimal start time for statins (as outlined in Chapter 3). These constraints represent the value function equations for the MDP as presented in Equation 3.7, where constraints 5.2 and 5.3 represent the value functions for patients not yet on statins that remain off statins or elect to begin statins in the next epoch. Constraint 5.4 represents the value function for patients on statins. Our model also includes constraints that define the ATP III guidelines in the same form (constraints 5.5 and 5.6). Constraint 5.5 represents the value function for patients not currently on statins, transitioning to on statins in the next epoch if optimal according to the guidelines, and constraint 5.6 represents the value function for patients on statins according to the guidelines. Together these constraints define the value functions given the optimal initiation of statins and initiation based on the ATP III guideline respectively. The objective of our linear program is to minimize the difference in expected discounted future rewards from age 40 between the optimal policy and the ATP III policy (5.1). We allow R_0 to be a decision variable for each of the decision epochs from age 40 to age 80. The inverse optimization problem can be formulated as follows:

$$min \sum_{s_{40}} |v^M_{40,s_{40}} - v^G_{40,s_{40}}| \tag{5.1}$$

$$v^M_{t,s^0_t} - d_{t,s^0_t} R_t - \lambda \sum_{\forall s^0_{t+1}} p_t(s^0_{t+1}|s^0_t) v^M_{t,s^0_{t+1}} \geq -c_{t,s^0_t} \tag{5.2}$$

$$v^M_{t,s^0_t} - d_{t,s^0_t} R_t - \lambda \sum_{\forall s^1_{t+1}} p_t(s^1_{t+1}|s^0_t) v^M_{t,s^1_{t+1}} \geq -c_{t,s^0_t} - c^{ST} \tag{5.3}$$

$$v^M_{t,s^1_t} - d_{t,s^1_t} R_t - \lambda \sum_{\forall s^1_{t+1}} p_t(s^1_{t+1}|s^1_t) v^M_{t,s^1_{t+1}} = -c_{t,s^1_t} - c^{ST} \tag{5.4}$$

$$v^G_{t,s^0_t} - d_{t,s^0_t} R_t - \lambda \sum_{\forall s^{a_0}_{t+1}} p_t(s^{a_0}_{t+1}|s^0_t) v^G_{t,s^{a_0}_{t+1}} = -c_{t,s^0_t} - c^{ST} \cdot a^G_{t,s^0_t} \tag{5.5}$$

$$v^G_{t,s^1_t} - d_{t,s^1_t} R_t - \lambda \sum_{\forall s^1_{t+1}} p_t(s^1_{t+1}|s^1_t) v^G_{t,s^1_{t+1}} = -c_{t,s^1_t} - c^{ST} \tag{5.6}$$

$$R_t \geq 0$$

$$v^M_{t,s^0_t}, v^M_{t,s^1_t} \geq 0$$

$$v^G_{t,s^0_t}, v^G_{t,s^1_t} \geq 0$$

Note that 5.1 can be linearized with one additional variable and two additional constraints to eliminate the absolute value. In this formulation, we have the following model parameters: d_{t,s_t} represents the decrements to the yearly reward, c_{t,s_t} represents the costs for stroke, CHD, and other costs, and c^{ST} represents the cost of statins. The states are represented by the vector s_t: s^0_t are the states where the patient is off statins, and s^1_t are the states where the patient is on statins. R_t represents the array of decision variables for the reward value, based on the year of the patient's life. Note that R_t corresponds to the single parameter, R_0, in our MDP model of Chapter 3. The expected discounted future rewards associated with the MDP and the guidelines are the decision variables represented by v^M_{t,s_t} and v^G_{t,s_t}, $\forall(t, s_t)$.

We solve this linear program using CPLEX 11.0 Concert Technology Library with C++. The entire C++ program (including the MDP model) takes approximately 26 seconds to run on an Intel Core 2 CPU 6300 @1.86GHz with 2.00 GB of RAM.

5.4 Results

Our analysis found that R_t varies between \$117,438 and \$152,870 for females and between \$123,736 and \$160,257 for males over a patient's lifetime, as shown in Figures 5.2 and 5.1, respectively. These ranges do not include the values for the last two years of the horizon. The last two values for both males and females drop sharply due to the end of horizon value approximation for years of life past age 80.

The mean annual reward is \$135,327 for males and \$132,603 for females. There is a pronounced upward trend in the reward value with respect to age with older patients having higher implied rewards per QALY. This trend is consistent with the results found by Lee et al. [25]. Older patients and patients with more comorbid conditions had the higher cost-effectiveness ratios in Lee's model.

With a small change in the above formulation of the linear program we are able to estimate a single reward value for QALYs for both males and females. We fix the R_t decision variables to a single value by adding constraints $R_t = R_{t'}, \forall(t, t')$. The single value was found to be \$136,530 for females and \$137,380 for males, as depicted in Figures 5.2 and 5.1, respectively.

5.5 Discussion

Although we used different methods and different diseases for analysis than Lee et al. [25] and Braithwaite et al. [66], we found comparable results. Our results along with these other studies highlight the potential need for a new standard for the accepted monetary reward for a QALY. The implied reward per QALY is indeed higher than the commonly used value of \$50,000. Based on our results, a value between \$125,000 and \$150,000 would be consistent with the ATP III guidelines.

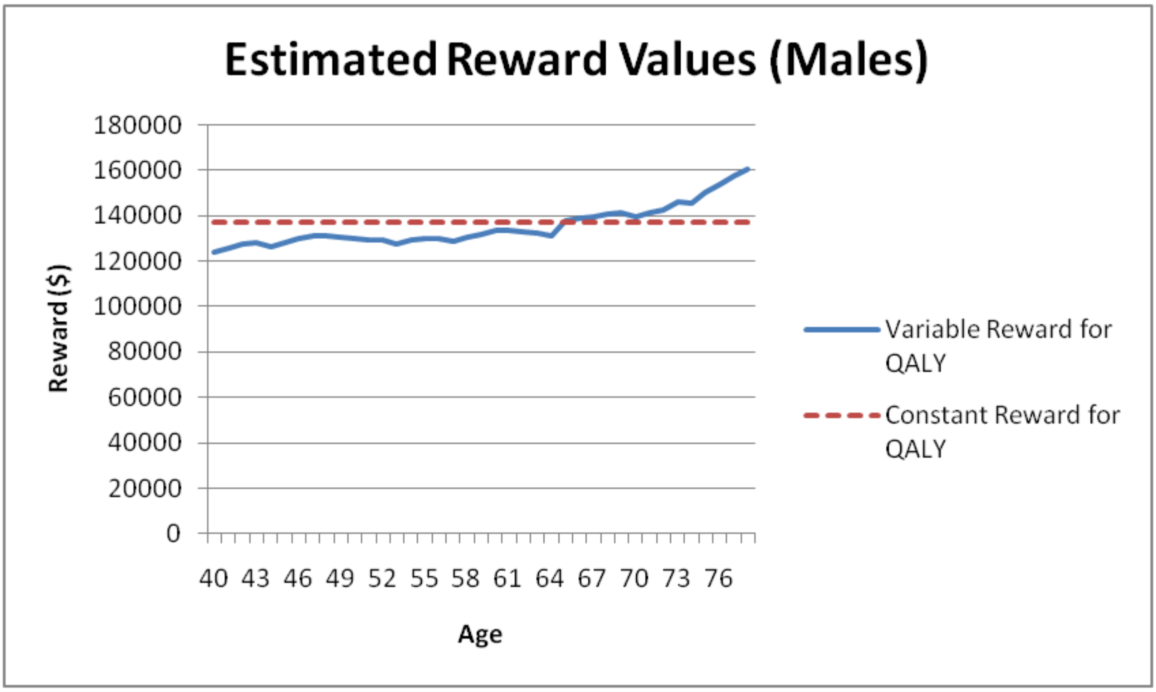

Figure 5.1: Estimated monetary reward for QALYs for males as a function of age.

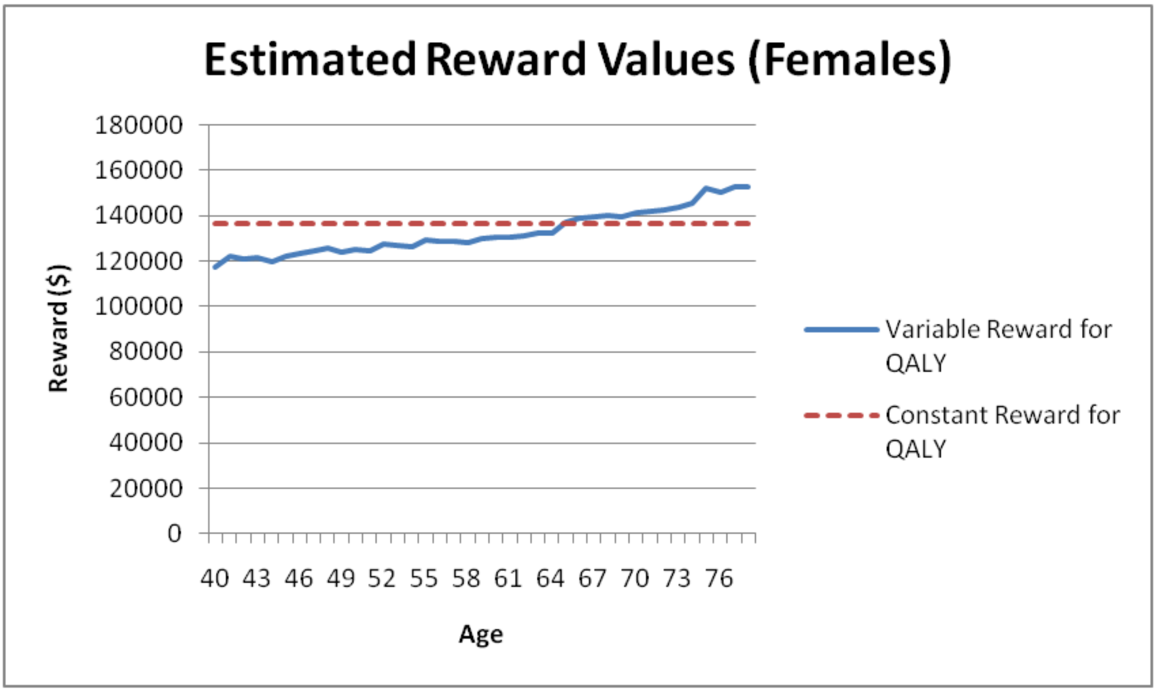

Figure 5.2: Estimated monetary reward for QALYs for females as a function of age.

Chapter 6

Conclusions

We studied two important factors affecting statin treatment for patients with type 2 diabetes. First, we studied the adherence behavior to statins based on a large cohort of diabetic patients. We formulated an MDP model that includes a Markov model for adherence to determine the optimal start time of statin treatment for patients with type 2 diabetes. Second, we analyzed the model from three different perspectives: the patient, the third-party payer, and society. Finally, we used inverse optimization to determine the implied monetary reward for a quality year of life.

Our models provided many interesting results. With the original model parameters we found that all males and females in most health states should initiate statins as early as age 40 with both stochastic and perfect adherence. Although the optimal start times were equivalent, we found the expected future discounted rewards associated with these policies to differ significantly. Patients with perfect adherence added as much as half a year to their expected future QALYs from age 40. This demonstrates the importance of improving adherence.

We implemented three different reward functions to reflect three different decision makers perspectives: society, patient, and third-party payers. We found three different policies with the earliest optimal times associated with the patient perspective and the latest optimal start times associated with the third-party payer perspective. For both the patient and third-party payer perspectives it is optimal for older patients to initiate statin treatment when it is not optimal for patients to begin treatment with the society perspective.

Finally, we found the reward for QALYs to be between \$120,000 and \$160,000, increasing during the patient's lifetime. The average reward was around \$137,000 for both males and females.

This research offers many opportunities for future work. While there is no evidence that a Markov model for adherence is inappropriate, we have not tested the appropriateness of the Markov assumption. Our model is a reasonable approximation of the long-term adherence behavior of a population as compared to the results of observational studies of elderly patients. Benner et al. [29] found only 25% of patients remained highly adherent after five years, and Jackevicius et al. [37] found only 25.4% of primary prevention patients were highly adherent after two years. We will test the Markov assumption in the future and consider using a hidden Markov model to model the adherence behavior as we rely on pharmacy claims data to determine a patient's adherence level, not the actual adherence data.

The model we propose could be valuable in planning multiple educational, behavioral, and provider intervention strategies to improve outcomes [32] [67]. The model could serve as motivation for improving adherence through employer benefit plans. Since patients with type 2 diabetes have to manage more than just cholesterol, it would be beneficial to add additional medications for managing blood pressure and glucose to the MDP model to determine the optimal sequence and timing of multiple treatments for a patient. This model would need stochastic blood pressure and HbA1c states. We would also want to understand patients' adherence to the different medications and determine whether multiple medications improve or degrade their overall adherence. Adding additional adverse events associated with diabetes such as kidney failure, blindness, and limb amputation would also make the model more realistic since patients with diabetes are at a greater risk for these events. With these additions, our model would have a much larger state space. Other methods such as approximate dynamic programming might be necessary to solve the multiple medication problem.

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Appendices

APPENDIX A: Percentage Change in Cholesterol

We first examine the percent change in total cholesterol from pre-initiation ($t = 0$) to post-initiation ($t = 1$). A linear regression model was fit to the raw adherence values y_1, the plot of which is shown in Figure A1. The slope of -0.235 has a significant p-value of less than 2e-16. The standard error of the residuals is 0.144 on 547 degrees of freedom, and the adjusted R-squared value is 0.214. Although this single-term model is inadequate for explaining the majority of the variability in the observations, it does show that adherence has a significant effect on lowering total cholesterol. Pursuing this idea, we performed one-sided t-tests for each of the four categorized adherence states. For each state X_1, our test is

$$H_0 \colon \mu_{X_1} = 0 \tag{A1}$$

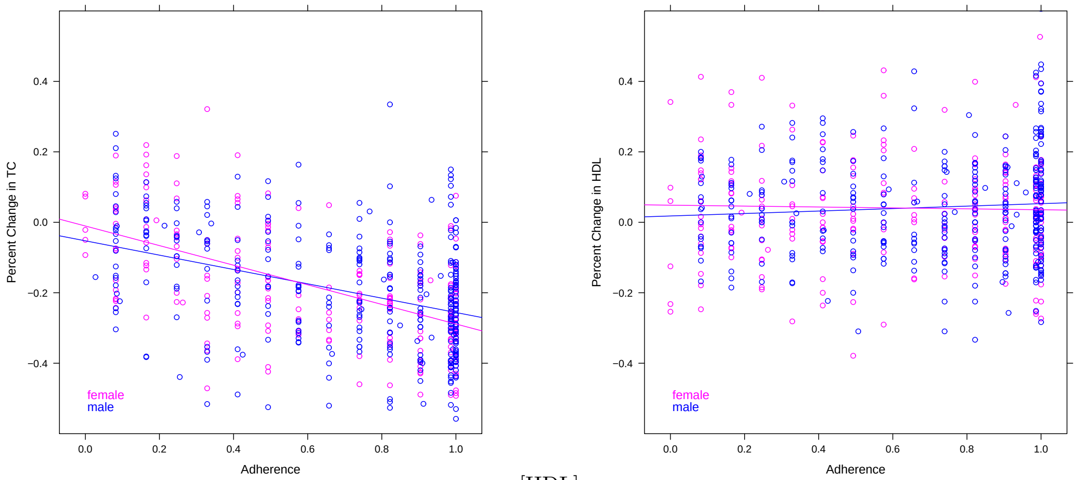
$$H_1 \colon \mu_{X_1} < 0 \tag{A2}$$

where μ_{X_1} is the mean of all readings for adherence state X_1, and the convention that a decrease in total cholesterol results in a negative percent change. The results presented in Table A1 are for a confidence level $\alpha = 0.01$, and show that statins are effective at each adherence state. The adherence state $X_1 =$ non that models zero to 10% of days supply is just significant for $\alpha = 0.01$. This is probably due to the fact that initial doses of statin medications have a larger impact on cholesterol levels than do doses in subsequent years.

To further examine the distribution of the change in cholesterol levels, the bean-plot [68] in Figure A2 simultaneously shows a scatter plot, mean, and shape of the density functions for each adherence state X_1, grouped by gender. The densities are similar to the Normal distribution; they are (mostly) symmetric with mass concentrated near the mean. Quantile-quantile plots to compare the observations in each adherence state to a standard Normal distribution are show in Figure A3. Maximum likelihood estimates for fitted Normal distributions are given in Table A2.

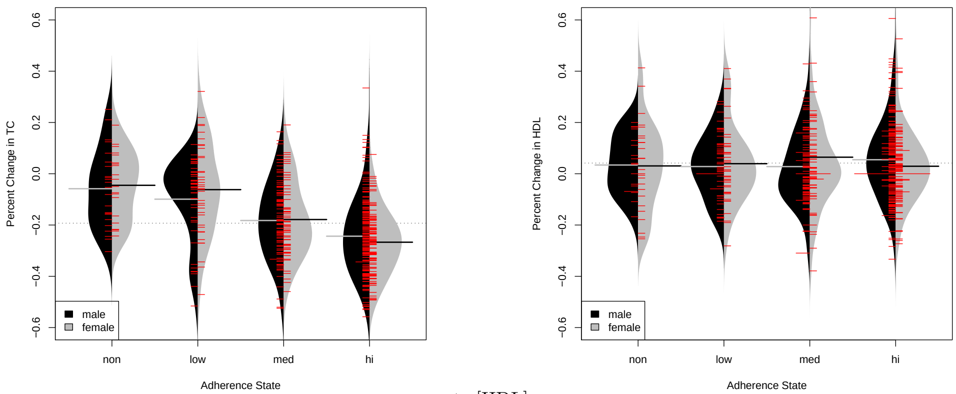
Table A1: Results of t-tests

Lab	Gender	X_1	t-statistic	d.o.f.	p-value	Decision
TC	both	non	-2.4198	42	0.009968	reject H_0
		low	-4.3969	80	1.673e-05	reject H_0
		med	-14.8141	144	<2.2e-16	reject H_0
		hi	-30.1718	279	<2.2e-16	reject H_0
TC	male	non	-1.8356	22	0.03999	accept H_0
		low	-4.1732	43	7.168e-05	reject H_0
		med	-11.336	85	<2.2e-16	reject H_0
		hi	-21.2168	173	<2.2e-16	reject H_0
TC	female	non	-1.5378	19	0.07029	accept H_0
		low	-2.0929	36	0.02173	accept H_0
		med	-9.463	58	1.152e-13	reject H_0
		hi	-23.2699	105	<2.2e-16	reject H_0
HDL	both	non	1.4214	43	0.08121	accept H_0
		low	2.312	88	0.01156	accept H_0
		med	2.8002	152	0.002885	reject H_0
		hi	5.2029	290	1.858e-07	reject H_0
HDL	male	non	1.2816	17	0.1086	accept H_0
		low	1.6155	47	0.05644	accept H_0
		med	1.6405	87	0.05225	accept H_0
		hi	4.7904	177	1.753e-06	reject H_0
HDL	female	non	0.9039	25	0.1873	accept H_0
		low	1.6455	40	0.05386	accept H_0
		med	2.2782	64	0.01303	accept H_0
		hi	2.2658	112	0.01269	accept H_0



[TC] [HDL]

Figure A1: Linear Models by Gender



[Total Cholesterol] tc [HDL]

Figure A2: Densities by Adherence State and Gender

Table A2: Maximum likelihood estimates.

Lab	Gender	X_1	$\hat{\mu}_{X_1}$	$\hat{\sigma}_{X_1}$
TC	both	non	-0.0522	0.1397
		low	-0.0821	0.1670
		med	-0.1808	0.1465
		hi	-0.2525	0.1398
TC	male	non	-0.0583	0.1490
		low	-0.0992	0.1558
		med	-0.1824	0.1483
		hi	-0.2436	0.1510
TC	female	non	-0.0451	0.1278
		low	-0.0619	0.1775
		med	-0.1786	0.1437
		hi	-0.2670	0.1176
HDL	both	non	0.0320	0.1475
		low	0.0333	0.1350
		med	0.0435	0.1915
		hi	0.0448	0.1468
HDL	male	non	0.0340	0.1096
		low	0.0281	0.1193
		med	0.0279	0.1588
		hi	0.0547	0.1520
HDL	female	non	0.0305	0.1688
		low	0.0393	0.1510
		med	0.0646	0.2267
		hi	0.0293	0.1367

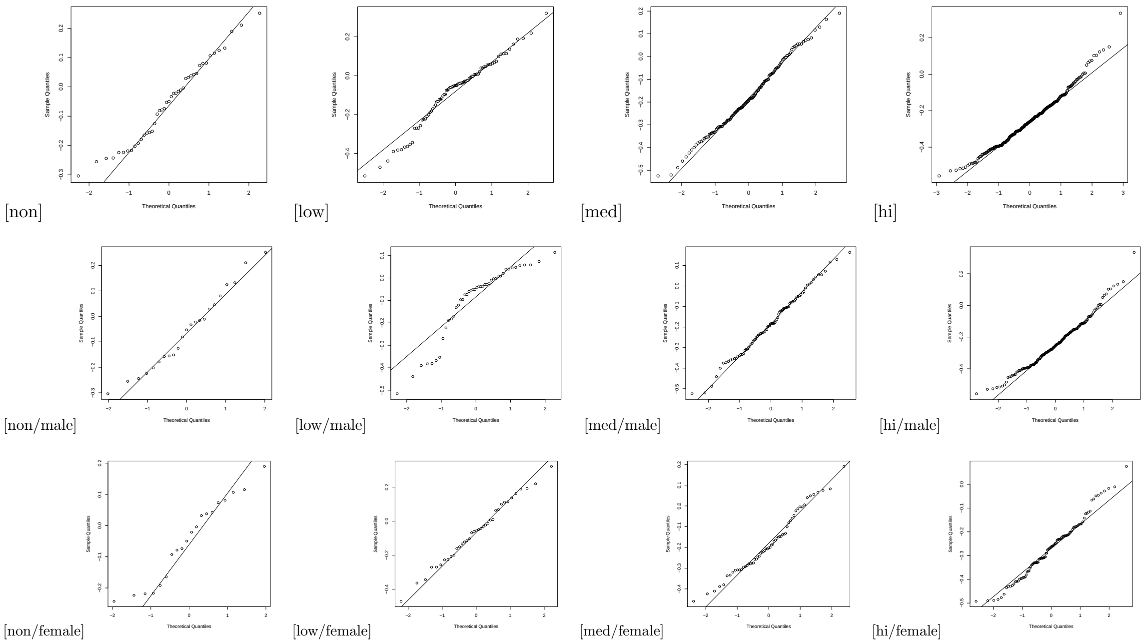


Figure A3: Quantile-quantile plots

APPENDIX B: Adherence Transition Probabilities by Gender

Although the transition probabilities were not significantly different according to gender, we include the probabilities below. The following probabilities are the initial probabilities and transition probability matrices for the adherence levels for males and females. Since the differences by gender were not significant, we used probabilities from the entire population.

$$\mathbf{p}_{\text{males}} = (0.084, 0.155, 0.251, 0.510) \tag{A3}$$

$$\mathbf{p}_{\text{females}} = (0.101, 0.177, 0.267, 0.455) \tag{A4}$$

$$\mathbf{P}_{\text{males}} = \begin{bmatrix} 0.781 & 0.107 & 0.085 & 0.027 \\ 0.486 & 0.203 & 0.217 & 0.094 \\ 0.188 & 0.147 & 0.392 & 0.273 \\ 0.027 & 0.043 & 0.176 & 0.754 \end{bmatrix} \tag{A5}$$

$$\mathbf{P}_{\text{females}} = \begin{bmatrix} 0.795 & 0.105 & 0.079 & 0.022 \\ 0.512 & 0.206 & 0.209 & 0.073 \\ 0.211 & 0.163 & 0.388 & 0.238 \\ 0.028 & 0.052 & 0.209 & 0.711 \end{bmatrix} \tag{A6}$$

Table A3: Mean first passage times to the nonadherent state.

MFPT to NonAdherence		
m_{21}	m_{31}	m_{41}
3.9701	6.5059	9.1720

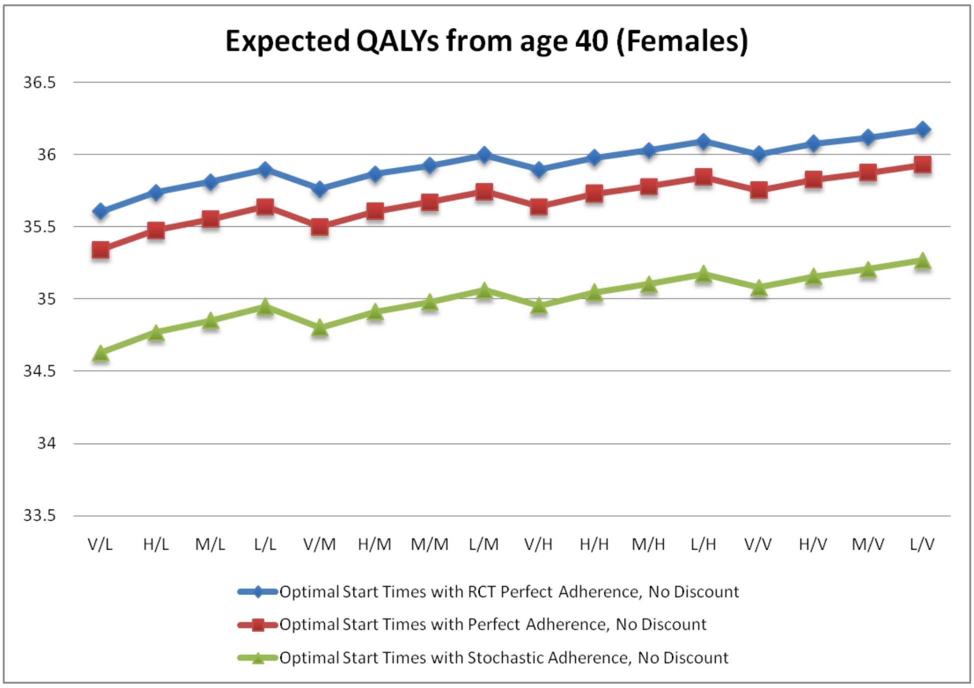


Figure A4: Expected QALYs from age 40 for females with no discount factor, $d^{ST} = 0.003$, and $C^{ST} = \$234$.

APPENDIX C: Mean First Passage Times

In Table A3, we have the mean first passage times from the low, medium, and high adherence states to the nonadherent state. For example, it will take an average of 6.5 years for a patient that starts in the medium adherence state to initially reach the nonadherence state.

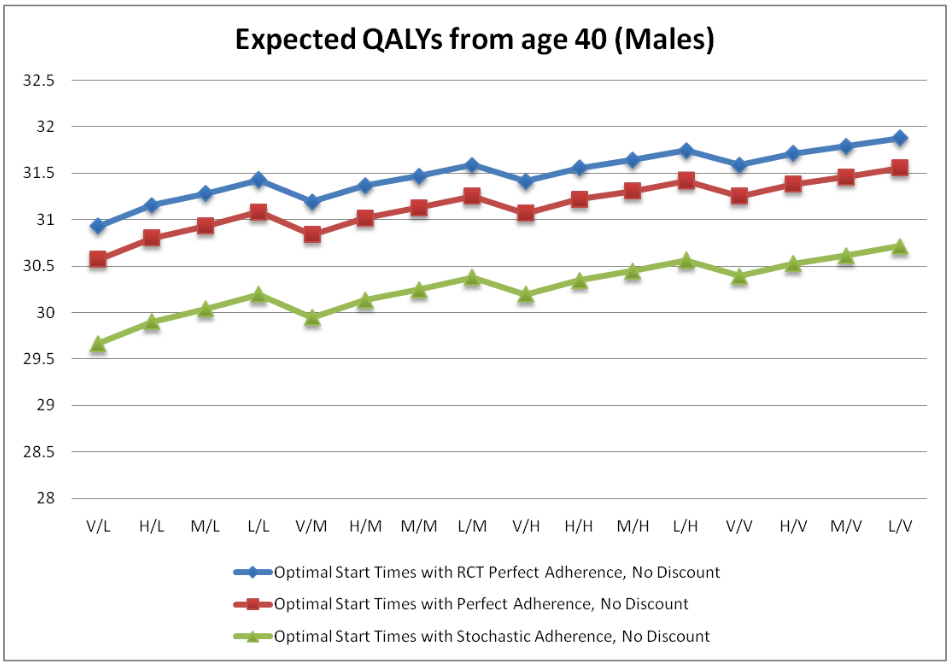


Figure A5: Expected QALYs from age 40 for males with no discount factor, $d^{ST} = 0.003$, and $C^{ST} = \$234$.

APPENDIX D: Results with No Yearly Discount Factor

To get a better view of the differences in expected QALYs between the perfect and stochastic adherence cases, we now look at the model while leaving out the discount factor. In Figures 6 and 6 we can see a greater difference between the expected QALYs without the discount factor. Since we are considering the future QALYs from age 40 to age 80, it makes sense that removing the discount factor will change the results fairly significantly. Now the rewards and costs of events in the future are valued the same as events that occur when the patient is 40 years old, which is not an unreasonable assumption for an individual.

APPENDIX E: Additional Female Sensitivity Analysis

In Tables A4 and A5 we present the female sensitivity analysis results for the cost of statins and the reward for life years. We can see that there are few changes in the optimal start times for females when the statins cost is increased. This is likely due to the fact that very few female patients should start statins with the initial parameters. We see similar results with the changing reward for life years.

Table A4: Optimal start times for females based on TC/HDL with sensitivity analysis for the cost of statins, assuming all other parameters are as defined in Table 3.2.

C^{ST}	V/L	H/L	M/L	L/L	V/M	H/M	M/M	L/M	V/H	H/H	M/H	L/H	V/V	H/V	M/V	L/V
\$234	40	40	40	40	40	40	40	42	40	40	42	46	40	40	45	51
\$713	40	40	40	45	40	41	45	49	40	46	49	54	45	51	54	58
\$1435	40	45	47	51	46	49	52	58	51	53	57	61	54	57	61	65

Table A5: Optimal start times for females based on TC/HDL with sensitivity analysis for the reward for life years, assuming all other parameters are as defined in Table 3.2.

R_0	V/L	H/L	M/L	L/L	V/M	H/M	M/M	L/M	V/H	H/H	M/H	L/H	V/V	H/V	M/V	L/V
\$25,000	40	44	46	50	44	47	51	56	49	51	55	61	52	55	58	65
\$50,000	40	40	40	41	40	40	42	46	40	44	47	51	40	47	51	55
\$75,000	40	40	40	40	40	40	40	44	40	40	44	47	40	43	47	54
\$100,000	40	40	40	40	40	40	40	42	40	40	42	46	40	40	45	51
\$125,000	40	40	40	40	40	40	40	41	40	40	42	45	40	40	45	49
\$150,000	40	40	40	40	40	40	40	40	40	40	40	45	40	40	44	49
\$175,000	40	40	40	40	40	40	40	40	40	40	40	44	40	40	43	47
\$200,000	40	40	40	40	40	40	40	40	40	40	40	44	40	40	43	47
\$225,000	40	40	40	40	40	40	40	40	40	40	40	44	40	40	43	46
\$250,000	40	40	40	40	40	40	40	40	40	40	40	44	40	40	43	46