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Using claims data linked with electronic health records to monitor and improve adherence to medication

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ABSTRACT

Poor adherence to medication is a serious problem in the United States, leading to complications and preventable hospitalizations, particularly for patients with chronic diseases. Interventions have been proposed as a means to improve adherence to medication, but the optimal time to perform an intervention has not been well studied. We provide a use case for how claims data linked with electronic health records (EHRs) can be used to monitor patient adherence to medication and provide a source of information to help decide when to perform an intervention. We propose a Markov decision process (MDP) model to determine when to perform adherence-improving interventions based on a patient's EHR. We consider the the societal perspective where we trade off maximization of time to first adverse health event and minimization of cost of interventions, medication, and adverse events. We use our model to evaluate the costs and benefits of implementing an EHR-based active surveillance system for adherence-improving interventions in the context of cardiovascular disease management for patients with type 2 diabetes. We also provide some theoretical insights into the structure of the optimal intervention policy and the influence of health risks and costs on intervention decisions.

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Claims data; electronic health records; medication adherence; Markov decision process; intervention

1. Introduction

Poor medication adherence has been estimated to cost approximately $100 billion per year in preventable hospitalizations in the United States alone (Osterberg and Blaschke, 2005). Studies show that while improving adherence results in an increase in medication costs, there are significant overall cost savings, particularly among patients with chronic diseases (Sokol *et al.*, 2005; Ho *et al.*, 2006). Improved adherence can also reduce the risk of adverse events and improve the quality and length of life for many patients. In particular, improving adherence to glucose medications among patients with diabetes in the United States could save $4.68 billion annually in avoided hospitalizations and emergency department visits (Jha *et al.*, 2012). In spite of the benefits of high adherence, poor adherence is recognized as a major challenge in the medical community (Cutler and Everett, 2010; Bosworth *et al.*, 2011). In 2007, the National Institutes of Health (NIH) implemented the *Adherence Research Network* to promote research on adherence (National Institutes of Health, 2011). The initiative supports 14 institutes and centers across NIH, highlights NIH funding for adherence research, synthesizes current scientific findings on adherence, and provides leadership on future research directions.

While it is difficult to directly measure the medication taken by patients, there are widely accepted proxy measures of adherence, including patient self-reporting, electronic medication monitors on pill canisters, and rates of prescription refills calculated from claims data. Based on prescription refill estimates of adherence, studies suggest that only 25% of patients remain highly adherent to common treatments such as cholesterol-lowering medication (Benner *et al.*, 2002; Mason *et al.*, 2012). Adherence-improving interventions, such as collaborative decision making and the use of decision aids to choose medications, have been shown to improve adherence (Weymiller *et al.*, 2007). However, barriers to such interventions include that they are often not reimbursed by third-party payers and the perception that they take time and effort. Furthermore, information about an individual patient's adherence to their prescribed medications is normally unavailable to physicians at the time of encounter with a patient.

Recently, considerable attention has been given to the use of electronic health records (EHRs) to improve efficiency and effectiveness of health care delivery. EHRs are systematic collections of patient health information that can aid physicians in making medical decisions. In the United States, the Centers for Medicare and Medicaid Services (CMS) have introduced the Meaningful Use initiative (US HHS Department, 2011). The goals of the initiative are to improve safety and efficiency of health care delivery through the use of EHRs. Due to incentives created by this program, health care managers are under pressure to meet the objectives of the Meaningful Use initiative and to submit clinical quality measures (CQMs) using certified EHR technology. In addition, in 2012, CMS added new adherence quality measures for oral diabetes medications, some blood pressure medications, and cholesterol medications

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/uhse.

(statins) based on the percentage of patients who refill at least 80% of their prescriptions over the measurement period (CMS, 2012). In light of these quality measures, there is an increasing need to use measures of adherence to guide the use of interventions at the point of care (Steiner, 2012).

Displaying pharmacy claims data within EHRs could enable monitoring of adherence and identification of patients who would benefit most from an adherence-improving intervention; Dixon *et al.* (2013) present an informatics approach for integrating medication adherence information into the EHR, and Danford *et al.* (2013) show the feasibility of measuring adherence to lipid management goals using EHRs. By using claims data within the EHR to actively monitor an individual patient's adherence to medications using metrics including the percentage of refills a patient has received, which we refer to as *active adherence surveillance* (AAS), health care providers could make such decisions in real time at the point of care. However, implementation of a surveillance system comes at a cost. Therefore, in this article we aim to answer the following research question: What are the potential cost and quality of life benefits of using claims data within EHRs to identify the optimal timing of interventions to improve adherence to medication? To answer this question, we use pharmacy claims data for a large population to estimate patient adherence levels to the most commonly used medication for cholesterol control. We present a Markov decision process (MDP) model to determine the optimal timing of adherence-improving interventions based on AAS of an individual patient's adherence. Our model is presented from the societal perspective, a perspective in medical decision–making applications that considers objectives of multiple stakeholders, including patients and third-party payers. Specifically, we incorporate the patient perspective into our model by prioritizing prevention of adverse health events related to poor adherence. We also incorporate minimization of costs of interventions, medication, hospitalizations, and follow-up care for adverse events related to poor adherence; these costs would be incurred in part by patients and in part by third-party payers (health insurers). These two perspectives are combined into a single weighted objective function by using a willingness-to-pay weighting factor to transform patient quality-adjusted life years (QALYs) to monetary rewards. We present structural properties of our model, including conditions under which a control limit policy exists, and how the control limit policy changes based on a patient's health status and the effectiveness of an intervention.

There are many prescription medications for which poor adherence is recognized as a challenge in preventing the onset or progression of disease (e.g., blood pressure control medications, asthma medications). In this article, we provide a specific example based on adherence to *statins*, the most common cholesterol-lowering medication. We evaluate the costs and benefits associated with AAS by using our MDP model to determine the following: (a) medication and intervention costs and costs associated with the occurrence of strokes and coronary heart disease (CHD) events (the most significant outcomes associated with cholesterol control) or death; and (b) the expected time before a stroke, a CHD event (such as a heart attack). To estimate the marginal benefits of implementing the joint claims data/EHR-based system, we compare AAS with a much simpler, and easier to implement, schedule of interventions at regularly spaced intervals (e.g., yearly interventions), which we refer to as *inactive adherence surveillance* (IAS). We also compare our results with outcomes for patients who receive no interventions. In addition, we estimate the potential yearly benefits of applying AAS to the US population.

Our findings have the potential to influence several different stakeholders. First, our findings could help inform CMS about the potential benefits of AAS, and whether such implementations should be added to the list of objectives for their Meaningful Use or other future initiatives. Understanding and improving medication adherence is a natural extension to the current Meaningful Use requirement of *medical reconciliation*, which requires an accurate list of medications the patient is currently taking. In addition, the goal of our work aligns with CMS's goal of "healthier people" by addressing an underlying cause of a lack of prevention of adverse health events (CMS, 2016). Second, our results could help inform third-party health insurers about the potential benefits of reimbursing health care providers for adherence-improving interventions. Minimization of the costs in our model would be strongly aligned with the goals of third-party payers. Third, physicians may benefit from an improved understanding of the relative benefits of addressing adherence to medications for chronic conditions. Finally, patients could directly benefit from improved quality of life and the lower costs that can be achieved by improved adherence.

2. Background on medication adherence

Motivation for understanding adherence to medication is summed up in a quote by C. Everett Koop, M.D.: "Drugs don't work in patients who don't take them" (Thomas, 2014). Osterberg and Blaschke (2005) cite patient forgetfulness and lack of understanding as possible causes of poor adherence. The authors describe several types of interventions for improving medical adherence, including patient education, increased access to medical care, and improved communication between patients and physicians. For example, interventions such as performing screening tests and reviewing a patient's risk of an adverse health event (e.g., 10-year risk of a stroke or CHD event), or educating a patient about the risk reduction associated with a particular medication, have been shown to improve patient adherence (Weymiller *et al.,* 2007). Behavioral interventions involving monitoring of adherence and tailored recommendations from health care providers on how to improve adherence have also been shown to improve clinical outcomes for patients with chronic conditions (Kripalani *et al.,* 2007). However, these interventions can be associated with high costs. Lower cost interventions using electronic reminders (e.g., text messages, e-mails) to improve adherence to medication can provide benefits to patient adherence in the short term, but in a review of interventions using electronic reminders, two of the three studies of with a follow-up greater than six months showed no effect of the interventions (Vervloet *et al.,* 2012). Thus, in this article we do not consider interventions comprised exclusively of electronic reminders.

A common method for measuring patient adherence is to observe the percentage of days covered (PDC) by prescription refills over time. Prescription refills can be observed from pharmacy claims data, a portion of administrative claims data generated as a result of a patient's encounter with the health system.

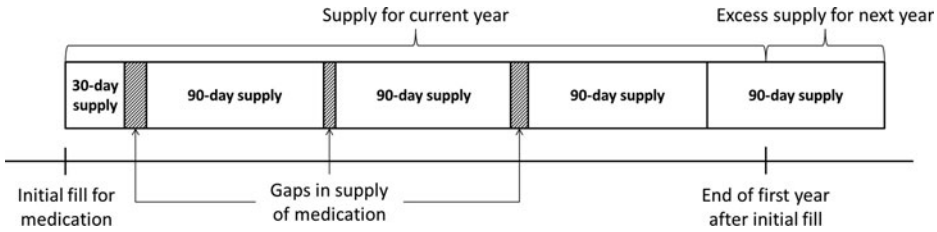

Figure 1. Diagram of prescription refills used to calculate the percentage of days covered (PDC).

Claims data is an important part of the extended EHR that is collected by third-party payers for payment purposes. If Meaningful Use program objectives are met, then more than 80% of patients will have pharmacy refills recorded as structured data.

The standard formula for PDC is as follows (Caetano *et al.*, 2006):

$$\text{PDC} = 100 \times \left(\frac{\text{days with an available supply of medication in the time period}}{\text{days in time period}} \right)\%.$$

Figure 1 provides an example of a patient's pharmacy claims for which PDC is estimated over a one-year period. In this example, the patient begins taking the medication with a 30-day supply. The patient makes four refills, each with 90-day supply, during the year. Gaps between the end of the days' supply for one prescription fill and the beginning of the next fill are interpreted as gaps in the patient's adherence to the medication. As shown in Fig. 1, refills that have supply exceeding the amount of time to the end of the year (time period) are carried over to the calculation of the PDC for the next time period. Note that this method for computing PDC is not restricted by the days' supply of refills or the refill method (by mail or local pharmacy).

Combining pharmacy claims data with laboratory data (e.g., cholesterol, blood sugar, blood pressure) and other sources of data in the EHR is often necessary to measure the effects of adherence. For example, the PDC can be linked with the patient's percentage change in metabolic values over the same time period. We illustrate this with a specific example. Consider the case of patients initiating statins to lower their cholesterol and therefore lower their risk of stroke and CHD events. States for the PDC over the course of a year after initiation are defined by the four categories given in Table 1. The adherence states are defined as follows: NON ($0\% \leq \text{PDC} \leq 10\%$); LOW ($10\% < \text{PDC} \leq 40\%$); MED ($40\% < \text{PDC} \leq 80\%$); and HIGH ($80\% < \text{PDC} \leq 100\%$). These specific choices of adherence states are based on those commonly used in the health services research literature (for example, see Rasmussen *et al.* (2007)). The threshold for high adherence is consistent with the adherence requirement from the National Committee for Quality Assurance (NCQA) Healthcare Effectiveness Data and Information Set (HEDIS) measure for patients with cardiovascular disease being treated with statin medication (National Committee for Quality Assurance, 2015). By using laboratory data, we link these adherence states with changes in total cholesterol (TC) from initiation to one year after initiation. Large data sets that combine pharmacy claims data with laboratory data for a large sample of patients can thus be used to estimate the expected change in TC for each PDC level.

Table 1. Adherence states defined by percentage of days covered (PDC) and the corresponding percentage change in total cholesterol (TC) for patients who initiate statins (Mason *et al.*, 2012).

Adherence State	PDC	Change in TC
NON	0% – 10%	– 5.22%
LOW	10% – 40%	– 8.21%
MED	40% – 80%	– 18.08%
HIGH	80% – 100%	– 25.25%

The results in Table 1 are based on a study reported by Mason *et al.* (2012). Table 1 establishes the link between a patient's percentage change in TC and the patient's adherence to medication. Since the patient's risk of cardiovascular events is affected by TC, that risk is also correlated with the patient's adherence to medication (Kothari *et al.*, 2002; Stevens *et al.*, 2001). For this reason, interventions that improve adherence have the potential to reduce cardiovascular risk over time. A method to estimate a stochastic model for changes in PDC and its effect on cardiovascular risk over time is elaborated in Section 6.

3. Literature review

The objective of this literature review is to highlight related Markov models used for medical decision making and outline the contributions of this article to the literature. The problem of finding the optimal time to perform an intervention to improve a patient's adherence to a medical treatment is analogous to problems studied in the machine maintenance literature. Pioneering work on maintenance systems was done by Klein (1962), who considers a stochastically deteriorating system that can be replaced or kept after inspection by a manager. This literature has been discussed previously (see section 5.3.1 of Mason (2012)).

3.1. Markov models for medical decision making

The prevalence of type 2 diabetes has stimulated modeling efforts for this chronic disease for many years. The CDC Disease Cost-Effectiveness group present a Markov model for the progression of type 2 diabetes over time and the cost incurred through treatment in order to evaluate the cost effectiveness of certain treatment programs (The CDC Diabetes Cost-Effectiveness Group, 2002). The intensive interventions targeted blood glucose, blood pressure, and cholesterol. Earnshaw *et al.* (2002) extend this work by using outputs from the CDC's diabetes progression Markov model as inputs for their linear programming model to determine an optimal mix of treatment programs to maximize QALYs for a population given

budget constraints and equity considerations. The resource allocation model shows that additional QALYs can be gained without increasing cost by using intensive therapy over regular therapy. Results also show that an increased budget can increase benefits to newly diagnosed diabetes patients but with diminishing marginal returns.

MDPs have been used in a number of medical applications for determining when a particular treatment should start or a specific procedure should take place. For example, Alagoz *et al.* (2004) consider the optimal timing of liver transplantation using a live donor in order to maximize the patient's total reward. The authors use an infinite-horizon MDP model to determine the optimal timing of this one-time decision. Structural properties are derived, including the existence of a control-limit policy under certain assumptions. Shechter *et al.* (2008) also present an infinite-horizon MDP model to determine the optimal timing of HIV therapy. The states in the model represent the patient's CD4 count, and the objective is to maximize life years (LYs) or QALYs over the patient's lifetime. Results suggest earlier treatment is optimal, contrary to treatment trends at the time of publication.

Maillart *et al.* (2008) present a partially observable Markov chain model to evaluate various breast cancer screening policies considering implications of patient adherence to screening guidelines and differences in breast cancer incidence and aggression as women age. Evaluation, rather than optimization of policies, is used to selectively compare easy-to-implement policies. Efficient policies are identified based on the trade-off between lifetime breast mortality risk and the expected number of mammograms over a woman's lifetime. Chhatwal *et al.* (2010) present a finite-horizon discrete-time MDP to determine the optimal timing of breast biopsy given the outcome of a mammogram and the patient's demographic features. The decision epochs are years after age 40, the states represent the patient's risk score determined after a mammogram, and the actions are to have a biopsy or to have another mammogram the following year. Once the action of biopsy is taken, the patient leaves the decision process. Rewards are defined by QALYs accrued by patients. Chhatwal *et al.* prove structural properties for their model, including the existence of a control-limit type policy. Results suggest that the decision to biopsy should depend on the patient's age.

Denton *et al.* (2009) propose an MDP model to find the optimal time to initiate statins in patients with type 2 diabetes for the prevention of cardiovascular events. The states represent the patient's metabolic risk factors. The rewards are monetary rewards for QALYs minus costs of medication and treatment for cardiovascular events, and the action to initiate or defer initiation of treatment is revisited each year. The authors consider the effects of using different cardiovascular risk models to estimate the probability of adverse events, concluding that the risk model chosen can dramatically affect the optimal start times. Their model assumes perfect adherence to treatment. Mason *et al.* (2012) propose a related MDP model to find the optimal time to initiate statins given the possibility of imperfect adherence. The authors incorporate a Markov model for adherence after the patient begins statins. The authors conclude that timing of initiation does not have as great an effect on patient outcomes as improving adherence; however, they note that adherence-improving interventions can be costly. This study provides motivation for the study of the optimal time of adherence-improving interventions once treatment has begun.

3.2. Contributions of this article to the literature

To our knowledge, the problem of finding the optimal time to perform an intervention to improve medication adherence has not been studied before. This problem is analogous to problems studied in the machine maintenance literature; however, there are two main differences: we consider a system that is deteriorating in a nonstationary fashion over a finite horizon, and in our model there is no available action to replace the system; only preventative maintenance may be performed. Our model also differs in several ways from the literature on MDP models for medical decision making described earlier: the decision to initiate an adherence-improving intervention is a recurring decision and not a one-time decision as considered by Alagoz *et al.* (2004), Shechter *et al.* (2008), Denton *et al.* (2009), and Chhatwal *et al.* (2010); the use of net benefit as a reward function; and our study is unique in its specific application and the research question we answer.

We present new structural properties that provide insight into optimal policies of an MDP in the context of recurring interventions, and which could be generalized to other medical decision–making problems. Proving the structural properties was made more difficult given the use of net benefit as a reward function, which combines costs and QALYs, rather than using just one metric or the other as many medical decision–making MDP models do. Our findings include a surprisingly simple but counterintuitive result about how to prioritize interventions among different types of interventions. We primarily parameterized this MDP model for determining adherence-improving interventions using transition probabilities and medication effectiveness inputs from Mason *et al.* (2012). While the MDP model solved by Mason *et al.* has a different purpose—determining the optimal start time of statins considering adherence behavior—the Markov-chain model describing adherence behavior and the effects of adherence levels on cholesterol levels from this previous work are relevant to the model presented in this article. Additional details are provided in Section 6 and in Appendix B to describe how these parameters of the MDP model were estimated from a large data set that combines pharmacy claims data with the relevant laboratory data from an EHR. We present results based on the MDP model for a specific example in the context of statin treatment for a population of patients at high risk of stroke and CHD events. To our knowledge, these results are the first estimates of the potential benefits that may be derived from active surveillance of patient adherence to medication using claims data and EHRs.

The technical development complements the case study and highlights methods for establishing key properties of optimal policies for MDPs with special structure when the standard results of Puterman (1994) cannot be applied directly. Based on a large-scale, real-world data set, the case study clearly illustrates the potential benefits of AAS while also revealing the strengths and limitations of the technical development and the potential robustness of the results based on that development.

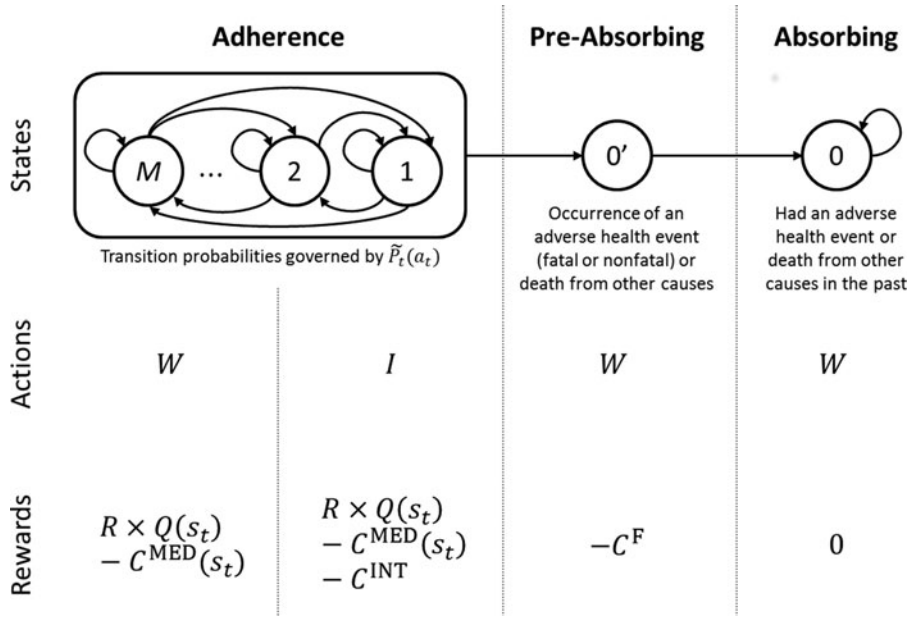

Figure 2. Diagram of the Markov decision process (MDP) model.

4. Model formulation

In each of a set of discrete decision epochs, a patient on a particular medication is observed to be in a specific health state. The health states are divided into *adherence states*, a *pre-absorbing state*, and an *absorbing state*. The adherence states represent the patient's level of adherence to the medication (e.g., statins), the transient pre-absorbing state represents the first occurrence of adverse health events that the treatment aims to prevent (e.g., a stroke or CHD event) or death from other causes, and the absorbing state indicates that an event or death has occurred previously. At each decision epoch, the decision maker (e.g., the physician) must decide whether or not to implement an intervention with the patient. Thus, one of two possible actions is taken: *implement an intervention* or *defer the decision until the next epoch*. This decision is faced at each decision epoch, provided the patient does not enter the pre-absorbing or absorbing states. Figure 2 provides an overview of the MDP model, and the following subsections provide a detailed description of each component.

4.1. Decision epochs

The decision to initiate an adherence-improving intervention is revisited periodically over a finite horizon with T yearly decision epochs. The decision epochs are indexed by $t = 0, 1, 2, \ldots, T-1$, where decision epoch (time) t is associated with the time interval $[t, t+1)$ in the sense that the effect of any decision made at decision epoch t applies only during the time interval $[t, t+1)$; for simplicity, we refer to this time interval as period t. Time $t = 0$ represents the initial epoch when the patient begins surveillance (the patient begins taking the medication), and T is chosen as a reasonable upper bound on a typical patient's age (e.g., 100 years).

4.2. States

The states of the patient are represented by the set $S \equiv \{0, 0', 1, 2, \ldots, M\}$; for each time $t = 0, \ldots, T$, we let $s_t \in S \setminus \{0, 0'\}$ denote the patient's adherence level over the period $[t, t+1)$, while the pre-absorbing state $s_t = 0'$ indicates that the patient had an adverse health event (fatal or nonfatal), or that the patient died from other causes at time t. The pre-absorbing state is needed given the one-time cost assessed after patients have had an adverse health event (the reward structure is described fully in Subsection 4.5). The absorbing state $s_t = 0$ indicates that the patient had an adverse health event or death from other causes before time t. For $s_t \in S \setminus \{0, 0'\}$, a larger value of s_t corresponds to an increased (improved) level of adherence for the patient over the period $[t, t+1)$.

4.3. Actions

An intervention may be initiated or deferred at any decision epoch, $t \in \{1, \ldots, T-1\}$, and in any state, $s_t \in S \setminus \{0, 0'\}$. The possible set of actions is defined as the following:

$$A_t(s_t) = \begin{cases} \{W, I\} & \text{for } s_t \in S \setminus \{0, 0'\} \text{ and } t = 1, \ldots, T-1, \\ \{W\} & \text{for } s_t \in \{0, 0'\} \text{ or } t = T, \end{cases}$$

so that $a_t(s_t) \in A_t(s_t)$ denotes the action taken at time t when the patient is in state s_t, where the action $a_t = I$ denotes an intervention and the action $a_t = W$ denotes the action of waiting, or deferring the decision until the next decision epoch. The total action space is defined by $A = \{W, I\}$. Actions are dependent on a patient's adherence state over the period $[t, t+1)$, with the effect of the intervention being reflected in the patient's adherence state s_{t+1} at time $t+1$.

4.4. Transition probability matrix (TPM)

There are three types of one-step transitions: (1) transitions between adherence states; (2) transitions from adherence states to the pre-absorbing state; and (3) the (certain) transition from the pre-absorbing state to the absorbing state. Given avoidance of state $0'$, the conditional transition probabilities between the adherence states are represented by the matrix $\tilde{P}_t(a_t) \in \mathbb{R}^{M \times M}$ so that $[\tilde{P}_t(a_t)]_{i,j}$, the (i, j) element of $\tilde{P}_t(a_t)$, is equal to the

conditional probability $\Pr\{s_{t+1} = j \mid s_t = i$, action a_t is taken at time t, and $s_{t+1} \neq 0'\}$ for $1 \leq i, j \leq M$. Transitions from adherence states to the pre-absorbing state are represented by the vector $\bar{p}_t \in \mathbb{R}^M$ so that $[\bar{p}_t]_i$, the ith element of the $M \times 1$ (column) vector $\bar{p}_t$, is equal to the conditional probability $\Pr\{s_{t+1} = 0' \mid s_t = i\}$ for $1 \leq i \leq M$. Thus, this adverse health event would occur at time $t+1$, the beginning of decision epoch $t+1$, when patients enter the pre-absorbing state. Note that the probability of entering the pre-absorbing state from each adherence state does not depend on the action taken at time t; rather, if a patient has improved medication adherence from a previous intervention, then the patient's probability of entering the pre-absorbing state is reduced due to that patient being in an improved adherence state at time t. Improved adherence leads to an improved cholesterol level, which reduces a patient's probability of having an adverse health event. Notice also that by the definition of the transient pre-absorbing state $0'$, it is impossible for a patient to make a one-step transition from an adherence state to the absorbing state 0; therefore, all these one-step transition probabilities must be zero. Moreover, after entering the pre-absorbing state, the patient spends one period in that state before making a transition to the absorbing state with probability 1. The complete one-step transition probability matrix (TPM) is

$$P_t(a_t) = \begin{bmatrix} 1 & 0 & \mathbf{0}_M^{\mathsf{T}} \\ 1 & 0 & \mathbf{0}_M^{\mathsf{T}} \\ \mathbf{0}_M & \bar{p}_t & \operatorname{diag}[\mathbf{1}_M - \bar{p}_t]\tilde{P}_t(a_t) \end{bmatrix}, \qquad (1)$$

where $\mathbf{0}_M$ is the $M \times 1$ (column) vector of zeros and $\mathbf{1}_M$ is the $M \times 1$ (column) vector of ones.

4.5. Rewards

There are many possible reward structures for our model, depending on the decision maker's perspective. In this article, we define a flexible reward structure that is composed of four parts: (1) a reward for quality-adjusted time gained in the most recent period (e.g., a QALY for an annual decision epoch); (2) a cost associated with an adherence intervention; (3) a state-dependent cost of medication; and (4) a penalty cost for entering the pre-absorbing state. We define $r_t(s_t, a_t)$ to be the reward accrued at time t in state s_t given action a_t is taken. For $t = 1, \ldots, T-1$, the reward function is defined as

$$r_t(s_t, a_t) = \begin{cases} R \times Q(s_t) - C^{\mathrm{MED}}(s_t) & \text{for } a_t = W \text{ and } s_t = 1, \ldots, M, \\ R \times Q(s_t) - C^{\mathrm{MED}}(s_t) - C^{\mathrm{INT}} & \text{for } a_t = I \text{ and } s_t = 1, \ldots, M, \\ -C_t^{\mathrm{F}} & \text{for } s_t = 0', \\ 0 & \text{for } s_t = 0, \end{cases} \qquad (2)$$

where R is the *willingness-to-pay* factor defining a monetary value per QALY and $Q(s_t)$ represents the QALYs accumulated for a patient in state s_t during time epoch t. The quantity $C^{\mathrm{MED}}(s_t)$ denotes the cost of medication for period t; this cost depends on the patient's adherence state, since costs are not incurred for medication patients do not have in their possession. The quantity C^{INT} denotes the cost of an adherence-improving intervention. The quantity C_t^{F} represents a one-time lump sum for the expected future costs of a patient entering the pre-absorbing state $0'$ at time t, dependent on the probability of having a nonfatal or fatal stroke or CHD event or death from other causes. This cost penalty reflects a loss associated with failure to avoid an adverse health event. This loss could include costs associated with hospitalization (for fatal and nonfatal events) and/or future treatment. The quantity C_t^{F} is estimated in practice by multiplying the probability of each type of absorbing event occurring and the expected future costs associated with that absorbing event. When a nonfatal event occurs, the cost consists of the initial cost of an event plus expected future costs of follow-up for that event. When patients die from an event, the cost consists of only the hospitalization cost for that event, while there is no cost for patients who die from other causes.

The reward structure presented earlier represents a combination of the patient objective of maximizing quality-adjusted time to the first adverse health event (which is frequently the clinical intent of preventive treatment (Cleeman *et al.,* 2001)) and the objective of minimizing costs of treatment, considering both costs before the patient enters the absorbing state and expected costs after the patient enters the absorbing state. Additional assumptions about the reward structure are provided in Section 5, and specific values for rewards are provided in Section 6 in the context of cardiovascular disease prevention.

For a patient in state $s_t \in S$ in epoch t, the optimality equations can be written as

$$v_t(s_t) = \max_{a_t \in A_t(s_t)} \left\{ r_t(s_t, a_t) + \lambda \sum_{s_{t+1} \in S} p_t(s_{t+1} | s_t, a_t) v_{t+1}(s_{t+1}) \right\}, \quad \text{for every } t = 1, \ldots, T-1, \qquad (3)$$

where $p_t(s_{t+1}|s_t, a_t)$ is the (s_t, s_{t+1}) element of $P_t(a_t)$, $v_t(s_t)$ is the optimal value function, and $\lambda \in (0, 1]$ is the discount factor used to calculate the value at time t of rewards received at time $t+1$. For a patient who has not entered the absorbing state at time T, a reward is obtained that estimates the benefits and costs associated with the patient's future survival, based on an estimate of the patient's future remaining QALYs. The end-of-horizon boundary condition is

$$v_T(s_T) = \begin{cases} \mathrm{E}[\mathrm{PDHR} \mid s_T] & \text{for } s_T = 0', \ 1, \ldots, M, \\ 0 & \text{for } s_T = 0, \end{cases} \qquad (4)$$

where $\mathrm{E}[\mathrm{PDHR} \mid s_T]$ represents the expected future difference between the rewards for quality-adjusted survival benefits and the associated costs, assuming no future interventions. Note that $\mathrm{E}[\mathrm{PDHR} \mid s_T = 0'] = -C_T^{\mathrm{F}} < 0$. In Section 6, we provide the particular finite horizon approximation of post–decision horizon rewards used in the numerical experiments. The last decision epoch, T, is selected to represent a reasonable upper bound on the age at which adherence-improving interventions would no longer be advisable due to high competing risks of death from other causes. This end-of-horizon assumption has been made in a number of other medical decision–making studies (Denton *et al.,* 2009; Chhatwal *et al.,* 2010; Kurt *et al.,* 2011).

5. Model properties and insights

This section provides insights into the structure of our model. First, we discuss some of the assumptions of our model. Next,

we present some properties of our model that can reduce the computational effort to solve the MDP, and that provide some insight into the optimal policy for interventions defined by our model. We prove the existence of an optimal control-limit policy. In Appendix A, we present a property, Proposition 1 relating the effectiveness of interventions to the optimal control limits for the interventions and a property, Proposition 2, comparing the optimal control limits for two patients where one patient is at a greater risk for adverse health events than the other. Proofs of the properties presented in this section and additional model properties are provided in Appendix A.

5.1. Model assumptions

There are many possible choices for the reward function to use in our MDP model. We chose to blend two criteria for our reward function: (1) the patient's reward for quality-adjusted time to the first adverse health event; and (2) the cost of treatment, intervention, and care associated with an adverse health event, incurred in part by patients and in part by third-party payers. We make the following assumptions about our model:

- $\mathbf{A}_1$: $\tilde{P}_t(a_t)$ has the increasing failure rate (IFR) property for every $a_t \in A$, and for every $t = 1, \ldots, T-1$;
- $\mathbf{A}_2$: $\mathrm{E}[\mathrm{PDHR}|s_T]$ is nondecreasing in $s_T \in S \setminus \{0\}$;
- $\mathbf{A}_3$: $[\tilde{p}_t]_i \equiv \Pr\{s_{t+1} = 0' | s_t = i \in S \setminus \{0, 0'\}\}$ is nonincreasing in s_t for $t = 1, \ldots, T-1$; and
- $\mathbf{A}_4$: $r_t(s_t, a_t)$ is a nondecreasing function of s_t for $t = 1, \ldots, T-1$, $s_t \in S \setminus \{0\}$, and $a_t \in A$.

Assumption $\mathbf{A}_1$ states that the Markov chain defining a patient's adherence exhibits the IFR property (see Barlow and Proschan (1965) for a definition of this property). This can be interpreted to mean that the better a patient's adherence level, the better it is likely to be in the next period. Our study using observational data (see Section 6) suggests that this is a reasonable assumption. This property has also been observed for a number of other health characteristics (Alagoz *et al.,* 2004; Kurt *et al.,* 2011; Chhatwal *et al.,* 2010). Assumption $\mathbf{A}_2$ states that a patient's expected post–decision horizon rewards for QALYs minus costs, assuming no future interventions, do not decrease as her adherence improves. This assumption is reasonable since improved adherence causes treatment to be more effective at preventing adverse events. Assumption $\mathbf{A}_3$ states that the probability of moving to the pre-absorbing state is nonincreasing in the adherence state. Finally, assumption $\mathbf{A}_4$ states that the difference between $R \times Q(s_t)$, the reward for living through period t, and $C^{\mathrm{MED}}(s_t)$, the cost of medication for period t, is a nondecreasing function of the adherence state s_t for $s_t \in S \setminus \{0, 0'\}$. This assumption is perhaps a limitation, given that patients who have higher adherence to medication may have nonincreasing quality of life (e.g., increased side-effects); however, some medications for chronic conditions have been shown to improve quality of life (e.g., antidepressants (Skevington and Wright, 2001)). We have provided an explanation in Appendix A of the conditions under which assumption $\mathbf{A}_4$ will hold. In addition to the previous assumptions, we assume that R, $Q(s_t)$, C^{INT}, C_t^{F}, $C^{\mathrm{MED}}(s_t)$, and $\mathrm{E}[\mathrm{PDHR}|s_t]$ are nonnegative for every $t \in \{1, \ldots, T\}$ and $s_t \in S \setminus \{0, 0'\}$.

5.2. Model properties

We now discuss some properties associated with the optimal adherence intervention policy and draw comparisons between different types of patients and interventions. We begin by presenting two lemmas that are used to prove our main results.

Lemma 1. *If $\tilde{P}_t(a_t)$ is IFR and assumption $\mathbf{A}_3$ holds, then $P_t(a_t)$ is IFR for $t = 1, \ldots, T-1$.*

This lemma establishes an important connection, in the form of the IFR property, between patient health states and the probability of health outcomes conditioned on those health states. Lemma 1 is useful for other types of medical decision–making problems for which the IFR property exists among ordered health states.

Lemma 2. *The value function $v_t(s_t)$ is nondecreasing in s_t, for $t = 1, \ldots, T$ and $s_t \in S \setminus \{0\}$.*

Lemma 2 shows that the patient's expected future rewards do not decrease as adherence to treatment improves. Lemma 2 is used to prove Theorem 1, which states that the optimal intervention policy has a simple control-limit structure for the adherence states $s_t = 1, \ldots, M$.

Theorem 1. *If the effect of an intervention at time t is independent of the patient's current adherence state $s_t \in S \setminus \{0, 0'\}$ for $t \in \{1, \ldots, T-1\}$, then there exists an optimal control limit $s_t^* \in S \setminus \{0, 0'\}$, for every $t \in \{1, \ldots, T-1\}$, such that the optimal action $a_t^*(s_t)$ is given by*

$$a_t^*(s_t) = \left\{ \begin{array}{ll} I, & \text{if } s_t \le s_t^*, \quad \text{and } s_t \in S \setminus \{0, 0'\}, \\ W, & \text{otherwise,} \end{array} \right\} \quad \text{for } t = 1, \ldots, T-1. \tag{5}$$

Theorem 1 provides sufficient conditions under which the optimal intervention policy has a simple structure, which is important for clinical applications in practice. For example, this structure would be valuable for implementing findings through a clinical decision support system for real-time interventions. This theorem applies in the setting of a perfect intervention, an intervention in which all patients transition to high adherence. In contrast, an imperfect intervention is one in which not all patients transition to high adherence after the intervention. In the case study presented in Section 6, we present numerical results for perfect and imperfect interventions that satisfy the independence assumption, and we empirically show that this optimal control limit structure exists.

6. Case study: Statin adherence for patients with type 2 diabetes

In this section, we present a case study to illustrate the application of our model to evaluate a hypothetical EHR-based AAS system in the context of preventive treatment for cardiovascular disease. Specifically, we investigate adherence interventions for statin treatment among patients with type 2 diabetes. Statins are particularly important for patients with diabetes, since these patients are at two to four times' higher risk for stroke and

CHD events over patients without diabetes (CDC, 2011). Furthermore, long-term adherence to statins is known to be poor (Benner *et al.,* 2002; Mason *et al.,* 2012).

In Section 6.1, we provide our data sources and model parameters. Additional details regarding parameter estimation are provided in Appendix B. In Section 6.2, we compare active and inactive surveillance policies using the MDP model described in Section 4. We present the optimal policies and expected LYs and costs associated with these policies. We also explore the effects of gender, the patient's health risk, the cost of an intervention, the willingness-to-pay factor, and the type of intervention on the optimal policy. We conclude this section with an estimate of total benefits of AAS to the US diabetes population.

6.1. Data and model parameter estimation

The transition probabilities among adherence states were computed from the administrative medical and pharmacy claims data from a large health insurance company that insures patients across the United States. A cohort of 54 036 diabetes patients from this dataset were identified using HEDIS criteria for diagnosis of diabetes (National Committee for Quality Assurance, 2007). Patients included in the set were required to have five years of continuous enrollment, with first encounter dates ranging from January 1995 to June 2004. The PDC by pharmacy fills, described in Section 2, was used as a proxy for patient adherence rates. Once the PDC was computed for each patient, the transition probabilities were computed by counting the number of patients in each adherence state who transitioned to each adherence state in the next year. The associated effect of statins on the patient's TC level for each adherence level was derived from this observational data set as well. See Mason *et al.* (2012) for a detailed description of the calculations for the initial probability vector for entering adherence states after initiating statins, the one-step transition probability matrix among adherence states, and the adherence-dependent effect of statins on the patient's TC level. Note that the estimation of the one-step transition probability matrix under the action wait implicitly assumes that the patients included in the administrative pharmacy claims dataset received no adherence-improving interventions during the data collection period; however, we have no way to ensure that this is the case. Thus, our estimate for this transition probability matrix may be biased, potentially leading to overestimating the number of patients in favorable adherence states (e.g., high– and medium–level adherence) under the action of wait in our model.

The transition probabilities for stroke and CHD events were derived from the UKPDS risk models (Kothari *et al.,* 2002; Stevens *et al.,* 2001), and the probabilities for death from other causes were calculated from the CDC mortality tables (National Center for Health Statistics, 2007). The state of the patient's health (other than their adherence level), which we used to estimate stroke and CHD event probabilities with the UKPDS model, was based on observations from a large cohort of 663 patients receiving treatment for type 2 diabetes at Mayo Clinic, Rochester, MN. Approximately 15,000 measurements of HbA1c (a patient's average blood sugar over two to three months), blood pressure, and cholesterol were collected between 1997 and 2006 through the Mayo Clinic Diabetes Electronic Management System (DEMS) (Gorman *et al.,* 2000). The evolution of blood glucose and blood pressure was estimated based on empirical estimates from the Mayo cohort for diabetes patients under treatment for blood glucose and blood pressure. The evolution of cholesterol states (TC and HDL) was estimated based on data from untreated patients; for the simplicity of this model, the majority of numerical experiments are based on deterministic evolution of cholesterol. We also present sensitivity analysis results using stochastic evolution of cholesterol; the methods for estimating the transition probabilities among cholesterol states has been described previously (Kurt *et al.,* 2011). Given that the evolution of cholesterol states was estimated based on data from untreated patients, the percentage changes in TC (shown in Table 1) are applied annually to the untreated TC values according to the patients adherence state.

For all our experiments, we assumed a maximum age of $T = 100$ as the age at which interventions would be discontinued and a discount factor of $\lambda = 0.97$, which corresponds to a 3% yearly discount rate (Gold *et al.,* 1996). Since we are only considering LYs in the case study, $Q(s_t) = 1$ for all $s_t \in S \setminus \{0, 0'\}$. For the base case, we assumed a willingness to pay of $R = \$100{,}000$ (Evans *et al.,* 2004) and a cost of statins of $C^{\text{MED}}(s_t) = \$212 \times \delta(s_t)$, where $\delta(s_t)$ represents the mean PDC of a patient in adherence state s_t (Red Book, 2009). The cost of an intervention for the base case was estimated to be $C^{\text{INT}} = \$90$ (Chapman *et al.,* 2010). This intervention cost includes telephone counseling to improve medication adherence and reinforcement of the message by a pharmacist. The initial and follow-up costs of stroke and CHD events were drawn from sources in the health services research literature provided in Table 2. The one-time penalty of entering the absorbing state, C_t^{F}, is computed with a Markov chain using these costs and probabilities governing patient survival. The event and death transition probabilities represented by the vector $\bar{p}_t$ were calculated by summing the probabilities of stroke, CHD events, and death for each adherence state. The expected post–decision horizon reward (i.e., expected rewards accrued after age 100) is given by the following 20-year finite-horizon approximation:

$$\mathrm{E}[\mathrm{PDHR}|s_T] = \left[\sum_{i=0}^{19} \lambda^{i+1}(i+1)\left(1 - [\bar{p}_T]_{s_T}\right)^i\right] \times [R \times Q(s_T) - C^{\text{MED}}(s_T)]([\bar{p}_T]_{s_T}). \quad (6)$$

The adherence states used in the numerical experiments are NON ($0\% \leq \text{PDC} \leq 10\%$), LOW ($10\% < \text{PDC} \leq 40\%$), MED ($40\% < \text{PDC} \leq 80\%$), and HIGH ($80\% < \text{PDC} \leq 100\%$) (Mason *et al.,* 2012). The transition probability matrices, $\tilde{P}_t(a_t)$,

Table 2. Initial hospitalization costs and follow-up events for adverse events.

Parameter	Cost	Citation
Initial Hospitalization for Stroke	\$13,204	AHRQ (2006)
Initial Hospitalization for CHD	\$18,590	AHRQ (2006)
Yearly Follow-up for Stroke	\$1664	Thom *et al.* (2006)
Yearly Follow-up for CHD	\$2576	Thom *et al.* (2006)

were estimated to be

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

and

$$\tilde{P}_t(I) = \begin{array}{c} \\ \text{NON} \\ \text{LOW} \\ \text{MED} \\ \text{HIGH} \end{array} \begin{array}{c} \begin{array}{cccc} \text{NON} & \text{LOW} & \text{MED} & \text{HIGH} \end{array} \\ \begin{pmatrix} 0.091 & 0.165 & 0.257 & 0.487 \\ 0.091 & 0.165 & 0.257 & 0.487 \\ 0.091 & 0.165 & 0.257 & 0.487 \\ 0.091 & 0.165 & 0.257 & 0.487 \end{pmatrix} \end{array}.$$

Note that $\tilde{P}_t(W)$ was estimated from adherence data for patients on statins after removal of patients who discontinued treatment due to intolerance (Mason *et al.*, 2012). The matrix $\tilde{P}_t(I)$ was estimated based on the proportion of patients occupying each of the adherence states in their first year of treatment. This assumption was made since an imperfect intervention may act to "reset" a patient's adherence level to the level it was when the patient initially began treatment. In addition, we considered the more optimistic case that a patient moves to state HIGH with probability 1. Use of this intervention provides a conservative estimate of the improvement achievable through interventions. The use of real observational data to estimate the probabilities among the adherence states inherently includes the effects of diet, exercise, and other behavioral changes.

The majority of the assumptions made in order to prove the structural properties also hold for our numerical experiments. Assumptions $\mathbf{A}_1$, $\mathbf{A}_2$, and $\mathbf{A}_3$ all hold. Given that there are no estimates in the literature of QALY decrements for statin medication adherence states, we only consider LYs in the case study. Thus, $Q(s_t) = 1$ for all $s_t = 1, \ldots, M$ and for all $t = 1, \ldots, T-1$, and assumption $\mathbf{A}_4$ does not hold. Also, the assumption made to prove Theorem 1 that the effect of an intervention at time t is independent of the patient's current adherence state holds for both of the intervention transition probability matrices used in the numerical experiments. In what follows, the TPM $P_t^{(1)}(a_t)$ *stochastically dominates* the TPM $P_t^{(2)}(a_t)$, represented as $P_t^{(1)}(a_t) \succcurlyeq P_t^{(2)}(a_t)$, if for each row of these TPMs, the associated complimentary cumulative distribution function of $P_t^{(1)}(a_t)$ dominates that of $P_t^{(2)}(a_t)$; see also Definition 1 and Proposition 1 in Appendix A.3. For Proposition 1, $P_t^{(1)}(I_1) \succcurlyeq P_t^{(2)}(I_2)$ is satisfied when interventions I_1 and I_2 are the perfect and imperfect interventions, respectively, outlined earlier; however, $P_t^{(2)}(I_2) \succcurlyeq P_t^{(2)}(W)$ is not satisfied. Also, the inequality for the difference in value function values is satisfied for all $t \in \{1, \ldots, T-1\}$ except for the case of $s_t = M - 1$. However, transition probability matrices for other interventions may satisfy all assumptions for Proposition 1 of Considering types A and B to represent men and women, respectively, all conditions for the theorem are satisfied except for $\tilde{P}_t^{(B)}(I) \succcurlyeq \tilde{P}_t^{(B)}(W)$ and $v_t^{(A)}(s_t+1) - v_t^{(A)}(s_t) \leq v_t^{(B)}(s_t+1) - v_t^{(B)}(s_t)$ (other than when t is close to T). However, other categories of patients may satisfy the conditions of Proposition 1.

6.2. Numerical results

Numerical experiments were conducted to find the optimal policy for adherence-improving interventions based on the previous model parameters. The model was solved using backwards recursion, implemented in C/C++. Each experiment took less than 10 s to run using a 2.83GHz PC with 8GB of RAM. Experiments were run for males and females, starting at age 40, assuming a variety of different risk states and different intervention cost estimates. The perfect and imperfect interventions described in Section 6.1 were both evaluated. We represent different risk states by the patient's TC and high-density lipoprotein (HDL), also known as "good" cholesterol, each given as one of low (L), medium (M), high (H), and very high (V). These are the most significant metabolic factors influencing a patient's risk of stroke or CHD events according to the UKPDS model. While there are a total of 16 patient risk states defined by clinically relevant thresholds (Cleeman *et al.*, 2001), for brevity we provide policies and numerical results for representative patients with low risk (low TC and very high HDL), medium risk (medium TC and medium HDL), and high risk (very high TC and low HDL).

6.2.1. Active vs. inactive surveillance

To estimate the potential benefits of using EHRs to improve adherence to medication at the population level, we compared the expected LYs from age 40 prior to an event or death and the expected discounted total costs comprising the costs of intervention, statin treatment, and hospitalizations and follow-up care for CHD events and stroke found using the optimal AAS policy and the IAS policy. IAS involves periodic interventions that do not rely on a patient's adherence level. We considered interventions that occur every k years ($k = 1, 2, 3, 4$, or 5) after a patient begins taking medication, regardless of the patient's adherence state. The IAS policy is useful for comparison since it requires no pharmacy or laboratory data and is therefore much easier to implement in practice. We also considered the use of no interventions.

Figures 3 and 4 show the expected LYs vs. costs for AAS, IAS, and no treatment, for females and males. Imperfect interventions were used for these results. We evaluated different AAS policies by varying the willingness-to-pay factor from $R = \$0$

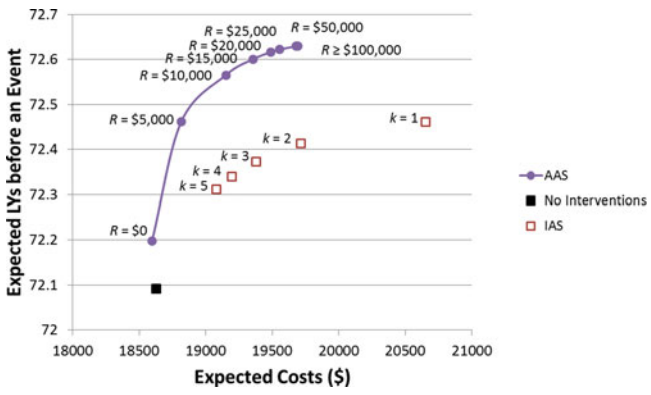

Figure 3. Comparison of expected LYs versus costs for medication, interventions, and treatment of events for active adherence surveillance (AAS) policies (with varying R values) and inactive adherence surveillance (IAS) policies (when interventions occur every k years) for female patients using imperfect interventions. Results are a weighted average of LYs and costs for the 16 possible risk states.

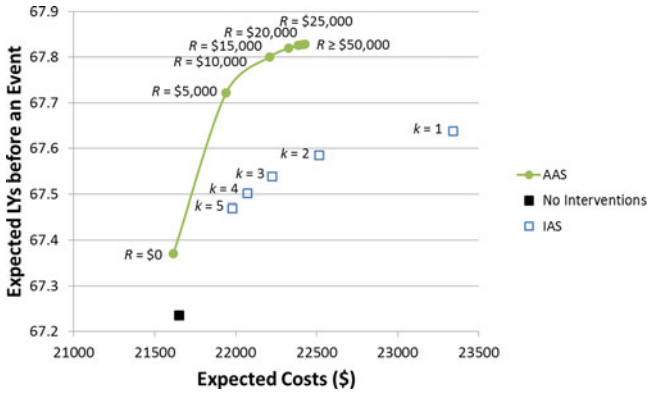

Figure 4. Comparison of expected LYs versus costs, as shown in Fig. 3, for male patients.

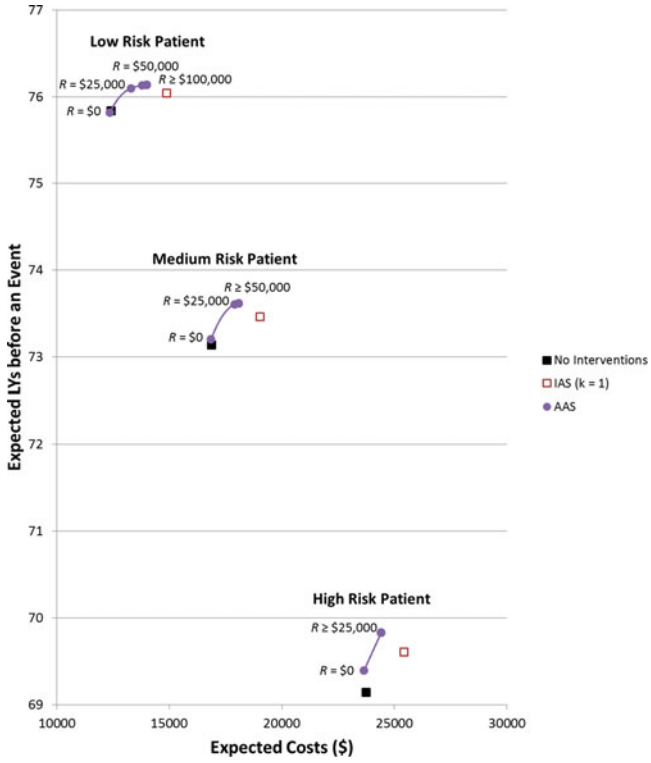

Figure 5. Comparison of expected LYs versus costs for medication, interventions, and treatment of events for active adherence surveillance (AAS) policies (with varying R values) and yearly inactive adherence surveillance (IAS) for female patients using imperfect interventions. Results are compared for low-, medium-, and high-risk patients.

to $R = \$1{,}000{,}000$. When the willingness-to-pay factor is varied, different weights are placed on LYs and costs. An R value of \$0 or close to \$0 may align with the payer perspective of minimizing costs. As this factor increases, a larger weight is placed on maximizing the patient's LYs rather than minimizing costs. We observe that AAS outperforms IAS, for females and males, yielding greater expected LYs before an event or death and lower expected costs when $R \geq \$5{,}000$. In fact, the exact threshold value for R for which AAS provides greater LYs than IAS is less than \$5,000 for males. When $R = \$100{,}000$, the base case value for our experiments, the average female patient using AAS receives an expected 0.17 additional LYs with a \$960 reduction in costs over IAS ($k = 1$), and the average male patient using AAS receives an expected 0.19 additional LYs with a \$913 reduction in costs over IAS ($k = 1$). AAS resulted in no interventions for patients with HIGH adherence. The higher expected costs incurred by IAS are presumably due, in part, to unnecessary interventions for patients with HIGH adherence to treatment, highlighting the benefit of AAS. It is particularly interesting that there are major gender differences in the expected LYs before an event or death. Based on our results, we observe that males are expected to have an adverse event or death approximately five years earlier than females.

While AAS dominates IAS for all 16 risk states, there are significant differences in the magnitude of the differences in expected cost and LYs for patients with different risk of CHD events and stroke. Figure 5 presents results for females with low, medium, and high risk in a format similar to Fig. 3. Patients with low risk can expect to have their first event or death later in life than patients with medium or high risk. Also, as a patient's risk increases, her benefit over no treatment and her benefit over IAS increase. Thus, it appears the benefit of AAS is increasing in patient risk. We also note that the expected costs and LYs are less sensitive to changes in the willingness-to-pay factor as risk increases. The observations for males are consistent with the results for females.

6.2.2. Sensitivity to the effectiveness of an intervention

We performed sensitivity analysis on the type of intervention. When a perfect intervention is considered, AAS (for $R = \$100{,}000$) and IAS (for $k = 1$) achieve nearly the same expected LYs before an adverse health event or death, with AAS providing 0.00037 fewer LYs for females and the same expected LYs for males. AAS results in an average reduction in costs of \$23 for females and no reduction for males. Thus, we conclude that if perfect interventions were achievable, the incremental benefit of AAS compared with IAS would be small.

Next, we explored the use of an imperfect transition probability matrix that is independent of the patient's current adherence state and does not result in high-adherence patients having a lower rate of remaining in high adherence after an intervention than after no intervention. This imperfect transition probability matrix is as follows:

$$\tilde{P}_t(I^{\mathrm{H}}) = \begin{array}{c} \\ \mathrm{NON} \\ \mathrm{LOW} \\ \mathrm{MED} \\ \mathrm{HIGH} \end{array} \begin{array}{c} \begin{array}{cccc} \mathrm{NON} & \mathrm{LOW} & \mathrm{MED} & \mathrm{HIGH} \end{array} \\ \begin{pmatrix} 0.02 & 0.04 & 0.18 & 0.76 \\ 0.02 & 0.04 & 0.18 & 0.76 \\ 0.02 & 0.04 & 0.18 & 0.76 \\ 0.02 & 0.04 & 0.18 & 0.76 \end{pmatrix} \end{array}.$$

Under this intervention transition probability matrix, the optimal actions ($R = \$100{,}000$) result in reduced costs (\$899 for males, and \$1164 for females) and small reductions in LYs (0.0112 for males, and 0.0128 for females). These results show that, in some situations (though not all), it is optimal for patients with high adherence to have interventions. For males with the worst underlying health, interventions for patients with high adherence should start at age 51; however, for males with the best underlying health, it is never optimal to have interventions when the patient has high adherence. For females with the worst underlying health, interventions for patients with high adherence should start at age 61; again, we find that it is not optimal

Table 3. Optimal ages to begin having interventions within a particular adherence state for female patients using active surveillance. Imperfect (probabilistic) interventions are assumed. Note: "–" denotes it is never optimal for the patient to have interventions.

	Low Risk				Medium Risk				High Risk		
	$10	$90	$142		$10	$90	$142		$10	$90	$142
NON	41	41	41	NON	41	41	41	NON	41	41	41
LOW	41	41	41	LOW	41	41	41	LOW	41	41	41
MED	41	41	45	MED	41	41	41	MED	41	41	41
HIGH	—	—	—	HIGH	—	—	—	HIGH	—	—	—

for healthier patients to have interventions when the patient has high adherence.

We also explored the use of alternative imperfect interventions in which the effect of an intervention is dependent on a patient's current adherence state. We created an upper-triangular transition probability matrix from $\tilde{P}_t(I)$, thereby ensuring that patients would have the same or better adherence after the intervention. For each adherence level (for each row), the probabilities of entering lower adherence states were set to 0. We then ensured that each row of the transition probability matrix summed to 1 by normalizing the remaining entries. The upper-triangular imperfect transition probability matrix is as follows:

$$\tilde{P}_t(I^{\mathrm{UT}}) = \begin{array}{c} \\ \text{NON} \\ \text{LOW} \\ \text{MED} \\ \text{HIGH} \end{array} \begin{array}{c} \begin{array}{cccc} \text{NON} & \text{LOW} & \text{MED} & \text{HIGH} \end{array} \\ \begin{pmatrix} 0.091 & 0.165 & 0.257 & 0.487 \\ 0 & 0.182 & 0.283 & 0.536 \\ 0 & 0 & 0.345 & 0.655 \\ 0 & 0 & 0 & 1 \end{pmatrix} \end{array}.$$

The results found using this transition probability matrix show that, for males, there is no benefit from AAS (for $R = \$100{,}000$) over IAS (for $k = 1$). For females, AAS differed from IAS only in the case of the healthiest patients (low TC, very high HDL) in which interventions were not optimal for ages 41 and 42.

When we alter this intervention transition probability matrix by varying the percentage of HIGH adherence patients who remain in HIGH adherence—versus moving to MED adherence—from 100% to 80%, we (unsurprisingly) observe that as the rate of remaining in HIGH adherence decreases, the starting age for interventions for HIGH adherence patients increases. The latest starting age for interventions for HIGH adherence female patients is age 58, resulting in an average of 0.002 fewer LYs and $133 less cost per patient than yearly IAS. For males, interventions start as late as age 45, resulting in 0.00006 fewer LYs and $4 less on average per patient compared to IAS. It is important to note that while these altered imperfect transition probability matrices do not satisfy the condition in Theorem 1 that an intervention is independent of a patient's current adherence state, these experiments show that the optimal policies are still control-limit policies. Overall, we found that the further an intervention is from a perfect intervention, the greater the value AAS provides in identifying patients who do not need interventions, thereby saving money and preventing patients with high adherence from undergoing interventions that would provide little benefit.

6.2.3. Sensitivity to cost of intervention

We performed sensitivity analysis on the cost of interventions using cost estimates for interventions from the literature (Chapman *et al.*, 2010). When interventions are free, we observe that patients should have yearly interventions starting at age 41 ($t = 1$), the earliest possible age for interventions to occur in our model, since there is no downside for free interventions. For $C^{\mathrm{INT}} = \$10$, $90, or $142, we observe female patients within a particular adherence state should have interventions starting at the ages listed in Tables 3 (for imperfect, $\tilde{P}_t(I)$, interventions) and 4 (for perfect interventions). The following scenario shows how these results would be applied to a patient in practice for low-risk female patients considering high cost ($142) interventions. A 41-year-old female patient in the LOW adherence state would receive an intervention. Given that she remains in the LOW adherence state at age 42, she would again receive an intervention. At age 43, her adherence improves to MED, so she would not receive an intervention; she would only be eligible for interventions in the MED adherence state once she is age 45 or older. At any point in time, if this patient enters the HIGH adherence state she will not have an intervention, since it is never optimal for interventions in this adherence state.

The optimal policy for male patients follows a similar pattern to the optimal policy for female patients, but male patients should start having interventions up to 13 years earlier than female patients, depending on the type and cost of intervention and the adherence state being considered. The differences between the policies for male and female patients are likely due to the fact that males generally have an earlier onset of risk for cardiovascular events than females.

The optimal policy, presented in Tables 3 and 4, exhibits a control limit structure across adherence states for a given age, as expected from Theorem 1. For example, when considering high-cost ($142) interventions for low-risk female patients who are 41

Table 4. Optimal ages to begin having interventions within a particular adherence state for female patients using active surveillance. Perfect interventions are assumed.

	Low Risk				Medium Risk				High Risk		
	$10	$90	$142		$10	$90	$142		$10	$90	$142
NON	41	41	41	NON	41	41	41	NON	41	41	41
LOW	41	41	41	LOW	41	41	41	LOW	41	41	41
MED	41	41	41	MED	41	41	41	MED	41	41	41
HIGH	41	49	58	HIGH	41	41	44	HIGH	41	41	41

Table 5. Yearly differences in costs (billions) and future LYs for newly diagnosed diabetes patients using yearly inactive adherence surveillance (IAS, $k = 1$) and active adherence surveillance (AAS) relative to no adherence interventions.

	Males		Females		Total Population	
	LYs	Cost (billions)	LYs	Cost (billions)	LYs	Cost (billions)
IAS ($k = 1$)	144,741	\$0.51	145,336	\$0.67	290,077	\$1.18
AAS	210,939	\$0.17	210,143	\$0.29	421,082	\$0.46

years old, the optimal control limit s_t^* is LOW. When considering perfect interventions for these patients, the optimal control limit changes to MED. We also observe that the control limit tends to increase with respect to age.

6.2.4. Sensitivity to individual patient risk factors

In general, female patients and patients with lower risk stop having interventions earlier due to lower risk of stroke and CHD events. The policies are very insensitive to changes in the cost of interventions, particularly for males and patients in higher risk states. We observe that the higher-cost interventions have a shorter range for which it is optimal to perform the interventions; that is, the interventions start later in life. The female patients have fewer interventions overall; this is likely due to the fact that being male is a risk factor for stroke and CHD events, the events statins help prevent.

When perfect interventions are considered, it is always optimal for male and female patients to have interventions when their adherence is less than HIGH. The use of perfect interventions for patients with HIGH adherence depends on the intervention cost and risk state. For imperfect interventions, however, patients with HIGH adherence should never have an intervention since the probability of remaining in the HIGH adherence state under an intervention is lower than the probability of remaining in the HIGH adherence state without an intervention.

We also tested the model for sensitivity to the modeling of the evolution of cholesterol states. This sensitivity analysis replaces the deterministic evolution of cholesterol states with Markov chains to describe the stochastic evolution of TC and HDL. While the choice for the method of modeling cholesterol does affect the LY values and costs under each IAS (k =1,2,3,4 or 5) and AAS (R = \$0, \$25,000, \$50,000, or $\geq$ \$100,000) scenario—under stochastic cholesterol state modeling LYs are from 0.406 to 0.420 higher and costs are from \$688 to \$739 lower than deterministic cholesterol state modeling—the relative benefit of AAS over IAS is almost identical under each cholesterol modeling assumption. The benefit of AAS (R = \$100,000) over IAS (k =1) under stochastic cholesterol states is 0.161 LYs and −\$954, compared with 0.168 LYs and −\$960 (for a difference of −0.007 LYs and \$6).

6.2.5. Potential yearly benefits of AAS to the US diabetes population

In order to estimate the benefits of AAS applied to all diabetes patients in the United States, we first estimated the prevalence of diabetes in the United States using population estimates, by age and gender, based on the 2010 US Census (US Census Bureau, 2011), and the estimated diabetes prevalence by state and age range reported by Danaei *et al.* (2009). Next, we estimated the number of newly diagnosed diabetes patients for each gender, for every state and the District of Columbia, and for each age, starting at age 40. Patients were defined as *newly diagnosed* in 2010 if they were a diabetes patient at age 40 or an older patient diagnosed later in life. Patients were identified as newly diagnosed past age 40 if the population of total patients diagnosed at earlier ages was less than the diagnosed population at the given age. This accounts for increases in population and diabetes prevalence with respect to age.

Table 5 provides a yearly estimate of the differences in expected LYs and costs over the remaining years of life for newly diagnosed diabetes patients aged 40 or older with IAS ($k = 1$) and AAS relative to no interventions. According to our model, the implementation of IAS ($k = 1$), compared with no interventions, would increase LYs for the US population at a cost of \$4075/LY. In comparison, AAS would increase LYs over no interventions for the US population at a cost of \$1102/LY. Using AAS in place of IAS ($k = 1$) would result in over 131,000 additional LYs among adults newly diagnosed with diabetes while saving over \$717 million per year.

7. Conclusions

The CMS Meaningful Use initiative has the potential to encourage improved efficiency and effectiveness of health care delivery through the use of EHRs. Based on our results, we found that using an adherence-improving model linking claims data with EHRs has the potential to significantly delay the onset of adverse events or death, and reduce expected costs of treatment, hospitalization, and follow-up care associated with adverse events such as stroke and CHD. From the population perspective, we found that AAS is cost-effective compared with no interventions at a cost of \$1102 spent per LY added prior to CHD, stroke, or death. This cost per LY added is very low with respect to commonly used thresholds (Evans *et al.*, 2004). In addition, AAS results in significant cost savings over annual IAS ($k = 1$) while providing more than 131,000 additional event-free LYs to newly diagnosed diabetes patients each year at a savings of \$717 million per year. These estimated annual benefits highlight the potential benefits of AAS. Our study considers the use of AAS for a subpopulation in the United States that is at a high risk of stroke and CHD events; however, AAS could be used for the broader US population and for patients on other medications, yielding additional savings.

From the third-party payer perspective, our model results—using a willingness-to-pay value of R = \$0 or very close to \$0—could be used to inform a third-party payer's coverage of all or part of the cost of adherence-improving interventions. From the individual patient perspective, males receive an

average of 0.19 additional LYs per patient before an event or death over annual IAS at a reduction in costs of $913, and females receive 0.17 additional LYs per patient at a cost savings of $960 over annual IAS. These increases in LYs over annual IAS are an order of magnitude greater than the benefits seen through some prevention programs that are part of standard practice in the United States. For example, childhood vaccination against measles, mumps, and rubella results in an increase of 0.017 LYs per person (Wright and Weinstein, 1998). In addition, the increase in LYs from AAS over no interventions is even greater. The benefits of AAS over IAS and no interventions increase with increasing patient risk. In other words, patients at higher risk of adverse events stand to have greater benefit from AAS. In addition, we have found that the further an intervention is from a perfect intervention, the greater the value AAS provides in identifying patients who do not need interventions.

We found the optimal policy for adherence-improving interventions to exhibit a control-limit structure. This is consistent with the theoretical results we presented. This simple structure is intuitively appealing and could be exploited to achieve computational advantages in the context of large MDPs requiring fast solutions. From our numerical experiments, it appears that the control limit is increasing with respect to age. Once a patient begins having interventions, it is generally optimal to continue having yearly interventions until very late in life. Such a simple policy is encouraging for the application of AAS system in the already complex clinical environment.

We proved several new structural properties, for finite horizon nonstationary MDPs, related to the optimal control limit when interventions of different effectiveness are considered, and when patients of different levels of risk are considered. Proposition 1, in particular, provides insight through a simple yet counterintuitive rule for prioritizing patient interventions. While we presented Theorem 1 and Proposition 1 (presented in Appendix A) in the context of the problem to which we are applying our model (the optimal timing of adherence-improving interventions for patients with type 2 diabetes), these theoretical properties and our model are generalizable to many other contexts. For example, in the context of machine maintenance, Proposition 1 could be useful in scheduling maintenance for different types of machines that have different levels of reliability.

Although the outcomes of the AAS policy dominated the easier-to-implement IAS outcomes, our model did not account for the possibility of initial set-up costs and ongoing maintenance costs for such a system. While our model requires data that are generally available in administrative claims systems and laboratory information systems, the development of a decision support system that collects and utilizes the data would have some cost associated with instantiation of the system in a clinical environment. Since these costs are likely to vary significantly among implementations, we did not consider this in our analysis; however, it is worth noting that our model can easily be modified to incorporate any maintenance costs that would be necessary to use AAS. In addition, our model could be used to estimate the payback time for the initial costs of the system by calculating expected return on investment of using AAS over IAS. Furthermore, CMS incentives for participation in the Meaningful Use program may offset some of the costs of implementation.

There are benefits and limitations associated with using claims data. Administrative claims data sets can provide information about many aspects of a patient's interactions with the health care system, including diagnoses, procedures, medications, and providers. Claims data offer a cost-effective tool for studying clinical care and outcomes for a large population of patients. At the same time, important limitations do exist including the following: only insured patients are represented in claims data, not all diagnoses appear in the patient record (e.g., hypertension), and not all information about a patient encounter is collected (e.g., no clinical measurements such as blood pressure). One additional limitation related to pharmacy claims may lead to overestimation of medication adherence. Dates of filled prescriptions and pill counts are included in pharmacy claims data, but the claims data are not able to reflect how many pills the patient actually took from the prescription.

There are also some practical challenges associated with the use of claims and EHR data for applications such as we discuss. First, patients do not always stay with the same insurance provider. There may be a limited amount of time for which there is continuous information for each patient. This challenge may eventually be overcome by the development of a universal EHR that could be linked with claims data from multiple insurance providers. Second, our model assumes population-level data can be used to estimate parameters for individual patients. In the case of adherence to medical treatments, such as statin therapy, this is reasonable because researchers have not been able to identify ways to predict adherence on the basis of available health data. Nevertheless, the use of population-level data represents a barrier to more accurate prediction of adherence that might be possible with additional data. Third, in order for AAS to be implemented at the point of care, EHRs will need to be linked to pharmacy claims data to compute patient information such as PDC for prescribed medications (to estimate the patients adherence level), and patient health information from the EHR (such as blood pressure and cholesterol) to estimate the risk of adverse events. While we have demonstrated, in this article, that it is possible to use claims and EHR data from two different sources in a unified model, the ability to rapidly collect and combine such data presents a challenge for health systems. Models for combining claims and EHR data, utilizing a common data format, have been developed for the following: (1) drug safety monitoring (beginning in 2008, the public-private Observational Medical Outcomes Partnership, and beginning in 2009, the US Food and Drug Administration–funded program Mini-Sentinel); and (2) comparative effectiveness research (PCORnet, an innovative initiative of the Patient-Centered Outcomes Research Institute) (Curtis *et al.,* 2014; Rho *et al.,* 2016). While governance and technological challenges exist, combination of claims data and EHR data is needed to generate a fuller picture of a patient's health status and move toward a learning health system (Wallace *et al.,* 2014; West *et al.,* 2014; Haynes *et al.,* 2016).

In addition to the practical challenges highlighted earlier, we acknowledge that there are additional steps needed to improve medication adherence, including identification of effective interventions. Our modeling efforts provide independent confirmation of the importance of identifying effective interventions. As more information becomes available about the length

of time an intervention affects a patient's behavior, the model could be altered to incorporate this effectiveness information.

Future research could build on our model in several ways. For example, we considered interventions for a single medical treatment; future studies could extend the current model to include the optimal timing of interventions for patients on multiple medications. This extension suggests a number of interesting questions. Would there be interactions between interventions? In other words, could an intervention for one medication influence adherence to another medication? Could an intervention be designed that would simultaneously improve adherence to multiple medications? Furthermore, interesting questions arise about the relative importance of interventions. Our model could be extended to include more than one type of intervention in the action space for the one-medication problem to help prioritize among different types of interventions with varying costs and levels of effectiveness. In addition, our model could be amended to help prioritize interventions for different medications. Additional variations on our model could include different assumptions about the effectiveness of interventions. Although there is no evidence at present, it is possible that interventions may provide diminishing improvement to adherence over time or the adherence behavior of patients in the absence of interventions may be nonstationary. As we pointed out in the introduction, the recent substantial commitment of resources and efforts by the medical community to improve the current state of knowledge about medication adherence presents a number research opportunities for the OR community. Our model lays the foundation for some of these future studies.

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Appendix A: Proofs of lemmas and theorem from Section 5, and additional structural properties

A.1. A note about Assumption $\mathbf{A}_4$

In this subsection, we detail a situation in which Assumption $\mathbf{A}_4$ holds. Suppose that the disutility associated with statin use has the form

$$D^{\text{MED}} \times g(u),$$

where D^{MED} is the "baseline" discount in QALYs associated with statin use, and $g(u)$ is differentiable and nonincreasing in the adherence percentage a. For example, suppose that

$$g(u) = 1.0 - 1.0u$$

for $0 \leq u \leq 1$ so that the disutility associated with statin use is actually decreasing as the adherence percentage increases. Then, we have

$$R \times Q(u) - C^{\text{MED}}(u) = R \times [1 - D^{\text{MED}} g(u)] - C^{\text{MED}}(u) \quad \text{(A1)}$$

$$= R - [R \times D^{\text{MED}} \times g(u) + C^{\text{MED}} \times (u)], \quad \text{(A2)}$$

where $C^{\text{MED}}(u)$ is the full cost of statins for adherence percentage (a). A sufficient condition for Assumption $\mathbf{A}_4$ to hold is that

$$\frac{d}{du}g(u) \leq -\frac{\frac{d}{du}C^{\text{MED}}(u)}{(R \times D^{\text{MED}})}$$

for $0 \leq u \leq 1$.

Assuming statins cost $C^{\text{MED}}(u) = \$212u$ and the disutility associated with statin use is $D^{\text{MED}} = 0.003$, Assumption $\mathbf{A}_4$ will hold when $R \geq \$70{,}667$. Thus, Assumption $\mathbf{A}_4$ will hold for the base case value of $R = \$100{,}000$. On the other hand, Assumption $\mathbf{A}_4$ will not hold if $R = \$50{,}000$ unless the cost $C^{\text{MED}}(u)$ is less than or equal to \$150, assuming D^{MED} stays constant.

A.2. Proofs of the main lemmas and theorem

Proof of Lemma 1. Since $\tilde{P}_t(a_t)$ is IFR by assumption $\mathbf{A}_1$, with (i, j) element $\tilde{p}_t(j|i, a_t) \equiv [\tilde{P}_t(a_t)]_{i,j}$, it follows that for each $k \in \{1, \ldots, M\}$, the quantity $\tilde{q}_t(k|i, a_t) = \sum_{j=k}^{M} \tilde{p}_t(j|i, a_t)$ is nondecreasing in i for $i = 1, \ldots, M$. The matrix multiplication $\text{diag}[\mathbf{1}_M - \bar{p}_t]\tilde{P}_t(a_t)$ involves multiplying the ith row of $\tilde{P}_t(a_t)$ through by $1 - [\bar{p}_t]_i$ for $i \in \{1, \ldots, M\}$. Therefore, since $1 - [\bar{p}_t]_i$ is nondecreasing in i by assumption $\mathbf{A}_3$, it follows that the $(M + 2) \times M$ matrix

$$Y \equiv \begin{bmatrix} \mathbf{0}_M^{\intercal} \\ \mathbf{0}_M^{\intercal} \\ \text{diag}[\mathbf{1}_M - \bar{p}_t]\tilde{P}_t(a_t) \end{bmatrix} \tag{A3}$$

with (u, v) element $Y_{u,v}$ for $u \in \{0, 0', 1, \ldots, M\}$ and $v \in \{1, \ldots, M\}$ satisfies the following IFR-like property: for each fixed $k \in \{1, \ldots, M\}$, the function $y(u) \equiv \sum_{v=k}^{M} Y_{u,v}$ is nondecreasing in u for $u \in \{0, 0', 1, \ldots, M\}$. Similarly, it follows that the $(M + 2) \times (M + 1)$ matrix

$$Z \equiv \begin{bmatrix} 0 & \mathbf{0}_M^{\intercal} \\ 0 & \mathbf{0}_M^{\intercal} \\ \bar{p}_t & \text{diag}[\mathbf{1}_M - \bar{p}_t]\tilde{P}_t(a_t) \end{bmatrix} \tag{A4}$$

with (u, v) element $Z_{u,v}$ for $u \in \{0, 0', 1, \ldots, M\}$ and $v \in \{0', 1, \ldots, M\}$ satisfies the following IFR-like property: for each fixed $k \in \{0', 1, \ldots, M\}$, the function $z(u) \equiv \sum_{v=k}^{M} Z_{u,v}$ is nondecreasing in u for $u \in \{0, 0', 1, \ldots, M\}$ because of the following observations: (1) the matrix Z is obtained by concatenating the $(M + 2)$-dimensional column vector $[0, 0, \bar{p}_t^{\intercal}]^{\intercal}$ and the $(M + 2) \times M$ matrix Y, which has just been shown to satisfy the required IFR-like property; and (2) for each of the last M rows of Z, the row sums to 1 because a one-step transition from the associated adherence state to the absorbing state is impossible. Finally, we observe that $P_t(a_t)$ is obtained by concatenating the $(M + 2)$-dimensional column vector $[1, 1, \mathbf{0}_M^{\intercal}]^{\intercal}$ and the $(M + 2) \times (M + 1)$ matrix Z, which has just been shown to satisfy the IFR-like property; therefore $P_t(a_t)$ satisfies the required IFR property because each row of the latter matrix sums to 1. □

Proof of Lemma 2. The proof of Lemma 2 parallels the argument justifying Proposition 4.7.3 of Puterman (1994) after properly accounting for the exclusion of the absorbing state from assumptions $\mathbf{A}_2$ and $\mathbf{A}_4$. Now $r_t(0, a_t) = 0$ for $t \in \{1, \ldots, T - 1\}$ and for $a_t \in A_t(0)$ by (2), and we have $v_T(0) = 0$ by (4); therefore, from the optimality Eq. (3) for state 0, we see that

$$v_t(0) = 0 \quad \text{for } t \in \{1, \ldots, T - 1\}. \tag{A5}$$

The rest of the proof that $v_t(s_t)$ is nondecreasing in s_t for $s_t \in S \setminus \{0\}$ and $t \in \{1, \ldots, T\}$ requires us to exploit the optimality Eq. (3) for state s_t and any other state $s_t^{\dagger} \geq s_t$ together with the IFR property of $P_t(a_t)$, Eq. (A5), and Lemma 4.7.2 of Puterman (1994) in a backward induction argument that proceeds as follows. First, we observe that at time T, assumption $\mathbf{A}_2$ and Eq. (4) ensure that $v_T(s_T)$ is nondecreasing for $s_T \in S \setminus \{0\}$. Now we assume that $v_u(s_u)$ is nondecreasing in s_u for $s_u \in S \setminus \{0\}$ and $u \in \{t + 1, \ldots, T\}$. From the optimality equation for state $s_t \in S \setminus \{0\}$ with optimal action $a_t^*(s_t)$, we have by (A5) that

$$v_t(s_t) = r_t\left(s_t, a_t^*(s_t)\right) + \lambda \sum_{j \in S \setminus \{0\}} p_t\left(j|s_t, a_t^*(s_t)\right) v_{t+1}(j). \tag{A6}$$

We choose another adherence state $s_t^{\dagger} \geq s_t$ arbitrarily. To show that $v_t(s_t^{\dagger}) \geq v_t(s_t)$, we exploit the IFR property of $P_t(a_t)$ to conclude that for $s_u^{\ddagger} \in S \setminus \{0\}$, the function

$$q_u\left(k|s_u^{\ddagger}, a_u\right) \equiv \sum_{j=k}^{M} p_u\left(j|s_u^{\ddagger}, a_u\right) \tag{A7}$$

is nondecreasing in $s_u^{\ddagger}$ for all $k \in S$, $a_u \in A_u(s_u^{\ddagger})$, and $u \in \{1, \ldots, T\}$. We apply Puterman's Lemma 4.7.2 in which we make the associations $x_j' \leftrightarrow p_t(j|s_t, a_t^*(s_t))$, $x_j \leftrightarrow p_t(j|s_t^{\dagger}, a_t^*(s_t))$, and $v_j \leftrightarrow v_{t+1}(j)$ for $j \in S \setminus \{0\}$. With the latter assignments, we can combine Eq. (2), assumption $\mathbf{A}_4$, Eq. (A6), and the definition (A7) of $q_u(k|s_u^{\ddagger}, a_u)$ to conclude from Puterman's Lemma 4.7.2 that

$$\begin{aligned} v_t(s_t) &\leq r_t\left(s_t^{\dagger}, a_t^*(s_t)\right) + \lambda \sum_{j \in S \setminus \{0\}} p_t\left(j|s_t^{\dagger}, a_t^*(s_t)\right) v_{t+1}(j) \\ &\leq \max_{a_t \in A_t(s_t^{\dagger})} \left\{ r_t\left(s_t^{\dagger}, a_t\right) + \lambda \sum_{j \in S} p_t\left(j|s_t^{\dagger}, a_t\right) v_{t+1}(j) \right\} = v_t\left(s_t^{\dagger}\right) \end{aligned}$$

by (A5) and the optimality Eq. (3) for state $s_t^{\dagger}$. Thus we see that $v_t(s_t)$ is nondecreasing in s_t for $s_t \in S \setminus \{0\}$ so the induction hypothesis is satisfied. □

Proof of Theorem 1. The proof parallels the analysis establishing Theorem 4.7.4 of Puterman (1994) after making suitable adjustments to handle states 0 and 0′ separately. For convenience, we make the assignment $a_t(s_t) = 0$ when taking the action W at time t given than the patient is in health state $s_t \in S$; similarly, we assign $a_t(s_t) = 1$ when taking action I at time t given the patient's health state $s_t \in S$ for $t \in \{1, \ldots, T - 1\}$. Because $A_t(s_t) = \{W\}$ for $s_t \in \{0, 0'\}$, we have $a_t^*(s_t) = 0$ for $s_t \in \{0, 0'\}$ and $t \in \{1, \ldots, T - 1\}$.

Paralleling the proof of Theorem 4.7.4 of Puterman (1994), the following properties are essential to the argument for each $t \in \{1, \ldots, T - 1\}$:

- $\mathbf{B}_1$: $r_t(s_t, a_t)$ is nondecreasing in s_t for $s_t \in S \setminus \{0, 0'\}$ and $a_t \in \{0, 1\}$;
- $\mathbf{B}_2$: $q_t(k|s_t, a_t)$ as defined by Eq. (A7) is nondecreasing in s_t for $s_t \in S \setminus \{0, 0'\}$ and for all $k \in S$, $a_t \in \{0, 1\}$;

$\mathbf{B}_3$: $r_t(s_t, a_t)$ is a subadditive function on $[S \setminus \{0, 0'\}] \times \{0, 1\}$;

$\mathbf{B}_4$: $q_t(k|s_t, a_t)$ is a subadditive function on $[S \setminus \{0, 0'\}] \times \{0, 1\}$ for all $k \in S$; and

$\mathbf{B}_5$: the terminal value function $v_T(s_T)$ is nondecreasing in s_T for $s_T \in S \setminus \{0, 0'\}$.

Property $\mathbf{B}_1$ follows immediately from Eq. (2) and assumption $\mathbf{A}_4$. Properties $\mathbf{B}_2$ and $\mathbf{B}_5$ follow from Lemmas 1 and 2, respectively. Verifying property $\mathbf{B}_3$ is equivalent to showing that for every $\eta \in \{1, \ldots, M-1\}$ and $s_t \in \{1, \ldots, M-\eta\}$ and for $a_t = 0$, the second partial difference

$$\underset{s_t}{\Delta}\underset{a_t}{\Delta}\, r_t(s_t, 0) \equiv r_t(s_t + \eta, 1) - r_t(s_t + \eta, 0) - r_t(s_t, 1) + r_t(s_t, 0)$$

is nonpositive. By (2) we have

$$\begin{aligned}\underset{s_t}{\Delta}\underset{a_t}{\Delta}\, r_t(s_t, 0) &= [R \times Q(s_t + \eta) - C^{\mathrm{MED}}(s_t + \eta) - C^{\mathrm{INT}}] \\ &\quad - [R \times Q(s_t + \eta) - C^{\mathrm{MED}}(s_t + \eta)] \\ &\quad - [R \times Q(s_t) - C^{\mathrm{MED}}(s_t) - C^{\mathrm{INT}}] \\ &\quad + [R \times Q(s_t) - C^{\mathrm{MED}}(s_t)] \\ &= 0 \quad \text{for } \eta \in \{1, \ldots, M-1\}, \\ &\quad s_t \in \{1, \ldots, M-\eta\}, \quad \text{and} \\ &\quad t \in \{1, \ldots, T-1\}.\end{aligned}$$

The verification of condition $\mathbf{B}_4$ is similar to the verification of condition $\mathbf{B}_3$. For $\eta \in \{1, \ldots, M-1\}$, $s_t \in \{1, \ldots, M-\eta\}$, $k \in S$, and $t \in \{1, \ldots, T-1\}$, the second partial difference

$$\underset{s_t}{\Delta}\underset{a_t}{\Delta}\, q_t(k|s_t, 0) = [q_t(k|s_t + \eta, 1) - q_t(k|s_t, 1)] - [q_t(k|s_t + \eta, 0) - q_t(k|s_t, 0)] \quad \text{(A8)}$$

must be nonpositive for the following reasons: (1) by assumption, the effect of an intervention at time t is independent of the patient's health state at that time so that the first term in square brackets on the right-hand side of Eq. (A8) must vanish; and (2) Lemma 1 ensures that the second term in square brackets is nonnegative. Thus we see that $\Delta_{s_t}\Delta_{a_t}\, q_t(k|s_t, 0) \leq 0$ for $\eta \in \{1, \ldots, M-1\}$, $s_t \in \{1, \ldots, M-\eta\}$, $k \in S$, and $t \in \{1, \ldots, T-1\}$ so that property $\mathbf{B}_4$ follows.

To complete the proof of Theorem 1, we need to establish that the function

$$w_t(s_t, a_t) \equiv r_t(s_t, a_t) + \sum_{j=1}^{M} p_t(j|s_t, a_t) v_{t+1}(j)$$

is subadditive on $[S \setminus \{0, 0'\}] \times \{0, 1\}$. By the subadditivity of $q_t(k|s_t, a_t)$ on $[S \setminus \{0, 0'\}] \times \{0, 1\}$ for all $k \in S$, we have for $1 \leq s_t^- \leq s_t^+ \leq M$, $0 \leq a_t^- \leq a_t^+ \leq 1$, and $k \in S$,

$$\sum_{j=k}^{M} \left[p_t\left(j|s_t^-, a_t^-\right) + p_t\left(j|s_t^+, a_t^+\right)\right] \leq \sum_{j=k}^{M} \left[p_t\left(j|s_t^-, a_t^+\right) + p_t\left(j|s_t^+, a_t^-\right)\right]. \quad \text{(A9)}$$

By Lemma 2, the value function $v_{t+1}(j)$ is nondecreasing for $j \in S \setminus \{0, 0'\}$; therefore, we can apply Lemma 4.7.2 of Puterman (1994) to obtain

$$\sum_{j=1}^{M} \left[p_t\left(j|s_t^-, a_t^-\right) + p_t\left(j|s_t^+, a_t^+\right)\right] v_{t+1}(j) \leq \sum_{j=1}^{M} \left[p_t\left(j|s_t^-, a_t^+\right) + p_t\left(j|s_t^+, a_t^-\right)\right] v_{t+1}(j). \quad \text{(A10)}$$

For $\eta \in \{1, \ldots, M-1\}$ and $s_t \in \{1, \ldots, M-\eta\}$, we can express (A10) as

$$0 \geq \sum_{j=1}^{M} \left[\underset{s_t}{\Delta}\underset{a_t}{\Delta} p_t(j|s_t, 0)\right] v_{t+1}(j) = \underset{s_t}{\Delta}\underset{a_t}{\Delta} \left[\sum_{j=1}^{M} p_t(j|s_t, 0) v_{t+1}(j)\right]; \quad \text{(A11)}$$

and from property $\mathbf{B}_3$ we obtain the analogous result

$$\underset{s_t}{\Delta}\underset{a_t}{\Delta} r_t(s_t, 0) \leq 0 \quad \text{for } \eta \in \{1, \ldots, M-1\}, s_t \in \{1, \ldots, M-\eta\}, \text{ and } t \in \{1, \ldots, T-1\}. \quad \text{(A12)}$$

Combining (A11) and (A12) we see that $\Delta_{s_t}\Delta_{a_t} w_t(s_t, 0) \leq 0$ for $\eta \in \{1, \ldots, M-1\}$, $s_t \in \{1, \ldots, M-\eta\}$, and $t \in \{1, \ldots, T-1\}$, so that $w_t(s_t, a_t)$ is subadditive on $[S \setminus \{0, 0'\}] \times \{0, 1\}$. Applying Lemma 4.7.1 of Puterman (1994), we see that there exists a control limit s_t^* for $t \in \{1, \ldots, T-1\}$ such that Eq. (5) holds. □

A.3. Intervention effectiveness

This subsection and the following subsection present propositions based on the comparison of optimal policies for different types of interventions and different types of patients. Note that although these propositions both have shortcomings since they depend on the optimal value function, we feel they are valuable to include, given that they provide intuition about the structure of the problem being solved. We begin with a definition of stochastic dominance relevant to the two propositions.

Definition 1. Given $t \in \{1, \ldots, T-1\}$, $s_t \in S$, and $a_t \in A_t(s_t)$, the one-step transition probability matrix $P_t^{(1)}(a_t)$ is said to stochastically dominate $P_t^{(2)}(a_t)$, denoted by $P_t^{(1)}(a_t) \succcurlyeq P_t^{(2)}(a_t)$, if

$$\sum_{j=k}^{M} P_t^{(1)}(j|i, a_t) \geq \sum_{j=k}^{M} P_t^{(2)}(j|i, a_t) \quad \text{for every } i, k \in S,$$

where successive values of j and k are always understood to be taken in the order $0, 0', 1, 2, \ldots, M$.

In the context of the following two propositions, stochastic dominance represents that a transition probability matrix for a particular action is superior to a transition probability matrix for another action in terms of the probability of remaining in high adherence states. In order to differentiate the control limits for two interventions, we introduce the following notation: $s_t^*(I_\ell)$ represents the optimal control limit for intervention I_ℓ for $\ell = 1, 2$. In addition, we use a superscript to differentiate probabilities, actions, and value functions from the two MDPs in the following lemma and proposition.

Lemma 3. *Given two MDPs, MDP$_1$ with intervention I_1 and MDP$_2$ with intervention I_2, for which $P_t^{(1)}(I_1) \succcurlyeq P_t^{(2)}(I_2)$ and $P_t^{(1)}(W) \equiv P_t^{(2)}(W)$, the following is true:*

$$v_t^{(1)}(s_t) \geq v_t^{(2)}(s_t) \quad \text{for all } t \text{ and for all } s_t \in S. \tag{A13}$$

Thus, when one intervention dominates another, the expected future rewards can be no worse.

Proposition 1. *Given MDP$_1$ with intervention I_1 and MDP$_2$ with intervention I_2, if $v_t^{(2)}(s_t+1) - v_t^{(2)}(s_t) \leq v_t^{(1)}(s_t+1) - v_t^{(1)}(s_t)$ for all $s_t \in \{1,\ldots,M-1\}$ for $t \in \{1,\ldots,T-1\}$ and if the two MDPs are identical except that $P_t^{(1)}(I_1) \succcurlyeq P_t^{(2)}(I_2)$ and $P_t^{(2)}(I_2) \succcurlyeq P_t^{(2)}(W)$ for $t \in \{1,\ldots,T-1\}$, then $s_t^*(I_1) \geq s_t^*(I_2)$ for $t \in \{1,\ldots,T-1\}$.*

Proposition 1 can be interpreted as follows. If intervention I_1 is more effective than intervention I_2, then the optimal control limit for I_1 in MDP$_1$ should be greater than or equal to the optimal control limit for I_2 in MDP$_2$. In other words, under the optimal policy, intervention I_1 would be implemented for a wider range of adherence states. Intervention I_1 may be used for patients in better adherence states than I_2. The condition that $v_t^{(2)}(s_t+1) - v_t^{(2)}(s_t) \leq v_t^{(1)}(s_t+1) - v_t^{(1)}(s_t)$ for all $s_t \in \{1,\ldots,M-1\}$ for $t \in \{1,\ldots,T-1\}$ intuitively means that, under intervention I_1, the improvement in the value function realized by being in adherence state s_t+1 rather than state s_t at time t is at least as large as the corresponding improvement in the value function under intervention I_2. In general, the value-function increments $v_t^{(2)}(s_t+1) - v_t^{(2)}(s_t)$ and $v_t^{(1)}(s_t+1) - v_t^{(1)}(s_t)$ will decrease with increasing $s_t \in \{1,\ldots,M-1\}$; and the assumed condition merely requires that the increment $v_t^{(1)}(s_t+1) - v_t^{(1)}(s_t)$ for the more effective intervention decreases no faster than does the corresponding increment $v_t^{(2)}(s_t+1) - v_t^{(2)}(s_t)$ for the less effective intervention I_2 as the adherence state s_t improves (increases). The result of Proposition 1 is partly due to this assumption holding and the corresponding benefit provided by the value function being in an improved adherence state. This result also depends on the costs of interventions I_1 and I_2; in order for the conclusion of Proposition 1 to hold in general, the cost of intervention I_1 must not exceed that of intervention I_2.

Proof of Lemma 3. First we establish Eq. (A13) for the absorbing and pre-absorbing states $\{0, 0'\}$ separately, and then we use backward induction to establish (A13) for the adherence states. From Eqs. (2) and (4), we see that

$$v_T^{(1)}(s_T) = v_T^{(2)}(s_T) = \begin{cases} -C_T^{\mathrm{F}}, & \text{if } s_T = 0', \\ 0, & \text{if } s_T = 0. \end{cases} \tag{A14}$$

From Equation (A5), we have

$$v_t^{(1)}(0) = v_t^{(2)}(0) = 0 \text{ for } t \in \{1,\ldots,T-1\}. \tag{A15}$$

Moreover from Eq. (2) and the optimality Eq. (3) for the pre-absorbing state $0'$, we see that

$$v_t^{(1)}(0') = v_t^{(2)}(0') = -C_t^{\mathrm{F}} \quad \text{for } t \in \{1,\ldots,T-1\}. \tag{A16}$$

Combining (A14), (A15), and (A16), we see that Eq. (A13) holds for $s_t \in \{0, 0'\}$ and $t \in \{1,\ldots,T\}$.

To handle the adherence states, we start by noting that Eq. (4) yields $v_T^{(1)}(s_T) = \mathrm{E}[\mathrm{PDHR}|s_T] = v_T^{(2)}(s_T)$, for $s_T \in S \setminus \{0, 0'\}$. Thus, $v_T^{(1)}(s_T) \geq v_T^{(2)}(s_T)$ for $s_T \in S \setminus \{0, 0'\}$. For the inductive step, we assume $v_\tau^{(1)}(s_\tau) \geq v_\tau^{(2)}(s_\tau)$ for $s_\tau \in S \setminus \{0, 0'\}$ and $\tau \in \{t+1,\ldots,T\}$. Now we must show $v_t^{(1)}(s_t) \geq v_t^{(2)}(s_t)$ for $s_t \in S \setminus \{0, 0'\}$. Let $a_t^{(2)*}(s_t)$ be the optimal action for MDP$_2$ at time t for a patient in state $s_t \in S \setminus \{0, 0'\}$. It follows that

$$\begin{aligned} v_t^{(1)}(s_t) &\geq r_t\big(s_t, a_t^{(2)*}(s_t)\big) \\ &\quad + \lambda \sum_{s_{t+1}=0}^{M} p_t^{(1)}\big(s_{t+1}|s_t, a_t^{(2)*}(s_t)\big) v_{t+1}^{(1)}(s_{t+1}) \end{aligned} \tag{A17}$$

$$\begin{aligned} &\geq r_t\big(s_t, a_t^{(2)*}(s_t)\big) \\ &\quad + \lambda \sum_{s_{t+1}=0}^{M} p_t^{(2)}\big(s_{t+1}|s_t, a_t^{(2)*}(s_t)\big) v_{t+1}^{(1)}(s_{t+1}) \end{aligned} \tag{A18}$$

$$\begin{aligned} &\geq r_t\big(s_t, a_t^{(2)*}(s_t)\big) \\ &\quad + \lambda \sum_{s_{t+1}=0}^{M} p_t^{(2)}\big(s_{t+1}|s_t, a_t^{(2)*}(s_t)\big) v_{t+1}^{(2)}(s_{t+1}) \end{aligned}$$

$$= v_t^{(2)}(s_t) \quad \text{for } s_t \in S. \tag{A19}$$

Inequality (A17) follows from the fact that $v_t^{(1)}(s_t)$, the optimal value function for MDP$_1$, is bounded below by the value function for any other policy (in this case, the optimal policy for MDP$_2$). To establish (A18), we observe that $P_t^{(1)}(I_1) \succcurlyeq P_t^{(2)}(I_2)$ and $P_t^{(1)}(W) \equiv P_t^{(2)}(W)$ together imply that

$$\sum_{s_{t+1}=k}^{M} p_t^{(1)}(s_{t+1}|s_t, a_t^{(2)*}(s_t)) \geq \sum_{s_{t+1}=k}^{M} p_t^{(2)}\big(s_{t+1}|s_t, a_t^{(2)*}(s_t)\big) \text{ for } s_t \in S \setminus \{0, 0'\} \text{ and } k \in S; \tag{A20}$$

and (A20) is a strict equality for $k = 0'$. Because $v_t^{(1)}(s_t)$ is non-decreasing in s_t for $s_t \in S \setminus \{0\}$ by Lemma 2 earlier, we can apply Puterman's Lemma 4.7.2 to Eq. (A20), thereby showing that

$$\begin{aligned} &\sum_{s_{t+1}=0'}^{M} p_t^{(1)}\big(s_{t+1}|s_t, a_t^{(2)*}(s_t)\big) v_{t+1}^{(1)}(s_{t+1}) \\ &\quad \geq \sum_{s_{t+1}=0'}^{M} p_t^{(2)}\big(s_{t+1}|s_t, a_t^{(2)*}(s_t)\big) v_{t+1}^{(1)}(s_{t+1}); \end{aligned} \tag{A21}$$

and in view of Eq. (A15), we see that the summations on both sides of (A21) can be extended to start at the absorbing state 0, so that, for $s_t \in S \setminus \{0, 0'\}$, we have

$$\begin{aligned} &\sum_{s_{t+1}=0}^{M} p_t^{(1)}\big(s_{t+1}|s_t, a_t^{(2)*}(s_t)\big) v_{t+1}^{(1)}(s_{t+1}) \\ &\quad \geq \sum_{s_{t+1}=0}^{M} p_t^{(2)}\big(s_{t+1}|s_t, a_t^{(2)*}(s_t)\big) v_{t+1}^{(1)}(s_{t+1}); \end{aligned} \tag{A22}$$

and Inequality (A18) follows immediately from (A22). Inequality (A19) holds by the inductive hypothesis. Thus, $v_t^{(1)}(s_t) \geq v_t^{(2)}(s_t)$ for all t and for all $s_t \in S$. □

To prove Proposition 1, we must first establish the following variant of Lemma 4.7.2 of Puterman (1994) in which the summations $\sum x_j$ and $\sum x'_j$ are finite rather than infinite, and the summands $\{x_j\}$ and $\{x'_j\}$ are unconstrained in sign.

Lemma 4. *Let $\mathbb{J} \equiv \{0, 1, \ldots, L\}$ denote a finite index-set; and let $\{x_j : j \in \mathbb{J}\}$ and $\{x'_j : j \in \mathbb{J}\}$ be finite real-valued sequences satisfying $\sum_{j=k}^{L} x_j \geq \sum_{j=k}^{L} x'_j$ for $k \in \mathbb{J}$ and $\sum_{j=0}^{L} x_j = \sum_{j=0}^{L} x'_j$. If $v_{j+1} \geq v_j$ for $j = 0, 1, \ldots, L-1$, then $\sum_{j=0}^{L} x_j v_j \geq \sum_{j=0}^{L} x'_j v_j$.*

Proof of Lemma 4. If in the proof of Puterman's Lemma 4.7.2 we replace the infinite upper limit on each summation with the upper limit L, then all summations are finite and hence well–defined, even if some of the $\{x_j : j \in \mathbb{J}\}$ or $\{x'_j : j \in \mathbb{J}\}$ are negative; and the same analysis used for Puterman's Lemma 4.7.2 yields the desired conclusion. □

Proof of Proposition 1. The proof is by contradiction. If the desired conclusion of the proposition is false, then there is a time $u \in \{1, \ldots, T-1\}$ for which $s_u^*(I_1) < s_u^*(I_2)$; therefore, we can find an adherence state $s_u \in S \setminus \{0, 0'\}$ such that $s_u^*(I_1) < s_u \leq s_u^*(I_2)$ and

$$\begin{aligned} & R \times Q(s_u) - C^{\mathrm{MED}}(s_u) - C^{\mathrm{INT}} \\ & \quad + \lambda \sum_{s_{u+1}=0}^{M} p_u^{(1)}(s_{u+1}|s_u, I_1) v_{u+1}^{(1)}(s_{u+1}) \\ & < R \times Q(s_u) - C^{\mathrm{MED}}(s_u) \\ & \quad + \lambda \sum_{s_{u+1}=0}^{M} p_u^{(1)}(s_{u+1}|s_u, W) v_{u+1}^{(1)}(s_{u+1}), \end{aligned}$$

because, by the construction of the control limit $s_u^*(I_1)$ as specified in Lemma 4.7.1 of Puterman (1994), the right- and left-hand sides of the previous display cannot be equal; and from the previous inequality, it follows immediately that

$$\lambda \sum_{s_{u+1}=0}^{M} \left[p_u^{(1)}(s_{u+1}|s_u, I_1) - p_u^{(1)}(s_{u+1}|s_u, W) \right] v_{u+1}^{(1)}(s_{u+1}) < C^{\mathrm{INT}}. \tag{A23}$$

Moreover, because $s_u \leq s_u^*(I_2)$, we have

$$\lambda \sum_{s_{u+1}=0}^{M} \left[p_u^{(2)}(s_{u+1}|s_u, I_2) - p_u^{(2)}(s_{u+1}|s_u, W) \right] v_{u+1}^{(2)}(s_{u+1}) \geq C^{\mathrm{INT}}. \tag{A24}$$

From (A23), (A24), and the condition $\lambda \in (0, 1]$, it follows that

$$\begin{aligned} & \sum_{s_{u+1}=0}^{M} \left[p_u^{(1)}(s_{u+1}|s_u, I_1) - p_u^{(1)}(s_{u+1}|s_u, W) \right] v_{u+1}^{(1)}(s_{u+1}) \\ & \quad < \sum_{s_{u+1}=0}^{M} \left[p_u^{(2)}(s_{u+1}|s_u, I_2) - p_u^{(2)}(s_{u+1}|s_u, W) \right] v_{u+1}^{(2)}(s_{u+1}). \end{aligned} \tag{A25}$$

(Note that the formation of this inequality also relies on the condition that the cost of intervention I_1 must not exceed that of intervention I_2.) To contradict (A25), first we must show that the following two conditions always hold: (1) for all $t \in \{1, \ldots, T-1\}$ and for every $s_t \in S \setminus \{0, 0'\}$ and $k \in S$, we have

$$\begin{aligned} & \sum_{s_{t+1}=k}^{M} \left[p_t^{(1)}(s_{t+1}|s_t, I_1) - p_t^{(1)}(s_{t+1}|s_t, W) \right] \\ & \quad \geq \sum_{s_{t+1}=k}^{M} \left[p_t^{(2)}(s_{t+1}|s_t, I_2) - p_t^{(2)}(s_{t+1}|s_t, W) \right]; \end{aligned} \tag{A26}$$

and (2) we have

$$v_t^{(1)}(s_t) \geq v_t^{(2)}(s_t) \quad \text{for all } s_t \in S \quad \text{and } t \in \{0, 1, \ldots, T\}. \tag{A27}$$

Condition (A26) follows from the assumptions that $P_t^{(1)}(I_1) \succcurlyeq P_t^{(2)}(I_2)$ and $P_t^{(1)}(W) \equiv P_t^{(2)}(W)$ for $t \in \{1, \ldots, T-1\}$, and condition (A27) follows from Lemma 3. Now, we use conditions (A26) and (A27) to show that (A25) cannot be true. By Lemma 4, the following inequality holds for $t \in \{1, \ldots, T-1\}$:

$$\begin{aligned} & \sum_{s_{t+1}=0'}^{M} \left[p_t^{(1)}(s_{t+1}|s_t, I_1) - p_t^{(1)}(s_{t+1}|s_t, W) \right] v_{t+1}^{(1)}(s_{t+1}) \\ & \quad \geq \sum_{s_{t+1}=0'}^{M} \left[p_t^{(2)}(s_{t+1}|s_t, I_2) - p_t^{(2)}(s_{t+1}|s_t, W) \right] v_{t+1}^{(1)}(s_{t+1}). \end{aligned} \tag{A28}$$

(Note that Lemma 4.7.2 of Puterman (1994) is not sufficient to establish (A28) because the terms in square brackets in (A28) are not all guaranteed to be nonnegative; and in this situation Lemma 4 is required instead.) In view of Eq. (A15), we see that the summation on both sides of (A28) can be extended to start at the absorbing state 0, yielding

$$\begin{aligned} & \sum_{s_{t+1}=0}^{M} \left[p_t^{(1)}(s_{t+1}|s_t, I_1) - p_t^{(1)}(s_{t+1}|s_t, W) \right] v_{t+1}^{(1)}(s_{t+1}) \\ & \quad \geq \sum_{s_{t+1}=0}^{M} \left[p_t^{(2)}(s_{t+1}|s_t, I_2) - p_t^{(2)}(s_{t+1}|s_t, W) \right] v_{t+1}^{(1)}(s_{t+1}) \end{aligned} \tag{A29}$$

for $s_t \in S \setminus \{0, 0'\}$ and $t \in \{1, \ldots, T-1\}$. Finally, the following inequality holds by applying Lemma 4, the assumptions that $v_t^{(2)}(s_t + 1) - v_t^{(2)}(s_t) \leq v_t^{(1)}(s_t + 1) - v_t^{(1)}(s_t)$ for all $s_t \in \{1, \ldots, M-1\}$ and $t \in \{1, \ldots, T-1\}$, and $P_t^{(2)}(I_2) \succcurlyeq P_t^{(2)}(W)$ for $t \in \{1, \ldots, T-1\}$ together with condition (A27):

$$\begin{aligned} & \sum_{s_{t+1}=0}^{M} \left[p_t^{(2)}(s_{t+1}|s_t, I_2) - p_t^{(2)}(s_{t+1}|s_t, W) \right] v_{t+1}^{(1)}(s_{t+1}) \\ & \quad \geq \sum_{s_{t+1}=0}^{M} \left[p_t^{(2)}(s_{t+1}|s_t, I_2) - p_t^{(2)}(s_{t+1}|s_t, W) \right] v_{t+1}^{(2)}(s_{t+1}) \end{aligned} \tag{A30}$$

for every $s_t \in S \setminus \{0, 0'\}$ and $t \in \{1, \ldots, T-1\}$. We establish Eq. (A30) as follows. If in Lemma 4 we make the following associations: (i) $x_j \leftrightarrow p_t^{(2)}(s_{t+1} = j|s_t, I_2) - p_t^{(2)}(s_{t+1} = j|s_t, W)$ for $j = 0', 1, \ldots, M$; (ii) $x'_j \leftrightarrow 0$ for $j = 0', 1, \ldots, M$; and (iii) $v_j \leftrightarrow$

$v_{t+1}^{(1)}(s_{t+1}=j)-v_{t+1}^{(2)}(s_{t+1}=j)$ for $j=0',1,\ldots,M$, then we see from (A16) that

$$v_j=0 \quad \text{for } j=0', \tag{A31}$$

from Lemma 3 we have

$$v_j\geq 0 \quad \text{for } j=1,\ldots,M. \tag{A32}$$

From (A31), (A32), and the assumption that $v_t^{(2)}(s_t+1)-v_t^{(2)}(s_t)\leq v_t^{(1)}(s_t+1)-v_t^{(1)}(s_t)$ for all $s_t\in\{1,\ldots,M-1\}$ and $t\in\{1,\ldots,T-1\}$, we see that $v_j\leq v_{j+1}$ for $j=0',1,\ldots,M-1$. Therefore, all the hypotheses of Lemma 4 are satisfied, so that we have $\sum_{j\in S\setminus\{0\}}v_jx_j\geq\sum_{j\in S\setminus\{0\}}v_jx'_j$, from which we immediately have

$$\sum_{j=0'}^{M}\left[p_t^{(2)}(s_{t+1}=j|s_t,I_2)-p_t^{(2)}(s_{t+1}=j|s_t,W)\right]\times\left[v_{t+1}^{(1)}(s_{t+1}=j)-v_{t+1}^{(2)}(s_{t+1}=j)\right]\geq 0. \tag{A33}$$

Rearranging (A33), we have

$$\sum_{s_{t+1}=0'}^{M}\left[p_t^{(2)}(s_{t+1}|s_t,I_2)-p_t^{(2)}(s_{t+1}|s_t,W)\right]v_{t+1}^{(1)}(s_{t+1})\geq\sum_{s_{t+1}=0'}^{M}\left[p_t^{(2)}(s_{t+1}|s_t,I_2)-p_t^{(2)}(s_{t+1}|s_t,W)\right]v_{t+1}^{(2)}(s_{t+1}); \tag{A34}$$

and in view of (A15), we can extend the summation on both sides of (A34) so that they start at the absorbing state 0, yielding Eq. (A30). Therefore, from (A29) and (A30) we have

$$\sum_{s_{t+1}=0}^{M}\left[p_t^{(1)}(s_{t+1}|s_t,I_1)-p_t^{(1)}(s_{t+1}|s_t,W)\right]v_{t+1}^{(1)}(s_{t+1})\geq\sum_{s_{t+1}=0}^{M}\left[p_t^{(2)}(s_{t+1}|s_t,I_2)-p_t^{(2)}(s_{t+1}|s_t,W)\right]v_{t+1}^{(2)}(s_{t+1}) \tag{A35}$$

for every $s_t\in S\setminus\{0,0'\}$ and $t\in\{1,\ldots,T-1\}$. In view of Inequality (A35), we see that (A25) is false; and thus the desired conclusion follows immediately. □

A.4. Individual patient responses to interventions

In the final proposition, we use a superscript to index different types of patients in order to compare the optimal intervention thresholds for two types of patients. The superscript for a patient of type A is (A) and the superscript for a patient of type B is (B).

Proposition 2. *If* $\tilde{P}_t^{(A)}(I)=\tilde{P}_t^{(B)}(I)\succcurlyeq\tilde{P}_t^{(B)}(W)=\tilde{P}_t^{(A)}(W)$ *for* $t\in\{1,\ldots,T-1\}$ *and* $v_t^{(A)}(s_t+1)-v_t^{(A)}(s_t)\leq v_t^{(B)}(s_t+1)-v_t^{(B)}(s_t)$ *for all* $s_t\in\{1,\ldots,M-1\}$ *and* $t\in\{1,\ldots,T-1\}$, *then for two patient types that are identical except that*

$$[\tilde{p}_t^{(A)}]_i\geq[\tilde{p}_t^{(B)}]_i, \quad \text{for every } i=1,\ldots,M \text{ and for } t\in\{1,\ldots,T-1\}, \tag{A36}$$

and

$$v_T^{(A)}(s_T)\leq v_T^{(B)}(s_T), \quad \text{for every } s_T\in S, \tag{A37}$$

then we have

$$P_t^{(B)}(W)\succcurlyeq P_t^{(A)}(W), \quad P_t^{(B)}(I)\succcurlyeq P_t^{(A)}(I), \tag{A38}$$

and

$$s_t^{*(A)}\leq s_t^{*(B)} \quad \text{for } t\in\{1,\ldots,T-1\}. \tag{A39}$$

Proposition 2 states that if a patient of type A has a higher probability of moving to the pre-absorbing state than a patient of type B, then a patient of type B should have interventions in the same or better adherence states when compared with a patient of type A. Since $P_t^{(B)}(I)\succcurlyeq P_t^{(A)}(I)$, a patient of type A, the sicker patient, receives less benefit from interventions than a patient of type B. Interventions that are optimal for a patient of type B with better adherence may not be optimal for a patient of type A. This counterintuitive result provides a simple criterion for sorting patients on the basis of importance of an intervention, which could be useful for resource-constrained settings.

Proof of Proposition 2. To conserve space, we summarize the main points, with references to the relevant methods used in previous proofs. Equation (A38) is shown by an argument similar to that involving (A3) and (A4) in the proof of Lemma 1. We show Eq. (A39) using a proof by contradiction similar to the proof of Proposition 1. If the desired conclusion (A39) is false, then there is a time $u\in\{1,\ldots,T-1\}$ for which $s_u^{*(A)}>s_u^{*(B)}$; and by an argument similar to that involving Eqs. (A23)–(A25), we deduce from the latter inequality that

$$\sum_{s_{u+1}=0}^{M}\left[p_u^{(B)}(s_{u+1}|s_u,I)-p_u^{(B)}(s_{u+1}|s_u,W)\right]v_{u+1}^{(B)}(s_{u+1})<\sum_{s_{u+1}=0}^{M}\left[p_u^{(A)}(s_{u+1}|s_u,I)-p_u^{(A)}(s_{u+1}|s_u,W)\right]v_{u+1}^{(A)}(s_{u+1}). \tag{A40}$$

Then, by an argument paralleling Eqs. (A26)–(A35) we show that the following relation is always true for every time $t\in\{1,\ldots,T-1\}$:

$$\sum_{s_{t+1}=0}^{M}\left[p_t^{(B)}(s_{t+1}|s_t,I)-p_t^{(B)}(s_{t+1}|s_t,W)\right]v_{t+1}^{(B)}(s_{t+1})\geq\sum_{s_{t+1}=0}^{M}\left[p_t^{(A)}(s_{t+1}|s_t,I)-p_t^{(A)}(s_{t+1}|s_t,W)\right]v_{t+1}^{(A)}(s_{t+1}). \tag{A41}$$

Because (A41) contradicts (A40), the desired conclusion follows. □

Appendix B: Parameter estimation

B.1. Percentage of days covered (PDC)

We estimated the PDC for each individual for each year over a four-year period after his or her first prescription for statins.

Patients were required to have a one-year period with no statin use prior to the first statins prescription. The PDC for an individual can be calculated using the standard formula (Caetano *et al.*, 2006):

$$\text{PDC} = 100 \times \left(\frac{\text{days with an available supply of medication in the time period}}{\text{days in time period}} \right) \%. \tag{B1}$$

The numerator of Eq. (B1) is calculated using the statin prescription fill dates and the days of supply for each prescription. In the first year, the days of available supply are computed by summing the days of supply for each prescription filled during the first year, with two potential exceptions. If there is continuous coverage of medication (i.e., there are no days when all prior prescription days' supplies have been exhausted) and the total days' supply over the first year is greater than 365, then the supply above 365 will be carried forward to the following year. If there are gaps in prescription coverage but there is excess supply from the last prescription(s) of the year, the excess supply from the final prescription(s) will be carried forward to the following year. An example of this scenario is provided in Fig. 1. The days of available supply in subsequent years are computed in a similar manner, with the one difference being the fact that any excess supply from previous years is added to the beginning of the current year's supply. The denominator of Eq. (B1) was 365. This fraction was multiplied by 100 to obtain a percentage for each individual. Each patient's adherence in each of the four years after statin initiation was classified as NON, LOW, MED, or HIGH based on the PDC based on the adherence state definitions in Table 1.

B.2. Percentage change in total cholesterol (TC) by adherence state

The percentage change in TC was estimated for each patient by computing the mean TC from all readings prior to statin initiation and the mean TC during the period six months to one year after initiation. The percentage change in TC for each adherence state (as shown in Table 1) was computed by averaging the percentage change in TC among all the patients in each adherence state during the first year.

B.3. Adherence transition probabilities

The initial probability vector describing the proportion of patients who entered each adherence state in the first year after statin initiation was computed by dividing the number of patients in the particular adherence state in the first year by the total number of patients who initiated statins. The base case intervention transition probability matrix, $\tilde{P}_t(I)$, consists of the initial probability vector for each row of the matrix.

Two additional imperfect intervention transition probability matrices were also considered: $\tilde{P}_t(I^{\text{H}})$ and $\tilde{P}_t(I^{\text{UT}})$. The matrix $\tilde{P}_t(I^{\text{H}})$ was constructed to create a transition probability matrix that is independent of the patient's current adherence state and does not result in high-adherence patients having a lower rate of remaining in high adherence after an intervention than after no intervention. This was done by editing the HIGH adherence row of $\tilde{P}_t(W)$ to have slightly decreased probabilities of entering NON, LOW, and MED (rounded down to the nearest hundredth) and a slightly increased probability of entering HIGH (to maintain a vector whose elements summed to 1). The resulting vector was used for each row of $\tilde{P}_t(I^{\text{H}})$. The matrix $\tilde{P}_t(I^{\text{UT}})$ was constructed to ensure that patients would have the same or better adherence after the intervention. We amended $\tilde{P}_t(I)$ by setting all probabilities of entering a lower adherence state to 0 and normalizing the remaining nonzero entries on each row to create a valid transition probability matrix.

The no intervention transition probability matrix $\tilde{P}_t(W)$ was estimated using one-step transition data for the cohort of statin initiation patients from years 1 through 4 after initiation. Elements of each one-step transition matrix (for years 1 to 2, 2 to 3, and 3 to 4) were calculated by counting the number of patients in each beginning adherence state who transitioned to each adherence state in the next time period and dividing by the number of patients in the beginning adherence state. Since we only observed small differences in the three transition matrices, $\tilde{P}_t(W)$ was ultimately estimated by computing the average number of people who transitioned among the adherence states from one year to the next.