

A comparison of decision-maker perspectives for optimal cholesterol treatment

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Medical decisions often involve tradeoff among competing criteria. For example, patients with third-party health insurance are primarily concerned about maximizing their quality-adjusted lifespan, since the majority of the cost burden typically falls on the third-party payer. On the other hand, third-party payers are incented to minimize total healthcare-related costs. Therefore, third-party payers must weigh the short-term cost of treatment against the long-term benefits of avoiding more costly health outcomes associated with disease progression and adverse events. The goal of the societal perspective is to achieve a reasonable balance among these competing criteria of quality-adjusted lifespan and costs. Treatment of diabetes provides a good example of the need to apply multicriteria decision-making models to treatment decisions. Chronic diseases such as diabetes are associated with high medical costs and a large number of available treatment options. In this paper, we use a Markov decision process (MDP) to show how decision-maker perspectives can influence medical treatment decisions related to cardiovascular risk management in patients with type 2 diabetes. We compare optimal treatment decisions from three different perspectives: societal, patient, and third-party payer. We further formulate an inverse MDP model to estimate the implied monetary value of a year of life, from the societal perspective, according to current U.S. treatment guidelines.

Introduction

Medical treatment decisions typically involve several stakeholders including patients, physicians, and third-party health insurers. Patients with third-party health insurance are primarily concerned about maximizing quality-adjusted lifespan. On the other hand, third-party payers must weigh the short-term cost of treatment against the long-term benefits of avoiding more costly health outcomes associated with disease progression and adverse events. The goal of the societal perspective is to strike a balance among these competing criteria of quality-adjusted lifespan and costs. Chronic diseases, such as diabetes, are particularly good examples of contexts in which multicriteria decision-making models are needed, since many chronic diseases are

associated with high medical costs and a large number of available treatment options.

The Centers for Disease Control and Prevention (CDC) estimates that approximately 8% of the U.S. population has type 2 diabetes [1]. Diabetes has the potential to significantly influence a patient's long-term health and quality of life. For example, patients with diabetes are at much higher risk for adverse events related to cardiovascular disease such as heart attack and stroke [2]. Diabetes is also a very costly disease to treat. It is estimated that in 2010 alone, medical expenditures due to diabetes were \$198 billion in the United States; this expenditure is expected to grow to at least \$264 billion per year by 2030 [3]. These high costs necessitate careful consideration of the value of medical treatment. Therefore, in this paper we present a case study of the comparison of decision-maker perspectives based on an important treatment decision for type 2 diabetes.

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Much of the literature in health economics and related fields, such as health services research and public health, uses cost-effectiveness studies to assess the merit of medical treatment decisions. Such studies commonly estimate the incremental cost-effectiveness ratio (ICER) associated with treatment decisions. The ICER is the ratio of the change in costs associated with an intervention to the change in the effects associated with the intervention. The cost is typically measured in dollars, whereas the effects may be measured in life-years or quality-adjusted life years (QALYs). “Life-years” is defined as having a value of 1, for a year in perfect health, whereas “QALYs” takes a value between 0 and 1 to denote the loss associated with a reduced quality of life due to burden of disease or treatment (see Gold et al. [4] for a thorough explanation of methods such as this for estimating quality-adjusted lifespan). Thus, ICERs are measured in dollars per QALY. Typically, a threshold is used to define the ICER value that is deemed cost-effective. For example, a commonly used estimate in the health economics literature is \$50,000/QALY, but as Rascati [5] points out, the question “How much is a QALY worth?” has been the source of significant debate. An initiative developed by the World Health Organization (WHO), called WHO-CHOICE, reports on the costs and effects of a range of interventions in different geographical regions around the world [6].

Some health systems, such as in the United Kingdom, take a formal approach to the evaluation of cost-effectiveness of healthcare interventions. For example, in the United Kingdom, the National Institute for Health and Clinical Evidence (NICE) is responsible for making recommendations on the use of new and existing medical interventions. The typical ICER threshold used by NICE is £20,000/QALY to £30,000/QALY [7]. In other countries, such as the United States, there is no formally accepted practice for evaluating the cost-effectiveness of medical interventions. In fact, in the past, Medicare, the public funder of healthcare for U.S. citizens and permanent residents age 65 years and older, has been required by law to provide whatever medical services are “reasonable and necessary.” Nevertheless, as Gillick [8] points out with specific examples, cost is an implied consideration in determining the viability of offering certain high-cost interventions.

In this paper, we study the influence of different decision-maker perspectives on medical treatment decisions. There are many medical treatment options for patients with type 2 diabetes. Among the most common are HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase inhibitors (statins), which are an important part of the treatment plan for patients with type 2 diabetes. Statins lower a patient’s cholesterol and have been shown to reduce the risk of heart attack and stroke. However, the optimal time to initiate treatment is influenced by many factors. Considerations include the patient’s health status with respect

to cardiovascular disease, the cost of treatment, cost of hospitalization and follow-up care due to heart attack and stroke, side effects resulting from treatment, and the benefits associated with potentially extending a patient’s lifetime or increasing quality of life.

We use a Markov decision process (MDP) to investigate the influence of decision-maker perspectives on the control of cardiovascular risk in patients with type 2 diabetes. In contrast with the standard approach employed in health economic investigations, which computes the ICER for a predefined intervention, we define the value of QALYs a priori and use this to find the optimal intervention that maximizes a reward function representing the stakeholder’s perspective. We consider three different perspectives: societal, patient, and third-party payer. From the patient’s perspective, we assume the goal is to maximize expected QALYs over the patient’s lifetime. The third-party payer perspective minimizes expected costs of treatment over the patient’s lifetime. Finally, the societal perspective combines these criteria and maximizes a weighted difference in rewards for QALYs and costs.

We further formulate an inverse MDP model to estimate the implied value of a QALY, which we refer to as the societal willingness to pay (WTP). The goal of our inverse MDP model is to find the implied monetary value per QALY that is consistent with the current published U.S. guideline for cholesterol control in patients with diabetes. The decision variables in the model include the monetary reward per QALY, and the objective is to minimize the difference between the optimal value function and the expected rewards associated with the current U.S. guideline. The results from this model provide estimates of the implied value of QALYs in the U.S. health system in the context of cholesterol control for patients with type 2 diabetes.

The remainder of this paper is organized as follows: First, we provide some background on type 2 diabetes. Second, we review the relevant literature on models for optimal control of medical interventions, and methods for estimating WTP. Third, we present two models. The first is an MDP model for determining the optimal time to initiate statin therapy in patients with type 2 diabetes, and the second is the inverse MDP model to determine the implied WTP. Fourth, we present results from our models including 1) optimal policies for statin initiation for a male and a female base case, as well as sensitivity analysis, and 2) estimates of the implied WTP based on our inverse MDP model. Finally, we summarize some of the generalizable insights that can be drawn from our study, describe limitations of our work, and point out future research directions.

Background on diabetes treatment

The diagnosis of diabetes is straightforward when a patient presents with symptoms. Once diagnosed, a primary goal is to control blood glucose levels (glycemic control). This is

important for managing short-term effects such as thirst, frequent urination, muscle weakness, blurred vision, and other symptoms. It is also important for managing long-term risks, since high blood glucose levels, especially in the setting of hyperlipidemia (high cholesterol) and hypertension (high blood pressure), is associated with complications including coronary heart disease (CHD), stroke, blindness, kidney failure, limb amputation, and others. Glucose levels can be managed through diet and exercise; however, alone, this is typically not sufficient to control the disease. Recently, it has been recognized that cholesterol and blood pressure are particularly important factors in the design of treatment regimens for diabetes because patients with diabetes are at much higher risk of stroke and CHD events. In general, factors influencing risk in common risk models such as those we use in this paper include blood glucose, total cholesterol (TC), high-density lipoprotein [(HDL); often referred to as “good cholesterol”], and blood pressure (systolic and diastolic). Like blood glucose, the latter three factors are also controllable through medical treatment.

When patients are unable to manage their cholesterol by adhering to a diet and exercise regimen, medication may be necessary. Statins are currently considered the most important first line of treatment for controlling cholesterol levels [9]. A number of guidelines have been suggested for cholesterol control. In the United States, the Adult Treatment Panel III (ATP III) clinical guidelines were published by the National Cholesterol Education Program (NCEP) [9]. NCEP outlines goals for managing cholesterol and guidelines for achieving these goals in the U.S. population. ATP III has the stated 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. For diabetes patients, the treatment goal is to maintain LDL (low-density lipoprotein) cholesterol (also known as “bad cholesterol”) at a level of less than 100 mg/dL.

Literature review

There is an extensive literature on medical decision-making. Here, we provide a brief review of topics directly related to this paper. We focus on two particular areas: The first is research on the use of optimization models for medical treatment decisions, which are central to our own research; the second is research related to the estimation of societal WTP.

Models for treatment optimization

Quantitative models have been used for decades to help assist in medical decision-making. Markov models in particular are not new to medical decision-making. In 1993, Sonnenberg and Beck [10] highlighted that many clinical problems could be modeled using Markov chains. A more recent paper from 2006 presented a Markov model for

studying treatment options for preventing CHD events [11]. Pignone et al. [11] used their Markov model to determine the cost-effectiveness of aspirin, statins, or both for primary prevention of CHD events. Results showed that aspirin use was both more effective and less costly than no treatment, whereas the cost-effectiveness of adding statins depended on the patient’s 10-year risk of having a CHD event.

Recent years have seen an increase in extensions to treatment optimization based on MDPs. Schaefer et al. [12] 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 applicable to medical decision-making in many contexts. Following are some notable examples that have some similarity to our MDP model.

Shechter et al. [13] present an MDP model to determine the optimal timing of HIV (human immunodeficiency virus) therapy. The states are represented by the patient’s CD4 (cluster of differentiation 4) white cell count (the primary target of the virus), the decision to initiate treatment or defer the decision is made monthly, and the objective is to maximize the patient’s quality of life. Unlike with our model, their MDP is stationary and has an infinite horizon. Shechter et al. [13] show that if it is optimal to initiate therapy at a given CD4 count, it is also optimal for sicker patients (with lower CD4 counts) to begin therapy. Using their model, they conclude that aggressive treatment at an early stage is generally optimal.

Alagoz et al. [14] have written several papers on different versions of their MDP models for the optimal timing of liver transplantation, with the first model finding the optimal time for a patient to have a living donor transplantation. The states are the patient’s health status, defined by a scoring system [the MELD (Model for End-Stage Liver Disease) score] for patients with end-stage liver disease. The objective of this model is to determine when a patient should receive the transplant in order to maximize his quality-adjusted lifetime, assuming the living donor is available at any time and considering the QALYs before and after the transplantation. Subsequent models by Alagoz et al. consider the decision when cadaveric transplants are an option as well [15, 16].

Previous work has been done with consideration of different decision-maker perspectives. For example, Ross et al. [17] use a Monte Carlo simulation based on a Markov model to test different prostate-specific antigen test screening strategies for prostate cancer. Their analysis compared screening strategies in terms of health outcomes (effect on the patient) and resources used (effect on the healthcare system). They report the nondominated strategies and make further comparisons among these policies. Those

that were dominated were less effective and used more resources than the other strategies.

Some previous studies have focused on medical decisions related to the control of cholesterol and blood pressure for patients with type 2 diabetes. Denton et al. [18] formulated an MDP model, similar to the model we describe in this paper, to compute the optimal time to initiate statins. They used the model to compare the optimal treatment time for male and female patients based on three different risk models including the U.K. Prospective Diabetes Study (UKPDS) model [19, 20], the Framingham [21] model, and the Archimedes model [22]. Kurt et al. [23] also studied a similar problem with a focus on proving theoretical properties regarding the structure of optimal policies for statin initiation. Among other findings, the authors showed that a threshold policy defined by a patient's lipid ratio (the ratio of TC to HDL) is optimal. Finally, Mason et al. [24] combined an MDP model for statin initiation with a Markov model that represented the patient's (potentially) imperfect adherence to statin treatment. In their model, upon initiating treatment, patients probabilistically transition among health states defined by varying levels of adherence to statins. The resulting changes in adherence influence the patient's cholesterol levels and, therefore, indirectly influence the patient's probability of cardiovascular events. The authors used their model to evaluate the influence of imperfect adherence on optimal treatment decisions and to estimate the benefits associated with adherence-improving interventions.

Simulation has been used to study treatment decisions for patients with type 2 diabetes. Hayward et al. [25] used simulation to compare population-level policies for when to initiate statins for the primary prevention of coronary artery disease. The study compared the use of U.S. guidelines for cholesterol management based on risk factors and the patient's 10-year coronary artery disease risk—using both standard and intensive cholesterol treatment goals—and a treatment initiation plan based on the patient's 5-year coronary artery disease risk. Increasing doses of statins were used to intensify treatment as patients aged. The treatment strategy developed by the authors resulted in more events and deaths prevented and more QALYs saved than either of the U.S. guideline policies. This work differs from ours in that the authors compared a single alternative policy to the current guidelines, whereas our MDP model finds the optimal treatment policy among all possible treatment policies.

Estimation of willingness to pay

There has been significant debate about the appropriate monetary value of a QALY. The most commonly used value of \$50,000 in the health policy literature [5] dates back to the 1980s. The study estimated the WTP for dialysis therapy in Canada using a small sample of patients at a single medical center. In principle in the United States, there is

no standard practice for evaluating the cost-effectiveness of medical interventions.

Several approaches have been proposed to update the estimate of the value of a year of life. For example, a recent study suggested that the number be updated to \$93,500 by converting Canadian dollars to U.S. dollars and adjusting for inflation [26]. Another approach has been to estimate the incremental change in salary for workers to take on an increase in occupational risk. Hirth et al. [27] provide a review of estimates of WTP, including studies based on occupational risk. They found values vary widely across studies, ranging from \$21,294 to \$904,679, in 1997 U.S. dollars. Estimates varied on the basis of the data sources and the nationality of study participants. Braithwaite et al. [28] quantified the incremental costs and benefits of modern healthcare (post-1950s) and unsubsidized health insurance. Their results suggest that the appropriate amount per QALY should be between \$183,000 and \$264,000, suggesting that the commonly used value of \$50,000 per QALY is a poor estimate of the implied value of a QALY.

In a study more closely related to ours, Lee et al. [29] used a simulation model to estimate the treatment costs and QALYs for a population with end-stage renal disease. ICERs were estimated by comparing current practice with the next least costly option and with the case of no dialysis. 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, indicating ICERs varied significantly within the population they studied. For example, they observed significant differences based on age and the presence of comorbidities, suggesting inequity in the current dialysis practice.

The unique contributions of this paper are as follows. First, we use an MDP model to study the influence of three different decision-maker perspectives (patient, third-party payer, and societal) on the optimal policy for statin initiation for patients with type 2 diabetes. Second, we provide a new inverse MDP model, for evaluating WTP, which is applicable to other medical interventions such as those described above. Third, we provide estimates of the implied WTP for statin treatment in patients with type 2 diabetes. To our knowledge, we present the first estimates for statin therapy in this context. This is important because the U.S. guidelines for statin treatment affect a very large population, with current estimates from the CDC at 8% of the U.S. population. In contrast, end-stage renal disease, considered by Lee et al. [29], is less common, and using this disease may not be the best way to estimate the typical WTP used in policy research for treatments of all types of diseases. Thus, our results provide some insight into how the size of the affected population may influence the implied WTP. Such comparisons may help reveal biases or disparities among disease treatment indicating inequity within the health system.

Model formulation

For many diabetes patients, the most important controllable cardiovascular risk factors are cholesterol and blood pressure. Statins reduce cholesterol and are typically the first line of treatment. The decision to initiate statins 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 causes unrelated to diabetes.

Metabolic risk factors, including blood pressure, cholesterol, and HbA1c (an estimate of a patient's 2-to-3-month blood glucose concentration), evolve probabilistically over time as patients age. At each decision epoch, 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 risk factors and the occurrence of nonfatal cardiovascular events including CHD and stroke. Absorbing states include death from cardiovascular complications and other causes. In each epoch, a decision-maker selects one of two possible decisions: *initiate treatment* or *defer treatment until the next epoch*. The following subsections provide a description of the MDP model.

Time horizon

The decision to initiate statins is revisited periodically within a finite horizon with N (yearly) decision epochs, indexed by integer t , with nonstationary transition probabilities. In our model, N is a reasonable upper bound on the length of the decision horizon, that is, the portion of a patient's lifetime for which statin initiation would be considered.

Health states

The health states are defined for each of TC and HDL. We let $S^{\text{TC}} = \{1, 2, \dots, c\}$ define the TC states, indexed by decision epoch t by $\ell_t^{\text{TC}} \in S^{\text{TC}}$, where a lower index denotes lower risk of entering an absorbing state. We let $S^{\text{HDL}} = \{1, 2, \dots, h\}$ define the HDL states, indexed by decision epoch t by $\ell_t^{\text{HDL}} \in S^{\text{HDL}}$, where a higher index denotes a lower probability of entering an absorbing state. The patient's event history is also contained in the state definition. We let $S^{\text{CHD}} = \{0, 1, 2, \dots, 5\}$ define the possible number of CHD events, and $S^{\text{S}} = \{0, 1, 2, \dots, 5\}$ define the possible number of strokes (up to a maximum of 5), indexed by ℓ_t^{CHD} and ℓ_t^{S} , respectively. For simplicity of notation, we let ℓ_t represent the patient's overall health state, including history of events (ℓ_t^{CHD} and ℓ_t^{S}), TC (ℓ_t^{TC}), and HDL (ℓ_t^{HDL}).

Actions

At each decision epoch t , the decision-maker either elects to initiate statins or defer treatment. We denote the

decision to initiate (I) statins at epoch t by $a_t = I$ and the decision to wait (W) one more epoch by $a_t = W$. Initiating treatment is assumed to be a one-time, irreversible decision. In other words, we assume the treatment decision is irreversible because that is generally the clinical intention provided a patient tolerates statins. Once a patient with type 2 diabetes initiates statin treatment, clinical guidelines recommend the patient should continue treatment for the remainder of the patient's life [30, 31].

Transition probabilities

Several events are associated with possible health outcomes in our model including fatal CHD (FCHD), nonfatal CHD (NFCHD), fatal stroke (FS), nonfatal stroke (NFS), and death from other causes (FO). We group these into three types of probabilities in our model: 1) the probabilities of death from other causes $p_t(\text{FO})$, 2) the probabilities of fatal cardiovascular events [$p_t(\text{FCHD}|\ell_t, a_t)$ and $p_t(\text{FS}|\ell_t, a_t)$] and nonfatal cardiovascular events [$p_t(\text{NFCHD}|\ell_t, a_t)$ and $p_t(\text{NFS}|\ell_t, a_t)$], and 3) the transition probabilities among health states $q_t(\ell_{t+1}|\ell_t)$ given that statins are not initiated. Transition probabilities are estimated using a large longitudinal data set from the Mayo Clinic [32], U.S. CDC life tables [33], and the UKPDS cardiovascular risk model [19, 20]. We define the probability of dying as $p_t(D|\ell_t, a_t) = p_t(\text{FO}) + p_t(\text{FCHD}|\ell_t, a_t) + p_t(\text{FS}|\ell_t, a_t)$. The probability of being in state ℓ_{t+1} at time $t + 1$, given that a_t is taken in state ℓ_t at time t , is defined by the following:

$$p_t(\ell_{t+1}|\ell_t, a_t) = \begin{cases} q_t(\ell_{t+1}|\ell_t)[1 - p_t(D|\ell_t, a_t)] & \text{if the patient lives} \\ p_t(D|\ell_t, a_t) & \text{if the patient dies.} \end{cases}$$

The effects of statins are to modify the probability of dying and thus potentially extend the patient's lifespan.

Rewards

We consider three different reward functions to reflect the patient, third-party payer, and societal perspectives. Rewards are denoted by $r(\ell_t, a_t)$ for health state ℓ_t and action a_t . The objective for the societal perspective model is to maximize the dollar reward for patient QALYs minus costs of treatment and health services. The following reward function reflects these two criteria:

$$r(\ell_t, a_t) = d(\ell_t, a_t)R - c(\ell_t, a_t) - c^{\text{ST}}(a_t),$$

where $d(\ell_t, a_t)$ represents the patient's QALY when the patient is in state ℓ_t and action a_t is taken. QALY decrements are applied when a patient is on treatment or has suffered a stroke or CHD event. Parameter R represents the monetary value per QALY; $c(\ell_t, a_t)$ denotes the annual cost of standard diabetes care and treatment for adverse events; and $c^{\text{ST}}(a_t)$ represents the cost of statin treatment, applied if a patient has taken the action $a_t = I$. For the patient perspective

model, the objective is to maximize QALYs; the associated reward function is as follows:

$$r(\ell_t, a_t) = d(\ell_t, a_t).$$

For the third-party payer perspective model, the objective is to minimize costs. The reward function is given by the following:

$$r(\ell_t, a_t) = -c(\ell_t, a_t) - c^{\text{ST}}(a_t).$$

Note that minimizing costs is equivalent to maximizing negative costs. In each of the three reward functions, the initiation of statins results in a loss of QALYs (patient and societal perspectives) and/or a monetary cost of medication (societal and third-party payer perspectives).

Optimality equations

Based on the above definition of statins, actions, and rewards, the optimality equations for the optimal time to initiate statins can be written as follows:

$$v_t^M(\ell_t) = \max \left\{ r(\ell_t, W) + \lambda \sum_{\ell_{t+1} \in S} p_t(\ell_{t+1} | \ell_t, W) \times v_{t+1}^M(\ell_{t+1}), \mu_t(\ell_t) \right\}, \quad \forall \ell_t \in S, t \neq N,$$

where $v_t^M(\ell_t)$ denotes the value function for health state ℓ_t in epoch t associated with the MDP, and $\mu_t(\ell_t)$ denotes the post-treatment rewards for a patient that begins treatment in health state ℓ_t at epoch t . Thus, the above MDP involves deciding between the expected benefit of deferring treatment and the expected benefits of initiating treatment.

The boundary condition is given by $v_N^M(\ell_N) = E[\text{PDHR} | \ell_N, a_N]$, where $E[\text{PDHR} | \ell_N, a_N]$ represents the expected post-decision horizon rewards, defined as the expected rewards for QALYs minus costs received after the end of the decision horizon. These post-decision horizon rewards are accrued using a Markov model for $r(\ell_t, a_t)$ with the assumption that the patient's probabilities of death and events remain constant from the last year of the decision horizon. This quantity captures the expected rewards patients accrue between the end of the decision horizon and death. In our model, decision epochs are annual, the decision horizon extends to age 80, and the post-decision horizon extends from age 80 to 100.

The above MDP has the structure of an *optimal stopping time problem* reported by Denton et al. [18]. Puterman [34] gives a number of examples of other types of stopping time problems and a detailed description of solution methods and structural properties of MDPs such as this.

Implied societal willingness to pay

The combination of costs and rewards for QALYs requires a monetary estimate of the value of QALYs, i.e., the societal WTP. Since the most appropriate value of the WTP factor

is highly debated, we present an inverse MDP, based on the above MDP, to estimate the implied WTP based on the published ATP III cholesterol treatment guidelines in the United States [9]. For diabetes patients, the ATP III guideline has the goal of treatment when LDL cholesterol level is 100 mg/dL or higher. The inverse MDP can be expressed as a linear program (LP) in which the WTP factor, denoted by R_0 , is a decision variable. The objective of the LP is to find the WTP that generates an optimal policy with expected future rewards (denoted by the value-to-go function in the objective function) from a given starting age (e.g., initial diagnosis of type 2 diabetes) that is consistent with the expected rewards achieved when implementing published cholesterol treatment guidelines.

In the LP formulation provided below, a patient in state ℓ_t that is taking action a_t is denoted by $\ell_t^{a_t}$. The decision variable $v_t^G(\ell_t^{a_t})$ denotes the value function for health state ℓ_t in epoch t when the actions are according to the ATP III guideline, i.e., wait (W) or initiate (I) statins, and a_t^G represents the action taken according to the guideline for a patient at epoch t that is currently not on statins. The decision variable $v_t^M(\ell_t^{a_t})$ denotes the value function for health state ℓ_t associated with the MDP when action a_t is taken. The inverse MDP can be written as follows:

$$\begin{aligned} & \min \sum_{\ell_0} |v_0^M(\ell_0^W) - v_0^G(\ell_0^W)| \\ & v_t^M(\ell_t^W) - d(\ell_t^W)R_0 - \lambda \sum_{\ell_{t+1}^W} p_t(\ell_{t+1}^W | \ell_t^W) \\ & \quad \times v_{t+1}^M(\ell_{t+1}^W) \geq -c(\ell_t^W), \forall \ell_t, t \neq N \\ & v_t^M(\ell_t^W) - d(\ell_t^W)R_0 - \lambda \sum_{\ell_{t+1}^I} p_t(\ell_{t+1}^I | \ell_t^W) \\ & \quad \times v_{t+1}^M(\ell_{t+1}^I) \geq -c(\ell_t^W), \forall \ell_t, t \neq N \\ & v_t^M(\ell_t^I) - d(\ell_t^I)R_0 - \lambda \sum_{\ell_{t+1}^I} p_t(\ell_{t+1}^I | \ell_t^I) \\ & \quad \times v_{t+1}^M(\ell_{t+1}^I) = -c(\ell_t^I) - c^{\text{ST}}(I), \forall \ell_t, t \neq N \\ & v_t^G(\ell_t^W) - d(\ell_t^W)R_0 - \lambda \sum_{\ell_{t+1}^{a_t^G}} p_t(\ell_{t+1}^{a_t^G} | \ell_t^W) \\ & \quad \times v_{t+1}^G(\ell_{t+1}^{a_t^G}) = -c(\ell_t^W) - c^{\text{ST}}(a_t^G), \forall \ell_t, t \neq N \\ & v_t^G(\ell_t^I) - d(\ell_t^I)R_0 - \lambda \sum_{\ell_{t+1}^I} p_t(\ell_{t+1}^I | \ell_t^I) \\ & \quad \times v_{t+1}^G(\ell_{t+1}^I) = -c(\ell_t^I) - c^{\text{ST}}(I), \forall \ell_t, t \neq N \\ & v_t^M(\ell_t^{a_t^M}) = E[\text{PDHR} | \ell_t^{a_t^M}], \forall \ell_t, t = N \\ & v_t^G(\ell_t^{a_t^G}) = E[\text{PDHR} | \ell_t^{a_t^G}], \forall \ell_t, t = N \\ & R_0, v_t^M(\ell_t^W), v_t^M(\ell_t^I), v_t^G(\ell_t^W), v_t^G(\ell_t^I) \geq 0. \end{aligned}$$

The objective function is the absolute value of the difference in the value functions for the optimal policy and the ATP III guideline. The first two sets of constraints of the

Table 1 Description and sources of model input parameter values.

| <i>Parameter</i> | <i>Value</i> | <i>Source</i> |
|------------------------------------|--------------|---------------|
| Lower bound statins cost | \$212 | [37] |
| Upper bound statins cost | \$1,258 | [37] |
| Initial hospitalization for stroke | \$13,204 | [38] |
| Follow-up for stroke | \$1,664 | [39] |
| Initial hospitalization for CHD | \$18,590 | [38] |
| Follow-up for CHD | \$2,576 | [39, 40] |
| Willingness-to-pay factor | \$100,000 | [36, 41] |
| Discount factor | 3% | [41] |
| Statins QALY decrement | 0.997 | [42–44] |
| Stroke QALY decrement | 0.79 | [45, 46] |
| CHD QALY decrement | 0.93 | [45, 47] |

Table 2 Ranges of total cholesterol and high-density lipoprotein (HDL) for the low, medium, high, and very high states used in the numerical experiments. Healthier patients have lower values of total cholesterol and higher values of HDL.

| | <i>Low</i> | <i>Medium</i> | <i>High</i> | <i>Very high</i> |
|--------------------------|------------|---------------|-------------|------------------|
| <i>Total cholesterol</i> | <160 | 160–200 | 200–240 | >240 |
| <i>HDL</i> | <40 | 40–50 | 50–60 | >60 |

LP ensure the value function associated with the MDP for patients not currently on treatment is the larger of the value associated with delaying treatment and the value associated with initiating treatment. The third set of constraints defines the value function for the MDP for patients already on treatment. The next set of constraints defines the value function estimates associated with following the ATP III guideline for statin initiation for patients currently off statins. The fifth set of constraints defines the value function for the ATP III guideline for patients already on treatment. The remaining three sets of constraints set the value function for the final period equal to the expected post-decision horizon rewards and ensure the decision variables are all nonnegative, respectively. Overall, the goal of the LP formulation is to find a value of R_0 such that the difference between the optimal policy and the ATP III guideline is minimized.

Results

In this section, we present results for two types of numerical experiments. First, we present results illustrating the optimal statin initiation policy from the patient, third-party payer, and societal perspectives. For the societal perspective, we solve the MDP assuming a WTP of \$100,000/QALY [35, 36]. We provide results for male and female patients and contrast the two cases. Because of high variation in the cost of statins depending on the brand, we performed

sensitivity analysis with respect to medication cost. For the second set of numerical experiments, we present results of the solution to the inverse MDP model to provide estimates of the implied WTP based on current U.S. treatment guidelines for statin initiation in patients with type 2 diabetes.

All numerical experiments were performed using a personal computer with an Intel Core™ 2 Quad processor Q9550 at 2.83 GHz with 8.00 GB of RAM. For the solution of the MDP model, we use backward induction implemented in C++. Total computation time to solve the MDP was less than 5 seconds. For the inverse MDP described above, we solved instances of the linear program using IBM CPLEX® 11.0 Concert Technology Library with C++. Total computation time for the WTP numerical experiments was less than 10 seconds.

Table 1 provides a description of the base case model inputs and their sources for the reward function of the MDP (costs and disutilities). **Table 2** defines the TC and HDL ranges for low (L), medium (M), high (H), and very high (V) states used in all of the numerical experiments. These ranges are based on clinically relevant thresholds [9]. A total of 16 types of patients were defined on the basis of these states for TC and HDL, with the highest risk patient having very high TC and low HDL and the healthiest patient having low TC and very high HDL. Transition probabilities among health states were estimated from three sources. Transitions among TC and HDL states were estimated using a large

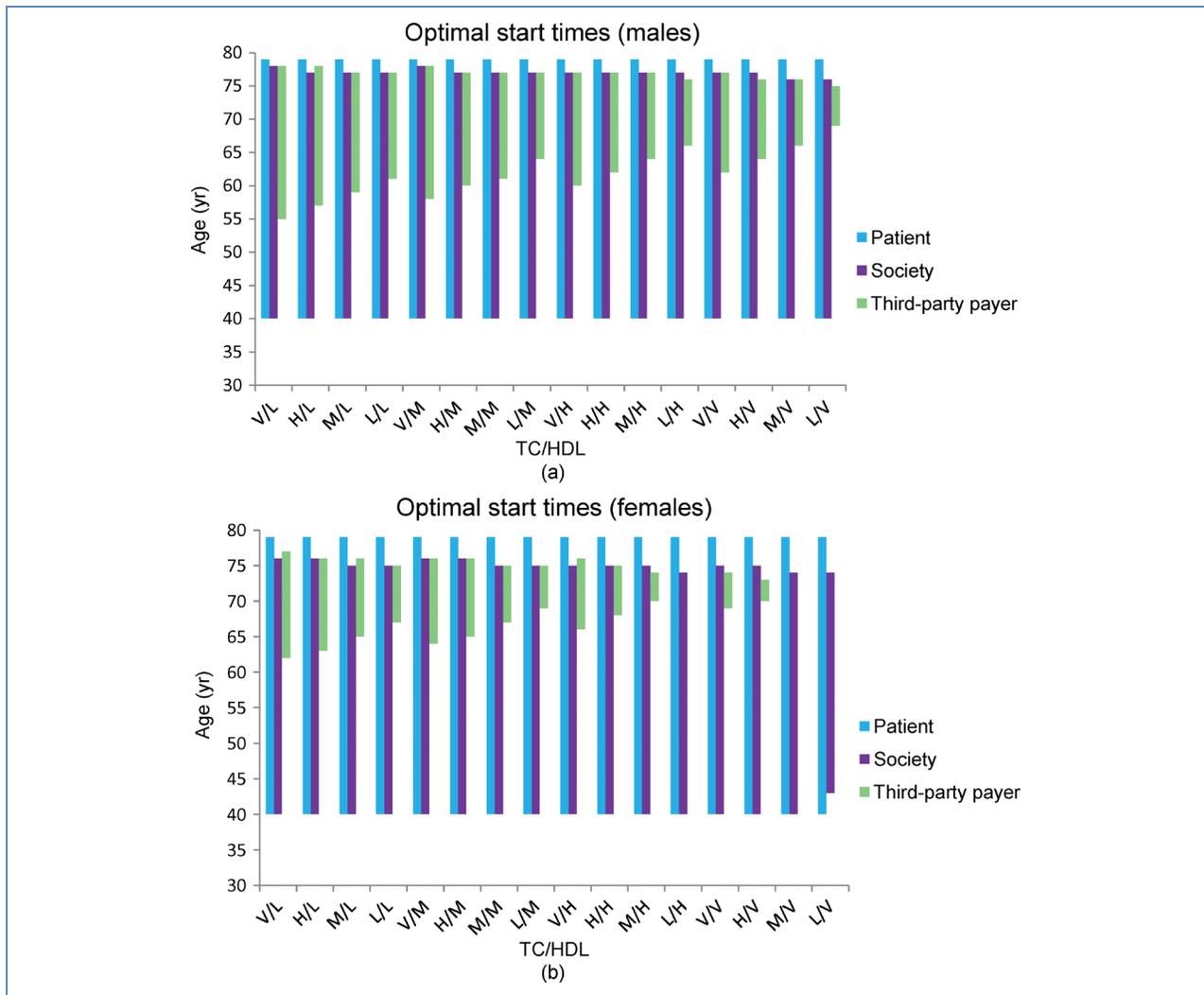


Figure 1

Optimal policies for statin initiation. (a) Illustration of the optimal policy for statin initiation at the lower bound of annual statin treatment costs for male patients from the patient, third-party payer, and societal perspectives. The x-axis is composed of risk states that are defined by total cholesterol (TC) and high-density lipoprotein (HDL), each of which can be low (L), medium (M), high (H), or very high (V). The ranges for these states are defined by Table 2. Each bar represents the age range for which statin initiation is optimal in patients that have not yet initiated treatment. (b) Illustration of the optimal policy for statin initiation for female patients for the lower bound on annual statin treatment costs.

clinical data set from Mayo Clinic composed of a longitudinal medical record for a cohort of patients with type 2 diabetes from 1993 to 2005 [32]. The data set includes laboratory measurements for TC, HDL, and other factors. Transitions from health states to states representing fatal and nonfatal cardiovascular events were estimated using the UKPDS model [19, 20]. Finally, transitions to the death state, representing all other cause mortality, were computed using CDC life tables based on subtracting the probabilities of death from CHD and stroke from the total probability of death. See Denton et al. [18] for a detailed description of the estimate of these transition probabilities.

Estimates of the effect of statins on TC and HDL were obtained using the Mayo Clinic data set. The statin effects were estimated using laboratory measurements for TC and HDL for patients who initiated statin treatment during the timeframe of the longitudinal data set. Estimates were based on the mean change using laboratory measurements from the 6-month periods immediately before and immediately after initiation. The effect of statins on TC was estimated as -13.97% , and the effect of statins on HDL was estimated as $+7.28\%$. See Kurt et al. [23] for a detailed description of the estimate of these treatment effects.

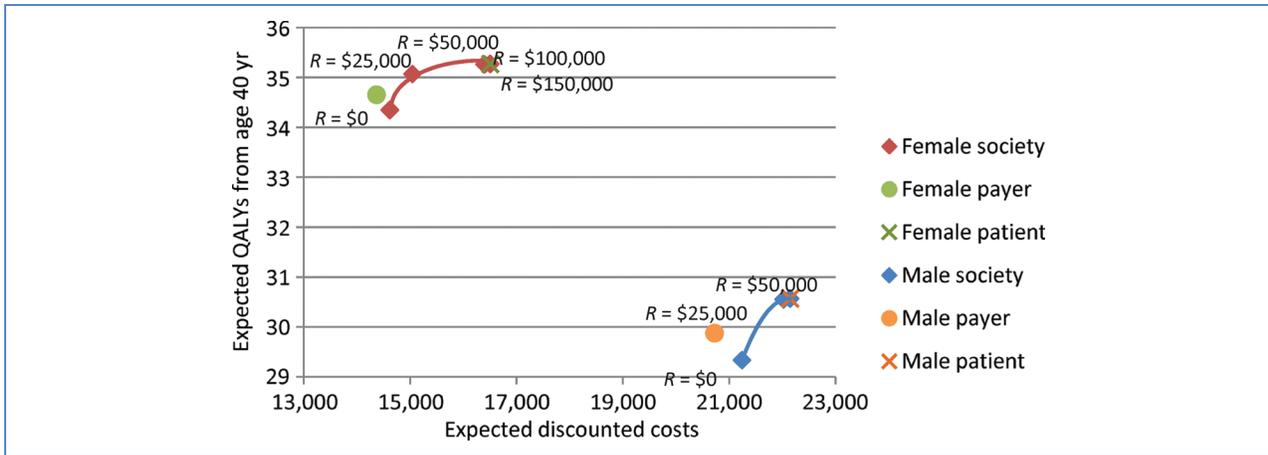


Figure 2

Comparison of expected QALYs from age 40 years and expected discounted costs of medications and hospitalizations from three perspectives: societal (R varying from 0 to 150,000), third-party payer, and patient.

Optimal policies from patient, third-party payer, and societal perspectives

We now compare the optimal policies for statin initiation from the patient, third-party payer, and societal perspectives for each of the 16 types of patients represented by the patient’s TC and HDL states. In **Figure 1(a)** and **(b)**, the bars for each state represent the age range for which statin initiation is optimal in patients who have not yet initiated treatment, according to each perspective. Based on our results, we observe that treatment decisions vary considerably depending on the decision-maker perspective. For example, compared with the patient perspective, maximizing quality-adjusted lifespan, the earliest optimal start times for the third-party payer perspective are 15 or more years later for males, as seen in Figure 1(a), and 23 or more years later for females, as seen in Figure 1(b), when the lowest cost generic statins are considered. When the highest cost brand statins are considered, it is never optimal to initiate statins from the third-party payer perspective.

There are small differences between optimal start times when comparing the patient and societal perspectives for low-cost generic statins; however, we observed significant differences (up to 23 years for females and up to 15 years for males) for the high-cost brand statins. For females in the lowest risk state (low TC and very high HDL), it is never optimal to start statins from the societal perspective when high-cost brand statins are considered. These significant differences between genders are related to the fact that males have an earlier onset of risk of heart attack and stroke compared with females. In addition, when high-cost brand statins are considered, it is never optimal for males or females, regardless of health state, to initiate statins from the third-party payer perspective, because the cost of

Table 3 Estimates of willingness-to-pay based on solving the inverse MDP for male and female patients and for the lower and upper bound on statin costs.

| | Low-cost statins | High-cost statins |
|---------|-------------------|-------------------|
| Males | $R_0 = \$114,773$ | $R_0 = \$116,183$ |
| Females | $R_0 = \$115,121$ | $R_0 = \$116,529$ |

medication does not outweigh the benefit of reducing the risk of costly adverse events.

To further compare the perspectives, we present the expected QALYs and costs separately from age 40 years in **Figure 2**. The y axis depicts the expected QALYs from age 40 years, and the x axis provides the expected discounted costs of medications and treatment of events from age 40 years. The comparison is presented for both males and females from the patient perspective, the third-party payer perspective, and the societal perspective by varying the WTP factor from $R = \$0$ to $R = \$150,000$. When $R = \$0$, the societal perspective outcomes are most closely aligned with the third-party payer perspective outcomes. As the WTP factor R is increased, the societal perspective objective becomes more aligned with the patient perspective objective. When $R \geq \$150,000$ for females and $R \geq \$50,000$ for males, the societal perspective outcomes are identical to the patient perspective outcomes. The commonly used value of $R = \$50,000/QALY$ results in lower expected QALYs and costs for females than our base case of $R = \$100,000$. However, for males the expected outcomes and policies are identical for $R = \$50,000$ and $R = \$100,000$.

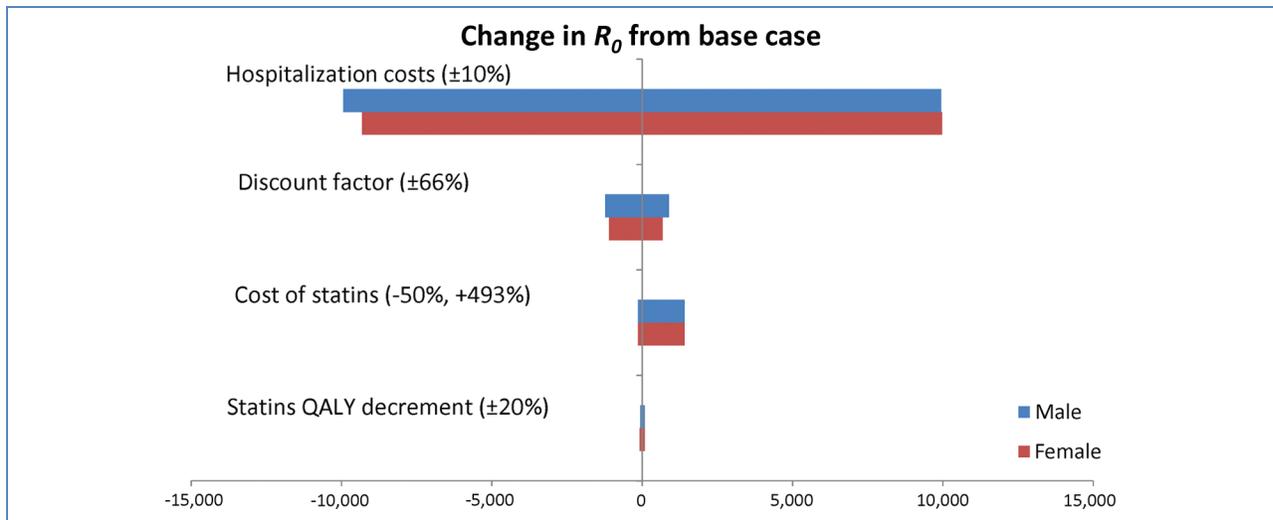


Figure 3

Effects of one-way sensitivity analysis on the implied willingness-to-pay factor R_0 .

In addition to the differences in QALYs and costs when different perspectives are used, it can be observed from Figure 2 that females achieve significantly greater expected QALYs than males at lower medication and treatment costs. This is likely due to females having longer expected lifespans than males and males being at a greater risk of CHD and stroke earlier in life than females.

WTP estimates using inverse MDP

Results based on our inverse MDP model, given in Table 3, provide estimates of the expected societal WTP, R_0 , of \$114,773 to \$116,529 per QALY. There are moderate differences with respect to gender, with the WTP estimate being slightly higher for females than males. This is consistent with the current U.S. policy, which does not differentiate on the basis of gender; however, it is somewhat counter-intuitive since risk models such as UKPDS reflect the fact that males are observed to be at higher risk at an earlier age than females. This suggests the differences are due to differences in all other cause mortality between males and females. Table 3 also shows there are small differences with respect to the cost of statins, with the higher cost estimates implying a larger WTP, as expected.

Figure 3 provides the effects of one-way sensitivity analysis on the implied WTP factor R_0 . We varied the initial and follow-up hospitalization costs, the 3% discount factor, the cost of statins, and the statins QALY decrement. The cost of statins was varied from the low-cost statins estimate provided in Table 1, with the reduced cost being one half of the low-cost statins estimate and the increased cost being the high-cost statins estimate from Table 1. We chose 5% as the upper bound for the discount factor because this value

is the second most common discount rate in the health services literature [48]. Of the factors we varied, hospitalization costs had the greatest impact on the implied WTP factor R_0 . As costs of treatment for events continue to rise, our results suggest that the implied WTP factor will continue to rise proportionately unless the guidelines are updated. Sensitivity analysis on the other factors produced little change in the implied WTP factor.

Based on the results in Table 3 and Figure 3, we conclude the implied reward per QALY is much higher than the commonly used value of \$50,000/QALY [5]. This original estimate can be traced back to a 1984 study of dialysis patients in Canada [48]. A more recent study has suggested that the value should be increased to \$93,500 because of inflation adjustments [49]. A recent study based on dialysis patients with updated costs, utility, and disease progression estimates suggests a range of \$110,000 to \$129,000 per QALY [29]. It is notable that our estimates also fall within this range.

Conclusions

In this paper, we discussed an MDP model for optimal timing of statin treatment initiation, and we further extended the model to an inverse MDP that can be used to compute the implied societal WTP that is consistent with a specific treatment guideline. Using the MDP model, we highlighted the differences in optimal policies for statin initiation when different decision-maker perspectives are considered. With a specified WTP of \$100,000/QALY, we found the societal perspective resulted in a policy much closer to the patient perspective than the third-party payer perspective, especially when the generic cost statins were considered. Our results define the optimal time to start statins according to each

perspective based on individual patient risk factors including gender, TC, and HDL. Our model provides more individualized guidelines than the current one-size-fits-all guidelines that suggest initiation of statins if a patient's LDL falls below 100 [9]. Using the inverse MDP model, the implied WTP estimates, based on the current U.S. guidelines for cholesterol control, agreed with other recent WTP estimates that are also much greater than the original WTP value of \$50,000/QALY. Consistent with previous studies based on dialysis therapy, our findings suggest that the generally accepted WTP value should be greatly increased from \$50,000/QALY to more than \$100,000/QALY.

Our study has some limitations. First, the data was derived from a relatively homogeneous population that may or may not be representative of the broader population. Second, we assumed that after initiation, patients remained on statins the rest of their lives. We failed to model the small portion of patients who do not tolerate statins well and may ultimately discontinue or change to another type of statin. Third, we consider a single cholesterol treatment, although additional treatments, albeit less commonly used, exist. Finally, we concentrated on a single set of outcomes, i.e., cardiovascular disease outcomes. Future models that consider multiple treatment decisions related to the broad range of potential diabetes outcomes, such as kidney failure, blindness, and neuropathy, represent a rich opportunity area for future research.

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