Optimizing Statin Treatment Decisions for Diabetes Patients in the Presence of Uncertain Future Adherence

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Background. *Statins are an important part of the treatment plan for patients with type 2 diabetes. However, patients who are prescribed statins often take less than the prescribed amount or stop taking the drug altogether. This suboptimal adherence may decrease the benefit of statin initiation.* ***Objective***. *To estimate the influence of adherence on the optimal timing of statin initiation for patients with type 2 diabetes.* ***Method***. *The authors use a Markov decision process (MDP) model to optimize the treatment decision for patients with type 2 diabetes. Their model incorporates a Markov model linking adherence to treatment effectiveness and long-term health outcomes. They determine the optimal time of statin initiation that minimizes expected costs and maximizes expected quality-adjusted life years (QALYs).* ***Results***. *In the long run, approximately 25% of patients remain highly adherent to statins. Based on the MDP model, generic statins lower costs in men and result in a small increase in costs in women relative to no treatment. Patients are able to noticeably increase their expected QALYs by 0.5 to 2 years depending on the level of adherence.* ***Conclusions***. *Adherence-improving interventions can increase expected QALYs by as much as 1.5 years. Given suboptimal adherence to statins, it is optimal to delay the start time for statins; however, changing the start time alone does not lead to significant changes in costs or QALYs.* ***Key words:*** *adherence; diabetes; statins; Markov decision process.* ***(Med Decis Making XXXX;XX:xxx–xxx)***

Patients with diabetes are at an increased risk of heart attack, stroke, and other complications such as blindness and kidney failure. Medical regimens and guidelines for management of diabetes are numerous and complex.[1,2] They have the potential to greatly influence an individual's health outcomes; however, they are highly dependent on an individual's ability to adhere to his or her prescribed treatments.[3–6] Patients may be less than highly adherent to their medication due to forgetfulness, lack of information about benefits and side effects, out-of-pocket costs, or other unknown factors.[7] The reasons for poor adherence are not well understood, but the observed effects of poor adherence can provide insight into the long-term health consequences.

Although inadequate management of lipids is associated with adverse outcomes (including greater probability of stroke and cardiovascular events), suboptimal adherence (or less than continuous high adherence) to lipid-lowering medications among diabetes patients is common.[8–11] Clinically, this leads to two important questions: is there an optimal time to initiate statins given a patient may have suboptimal adherence, and what are the potential benefits of improving adherence? To answer these questions, we developed a Markov decision process (MDP) model to determine the influence of

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adherence to statin treatment on intermediate outcomes (lipid levels) and long-term outcomes (cardiovascular events) in a large cohort of patients with type 2 diabetes. We used the United Kingdom Prospective Diabetes Study (UKPDS) model[12–14] to estimate how variation in adherence, and ultimately cholesterol, affects the patient's risk of cardiovascular events. Our model considered the implications of uncertainty in whether patients will take less than the prescribed dosage of statins.

We used our model to evaluate how suboptimal adherence influences the optimal time of statin initiation for each health state. We investigated whether the adverse effects of suboptimal adherence on quality-adjusted life years (QALYs) can be mitigated by changing the timing of initiation. We also used our model to estimate the incremental benefit possible from maintaining perfect adherence. This provides an estimate of the total potential benefits from an intervention to improve adherence.

METHODS

The optimal statin initiation problem was formulated as a discrete time, finite horizon, discounted MDP in which patients transitioned through health states corresponding to varying risks of future complications, their history of complications, and death from other causes unrelated to diabetes.[15] The solution of our MDP model produced a *policy*: a mapping that specifies the optimal decision (start statins or delay initiation) for every health state. States of our MDP model were defined by metabolic risk factors that influence the risk of complications, including blood pressure, cholesterol (total cholesterol [TC] and high-density lipoprotein cholesterol [HDL]), and long-term average plasma glucose concentration (HbA1c).

In our model, all 4 risk factors were defined to be gender dependent. Blood pressure and HbA1c values were age dependent but were assumed to be deterministic over time. This assumption is consistent with assumptions commonly made in other studies.[16–18] Furthermore, sensitivity analysis revealed that using stochastic blood pressure states resulted in a 0.57% to 1.3% reduction in the expected objective value, depending on the health state. TC and HDL evolved probabilistically over time according to a Markov process as patients aged. The Markovian assumption for cholesterol has been shown to be a reasonable approximation, particularly for long-term trends.[19] These risk factors were represented as a discrete set of states defined by clinically relevant thresholds,[20] as seen in Table 1 (low, *L*; medium, *M*; high, *H*; and very high, *V*).

At each of a set of annual decision epochs (yearly time periods where decisions must be made), the patient transitioned among health states that were grouped into 2 categories: *living states* and *absorbing states*. Living states defined the patient's current metabolic risk factors and the history of nonfatal cardiovascular events such as myocardial infarction (hereafter referred to as a coronary heart disease [CHD] event) and stroke. Absorbing states included death from cardiovascular complications and other causes.

Patients initiated statins in 1 of 2 ways: by choice before the occurrence of a nonfatal event or by default as the result of a nonfatal cardiovascular event. In each decision epoch, a decision maker (e.g., patient and/or physician) selected 1 of 2 possible decisions: *initiating statin treatment* or *deferring the decision until the next epoch*. If the decision maker (e.g., the patient) delayed the decision, then he or she faced the same decision in the next epoch, provided he or she did not enter an absorbing state. Once a patient had initiated statins, the living states also included the patient's level of adherence.

Figure 1 is a simplified state transition diagram. In our numerical experiments, patients started in one of the living states (*L*, *M*, *H*, or *V* in this simplified description of the model). Before initiation of statins, patients probabilistically moved between the living states and received a yearly reward capturing both the dollar amounts for QALYs and treatment. Patients initiated statins in 2 ways, either by choice or by default as a result of an event. Once a patient initiated statins, he or she progressed through health states based on a Markov model of adherence.

Natural History Model

Following is a brief description of our natural history model, which is similar to the model by Denton and others[15]:

Time horizon. The decision to initiate statins was revisited annually from ages 40 to 80.

States. The 2 categories of states, living states and absorbing states, are denoted by $\mathcal{L}$ and D, respectively. Living states define the patient's risk state based on several factors. We denote total cholesterol states by the set $L_{TC} = \{L, M, H, V\}$ and HDL states by the set $L_{HDL} = \{L, M, H, V\}$ as in Table 1. The

Table 1 Ranges for TC and HDL (mg/dL)

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

HDL, high-density lipoprotein cholesterol; TC, total cholesterol.

thresholds were derived from the thresholds used in the Adult Treatment Panel III cholesterol guidelines.[20] Also included in this state definition was the number of nonfatal CHD and stroke events (a maximum of 5 each) defined as $L_{CHD} = \{0, 1, \ldots, 5\}$ and $L_S = \{0, 1, \ldots, 5\}$, respectively. Thus, $\mathcal{L} = L_{TC} \times L_{HDL} \times L_{CHD} \times L_S$, and there were a total of 576 living states in our model. Patients transitioned to absorbing states, $D = \{D_{CHD}, D_S, D_O\}$, when they had a fatal CHD event (D_{CHD}), fatal stroke event (D_S), or death from other causes (D_O) not related to cardiovascular disease. The treatment status of the patient was defined by a binary indicator $m \in M = \{0, 1\}$, where 0 and 1 refer to not using and using statins, respectively. Patients who initiated statins transitioned probabilistically through a set of adherence states. Upon statin initiation, the patient's adherence level became part of the living state definition.

Transition probabilities. Our model employed 4 categories of probabilities: transition probabilities among health states, transition probabilities among adherence states, probabilities of CHD or stroke events, and probability of death from other causes. Details of the transition probabilities are found in the appendix.

Adherence

The level of adherence, y, was measured as the percentage of days covered[21] for each year using pharmacy claims data. The discrete adherence state A was defined as:

$$A = \begin{cases} NON & \text{if } y \leq 10\%, \\ LOW & \text{if } 10\% < y \leq 40\%, \\ MED & \text{if } 40\% < y \leq 80\%, \\ HIGH & \text{if } y > 80\%. \end{cases} \quad (1)$$

These thresholds for the adherence states are commonly used in the medical adherence literature, such as in the study by Rasmussen and others.[22] Our model implicitly assumed that the patient's health status did not influence his or her adherence level. This is supported by previous studies such as the one by Steiner and others,[23] which suggests that observed characteristics are not sufficient to predict future adherence behavior for patients.

We assumed that future adherence is unpredictable in advance, which is well supported by several studies.[10,23,24] Once a patient initiated statin treatment, he or she began the process in 1 of the 4 adherence states and then transitioned probabilistically between the adherence states every year after initiation. This Markov process implicitly defined the stochastic distribution among adherence states over time. Patients who discontinued statins due to intolerance were removed from adherence consideration. Patients who discontinued treatment due to poor adherence were included in the *NON* adherence state. Figure 2 illustrates the adherence Markov process. In our model, the cost of statin treatment depended on the adherence state. We assumed that the cost of the medication was consistent with the midpoint of the adherence range. For example, a patient who was adhering in the 40% to 80% range would have annual statin medication cost estimated at 60% of the full cost.

Each adherence state corresponded to an associated change in TC. The decreased TC levels of patients on statins translated to decreased probabilities of stroke and CHD events. Estimates are later shown of the association between adherence and cholesterol reduction due to statins. We assumed no significant change in the patient's HDL. Although some randomized controlled trials (RCTs) indicate moderate increases in HDL,[25] we did not observe this in our data set.

Treatment Decisions

We assumed the initiation of treatment was a one-time decision after which the patient stayed on statins. This assumption is consistent with clinical practice in which it is intended for patients to remain on statins permanently, provided they are tolerated (in a small number of cases, statins must be discontinued due to liver problems or myalgia). Statins have been observed to cause a proportional decrease in cholesterol based on results of clinical control trials.[25,26] In our model, high adherence to statin medications reduced the probability of transitioning to absorbing states by a corresponding reduction in the probability of fatal CHD and stroke events. Once statin treatment was initiated, the patient continued on treatment until he or she transitioned to an absorbing state, which terminated the process. The possible decisions that could be made at each decision epoch were as follows:

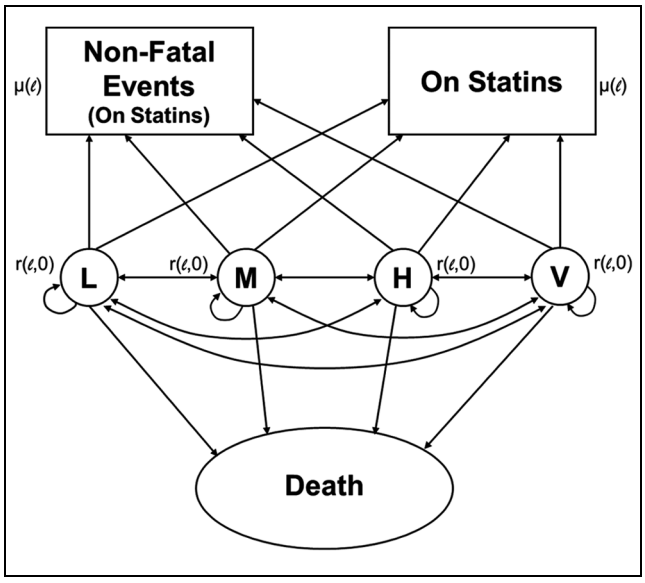

*Figure 1 Simplified state transition diagram. Patients probabilistically move among the health states (*L, M, H, *and* V*), receiving yearly, state-dependent rewards* r*(ℓ, 0). If a patient has an event or it is optimal for the patient to begin treatment, he or she moves into the "Nonfatal Events (On Statins)" box or the "On Statins" box, respectively, and receives the associated expected posttreatment reward μ(ℓ). Imbedded within these boxes is a Markov reward process for patients on statins.*

$$a_{(\ell,m)}=\begin{cases}\{I,W\} & \text{if } m=0 \text{ and } \ell\in\mathcal{L},\\ \{W\} & \text{if } m=1 \text{ and } \ell\in\mathcal{L},\end{cases} \qquad (2)$$

where I denotes initiating treatment and W deferring the decision until the next epoch when $m = 0$. If a patient had already initiated statins (i.e., $m = 1$), then we adopted the convention to specify the course of action as W. The decision, $a_{(\ell, m)}$, depended on the patient's health state, ℓ. We assumed that patients who had a stroke or CHD event started statins immediately after the event occurred, which is consistent with clinical practice.[25,27,28] In other words, once $L_{CHD} = 1$ or $L_S = 1$, the action I was taken.

Reward Model

Rewards, $r_t(\ell,m)$, included a dollar reward per QALY minus treatment costs as described in the following equation:

$$\begin{aligned} r_t(\ell,m) = {} & R(\ell,m) - C_t^O - (CF^S(\ell)+CF^{CHD}(\ell)) - \\ & mC^{ST}(A) - (C^S(\ell)+C^{CHD}(\ell)), \\ & \text{for } t=1,\ldots,T-1, \ell\in\mathcal{L}, m\in M, \end{aligned} \qquad (3)$$

where $R(\ell,m) = R_0(d^s(\ell))(d^{CHD}(\ell))(md^{ST}(A))$, $\ell \in \mathcal{L}$, $m \in M$ is the reward for 1 QALY, and A is the patient's adherence state. R_0 is the reward for a quality year of life. When a patient had an event or initiated statins, his or her quality of life was decreased. The decrement factors d^S, d^{CHD}, and d^{ST} represented the decrease in quality of life from a stroke, a CHD event, or statins initiation, respectively. There was an implicit assumption of no interaction of disutilities if a patient incurred both a stroke and a CHD event. Disutility factors for events were applied the year the event occured and all subsequent years. The statins disutility factor was applied every year the patient was on statins, scaled to correspond to his or her adherence level. The costs C^O, C^{ST}, C^S and C^{CHD}, and C^{FS} and CF^{CHD} represent the cost of other health care for diabetes patients, cost of statin treatment, cost of initial hospitalization for stroke and CHD events, and cost of follow-up treatment for stroke and CHD events, respectively. Initial hospitalization costs were incurred in the year the event occurred, and follow-up costs were incurred every subsequent year. Patients incurred the cost of statins every year they were taking the medication, scaled according to their adherence level. For $t = T$, we added 1 additional term to (3) to represent the expected postdecision horizon reward that estimated the discounted future expected rewards for a patient living past the decision horizon, up until age 100.

Optimization of Treatment Decisions

For a patient in state ℓ in epoch t, $v_t(\ell)$ denotes the patient's maximum total expected discounted rewards. The following recursive equation defines the optimal action in each state:

$$\begin{aligned} v_t(\ell) = \max\left\{ r_t(\ell,0) + \lambda \sum_{k'\in\mathcal{L}} p_t^W(k',0|\ell,0) v_{t+1}(k'), \mu_t(\ell) \right\}, \\ \forall \ell\in\mathcal{L}, t=1,\ldots,T-1, \end{aligned} \qquad (4)$$

where $\lambda \in [0,1)$ is the annual discount factor, which is commonly set to 97% in health economic evaluations (see chapter 7 of Gold and others[29] for a discussion of this). We defined $\mu_t(\ell)$ as the patient's *expected posttreatment reward* if treatment was initiated in state $\ell \in \mathcal{L}$ at epoch $t = 1, \ldots, T–1$. These rewards were determined recursively using the

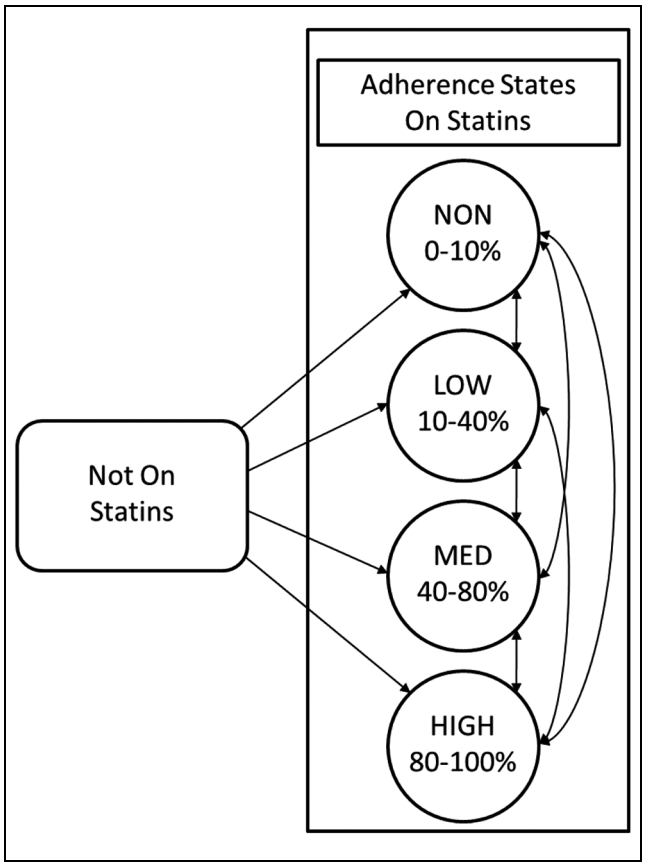

Figure 2 Markov model of adherence for patients initiating statins, including adherence states and transitions.

Markov model to estimate rewards for a person on statins. By equation (4), if treatment was initiated in health state $\ell \in \mathcal{L}$ at epoch $t = 1, \ldots, T-1$, the patient received the posttreatment reward $\mu_t(\ell)$ and left the decision process. The boundary condition $v_T(\ell)$ is set to the period T reward plus the expected postdecision horizon reward, $\forall \ell \in \mathcal{L}$.

In words, the decision problem reduced to selecting between 2 options: delaying the initiation of statins by at least 1 more year or deciding to initiate statins to maximize the expected future discounted rewards (see Puterman[30] for a detailed description of solution methods for MDPs such as this). In our model, there was a tradeoff resulting from treatment—reducing risk of events v. incurring cost of treatment and disutility from side effects. Because the cost and disutility of treatment were relatively small, it is our intuition that the imperfect nature of adherence decreased the posttreatment reward $\mu_t(\ell)$. Thus, uncertain future adherence affected expected discounted future rewards associated with statin treatment and possibly the optimal decision.

Data and Input Parameters

Descriptions and values of the model parameters are found in Table 2. All costs in the table were for 1 year. Other values drawn from the literature were the transition probabilities to absorbing states. Mortality tables[31] were used to estimate the probability of death from other causes. The UKPDS model[13,14,32] was used to compute probabilities of incurring a CHD event or stroke during the next decision epoch.

The transition probabilities among health states were computed from an observational data set based on medical records from the Mayo Electronic Medical Records (Mayo EMR) and Diabetes Electronic Management System (DEMS) for a large cohort of patients receiving treatment for type 2 diabetes at the Mayo Clinic, Rochester, Minnesota. The DEMS data set includes 663 patients with cholesterol, HbA1c, blood pressure, and other laboratory values.[44] A spline fit was used to interpolate missing laboratory values for cholesterol values to obtain an estimate of quarterly levels for these risk factors.[15]

Administrative medical and pharmacy claims data from United Healthcare (UHC) benefit plans were used to compute adherence transition probabilities as described in the appendix. These data are maintained by Igenix in a research-oriented database that is employed across United Health Group for longitudinal studies. It houses claims, membership, provider, and laboratory data for more than 25 million current members. The eligible population for our study consisted of members currently or previously enrolled in UHC commercial medical and pharmacy benefit plans. We used pharmacy claims and lab data to compute the adherence transition probabilities and subsequent effects on total cholesterol. A complete list of model inputs can be found in Table 3.

A cohort of 54,036 patients diagnosed with type 2 diabetes was identified by employing Healthcare Effectiveness Data and Information Set (HEDIS) criteria to the UHC data. HEDIS requirements for claim encounter data include 2 face-to-face encounters with different dates of service in an outpatient setting or nonacute inpatient setting or 1 face-to-face encounter in an acute inpatient setting or emergency department setting.[45] ICD-9 diagnosis codes were used to discern type 2 diabetes, and CPT procedure codes were used to discern the type of setting in face-to-face encounters. To be included in the cohort, we imposed a requirement that a member must have

Table 2 Description of Model Parameters Including Cost Inputs and Utility Decrements for the Reward Function of the MDP Model

Parameter Type	Parameter	Value	Source
Cost inputs	Initial hospitalization for stroke (C^S)	$13,204	33
	Initial hospitalization for CHD (C^{CHD})	$18,590	33
	Follow-up for stroke (CF^S)	$1664	34
	Follow-up for CHD (CF^{CHD})	$2576	34, 35
	Statin treatment (C^{ST})	$234	36
	Reward for a year of quality life (R_0)	$100,000	37
	Discount factor (λ)	0.97	29
Utility decrements	CHD decrement (d^{CHD})	0.93	38, 39
	Stroke decrement (d^S)	0.79	38, 40, 41
	Statins decrement (d^{ST})	0.997	16, 42, 43

CHD, coronary heart disease.

been continuously enrolled in medical and pharmacy plans for a minimum length of 5 years, with at least 1 year of enrollment before the first encounter date and at least 4 years of enrollment after the first encounter date. Patients were also required to have at least 1 prescription filled in each of these 4 years to ensure they did not discontinue treatment due to side effects. This cohort of patients contained 24,630 women and 29,406 men. Dates of first encounters ranged from January 1995 to June 2004.

We then identified a subset of 12,658 members who initiated statin treatment. To be included in this subset, we required that members have a minimum 1-year period with no statin prescriptions and a minimum 4-year period of pharmacy enrollment after the first statin prescription was filled. A timeline was established for each individual, with the date of the first prescription marking the beginning of year 1. We used possession of medication as a proxy for adherence. The formula used was percent of days covered: the ratio of the sum-of-days supply to 365.[21]

RESULTS

We solved our MDP model using the methods of dynamic programming, specifically backwards induction, which allowed us to efficiently and exhaustively search the space of all possible policies for initiation and choose the policy that minimized expected costs and maximized expected QALYs. We used the UHC cohort data to count the number of transitions among the states from year to year and estimate 3 transition matrices: years 1 to 2, 2 to 3, and 3 to 4. The absolute differences among the 3 transition matrices were small, which suggested

Table 3 Summary of Sources for Model Inputs

Model Input	Source
Probability among health states	Mayo EMR and DEMS
Adherence transition probabilities	UHC
Probability of death from other causes	CDC mortality tables
Probability of stroke and CHD events	UKPDS models
Cost and utility values	Secondary sources (see Table 2)

CDC, Centers for Disease Control and Prevention; CHD, coronary heart disease; DEMS, Diabetes Electronic Management System; EMR, Electronic Medical Records; UKPDS, United Kingdom Prospective Diabetes Study.

that the transition probabilities among adherence states were stationary. An estimate of the 1-step transition matrix was constructed by computing the average number of people who transition among the states from year to year. We calculated the 1-step transition matrices separately for men and women, as shown in the appendix in equations (10) and (11), although the differences were not significant. The initial probability vector for entering adherence states in year 1 was $p = (0.091, 0.165, 0.257, 0.487)$, and the 1-step transition matrix was given by the following:

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

This transition matrix corresponds to the states in the diagram of Figure 2.

Table 4 Percent Changes in Total Cholesterol (TC) from Preinitiation to Year 1 Postinitiation Based on Adherence Level

	Adherence States	% Change in TC
NON	≤10%	−5.217
LOW	10%–40%	−8.214
MED	40%–80%	−18.081
HIGH	>80%	−25.246

Effect of Adherence on Total Cholesterol

Statins are effective in reaching lipid level goals by lowering total cholesterol; however, the effects of adherence on cholesterol levels are less studied. We estimated these effects using laboratory data for those members of the diabetes cohort who initiated statin treatment. The mean of all laboratory readings prior to statin initiation was compared to the mean of all readings in the last 6-month period following initiation.

The correspondences between adherence level and mean percent change in TC are exhibited in Table 4. We applied these percent changes in TC from the natural history model each year a patient was on statins.

Long-Term Adherence

Using the adherence transition probability matrix, we computed the steady-state distribution of the adherence states. Table 5 shows that after a population started statins, an equilibrium was eventually reached in which approximately 25% of the patients would be in the *HIGH* adherence state. We observed that more than 45% of the population was, on average, in the *NON* adherence state. With such poor long-term adherence, most patients did not obtain the full benefit of statin treatment. Approximately 20 years were needed for the distribution to reach steady state, but after only 10 years, the percentage of highly adherent patients had already fallen to 27%.

Influence of Adherence on Treatment Decisions

We used our MDP model to calculate the optimal start times for statins for typical male and female patients based on the parameter estimates in Table 2. We compared the optimal policy for statin initiation for uncertain and perfectly predictable adherers based on gender. The former provided a policy consistent with our observational data, and the latter gave a policy that would appear to yield the largest achievable objective value (a combination of the largest expected QALYs and smallest expected discounted costs) among all adherence assumptions. We use the term *uncertain adherence* to reflect the fact that when a patient and physician are trying to determine when a patient should initiate statins, the patient's future adherence to statins is uncertain.

Table 5 Adherence Steady-State Distribution

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

The differences in start times between patients assumed to have high (A = *HIGH*) and uncertain adherence (A evolves according to the Markov process defined in the "Adherence" section) ranged from 0 to 11 years for women, with the largest gap in optimal start times for patients in the lowest risk states, as seen in Table 6. For women with high adherence, start times were early (e.g., age 40). Alternatively, female patients with uncertain adherence had a delayed optimal start time (up to 11 years) for any state associated with low or medium TC and high or very high HDL. This delay was likely because only 27% of patients remained highly adherent to statins after 10 years according to our data. Thus, many low-risk female patients stopped taking their full dose before their cardiovascular risk was high. Another study by Shechter and others[46] had similar findings in a different context. Their study found that HIV therapy initiation should be delayed for HIV patients with poor adherence. In both their study and ours, poor adherence led to worse health outcomes, and the models suggested delaying initiation of treatment when adherence was predicted to be poor.

The earliest optimal start time for men for both high and uncertain adherence was age 40, regardless of the health state. Two model parameters, with the statins cost of $234 per year and the statins decrement to quality of life of 0.997, explained why we see very early optimal start times, irrespective of the state and associated risk levels. This cost of yearly treatment was for a generic statin and was therefore a lower bound on the cost of branded statins. Men, in general, were at a higher risk of experiencing a stroke or CHD event. Because of this, men needed to initiate treatment earlier to prevent these earlier events.

To gain insight into the effects of different adherence assumptions, we calculated the expected QALYs

Table 6 Optimal Start Times for Women Based on Their TC/HDL State at Age 40

TC/HDL	V/L	H/L	M/L	L/L	V/M	H/M	M/M	L/M	V/H	H/H	M/H	L/H	V/V	H/V	M/V	L/V
Optimal start times for patients with uncertain adherence																
Age, y	40	40	40	40	40	40	40	42	40	40	42	46	40	40	45	51
Optimal start times for patients with high adherence																
Age, y	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40

L, M, H, and V represent the states low, medium, high, and very high for each of the metabolic factors. The parameters from Table 2 were used to obtain these results. HDL, high-density lipoprotein cholesterol; TC, total cholesterol.

and costs from age 40 for the optimal treatment policy under 5 different assumptions: uncertain, RCT, high, medium, and low adherence. Uncertain adherence represented the patient's adherence level probabilistically changing over time according to the Markov process defined in the ''Adherence'' section. The last 4 cases assumed the patient's adherence level remained fixed as he or she aged. RCT adherence corresponded to high adherence with the RCT outcomes of a 24% decrease in TC and an 8% increase in HDL as reported by Hebert and others,[26] and high, medium, and low corresponded to the decreases in TC in Table 4. For each adherence assumption, we found the change in QALYs and cost of treatment and hospitalization relative to the base case of no statin treatment. The results for the individual health states were combined using the probability distribution of the patients at age 40. Figure 3 has results for generic and branded statins for female patients. For all points on both graphs, we observed a simultaneous increase in expected QALYs and costs as adherence improved. Note that improved adherence raised yearly medication costs but lowered the probability of stroke and CHD events over time. This resulted in lower expected costs of future hospitalization and follow-up care associated with these events. Branded statins (C^{ST} = \$1435) showed a nearly linear relationship between the change in expected QALYs and costs.

Figure 4 provides the same results for men. With the branded statins (C^{ST} = \$1435), there is a nearly linear relationship between the change in expected QALYs and costs, similar to the female results. However, unlike for women, there are many points on the graphs for the generic statins that corresponded to an increase in QALYs and a decrease in costs from the base case. These points represent situations in which the base case is dominated; the patient's expected QALYs increase, and the expected costs decrease relative to no treatment. Only male patients with high adherence had a slight increase in expected costs from the base case when generic statins were considered. This was likely because these patients paid for more medication than those with medium or low adherence. It is ideal for patients to improve their adherence to high adherence from medium or low adherence to improve their expected QALYs even though there is an increase in costs. We also observed a larger potential increase in expected QALYs for male patients with both generic and branded statins. This was likely because men are at a higher risk for stroke and CHD events and therefore benefit more from statins at earlier ages.

When patients increased their level of adherence, their cost of treatment increased and their expected cost of events decreased (along with an increase in QALYs). Three of the 4 graphs (Figures 3 and 4) show increasing costs coupled with increasing QALYs. Thus, increased cost of medication outweighed the decreased expected costs of events. For men with low-cost statins, we observed the costs for low, uncertain, and medium adherence to be nearly constant; thus, we infer that the increase in cost of medication is nearly equal to the decrease in expected costs associated with events. This was likely because men benefitted from treatment more than women because they were at a higher risk for events earlier in life. Recall that the results presented in Figures 3 and 4 are an average across health states. The changes in cost were not equal for each individual health state across the 3 adherence cases, but the average was nearly equal.

Effects of Discounting

To obtain the results presented above, we used a 97% yearly discount factor. This is consistent with standard practice in the health policy literature.[47] We then extracted undiscounted expected future QALYs. Thus, the values in the figures are discounted expected costs and undiscounted expected QALYs. We observed that discounting greatly diminishes the value of rewards in the distant future. Because statins are a preventative medication, many of the benefits (i.e., preventing strokes and CHD events) are not realized until many years

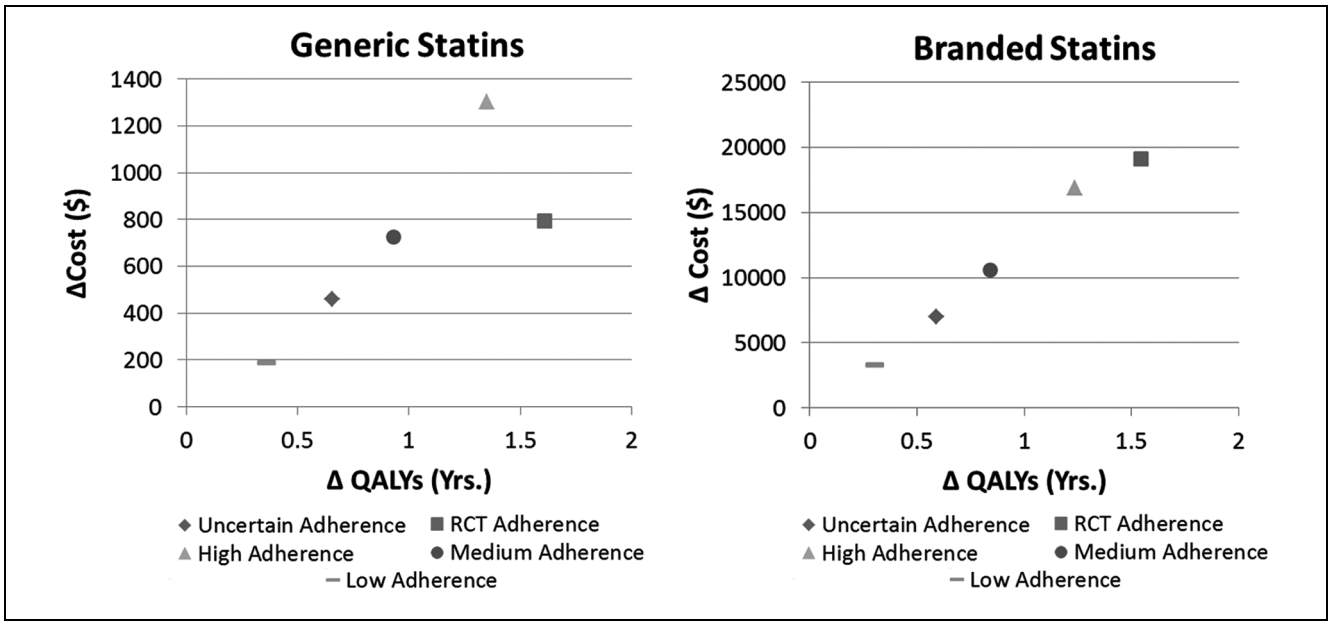

Figure 3 Changes in expected costs and quality-adjusted life years (QALYs) for women from age 40 compared to no treatment. Randomized controlled trial (RCT) adherence represents a 24% decrease in total cholesterol (TC) and an 8% increase in high-density lipoprotein cholesterol (HDL), whereas high, medium, and low adherence represent a 25.2%, 18.1%, and 8.2% decrease in TC, respectively, with no change in HDL. The uncertain adherence case corresponds to patient adherence following the Markov process outlined in the ''Adherence'' section.

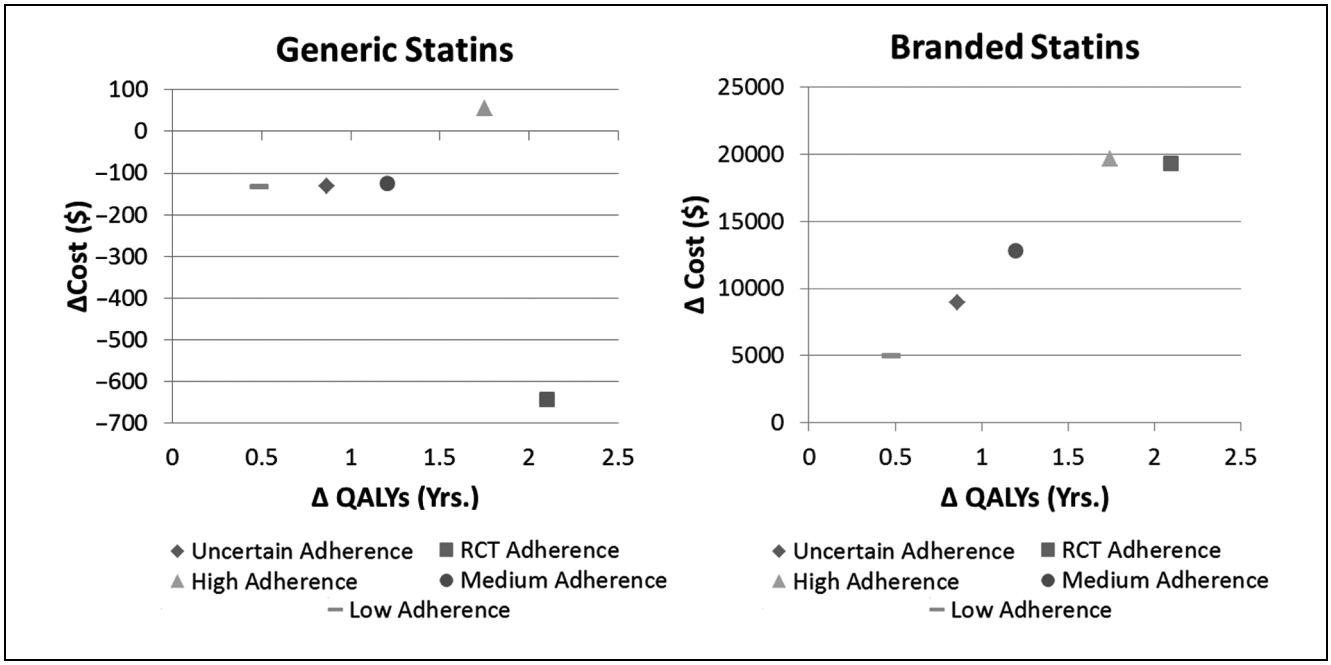

Figure 4 Changes in expected costs and quality-adjusted life years (QALYs) for men from age 40 compared to no treatment. Randomized controlled trial (RCT) adherence represents a 24% decrease in total cholesterol (TC) and an 8% increase in high-density lipoprotein cholesterol (HDL), whereas high, medium, and low adherence represent a 25.2%, 18.1%, and 8.2% decrease in TC, respectively, with no change in HDL. The uncertain adherence case corresponds to patient adherence following the Markov process outlined in the ''Adherence'' section.

into the future. Thus, we chose to compare the undiscounted expected QALYs to see the full benefit of adherence improvement.

DISCUSSION

Our study objective was to determine the effect of patient adherence on optimal statin initiation policies. We measured this by the total change in expected costs and improvement of expected QALYs over the patient's lifetime. We observed that patients who take less than their prescribed dosage of medication received a smaller percentage change in TC, and we found that in the long term, only 25% of patients remain highly adherent. Several other studies also indicate that long-term adherence to statin treatment is poor.[10,24,48,49] Furthermore, recent studies conclude that it is difficult to predict future adherence.[24] These results support the need for incorporating the possibility of suboptimal adherence into the decision-making process and the need for patient intervention programs for improving adherence to statin treatment.

In an effort to quantify the potential impact of an intervention on expected QALYs and cost, we found the change in expected QALYs and cost for each statin adherence assumption relative to the base case of no treatment. We found that highly adherent women can improve their expected QALYs up to 1.5 years. Women with low adherence could potentially improve their expected QALYs by more than 1 year by improving their adherence from low to high through interventions. The base case of no treatment was almost always dominated for men taking generic statins, with increases in expected QALYs and decreases in expected costs. We observed that highly adherent men could improve their expected QALYs by 2 years and by as much as 1.5 years by improving their adherence from low to high. The greater difference in expected QALYs for the men was reasonable because they are at a higher risk for strokes and CHD events than are women.

Rosen and others[50] point out the need for modeling of suboptimal medication adherence in cost-effectiveness analyses. They highlight that suboptimal adherence must be included for models to more closely reflect reality. The work of Cherry and others[51] and Nichol and others[52] is an example of one of a small number of cost-effectiveness models including adherence. They estimate the incremental cost per life year gained associated with various levels of adherence to statins and antihypertensive medications. Our study is novel in several ways. First, we considered the costs and QALYs of statin treatment in the context of optimal initiation by incorporating our adherence model into an MDP model. Second, we estimated the percentage change in TC with each adherence level, whereas the other 2 studies assumed a linear association between adherence and efficacy. To our knowledge, these are the first estimates of this relationship.

Finally, we used our model to evaluate the influence of uncertain adherence on the optimal start time and the potential benefits of adherence-improving interventions. From our results, it can be argued that initiation of generic statins provides value to the health system because they resulted in lower costs for men and greater QALYs over no statin treatment. For women, initiation of generic statins was also beneficial because there was improvement in QALYs with a small increase in costs over the base case. Although the expected cost for initiating branded statins was higher, initiating these drugs also provides additional QALYs from no treatment. Our study validated the decision to undergo statin treatment and to improve adherence of those patients who have already begun treatment through the use of interventions. By taking these steps, patients were able to noticeably increase their expected QALYs, by 0.5 to 2 years, depending on level of adherence. Thus, the potential benefits of an effective adherence-improving intervention were significant.

Our article addresses some important gaps in the literature. We proposed a decision model that considered the uncertain future adherence of diabetes patients and attempted to reduce its impact through better decision making. We found that the optimal time to initiate statins may be significantly later in life when uncertain adherence is considered. We provided results for upper bounds on the total benefit that could be gained from adherence-improving interventions. We hope to extend our research to include finding the optimal timing of adherence-improving interventions to balance their costs and benefits.

LIMITATIONS

Our study has some limitations. The Mayo Clinic data were derived from a relatively homogeneous population that may or may not be representative of the broader population. This population is also relatively young and healthy; it is possible that the calculated event probabilities are conservative. The

UHC population is broad and represents both large and small employers across a large geographic section of the United States; however, these commercial claims data may be biased toward healthy workers. These workers may be unusually loyal to the insurer and obtain care from an unusual set of providers with linked electronic laboratory records. Our use of claims data to estimate patient adherence is also a limitation because these data did not provide complete information about how often a patient took his or her medication. Our condition that patients must have filled at least 1 statin prescription in each of the 4 years after initiation to be included in the adherence study biased our study to more adherent patients. Nevertheless, it was necessary to eliminate patients who discontinued statins due to intolerance. Consistent with past studies,[53–55] we assumed that adherence follows a Markov process. However, it may be interesting to more rigorously validate this assumption as a future research direction. Finally, we assumed that after initiation, patients remained on statins the rest of their lives. We failed to model the patients who successfully made lifestyle changes that would result in discontinuation of statins. This consideration is left for future work.

APPENDIX

Definitions of Transition Probabilities

In the following section, we explain the transition probabilities summarized in the "Natural History Model" section in greater detail. At epoch $t = 1, \ldots, T-1$, death from other causes occured with probability $p_t(D_O)$. Otherwise, if the patient was in state $(\ell,\ m) \in \mathcal{L} \times M$, a nonfatal stroke or CHD event occured with probability $\pi_t^s(\ell,m)$ and $\pi_t^C(\ell,m)$, respectively, which depended on the patient's age, health state, and other risk factors such as race and gender. Fatal stroke and CHD events occured with probability $\overline{\pi_t^s}(\ell,m)$ and $\overline{\pi_t^C}(\ell,m)$, respectively. Given that the patient was in health state $\ell \in \mathcal{L}$, the probability of being in state ℓ' in the epoch following is denoted by $q_t(\ell'|\ell)$. The probabilities of nonfatal events, $\pi_t^s(\ell,m)$ and $\pi_t^C(\ell,m)$, were included in $q(\ell'|\ell)$. Given that the patient was in state (ℓ,m) at epoch t, the probability of moving into one of the absorbing states $d \in D$ at epoch $t+1$ is denoted by $p_t(d,m|\ell,m)$, where

$$p_t(d,m|\ell,m) = \begin{cases} p_t(D_O) & \text{if } d = D_O, \\ \overline{\pi_t^C}(\ell,m) & \text{if } d = D_{CHD}, \\ \overline{\pi_t^s}(\ell,m) & \text{if } d = D_S, \end{cases} \tag{5}$$

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

$$p_t^W(\ell',m'|\ell,m) = \begin{cases} [1 - \sum_{d \in D} p_t(d,m|\ell,m)]q_t(\ell'|\ell) & \text{if } m = m' \text{ and } \ell,\ell' \in \mathcal{L} \text{ and } d \in D, \\ p_t(d,m|\ell,m) & \text{if } m = m' \text{ and } \ell \in \mathcal{L}, \ell' = d \in D, \\ 1 & \text{if } \ell = \ell' = d \in D, \\ 0 & \text{otherwise.} \end{cases} \tag{6}$$

$$p_t^I(\ell',m'|\ell,m) = \begin{cases} [1 - \sum_{d \in D} p_t(d,1|\ell,1)]q_t(\ell'|\ell) & \text{if } m = 0, m' = 1 \text{ and } \ell,\ell' \in \mathcal{L} \text{ and } d \in D, \\ p_t(d,1|\ell,1) & \text{if } m = 0, m' = 1,\ \ell \in \mathcal{L} \text{ and } \ell' = d \in D, \\ 0 & \text{otherwise.} \end{cases} \tag{7}$$

Thus, $q(\ell'|\ell)$ are transitions over living states, conditioned on surviving that period. Transition probabilities $q_t(\ell'|\ell)$ were estimated from the Mayo Clinic data set,[15] the probabilities $p_t(D_O)$ were based on the US Centers for Disease Control and Prevention tables, and the probabilities $\pi_t^C(\ell,m)$, $\pi_t^s(\ell,m)$, $\overline{\pi_t^s}(\ell,m)$, and $\overline{\pi_t^C}(\ell,m)$ were based on the UKPDS risk engine model. The stroke and CHD deaths were omitted when computing the probability of death from other causes.

Adherence Transition Probabilities by Gender

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

Initial adherence state probabilities:

$$\mathbf{p}_{\text{males}} = (0.084, 0.155, 0.251, 0.510), \tag{8}$$

$$\mathbf{p}_{\text{females}} = (0.101, 0.177, 0.267, 0.455). \tag{9}$$

Transition probabilities for adherence states:

$$\mathbf{p}_{\text{males}} = \begin{bmatrix} 0.781 & 0.107 & 0.085 & 0.027 \\ 0.486 & 0.203 & 0.217 & 0.094 \\ 0.188 & 0.147 & 0.392 & 0.273 \\ 0.027 & 0.043 & 0.176 & 0.754 \end{bmatrix}, \tag{10}$$

$$\mathbf{p}_{\text{females}} = \begin{bmatrix} 0.795 & 0.105 & 0.079 & 0.022 \\ 0.512 & 0.206 & 0.209 & 0.073 \\ 0.211 & 0.163 & 0.388 & 0.238 \\ 0.028 & 0.052 & 0.209 & 0.711 \end{bmatrix}. \tag{11}$$

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