

At What Lipid Ratios Should a Patient with Type 2 Diabetes Initiate Statins?

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Type 2 diabetes is a leading cause of coronary heart disease (CHD) and stroke, which kill 650,000 Americans annually. Lipid abnormalities increase the risk of CHD and stroke for patients with Type 2 diabetes. Statins can be used to treat these abnormalities, but may have adverse side effects. In this paper, we consider the problem of the optimal timing of statin initiation for patients with Type 2 diabetes. We formulate an infinite-horizon Markov decision process model with a non-stationary decision horizon that maximizes the patient's quality-adjusted lifetime prior to the occurrence of the first CHD or stroke event. We describe the state of the process by the patient's lipid ratio levels and use the risk model developed by the United Kingdom Prospective Diabetes Study to estimate the patient's CHD and stroke probabilities. We derive structural properties of the model, including sufficient conditions for the optimality of control-limit policies and for the comparison of optimal treatment policies of two patients. We demonstrate the clinical implications of our results and using clinical data we present computational results for patients newly diagnosed with Type 2 diabetes.

Key words: diabetes; medical decision making; Markov decision processes; control-limit policy

History: _____

1. Introduction

Diabetes is the sixth-leading cause of death and a major underlying cause of cardiovascular complications in the U.S. (National Center for Health Statistics (NCHS) 2005). There are currently 20.8 million Americans with diabetes (American Diabetes Association (ADA) 2008), and this number is expected to grow to 39 million by 2050 (Honeycutt et al. 2003). Approximately 90 % of these patients have Type 2 diabetes, which is caused by insulin resistance combined with relative insulin deficiency. Because of this deficiency, patients often have difficulty maintaining their blood glucose levels within healthy ranges. While a primary goal of managing Type 2 diabetes has been the control of blood glucose levels, more recently the importance of cardiovascular risk has also been emphasized (The United Kingdom Prospective Diabetes Study (UKPDS) Group 1998a, Snow et al. 2004).

Type 2 diabetes has several significant complications, including coronary heart disease (CHD), stroke, kidney failure, amputation, and blindness, all of which can result in disabilities and work losses leading to poor productivity levels (Ng et al. 2001, Ramsey et al. 2002). These complications not only affect the patients' health-related quality of life but also account for a sizable portion of the total healthcare costs to society (Costa et al. 1997, Testa and Simonson 1998). Of these complications, CHD and stroke, which represent the leading causes of diabetic deaths in the U.S. (ADA 2008), carry significant importance for physicians in making treatment decisions, because Type 2 diabetes can increase the patient's CHD and stroke risks by a factor of five (Barrett-Connor et al. 1991, Manson et al. 1991, Koskinen et al. 1992, Stamler et al. 1993). Elevated total cholesterol (TC) and depressed high-density lipoprotein (HDL), which is also referred to as "good" cholesterol, have been reported to increase the overall risk of CHD and stroke. More specifically, the ratio of TC to HDL, which is defined as *lipid ratio* (LR), has been identified as a predictor of CHD and stroke risks, and increasing LR levels have been shown to increase the patient's CHD and stroke risks in clinical trials (Wannamethee et al. 2000, Goldstein et al. 2001, Vijan and Hayward 2004).

Several risk models predict CHD and stroke probabilities for patients with Type 2 diabetes. The most popular of these models has been calibrated based on data from the UKPDS (Turner 1998, Stevens et al. 2001, Kothari et al. 2002), which is the largest clinical study on diabetes, and is based on a 20-year surveillance of over 5,000 patients in the U.K. The UKPDS risk model predicts CHD and stroke probabilities based on several risk factors,

including the patient's age, gender, ethnicity, smoking status, presence of atrial fibrillation at the time of diagnosis, LR, systolic blood pressure (SBP) and hemoglobin A1c (HbA1c) levels (Wolf et al. 1987, Stegmayr and Asplund 1995, The UKPDS Group 1998a, 1998b, Davis et al. 1999, Adler et al. 2000 and Stratton et al. 2000). While other predictive models have been developed, e.g. Framingham (Anderson et al. 1991, D'Agostino et al. 2000) and Archimedes (Eddy and Schlessinger 2003a, 2003b), the UKPDS risk model is unique in that it has published equations governing risk probabilities that are specific to patients with Type 2 diabetes.

Several clinical trials have shown that cholesterol management using statins reduces the CHD and stroke risks of patients with Type 2 diabetes (Downs et al. 1998, The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial 2002, Collins et al. 2002, 2003; Colhoun et al. 2004, Briel et al. 2004). The results of these trials have also been confirmed in a large meta-analysis of the efficacy and safety of statin treatment, which showed a similar effect of statins both in diabetes and non-diabetes populations (Baigent et al. 2005).

Although statin treatment appears to reduce the risk of CHD and stroke in patients with Type 2 diabetes, it may have serious side effects, including muscle diseases with extreme muscle pain and liver problems. A large variety of other effects have also been reported with the use of statins, such as headaches, nausea, fever, fatigue, shortness of breath, memory loss, sexual dysfunction, rash and skin problems, irritability, and effects on nervous and immunity systems (Phillips et al. 2002, Pasternak et al. 2002).

Once a patient with Type 2 diabetes initiates statin treatment, clinical guidelines recommend that she should continue for the remainder of her life so that the initiation of statin treatment can be viewed as a one-time irreversible decision (Vijan and Hayward 2004, Snow et al. 2004). With the evidence that patients who may be most likely to benefit from statins are not prescribed statins, while patients who may incur only marginal benefits are prescribed statins, identifying the appropriate group that would have the greatest benefit from statin treatment is of utmost importance (Abookire et al. 2001, Ko et al. 2004, Smith et al. 2006).

The complexity of treatment decisions has led to the development of several national treatment guidelines (National Cholesterol Education Program (NCEP) 1994, 2001; National Heart Foundation of Australia 2001, New Zealand Guidelines Group 2003, The British Cardiac Society 2005, Fourth Joint Task Force 2007), and these guidelines do not make identical

recommendations for treatment initiation decisions. For instance, the U.K. guidelines (The British Cardiac Society 2005) recommend initiating lipid lowering agents such as statins when the 10-year CHD risk exceeds 15%, whereas New Zealand guidelines (New Zealand Guidelines Group 2003) recommend the initiation of treatment when the 5-year CHD risk exceeds 10%. Alternatively, one of the U.S. guidelines (ADA 2008) recommends initiating statins in all patients with Type 2 diabetes regardless of their long-term CHD risks.

In this paper, we consider the question of the optimal time to initiate statin treatment for a patient with Type 2 diabetes so as to maximize her quality-adjusted lifetime prior to her first CHD or stroke event. We model the progression of the patient’s LR levels as a discrete-time non-stationary Markov chain, which is calibrated by the patient’s CHD and stroke probabilities from the UKPDS risk model. We consider the trade-off between the benefits and adverse side effects of statin treatment, and formulate the optimal timing of statin initiation problem as an infinite horizon Markov decision process (MDP). To our knowledge, ours is the first optimization model that provides individualized recommendations for the optimal timing of statin initiation and demonstrates the influence of various CHD and stroke risk factors on the patient’s optimal treatment policy. Denton et al. (2007) is the only study we are aware of that models the optimal timing of statin initiation. In contrast to our patient-focused work, they consider the problem from a societal perspective and compare the optimal treatment policies under the UKPDS, Framingham and Archimedes risk models.

The remainder of this paper is organized as follows: In Section 2, we describe our MDP model. In Section 3 we derive structural properties the model, which are supported by a series of numerical experiments in Section 4. In Section 5 we present conclusions and summarize the current work with its limitations.

2. Model Formulation

We formulate a discrete-time, infinite-horizon MDP model for the optimal timing of statin initiation problem. We consider patients with Type 2 diabetes with no history of a CHD or a stroke event, and seek to maximize their quality-adjusted life years (QALYs) prior to their first CHD or stroke event. We assume the patient’s LR, SBP and HbA1c levels, and her age, gender, ethnicity and statuses of smoking and having an atrial fibrillation at diagnosis completely describe her CHD and stroke risk profile, where SBP and HbA1c levels change deterministically as a function of time. Following recent lipid management guidelines, we

assume that initiating statin treatment is a one-time irreversible decision. We describe our MDP model as follows:

Time Horizon: We assume the decision of initiating statin treatment is revisited periodically, and consider an infinite horizon with non-stationary transition probabilities for the first N decision epochs. We define $T = \{0, 1, 2, \dots, N\}$ as the set of decision epochs and assume the problem parameters at epoch $N - 1$ remain stationary beyond epoch $N - 1$. Therefore, the epochs beyond $N - 1$ are not differentiated and are represented by N . This modeling framework aims to access the time-horizon for which there is insufficient medical data due to low sample sizes for high ages and provides an approximation for a portion of the problem with stationary extrapolation of parameters. For notational simplicity, we define $T' = T \setminus \{N\}$ to denote the set of epochs in the non-stationary period, and let *stage* t refer to time interval between epochs t and $t + 1$. Without loss of generality, we assume the patient was diagnosed with the disease k years before epoch 0 and the length of each stage is τ years.

States: We discretize the continuous range of LR values into a set of states $\mathcal{L}' = \{1, 2, \dots, L\}$ where $\ell \in \mathcal{L}'$ corresponds to an *LR range* and lower indexed ranges indicate lower values of LR. We let LR_ℓ denote the patient’s off-treatment LR level in range $\ell \in \mathcal{L}'$. We add an absorbing state $L + 1$ to the set of LR ranges to denote a *terminal event*, e.g. a non-CHD or stroke-related death or a CHD or a stroke event, and let $\mathcal{L} = \mathcal{L}' \cup \{L + 1\}$. We describe the treatment status of the patient by a binary indicator $m \in \mathcal{M} = \{0, 1\}$, where “0” and “1” refer to *not using* and *using* statins, respectively.

Actions and Treatment Effect: The action in state $\ell \in \mathcal{L}$ is chosen from $\{W, I\}$, where W stands for waiting one more stage and I stands for initiating treatment immediately. We assume that treatment reduces the patient’s LR level by a factor $\omega \in (0, 1)$ which we call as the patient’s *treatment-effect factor*. More explicitly, we assume that the patient’s on-treatment LR level will be $(1 - \omega)$ times her off-treatment LR level.

Probabilities: We have four types of probabilities in our model: the probabilities of non-CHD or stroke-related death, CHD and stroke, and the transition probabilities among the LR ranges. At epoch $t \in T'$, a non-CHD or stroke-related death occurs with a state-independent probability $p_t(D)$. Otherwise, if the patient is in state $\ell \in \mathcal{L}'$ under treatment status $m \in \mathcal{M}$, a CHD event occurs with probability $\pi_t^C(\ell, m)$ and a stroke event occurs with probability $\pi_t^S(\ell, m)$. In practice $\pi_t^C(\ell, m)$ and $\pi_t^S(\ell, m)$ also depend on other risk factors, including the patient’s age at diagnosis, ethnicity, gender, SBP and HbA1c levels, and her smoking

status and presence of atrial fibrillation at the time of diagnosis. As the model assumes that SBP and HbA1c levels evolve deterministically and all other patient attributes are static, we suppress this dependence. We let $\pi_t^\nabla(\ell, m) = \pi_t^C(\ell, m) + \pi_t^S(\ell, m)$ denote the patient's probability of having a CHD or a stroke event in state $\ell \in \mathcal{L}'$ under treatment status $m \in \mathcal{M}$ in stage t ; that is, we ignore the possibility of the simultaneous occurrences of CHD and stroke events. Given the patient is in state ℓ under treatment status m at epoch $t \in T'$, the probability of moving into the absorbing state $L+1$ at epoch $t+1$ is denoted by $p_t^m(L+1|\ell)$, where $p_t^m(L+1|\ell) = p_t(D) + [1 - p_t(D)]\pi_t^\nabla(\ell, m)$ for $(\ell, m) \in \mathcal{L}' \times \mathcal{M}$ and $p_t^m(L+1|L+1) = 1$ for both $m \in \mathcal{M}$. Given the patient is in state $\ell \in \mathcal{L}'$ at epoch t and survives without incurring a terminal event in stage t , the probability of being in state $\ell' \in \mathcal{L}'$ at the next epoch is denoted by $q(\ell'|\ell)$, where $Q = [q(\ell'|\ell)]$ denotes the transition probability matrix among the LR ranges. We define $p_t^m(\ell'|\ell)$ to be the probability of being in state ℓ' at epoch $t+1$ given the patient is in state ℓ under treatment status $m \in \mathcal{M}$ at epoch $t \in T'$, which we write as:

$$p_t^m(\ell'|\ell) = \begin{cases} [1 - p_t^m(L+1|\ell)]q(\ell'|\ell) & \text{if } \ell, \ell' \in \mathcal{L}', \\ p_t^m(L+1|\ell) & \text{if } \ell \in \mathcal{L}', \ell' = L+1, \\ 1 & \text{if } \ell = \ell' = L+1, \\ 0 & \text{otherwise.} \end{cases} \quad (1)$$

Rewards: We define $r^m(\ell)$ to be the immediate reward in terms of QALYs accrued in state ℓ and under treatment status m . By isolating the effects of factors other than the patient's treatment status on the patient's health-related quality of life, we let $\sigma \in (0, 1)$ denote the *quality-adjustment factor* from the negative side effects of using statins and define $r^m(\ell) = \tau - m\sigma$ for $\ell \in \mathcal{L}'$ and $m \in \mathcal{M}$. Note that our approach for modeling the patient's immediate rewards is consistent with the studies that incorporate the patient's health-related quality of life into their analyses due to negative side effects of medications including statins (Tsevat et al. 2001, Pignone et al. 2006). Since our objective is to maximize the patient's QALYs prior to her first CHD or stroke event, we set all the immediate rewards associated with the absorbing state $L+1$ to zero, *i.e.*, $r^m(L+1) = 0$ for both $m \in \mathcal{M}$.

In our model, the patient continues to accumulate rewards prior to her first CHD or stroke event. Once she dies of a non-CHD or stroke-related reason or incurs either of these events she transitions into state $L+1$, which is absorbing and provides no rewards. Therefore, by the occurrence of a terminal event, accumulation of reward stops and the patient terminates the process. Recall that statin initiation is a one-time decision, and once the treatment

is initiated m switches from 0 to 1 and remains as such. Therefore, upon initiating the treatment, the patient's expected QALYs prior to her first terminal event is only dependent on her on-treatment rewards and transition probabilities. We define $\mu_t(\ell)$ as the patient's *expected post-treatment reward* in terms of QALYs if the treatment is initiated in state $\ell \in \mathcal{L}$ at epoch $t \in T$, which is recursively calculated as:

$$\mu_t(\ell) = r^1(\ell) + \lambda \sum_{\ell' \in \mathcal{L}} p_t^1(\ell'|\ell) \mu_{t+1}(\ell') \quad \text{for } \ell \in \mathcal{L}, t \in T', \quad (2)$$

$$\mu_N(\ell) = r^1(\ell) + \lambda \sum_{\ell' \in \mathcal{L}} p_{N-1}^1(\ell'|\ell) \mu_N(\ell') \quad \text{for } \ell \in \mathcal{L}, \quad (3)$$

where $\lambda \in [0, 1)$ is the discount factor per stage (Gold et al. 1996, Drummond et al. 1997). If the treatment is initiated in state $\ell \in \mathcal{L}'$ at epoch t , the patient receives the expected post-treatment reward and quits the process. Otherwise, she receives the immediate reward $r^0(\ell)$ and moves into state ℓ' with probability $p_t^0(\ell'|\ell)$. For a patient with no history of CHD or stroke in state ℓ at epoch t , we let $u_t(\ell)$ denote the patient's maximum total expected discounted QALYs prior to her first terminal event, which is defined by:

$$u_t(\ell) = \max \left\{ r^0(\ell) + \lambda \sum_{\ell' \in \mathcal{L}} p_t^0(\ell'|\ell) u_{t+1}(\ell'), \mu_t(\ell) \right\} \quad \text{for } \ell \in \mathcal{L}, t \in T', \quad (4)$$

$$u_N(\ell) = \max \left\{ r^0(\ell) + \lambda \sum_{\ell' \in \mathcal{L}} p_{N-1}^0(\ell'|\ell) u_N(\ell'), \mu_N(\ell) \right\} \quad \text{for } \ell \in \mathcal{L}. \quad (5)$$

Note that the expected post-treatment rewards can be seen as the parameters of the problem since they are determined recursively by a separate Markov reward chain. We define $a_t(\ell)$ as the optimal action in state ℓ at epoch t , which is characterized by (2) and (4) for $t < N$, and by (3) and (5) for $t = N$. Recall that the optimal action at epoch N remains stationary beyond epoch N , and note that (3) and (5) are the optimality equations of an infinite-horizon MDP with stationary rewards and transition probabilities, where (3) represents a set of linear equations. It can be also noticed that $u_t(L+1) = \mu_t(L+1) = 0$ for all $t \in T$, since $L+1$ is an absorbing state and provides no rewards because it denotes a terminal event.

3. Structural Properties

In this section we derive structural properties of our MDP model (we provide proofs of these properties in the electronic companion). In Subsection 3.1, we present sufficient conditions under which the optimal value function, $u_t(\ell)$, is monotone in $\ell \in \mathcal{L}$ and $t \in T$. We also

provide sufficient conditions for the optimality of control-limit policies. Such policies are consistent with guidelines and lend themselves to more efficient solution techniques (Puterman 1994). We also provide sufficient conditions by which we relate the optimal actions at successive epochs. In Subsection 3.2, we compare the optimal value functions and optimal policies of two different patients, and explore the sensitivity of a given patient’s optimal value function and optimal policy with respect to her quality-adjustment and treatment-effect factors. Note that depending on the context we use the terms LR and LR range interchangeably.

3.1. Optimality of Control-Limit Policies

In our problem context, we define a control-limit policy as follows: if the patient has not incurred a CHD or a stroke event at epoch t , she should initiate treatment if and only if her LR is above some threshold. In practice, lipid management guidelines follow threshold structures and we are unaware of any guideline that does not (NCEP 2001, National Heart Foundation of Australia 2001, New Zealand Guidelines Group 2003, The British Cardiac Society 2005, Fourth Joint Task Force 2007). Almost all of these guidelines define their thresholds in terms of the patient’s long-term risk for a major cardiovascular event. Of these, the British and New Zealand guidelines also use explicit LR thresholds for their treatment recommendations.

We assume the patient’s non-CHD or stroke-related death probability, $p_t(D)$, is nondecreasing in $t \in T'$. Note that this assumption is consistent with published mortality data (NCHS 2005). We begin our structural analysis by considering the following inequalities:

$$[1 - \pi_t^\nabla(\ell, m)] \sum_{\ell'=1}^k q(\ell'|\ell) \geq [1 - \pi_t^\nabla(\ell + 1, m)] \sum_{\ell'=1}^k q(\ell'|\ell + 1),$$

for all $\ell \in \mathcal{L}' \setminus \{L\}$, $k \in \mathcal{L}'$, $t \in T'$. (6)

Satisfying (6) under a given treatment status $m \in \mathcal{M}$ can be interpreted as follows: the lower the LR the patient has at the current epoch, the more likely she is to have a lower LR at the next epoch.

Definition 1 (Barlow and Proschan 1965) *An $n \times n$ stochastic matrix $H = [h(j|i)]$ is said to have the increasing failure rate (IFR) property if $\sum_{j=1}^k h(j|i)$ is nonincreasing in i for all $k = 1, \dots, n$.*

The IFR property may be viewed as the first order stochastic dominance relationship among the rows of a stochastic matrix and it appears to match closely clinical data in many contexts (Alagoz et al. 2004, 2007a, 2007b; Shechter et al. 2008, Kreke et al. 2008). In our problem, if Q is IFR, an intuitive explanation is as follows: given the patient does not incur a CHD or a stroke event, the lower the LR of the patient at the current epoch, the more likely it is to be lower at the next epoch.

Proposition 1 *If Q is IFR, then (6) holds for both $m \in \mathcal{M}$.*

Proposition 2 provides sufficient conditions under which the patient's expected post-treatment reward, $\mu_t(\ell)$, and the optimal value function, $u_t(\ell)$, are monotone in LR for all $t \in T$.

Proposition 2 *(i) If (6) holds for $m = 1$, then $\mu_t(\ell)$ is nonincreasing in $\ell \in \mathcal{L}$ for all $t \in T$.*

(ii) If $\mu_t(\ell)$ is nonincreasing in $\ell \in \mathcal{L}$ for all $t \in T$ and (6) holds for $m = 0$, then $u_t(\ell)$ is nonincreasing in $\ell \in \mathcal{L}$ for all $t \in T$.

Note that the condition on $\mu_t(\ell)$ in Proposition 2 (ii) need not follow from the condition of Proposition 2 (i). Also note that, by Proposition 1, Q being IFR is sufficient for Proposition 2 (i) and (ii) to hold.

We define $B_t(\ell)$ as the patient's *expected benefit loss* in QALYs from delaying the initiation of treatment to the next epoch in LR range $\ell \in \mathcal{L}'$ of epoch $t \in T'$, which we calculate as,

$$B_t(\ell) = \mu_t(\ell) - \lambda \sum_{\ell' \in \mathcal{L}} p_t^0(\ell'|\ell) \mu_{t+1}(\ell'), \quad \text{for } \ell \in \mathcal{L}' \text{ and } t \in T'. \quad (7)$$

Note that by definition (7) $B_t(\ell)$ is a composite parameter of the problem. In Proposition 3, we address the relationship between the patient's expected benefit loss and the effect of treatment on her transition probabilities when her expected post-treatment rewards are monotonically nonincreasing in her LR levels.

Proposition 3 *If $\mu_t(\ell)$ is nonincreasing in $\ell \in \mathcal{L}$ for all $t \in T'$, and*

$$\begin{aligned} [\pi_t^\nabla(\ell, 0) - \pi_t^\nabla(\ell, 1)] \sum_{\ell'=1}^k q(\ell'|\ell) &\leq [\pi_t^\nabla(\ell+1, 0) - \pi_t^\nabla(\ell+1, 1)] \sum_{\ell'=1}^k q(\ell'|\ell+1), \\ &\text{for all } \ell \in \mathcal{L}' \setminus \{L\}, k \in \mathcal{L}', t \in T', \end{aligned} \quad (8)$$

then $B_t(\ell)$ is nondecreasing in $\ell \in \mathcal{L}'$ for all $t \in T'$.

In Proposition 3, condition (8) implies that the higher the LR of the patient, the greater the increase she has by treatment in the likelihood of having a lower LR at the next epoch without incurring a CHD or stroke event. Theorem 1 provides sufficient conditions for the optimality of LR-based control-limit policies based on the comparison of the patient's expected benefit loss in different LR levels.

Theorem 1 *Suppose (6) holds for $m = 0$ and $B_t(\ell)$ is nondecreasing in $\ell \in \mathcal{L}'$ for all $t \in T'$. Then, there exists an LR threshold $\ell_t^* \in \mathcal{L}'$ for each $t \in T$ such that the optimal action in state ℓ at epoch t is to initiate treatment if and only if $\ell \geq \ell_t^*$, i.e., $a_t(\ell) = I$ for all $\ell \geq \ell_t^*$, and $a_t(\ell) = W$ otherwise.*

In practice, almost all guidelines explicitly consider the patient's age as a positive-risk factor for a CHD or a stroke event, which is also stated in the UKPDS risk model that each year spent after diagnosis of the disease increases the patient's CHD and stroke probabilities. Next, we focus on how the patient's optimal actions change as she ages. First, we consider the following inequalities:

$$p_{t+1}^m(L+1|\ell) \geq p_t^m(L+1|\ell) \text{ for all } \ell \in \mathcal{L}, t \in T' \setminus \{N-1\}. \quad (9)$$

Condition (9) states that the patient's probability of incurring a terminal event does not decrease under treatment status m as she ages.

Remark 1 *(9) is satisfied for those $(\ell, m) \in \mathcal{L}' \times \mathcal{M}$ for which $\pi_t^\nabla(\ell, m)$ is nondecreasing in $t \in T'$.*

In other words, the time behavior of the patient's CHD and stroke probabilities plays a critical role for her optimal value functions. Next, Proposition 4 explores the relationship between the time-monotonicity of the patient's terminal event probabilities and optimal value functions.

Proposition 4 *(i) If (9) holds for $m = 1$, then $\mu_t(\ell)$ is nonincreasing in $t \in T$ for all $\ell \in \mathcal{L}$.*

(ii) If $\mu_t(\ell)$ is nonincreasing in $t \in T$ for all $\ell \in \mathcal{L}$ and (9) holds for $m = 0$, then $u_t(\ell)$ is nonincreasing in $t \in T$ for all $\ell \in \mathcal{L}$.

By Proposition 4 (ii), if the patient's expected post-treatment rewards are nonincreasing and off-treatment terminal event probabilities are nondecreasing over time, her optimal value functions do not increase as she ages. Note that the patient's expected post-treatment rewards can be nonincreasing in time without satisfying (9) for $m = 1$.

Theorem 2 Suppose (9) holds for $m = 0$ and $B_t(\ell)$ is nondecreasing in $t \in T'$ for all $\ell \in \mathcal{L}'$. Then for $\ell \in \mathcal{L}'$ and $t \in T'$, $a_t(\ell) = I$ implies $a_{t+1}(\ell) = I$.

Theorem 2 demonstrates that if the patient's expected benefit loss from delaying the initiation of treatment to the next epoch does not decrease over time, she becomes more likely to initiate treatment as she ages. If the patient's optimal policy follows control-limit structure, then by Theorem 2 her optimal LR thresholds do not increase as she ages, but note that Theorem 2 applies even if the patient's optimal policy does not exhibit a control-limit structure.

3.2. Comparison of Optimal Policies of Two Patients & Sensitivity Analysis

In this section we compare the optimal policies of two patients. We specify the problem parameters for patient i by a pre-superscript, for $i = 1, 2$. By the following inequalities, which are related to the notion of the first order stochastic dominance among the patients' transition probabilities, under a given treatment status m , compared to patient 1, patient 2 is more likely to have a lower LR at the next epoch without incurring a CHD or a stroke event.

$$\sum_{\ell'=1}^k {}^2p_t^m(\ell'|\ell) \geq \sum_{\ell'=1}^k {}^1p_t^m(\ell'|\ell), \quad \text{for all } \ell, k \in \mathcal{L} \text{ and } t \in T', \quad (10)$$

Indeed, condition (10) is closely related to the patients' terminal event probabilities and their LR progression rates.

Definition 2 Let $H_1 = [h_1(j|i)]$ and $H_2 = [h_2(j|i)]$, $i, j = 1, \dots, n$, be two stochastic matrices. If $\sum_{j=k}^n h_1(j|i) \geq \sum_{j=k}^n h_2(j|i)$ for all $i, k = 1, \dots, n$, then we say H_1 stochastically dominates H_2 , and denote it by $H_1 \succeq H_2$.

Remark 2 Given ${}^1Q \succeq {}^2Q$, (10) holds for those $m \in \mathcal{M}$ for which ${}^1p_t^m(L+1|\ell) \geq {}^2p_t^m(L+1|\ell)$ for all $\ell \in \mathcal{L}'$ and $t \in T'$.

Proposition 5 compares the patients' expected post-treatment rewards and optimal value functions.

Proposition 5 *Consider two patients.*

(i) *Suppose ${}^2\sigma \leq {}^1\sigma$ and $\mu_t(\ell)$ is nonincreasing $\ell \in \mathcal{L}$ for all $t \in T$ for at least one of the patients. Then, if (10) holds for $m = 1$, ${}^1\mu_t(\ell) \leq {}^2\mu_t(\ell)$ for all $\ell \in \mathcal{L}$ and $t \in T$.*

(ii) *Suppose ${}^1\mu_t(\ell) \leq {}^2\mu_t(\ell)$ for all $\ell \in \mathcal{L}$ and $t \in T$, and (6) holds for $m = 0$ for at least one of the patients. Then, if (10) is satisfied for $m = 0$, ${}^1u_t(\ell) \leq {}^2u_t(\ell)$ for all $\ell \in \mathcal{L}$ and $t \in T$.*

Note that the condition on ${}^1\mu_t(\ell)$ and ${}^2\mu_t(\ell)$ in Proposition 5 (ii) need not follow from Proposition 5 (i). In the remainder of this section we relate the optimal policies of two patients. First, we present sufficient conditions to compare the patients' expected benefit losses, and establish an intuitive relationship by Proposition 6.

Proposition 6 *Consider two patients with ${}^1\sigma \leq {}^2\sigma$ and ${}^2\mu_t(\ell) \leq {}^1\mu_t(\ell)$ for all $\ell \in \mathcal{L}$ and $t \in T$. If $\mu_t(\ell)$ is nonincreasing in $\ell \in \mathcal{L}$ for all $t \in T$ for at least one of the patients and,*

$$\sum_{\ell'=1}^k [{}^2p_t^1(\ell'|\ell) - {}^2p_t^0(\ell'|\ell)] \leq \sum_{\ell'=1}^k [{}^1p_t^1(\ell'|\ell) - {}^1p_t^0(\ell'|\ell)], \text{ for all } \ell, k \in \mathcal{L} \text{ and } t \in T', \quad (11)$$

then ${}^1B_t(\ell) \geq {}^2B_t(\ell)$ for all $\ell \in \mathcal{L}$ and $t \in T'$.

In Proposition 6, condition (11) implies the following: by treatment the increase in the likelihood of having a lower LR at the next epoch without incurring a CHD or stroke event is higher for patient 1 than it is for patient 2. If (11) is satisfied and patient 1 has higher expected post-treatment rewards with a lower disutility effect of using statins than patient 2, then delaying the initiation of treatment for one more epoch will cost more for patient 1. Proposition 7 presents sufficient conditions for (11) to hold.

Proposition 7 *Consider two patients with the same treatment-effect factor, ω . Suppose*

$${}^2\pi_t^C(\ell, 0) \leq {}^1\pi_t^C(\ell, 0) \leq 1 - e^{-1} \text{ and } {}^2\pi_t^S(\ell, 0) \leq {}^1\pi_t^S(\ell, 0) \leq 1 - e^{-1} \\ \text{for all } \ell \in \mathcal{L}' \text{ and } t \in T'. \quad (12)$$

Then, if ${}^2Q \succeq {}^1Q$ and ${}^1p_t(D) \leq {}^2p_t(D)$ for all $t \in T'$, (11) holds.

Note that for an appropriately chosen stage length, *i.e.*, annual decision epochs, the patients do not have extremely high probabilities of incurring a CHD or a stroke event prior to the following decision epoch. Thus, condition (12) is not restrictive (we discuss the violation of this condition in the electronic companion). Next, Theorem 3 relates the patients' optimal actions to their expected benefit losses.

Theorem 3 Consider two patients. For at least one of them, suppose (6) holds for $m = 0$ and $B_t(\ell)$ is nondecreasing in $\ell \in \mathcal{L}'$ for all $t \in T'$. Then, if (10) holds for $m = 0$ and ${}^1B_t(\ell) \geq {}^2B_t(\ell)$ for all $\ell \in \mathcal{L}'$ and $t \in T'$, ${}^2a_t(\ell) = I$ implies ${}^1a_t(\ell) = I$ for $\ell \in \mathcal{L}'$ and $t \in T$.

In Theorem 3, at a given LR level the expected benefit loss from delaying the initiation of treatment one more epoch is higher for patient 1 than it is for patient 2, and therefore patient 1 is more likely to initiate treatment than patient 2. In Proposition 8, we address the relationship between the patient's optimal actions and their responses to treatment, which has been shown to be important in making treatment decisions with the evidence from recent investigations on the variability of the patients' pharmacogenetic profiles (Zineh 2007).

Proposition 8 Consider two patients with ${}^1\sigma \leq {}^2\sigma$. If

$${}^1p_t^0(\ell'|\ell) \leq {}^2p_t^0(\ell'|\ell), \text{ and } {}^1p_t^1(\ell'|\ell) \geq {}^2p_t^1(\ell'|\ell) \text{ for all } \ell, \ell' \in \mathcal{L}' \text{ and } t \in T', \quad (13)$$

then for $\ell \in \mathcal{L}'$ and $t \in T$, ${}^2a_t(\ell) = I$ implies ${}^1a_t(\ell) = I$.

In Proposition 8, condition (13) states that when both patients are off(on) treatment patient 2 is more(less) likely to have a lower LR than patient 1 without incurring a terminal event. Therefore, patient 1 benefits more from treatment in terms of increase in the likelihood of having a lower LR without incurring a CHD or a stroke event. Note that in Theorem 3 and Proposition 8, the patients' optimal policies need not exhibit control-limit structure.

In Corollary 1, we compare two patients who are identical except their quality-adjustment and/or treatment-effect factors. By such a comparison, we also explore the sensitivity of a patient's optimal value functions, $u_t(\ell)$, with respect to her quality-adjustment and treatment-effect factors.

Corollary 1 Consider two patients who are identical except ${}^2\sigma \geq {}^1\sigma$ and/or ${}^1\omega \geq {}^2\omega$. Then,

- (i) ${}^1\mu_t(\ell) \geq {}^2\mu_t(\ell)$ and ${}^1u_t(\ell) \geq {}^2u_t(\ell)$ for all $\ell \in \mathcal{L}$ and $t \in T$.
- (ii) For $\ell \in \mathcal{L}'$ and $t \in T$, ${}^2a_t(\ell) = I$ implies ${}^1a_t(\ell) = I$.

In Corollary 1, the patient's optimal value functions, $u_t(\ell)$, do not decrease as σ decreases and/or ω increases. Furthermore, if it is optimal to initiate treatment at a given LR level, it must be optimal to do so if the patient's disutility of using statins decreases and/or the treatment reduces her LR further.

Corollary 2 Consider two patients who are identical except ${}^2\sigma \geq {}^1\sigma$. For $\ell_1, \ell_2 \in \mathcal{L}'$, $\ell_1 \leq \ell_2$ and $t \in T$, suppose ${}^2a_t(\ell_1) = {}^2a_t(\ell_2) = I$. Then, if (6) holds for $m = 1$, ${}^1u_t(\ell_1) - {}^2u_t(\ell_1) \geq {}^1u_t(\ell_2) - {}^2u_t(\ell_2)$.

Corollary 2 reveals an important relationship between the negative side effects of using statins and LR levels of a patient who is currently on-treatment, and can be interpreted as follows: if the patient is currently on treatment and is more likely to incur a terminal event or have a higher LR at the next epoch, then the effect of reducing her quality-adjustment factor diminishes as her LR increases. Next, in Corollary 3, we focus on the adverse side effects of treatment over time for a patient who is currently on treatment with deteriorating terminal event probabilities.

Corollary 3 Consider two patients who are identical except ${}^2\sigma \geq {}^1\sigma$. For $\ell \in \mathcal{L}'$ and $t \in T'$, suppose ${}^2a_t(\ell) = {}^2a_{t+1}(\ell) = I$. Then if (9) holds for $m = 1$, ${}^1u_t(\ell) - {}^2u_t(\ell) \geq {}^1u_{t+1}(\ell) - {}^2u_{t+1}(\ell)$.

We interpret Corollary 3 as follows: reducing the adverse side effects of treatment has more substantial impacts at the early ages of a patient who is on treatment and has an increasing likelihood of incurring a terminal event over time.

We continue to analyze sensitivity of the patient's optimal value functions by Proposition 9, which we interpret as follows: the lower the quality-adjustment factor the patient has, the higher the benefit she gains as treatment reduces her LR further. This result can be intuitively explained as follows: by Corollary 1 (ii), as the efficacy of treatment in terms of reducing the patient's LR levels increases, the patient becomes more likely to initiate treatment, and as the disutility of using statins decreases the patient's on-treatment immediate rewards increases. Therefore, a decrease in the quality-adjustment factor has more impact on the patient's optimal value function when the treatment is more effective in reducing her LR levels.

Proposition 9 Consider two patients, who are identical except ${}^1\omega \geq {}^2\omega$. Let σ_1 and σ_2 be two quality-adjustment factors, with $\sigma_1 \geq \sigma_2$, and let ${}^{i,j}u_t(\ell)$ specify ${}^i u_t(\ell)$ when the quality-adjustment factor is σ_j , for $\ell \in \mathcal{L}$, $t \in T$ and $i, j = 1, 2$. Then, ${}^{1,2}u_t(\ell) - {}^{1,1}u_t(\ell) \geq {}^{2,2}u_t(\ell) - {}^{2,1}u_t(\ell)$ for all $\ell \in \mathcal{L}$ and $t \in T$.

Next, we analyze the rate of increase in the patient’s optimal value functions as her quality-adjustment factor decreases. To simplify the analysis, we introduce a third patient and let ${}^3\sigma$, ${}^3\mu_t(\ell)$ and ${}^3u_t(\ell)$ denote the quality-adjustment factor, the expected post-treatment reward and the optimal value function in state $\ell \in \mathcal{L}$ at epoch $t \in T$ for patient 3, respectively.

Proposition 10 *Consider three patients who are identical except ${}^1\sigma \geq {}^3\sigma$ and ${}^2\sigma = ({}^1\sigma + {}^3\sigma)/2$. Then, ${}^3u_t(\ell) - {}^2u_t(\ell) \geq {}^2u_t(\ell) - {}^1u_t(\ell)$ for all $\ell \in \mathcal{L}$ and $t \in T$.*

By Proposition 10, as the patient’s quality adjustment factor decreases, her optimal value function increases with an increasing rate, which reveals the importance of diminishing the negative side effects of using statins. We can also interpret Proposition 10 as the convexity of the patient’s optimal value function with respect to quality-adjustment factor intuitively as follows: as the disutility of using statins decreases the patient’s on-treatment immediate rewards increase and the patient becomes more likely to initiate treatment by Corollary 1 (ii). Therefore, decreasing the disutility of using statins increases the patient’s optimal value function with an increasing rate.

Finally, we provide a comparison that demonstrates the clinical implications of our structural results. The following proposition draws from the equations of the UKPDS risk model and provides insights for individualized treatment policies.

Proposition 11 *Consider two patients who are identical except as follows:*

1. *Patient 1 was diagnosed before patient 2, and/or*
2. *Patient 1 is male and patient 2 is female, and/or*
3. *Patient 1 is Caucasian or Asian-Indian, and patient 2 is Afro-Caribbean, and/or*
4. *Patient 1 was a smoker and patient 2 was a non-smoker when diagnosed, and/or*
5. *Patient 1 had atrial fibrillation and patient 2 did not when diagnosed, and/or*
6. *Patient 1 has a higher HbA1c than patient 2 for all $t \in T'$, and/or*
7. *Patient 1 has a higher SBP than patient 2 for all $t \in T'$.*

Then,

- (i) ${}^1\pi_t^C(\ell, m) \geq {}^2\pi_t^C(\ell, m)$ and ${}^1\pi_t^S(\ell, m) \geq {}^2\pi_t^S(\ell, m)$ for all $\ell \in \mathcal{L}'$, $m \in \mathcal{M}$ and $t \in T'$.
- (ii) ${}^1\mu_t(\ell) \leq {}^2\mu_t(\ell)$ and ${}^1u_t(\ell) \leq {}^2u_t(\ell)$ for all $\ell \in \mathcal{L}$ and $t \in T$.

(iii) If the patients have also different treatment effect factors, i.e., ${}^1\omega \neq {}^2\omega$, then there exists a function $f : \mathbb{R}_+ \rightarrow \mathbb{R}$ such that if ${}^1\omega \geq f({}^2\omega)$ then for $\ell \in \mathcal{L}'$ and $t \in T$, ${}^2a_t(\ell) = I$ implies ${}^1a_t(\ell) = I$.

Proposition 11 (iii) addresses the relationship between the patients' responses to the treatment in terms of reduction in their LR levels and their optimal actions. More explicitly, it can be interpreted as follows: given the reduction in patient 1's LR levels by treatment exceeds a certain threshold, which can be expressed as a function of the level of reduction in patient 2's LR levels, and if it is optimal to initiate treatment for patient 2, then it must be optimal to do so for patient 1. Note that the function $f({}^2\omega)$ depends on the parameters of the equations that the UKPDS risk model uses to predict the CHD and stroke probabilities, and any combination of cases 1-7 that metabolic profiles of the patients satisfy. In other words, $f({}^2\omega)$ is different for each combination of cases 1-7 that are satisfied (see the electronic companion for details). Also note that cases 6 and 7 are verifiable for $t \geq 0$ as we model the evolution of HbA1c and SBP deterministically. In other words, the patients' SBP and HbA1c levels can be compared at epoch 0 since they can be estimated as a function of time prior to analysis.

4. Numerical Study

We present a numerical study using our model calibrated with clinical data and the UKPDS risk model. We organize this section as follows: In Subsection 4.1, we describe the data sources on which we calibrate our MDP model, which is followed by the parameter estimation process in Subsection 4.2. In Subsection 4.3 we present the optimal value functions and treatment policies for two hypothetical patients. We also illustrate the sensitivity of the patients' optimal value functions and policies with respect to quality-adjustment and treatment-effect factors. We discuss the violations of the sufficient conditions that we present in Section 3 in the electronic companion.

4.1. Data Sources

We estimate the parameters of our MDP model by using the Mayo Clinic Diabetes Electronic Management System (DEMS) data (Gorman et al. 2000), the UKPDS risk model (Stevens et al. 2001, Kothari et al. 2002) and NCHS mortality rate tables (NCHS 2005). DEMS has been designed to track patients with Type 2 diabetes at Mayo Clinic and keeps longitudinal

medical records for such patients including the data for years 1993-2005. The patient data in DEMS are available quarterly with detailed treatment information and laboratory measurements for TC, HDL, SBP and HbA1c levels. The majority of the patients in DEMS are non-smoker Caucasian patients who had no atrial fibrillation at the age of diagnosis, and no prior CHD or stroke. Therefore, we limited our study to these patients leaving a data set of 663 patients.

4.2. Parameter Estimation

For our experiments, we assumed two patient profiles, one for each gender: non-smoker, Caucasian who was diagnosed with Type 2 diabetes at age 40 with no history of CHD, stroke, or atrial fibrillation. Our data set provides insufficient observations for patients older than 80. Therefore, we set annual decision epochs for a 40-year non-stationary decision horizon, which starts at age 40. This implies treatment decisions are age-dependent prior to age 79 and remain stationary after age 79 by our infinite horizon approximation, *i.e.*, $\tau = 1$, $k = 0$ and $N = 40$.

To describe the natural history of off-treatment LR levels, we develop a discrete-time Markov model, which has been applied in the context of several diseases (Sonnenberg and Beck 1993, Roberts and Sonnenberg 2000). Incomplete data is one of the most common challenges in building natural history models and estimating transition probability matrices (Craig and Sendi 2002, Welton and Ades 2005). To overcome this difficulty and maximize the utilization of sparsely available data, we first fit cubic splines to each patient’s sequence of TC and HDL measurements by using a similar approach as Alagoz et al. (2005) and Shechter (2006). We estimate the incomplete data points and obtain complete sequences of quarterly available TC and HDL levels, each with a size of 11,760 data points.

The effects of using statins on the patient’s LR levels have been reported as relative reductions in the patients’ TC and HDL levels in clinical trials (Hebert et al. 1997, Maron et al. 2000). Therefore, we implicitly estimate the treatment effect factor ω by assuming that treatment affects TC and HDL in proportion to their current levels. That is, using statins changes the patient’s current TC and HDL levels by factors c and h , respectively, where $0 < c < 1$ and $h > 1$. For instance, if the patient’s TC and HDL values are v_{TC} and v_{HDL} before treatment, then the treated levels are cv_{TC} and hv_{HDL} , respectively. This implies $\hat{\omega} = 1 - \frac{c}{h}$. To estimate the corresponding values of c and h , since the decision of initiating treatment is revisited annually, we observe the treatment’s impact on TC and HDL levels by focusing

on 6-month intervals before and after the initiation of treatment. Note that, although it is not clinically recommended (Vijan and Hayward 2004, Snow et al. 2004), in DEMS we observe some patients who gave up using statins and have initiated treatment more than once. We consider all initiations and re-initiations during estimating the factors c and h . We let $K(i)$ denote the number of times that patient i initiated treatment for $i = 1, \dots, N$, where $N = 663$ denotes the size of the sample. Then we let the pairs $[v_{TC}^i(j, k, 0), v_{HDL}^i(j, k, 0)]$ and $[v_{TC}^i(j, k, 1), v_{HDL}^i(j, k, 1)]$ denote the i^{th} patient's total cholesterol and HDL levels j quarters before and after the k^{th} initiation of treatment, respectively, for $i = 1, \dots, N$, $j = 1, 2$, and $k = 1, \dots, K(i)$, and estimate c and h by the following formulae:

$$c = \frac{\sum_{i=1}^N \frac{1}{K(i)} \sum_{k=1}^{K(i)} \frac{v_{TC}^i(1, k, 1) + v_{TC}^i(2, k, 1)}{v_{TC}^i(1, k, 0) + v_{TC}^i(2, k, 0)}}{N}, \quad h = \frac{\sum_{i=1}^N \frac{1}{K(i)} \sum_{k=1}^{K(i)} \frac{v_{HDL}^i(1, k, 1) + v_{HDL}^i(2, k, 1)}{v_{HDL}^i(1, k, 0) + v_{HDL}^i(2, k, 0)}}{N}. \quad (15)$$

In (15), each ratio term within the inner sum of the numerator corresponds to the ratio of the average TC or HDL level within 6 months after an initiation of treatment to that within 6 months before that initiation. Using (15) over the spline-fitted data we estimate $c = 0.86026$ and $h = 1.07284$, which implies 19.815 % reduction in LR levels by treatment, *i.e.*, $\hat{\omega} = 0.19815$.

To estimate the transition probability matrix Q for each gender, we use the patients' off-treatment LR levels. We calculate a corresponding off-treatment LR level for each spline-fitted on-treatment LR level. We assume $1/c$ and $1/h$ denote the factors for the inverse effects of treatment on TC and HDL levels. That is, stopping using statins changes the level of TC by a factor of $1/c$, and the level HDL by a factor of $1/h$. For instance, if the patient's on-treatment TC and HDL values are v_{TC} and v_{HDL} , then the estimated off-treatment levels are v_{TC}/c and v_{HDL}/h , respectively. By using the estimates $c = 0.86026$ and $h = 1.07284$, we normalize the patients' spline-fitted on-treatment TC and HDL levels so that we obtain sequences of TC and HDL estimates in which all patients are assumed to be off-treatment. We calculate the off-treatment LR levels over these sequences and discretize the continuous range of LR levels into $L = 13$ ranges. We let state $\ell \in \mathcal{L}'$ refers to range $[LB(\ell), UB(\ell))$, where the boundaries $\{LB(\ell), UB(\ell)\}$ for $\ell \in \mathcal{L}'$ are presented in Table 1.

Based on this discretization, for each patient, we calculate the number of off-treatment LR estimates in each LR range in all quarters and ages. Then, we count the number of transitions from each range to all other ranges between the same quarters of subsequent

Table 1: Boundaries of LR ranges

	LR Range (ℓ)												
	1	2	3	4	5	6	7	8	9	10	11	12	13
$LB(\ell)$	0	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5
$UB(\ell)$	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	∞

ages, and construct the Q matrices for the probabilistic movements among the LR ranges. Recall that we assume a single value, LR_ℓ , to denote the patient's off-treatment LR level in range $\ell \in \mathcal{L}'$. We calculate the gender specific LR averages in each range and assign these averages as the corresponding values of LR_ℓ for $\ell \in \mathcal{L}'$. With this approach, we increase the utilization of data by exploiting its quarterly availability. We formalize this process for male patients as follows: We let $b_{TC}^i(t, j)$ and $b_{HDL}^i(t, j)$ denote the off-treatment TC and HDL values of patient i in the j^{th} quarter of age t for $i = 1, \dots, N_m$, $j = 1, \dots, 4$ and $t = 40, \dots, 80$, respectively, where N_m is the number of male patients in the data set. We define two indicator functions: $\psi(z) = \{\ell \in \mathcal{L}' : z \in [LB(\ell), UB(\ell)]\}$, and

$$I_{t,j}^i(\ell) = \begin{cases} 1 & \text{if } \psi(b_{TC}^i(t, j)/b_{HDL}^i(t, j)) = \ell, \\ 0 & \text{otherwise,} \end{cases} \quad (16)$$

for $i = 1, \dots, N_m$, $j = 1, \dots, 4$, $t = 40, \dots, 80$ and $\ell, \ell' \in \mathcal{L}'$. Then the transition probability between ranges $\ell, \ell' \in \mathcal{L}'$ and average LR level in range $\ell \in \mathcal{L}'$ are estimated as follows:

$$q(\ell'|\ell) = \frac{\sum_{i=1}^{N_m} \sum_{j=1}^4 \sum_{t=40}^{79} I_{t,j}^i(\ell) I_{t+1,j}^i(\ell')}{\sum_{i=1}^{N_m} \sum_{j=1}^4 \sum_{t=40}^{79} \sum_{\ell' \in \mathcal{L}'} I_{t,j}^i(\ell) I_{t+1,j}^i(\ell')}, \quad LR_\ell = \frac{\sum_{i=1}^{N_m} \sum_{j=1}^4 \sum_{t=40}^{79} I_{t,j}^i(\ell) \left(\frac{b_{TC}^i(t, j)}{b_{HDL}^i(t, j)} \right)}{\sum_{i=1}^{N_m} \sum_{j=1}^4 \sum_{t=40}^{79} I_{t,j}^i(\ell)}.$$

We present gender specific average LR levels in each LR range in the following table.

Table 2: Gender specific LR_ℓ estimates.

		LR Range (ℓ)												
Patient		1	2	3	4	5	6	7	8	9	10	11	12	13
LR_ℓ	Female	2.61	3.26	3.75	4.24	4.74	5.24	5.73	6.22	6.73	7.24	7.73	8.22	9.97
	Male	2.63	3.29	3.77	4.25	4.75	5.25	5.73	6.24	6.73	7.24	7.74	8.24	10.87

Note that a similar approach has been used for other diseases in estimating the associated transition probability matrices (Alagoz et al. 2005, Shechter 2006).

We predict the patient’s yearly CHD and stroke probabilities by using the UKPDS risk model. A summary on how the UKPDS risk model predicts the patient’s yearly CHD and stroke probabilities is provided in the electronic companion. Recall that the UKPDS risk model considers SBP and HbA1c levels as explicit risk factors in estimating the patients’ CHD and stroke probabilities, and our model assumes deterministic evolution of these levels. In estimating the patients’ off and on-treatment yearly CHD and stroke probabilities, we use the gender specific SBP and HbA1c estimates from Denton et al. (2007), which models their progression as a function of age by a cubic spline.

Finally, we use the NCHS (2005) mortality rate tables to estimate the patients’ non-CHD or stroke-related death probabilities. We estimate the values of $p_t(D)$ by subtracting the probability of death due to a CHD or a stroke event from the probability of death due to all reasons. Note that the corresponding values of $p_t(D)$ are estimated as gender and age specific, but based on the availability of the data they are aggregated in 5-year intervals from age 40 to 80.

4.3. Numerical Results

We run our MDP model to derive the optimal treatment policies of the two hypothetical patients. For the quality-adjustment factor, we assume $\sigma = 0.02$ for our base case numerical experiments (Tsevat et al. 2001, Pignone et al. 2006), and perform a sensitivity analysis over σ . In all numerical experiments we assign $\lambda = 0.97$ as the annual discount factor (Gold et al. 1996).

Recall that the patients’ optimal value functions and actions remain stationary beyond age 79. Therefore, in the tables and figures that we present in this section we use 80+ to refer to all ages beyond 79. In Tables 3 and 4 we present the male and the female patient’s maximum expected quality-adjusted survivals prior to their first terminal events at ages 40, 50, 60, 70 and 80, respectively. Tables 3 and 4 show that the optimal value functions are monotonically nonincreasing in both LR and age (by Proposition 2 (ii) and Proposition 4 (ii), respectively). They also illustrate that the optimal value function of the male patient is less than that of the female at all LR ranges and ages, where the difference in the patients’ optimal value functions ranges from 2.09 to 2.69 QALYs. The differences in the maximum quality-adjusted survivals of the male and the female patients prior to their first terminal events are closely related to gender-based differences in CHD and stroke risks which may be attributed to pathophysiological processes for men and women (Pilote et al. 2007). From

Tables 3 and 4, it is also worth to mention that difference between the patients’ optimal value functions in two different LR ranges increase as they age. The optimal value function of the male patient has a range of 0.77 QALYs at age 40, whereas it is 2.58 QALYs at age 80 and beyond. Similarly, the optimal value function of the female patient has a range of 0.69 QALYs at age 40 and increases up to 2.67 QALYs by age 80. These imply that increasing LR levels have more significant effects on the patients’ optimal value functions as they get older.

Table 3: Male patient’s maximum expected QALYs prior to his first terminal event.

Age	LR Range (ℓ)												
	1	2	3	4	5	6	7	8	9	10	11	12	13
80+	5.93	5.69	5.47	5.29	5.08	4.92	4.74	4.59	4.47	4.35	4.26	4.01	3.65
70	7.60	7.41	7.22	7.07	6.89	6.76	6.60	6.47	6.37	6.28	6.21	5.99	5.73
60	11.10	10.94	10.78	10.65	10.50	10.38	10.24	10.14	10.05	9.97	9.92	9.73	9.52
50	14.87	14.75	14.63	14.54	14.42	14.34	14.23	14.16	14.10	14.04	14.01	13.87	13.73
40	18.44	18.36	18.26	18.19	18.11	18.05	17.98	17.93	17.89	17.86	17.84	17.75	17.67

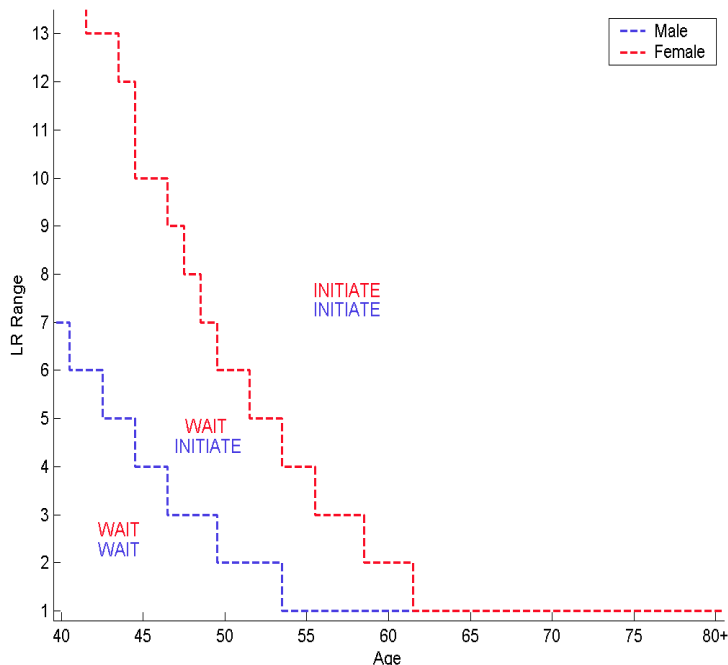
Table 4: Female patient’s maximum expected QALYs prior to her first terminal event.

Age	LR Range (ℓ)												
	1	2	3	4	5	6	7	8	9	10	11	12	13
80+	8.41	8.13	7.92	7.66	7.45	7.22	7.05	6.89	6.73	6.52	6.40	6.18	5.74
70	10.07	9.85	9.69	9.48	9.31	9.12	8.99	8.87	8.74	8.58	8.49	8.31	7.98
60	13.65	13.49	13.37	13.22	13.10	12.96	12.86	12.78	12.69	12.57	12.51	12.37	12.14
50	17.43	17.32	17.23	17.12	17.04	16.94	16.88	16.82	16.76	16.69	16.65	16.56	16.41
40	20.82	20.75	20.69	20.62	20.56	20.50	20.45	20.42	20.38	20.32	20.29	20.23	20.13

Figure 1 depicts the optimal LR thresholds to initiate treatment for both patients (by Theorem 1). For instance, the optimal policy at age 40 can be interpreted as follows: treatment should be initiated for the male patient if his LR level falls into any range that is higher than 6. On the other hand treatment is not recommended at any LR level for the female patient. Note that the optimal LR thresholds are nonincreasing in age for both patients which implies that the patients are more likely initiate treatment as they get older (by Theorem 2). Also note that the male patient’s optimal LR thresholds are not higher than those of the female patient, and the deviation between their optimal LR thresholds are more significant in the early ages after diagnosis. These results are consistent with a recent epidemiological study that has shown that relative cardiovascular risk reduction by treatment is less for

female patients than it is for male patients (Karp et al. 2007). Moreover, they also confirm a meta-analysis of clinical trials for lipid-lowering treatment agents which has demonstrated lesser benefit of treatment for female patients than for male patients (Walsh and Pignone 2004).

Figure 1: Patients' optimal LR range thresholds to initiate statin treatment when $\sigma = 0.02$ and $\omega = 0.19815$.



Although statin treatment has significant benefits in reducing the risk of cardiovascular complications for patients with Type 2 diabetes, there is no apparent clinical evidence that informs the use of statins for low-risk patients before age 55. Therefore, depending on the patient's LR levels, recent lipid management guidelines recommend the cautious use of statins before age 55 (Snow et al. 2004). Note that the optimal policies in Figure 1 are consistent with these recommendations.

To evaluate the effects of quality-adjustment and treatment-effect factors on the patients' optimal value functions and policies, we perform one-way and two-way sensitivity analyses. Figures 2 and 3 present the patients' optimal treatment policies under various quality-adjustment factors, and illustrate the fact that the patients become more likely to initiate treatment as the disutility of using statins decreases (by Corollary 1 (ii)).

Figure 2: Sensitivity of the male patient’s optimal policy with respect to σ , when $\omega = 0.19815$.

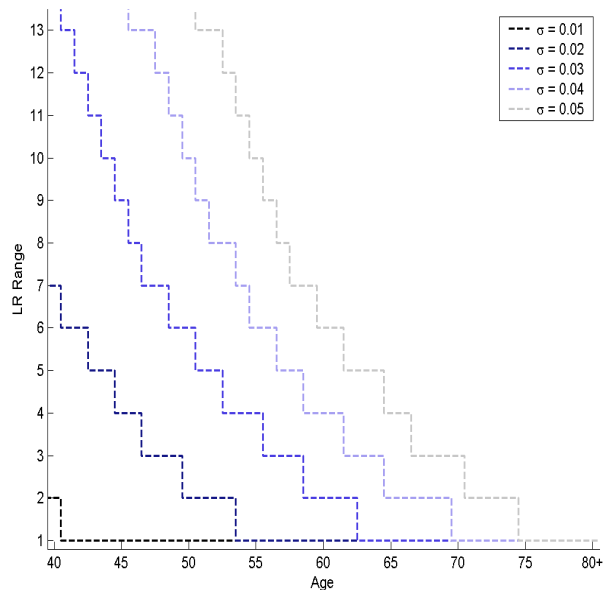
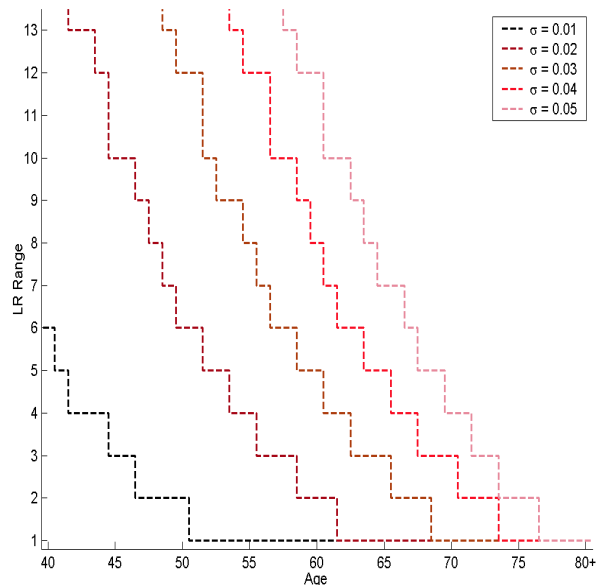


Figure 3: Sensitivity of the female patient’s optimal policy with respect to σ , when $\omega = 0.19815$.



It is clear that the optimal time to initiate statin treatment is quite sensitive to the patients’ quality-adjustment factors, and when both patients have the same factor, the optimal LR thresholds of the male patient are not higher than those of the female patient. Note that, when $\sigma = 0.01$, the patients do not lose more than 0.02 QALYs prior to their first terminal event if they immediately initiate treatment rather than following their optimal treatment policies. However, as shown in Table 5, as the disutility of using statins increases these losses can be significant, which may have consequential implications for some of the current guidelines that recommend the immediate initiation of statin treatment after diagnosis of the disease (Snow et al. 2004). Moreover, they highlight the importance of incorporating patients’ values and preferences when initiating statins since there may be considerable heterogeneity for the disutility of using statins experienced by patients. From Table 5, it is also worth to mention that the male patient’s quality-adjusted survival loss is less than that of the female patient in each LR range, which we can attribute to the fact that the male patient is more likely to initiate treatment than the female.

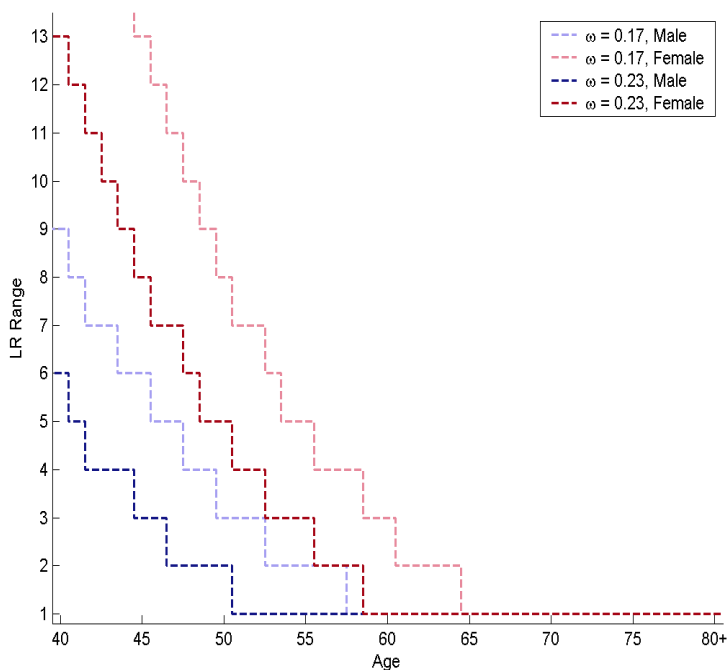
In Figure 4, we illustrate the sensitivity of the patients’ optimal policies with respect to treatment-effect factor, ω , within an approximate $\pm 3\%$ region around our point estimate

Table 5: Patients' QALY losses at the time of diagnosis from immediately initiating treatment rather than following their optimal treatment policies when $\sigma = 0.05$.

Patient	LR Range (ℓ)												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Male	0.411	0.391	0.369	0.352	0.332	0.317	0.302	0.286	0.276	0.268	0.262	0.243	0.231
Female	0.592	0.576	0.563	0.545	0.532	0.516	0.506	0.497	0.487	0.474	0.468	0.455	0.435

for ω . It depicts the fact that the patients become more likely to initiate treatment as it reduces their LR levels further (by Corollary 1 (ii)). It also depicts the region into which the patients' optimal LR thresholds are expected to fall if the level of reduction in the patient's LR levels by treatment is in between 17 % and 23 %. It is worth noting that the male patient is more likely to initiate treatment than the female patient even when his response to treatment in terms of reduction in his LR levels is less than that of the female.

Figure 4: Sensitivity of the patients' optimal policies with respect to treatment-effect factor ω , when $\sigma = 0.02$.



In Tables 6 - 9, we present the results from our two-way sensitivity analyses. It is clear that an increase in the treatment efficacy has more impact on the patients' optimal value

functions when the disutility effect of using statins is lower (by Proposition 9). It is also notable that when both patients have the same quality-adjustment factor, the increase in the treatment efficacy increases the male patient’s maximum quality-adjusted survival more than the female’s.

Table 6: Male patient’s QALY gain at the time of diagnosis when ω increases from 0.17 to 0.23.

σ	LR Range (ℓ)												
	1	2	3	4	5	6	7	8	9	10	11	12	13
0.01	0.182	0.190	0.196	0.201	0.205	0.209	0.213	0.217	0.219	0.221	0.223	0.228	0.232
0.02	0.154	0.159	0.167	0.174	0.183	0.193	0.204	0.211	0.217	0.219	0.220	0.225	0.228
0.03	0.122	0.125	0.130	0.133	0.138	0.142	0.148	0.153	0.157	0.160	0.163	0.180	0.191

Table 7: Female patient’s QALY gain at the time of diagnosis when ω increases from 0.17 to 0.23.

σ	LR Range (ℓ)												
	1	2	3	4	5	6	7	8	9	10	11	12	13
0.01	0.153	0.158	0.163	0.170	0.177	0.184	0.188	0.190	0.192	0.196	0.197	0.201	0.205
0.02	0.125	0.128	0.130	0.133	0.136	0.140	0.143	0.145	0.148	0.153	0.155	0.161	0.175
0.03	0.099	0.101	0.102	0.103	0.105	0.106	0.107	0.108	0.109	0.110	0.111	0.112	0.115

On the other hand, when treatment is more effective, reducing the negative side effects of statins increases the patients’ quality-adjusted survival gains more (by Proposition 9). From Tables 8 and 9, regardless of the efficacy of treatment, when the disutility of using statins decreases the male patient gains more quality-adjusted survival prior to the first terminal event than the female patient. It is also worth noting that the patients’ quality-adjusted survival gains with increasing treatment-effect and/or decreasing quality-adjustment factors increase as their LR levels increase. This implies that increasing treatment efficacy and decreasing disutility effect of using statins have more impact for high risk patients than they have for relatively low risk patients.

5. Conclusions

The existing risk models in the literature serve as a guide to clinicians for selecting the type of intervention and the aggressiveness of treatment. However, their use has so far focused

Table 8: Male patient’s QALY gain at the time of diagnosis when σ decreases from 0.05 to 0.01.

ω	LR Range (ℓ)												
	1	2	3	4	5	6	7	8	9	10	11	12	13
0.17	0.284	0.296	0.312	0.325	0.339	0.350	0.363	0.373	0.381	0.387	0.391	0.406	0.414
0.19815	0.341	0.358	0.376	0.390	0.407	0.420	0.435	0.446	0.455	0.462	0.467	0.484	0.493
0.23	0.399	0.419	0.440	0.455	0.475	0.489	0.506	0.519	0.529	0.537	0.543	0.561	0.573

Table 9: Female patient’s QALY gain at the time of diagnosis when σ decreases from 0.05 to 0.01.

ω	LR Range (ℓ)												
	1	2	3	4	5	6	7	8	9	10	11	12	13
0.17	0.225	0.231	0.236	0.244	0.250	0.259	0.265	0.272	0.279	0.289	0.294	0.304	0.318
0.19815	0.270	0.278	0.285	0.296	0.305	0.318	0.327	0.335	0.343	0.354	0.359	0.371	0.388
0.23	0.317	0.328	0.337	0.352	0.366	0.381	0.391	0.400	0.410	0.422	0.428	0.442	0.461

on providing raw information about the risk of complications to clinicians and patients, and unfortunately there has not been much emphasis on how to use these information to make treatment decisions. To our knowledge, ours is the first study in the literature that aims to balance the trade-off between the benefits and adverse side effects of statins. We consider patients with Type 2 diabetes with no prior CHD or stroke, and develop an infinite-horizon MDP model to maximize their quality-adjusted lifetimes prior to their first CHD or stroke events. We derive several structural properties of our model, including sufficient conditions that guarantee the monotonicity of the patient’s optimal value functions in LR levels and the optimality of LR-based control-limit treatment policies. We also provide sufficient conditions to relate the patient’s optimal actions across time periods and the optimal policies of two different patients. We analytically explore the sensitivity of the patient’s optimal value function with respect to treatment efficacy and disutility of using statins. By drawing from the UKPDS risk model’s CHD and stroke probability equations we address the clinical implications of our structural results and provide valuable insights for medical professionals.

By using clinical data from Mayo Clinic, we conduct a series of computational experiments to support our structural results for two hypothetical patients, one for each gender. In all of our computational tests, the optimal policy is of control-limit type, and the patients’ optimal LR-thresholds are nonincreasing in age. Our computational experiments also show that the

male patient’s quality-adjusted survival prior to his first terminal event is less than that of the female, whereas his optimal treatment policy is more aggressive than that of the female.

The treatment policies that we provide as a function of time and the patient’s LR level offer individualized guidelines which may motivate the patients to adhere to prescribed treatment regimens. The implications of these policies may also provide clinical insights to both patients and clinicians, and may establish a critical step in designing more patient-focused cholesterol treatment guidelines through explicit consideration of disutility of using statins by enhancing the analyses of results from clinical trials. Moreover, while the focus of our research has been on designing optimal statin treatment policies for patients with Type 2 diabetes, the model that we propose can also be used for the studies addressing the statin treatment decisions in the general population.

Our study has several limitations. Firstly, our model does not cover the probabilistic progression of SBP and HbA1c levels, which can be addressed by a more complicated model. Such a model can be developed through augmenting the current state space of our model, and can consider blood pressure and blood sugar treatment decisions. We leave the development of such an extensive model as a different branch of our future studies. Secondly, our model ignores the possibility of the simultaneous occurrences of CHD and stroke events. It is worth noting that none of the existing risk models in the literature has a published equation to calculate the probability of simultaneous occurrences of a CHD and a stroke event. Thirdly, the source data that we used to estimate the LR progression rates belong to a single medical center, and the population the data belongs to is likely to be healthier than a typical population that may not receive continuous access to health care. Lastly, a limitation for our numerical experiments is that we narrowed our focus only on Caucasian non-smoker patients due to availability of clinical data, but note that our model is generic so that it can be used for any Type 2 diabetes patient with no history of a CHD or a stroke event. It can also be used to address the problem under the other risk models mentioned in Section 1. Note that our structural results, excluding Propositions 1, 7, 8, 9 and 11, and Corollary 1, also hold for our model under the calibration of any other risk model.

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