Optimizing the Start Time of Statin Therapy for Patients with Diabetes

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Background. *Clinicians often use validated risk models to guide treatment decisions for cardiovascular risk reduction. The most common risk models for predicting cardiovascular risk are the UKPDS, Framingham, and Archimedes models. In this article, the authors propose a model to optimize the selection of patients for statin therapy of hypercholesterolemia, for patients with type 2 diabetes, using each of the risk models. For each model, they evaluate the role of age, gender, and metabolic state on the optimal start time for statins.* ***Method***. *Using clinical data from the Mayo Clinic electronic medical record, the authors construct a Markov decision process model with health states composed of cardiovascular events and metabolic factors such as total cholesterol and high-density lipoproteins. They use it to evaluate the optimal start time of statin treatment for different combinations of cardiovascular risk models and patient attributes.* ***Results***. *The authors find that treatment decisions depend on the cardiovascular risk model used and the age, gender, and metabolic state of the patient. Using the UKPDS risk model to estimate the probability of coronary heart disease and stroke events, they find that all white male patients should eventually start statin therapy; however, using Framingham and Archimedes models in place of UKPDS, they find that for male patients at lower risk, it is never optimal to initiate statins. For white female patients, the authors also find some patients for whom it is never optimal to initiate statins. Assuming that age 40 is the earliest possible start time, the authors find that the earliest optimal start times for UKPDS, Framingham, and Archimedes are 50, 46, and 40, respectively, for women. For men, the earliest optimal start times are 40, 40, and 40, respectively.* ***Conclusions***. *In addition to age, gender, and metabolic state, the choice of cardiovascular risk model influences the apparent optimal time for starting statins in patients with diabetes.* ***Key words:*** *diabetes; statins; Markov decision process.* ***(Med Decis Making 2009;29:351–367)***

Diabetes is one of the major underlying causes of stroke and coronary heart disease (CHD). According to the American Diabetes Association, there are currently 20.8 million children and adults in the United States who have diabetes (approximately 7% of the population).[1] Of the affected population, approximately 90% have type 2 diabetes. Currently, several risk models exist to predict the probability of complications related to type 2 diabetes. These models serve as a guide to clinicians for selecting the type of intervention and establishing the aggressiveness of treatment. They also motivate patients to adhere to prescribed treatment regimens. The most common models, which are the focus of this article, are cardiovascular risk models. One of these models has been calibrated based on data from the United Kingdom Prospective Diabetes Study (UKPDS).[2–4] Another, the Framingham model, is based on a North American population.[5] A third model, Archimedes, computes the risk of complications based on an aggregation of clinical studies using Monte Carlo simulation and other mathematical modeling methods.[6,7]

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All of the above referenced models predict the risk of complications; however, it is unclear if their predictions are similar and whether the differences would lead to clinically relevant differences in treatment. The models compute the probability of complications, such as myocardial infarction and stroke, but it is not clear how to use this information to make better decisions. For example, lipid abnormalities are commonly associated with diabetes and have been shown to have a strong relationship with all forms of vascular disease, but the optimal time to initiate treatment is commonly debated among physicians.[8–10] There are also a number of studies that identify overprescribing and underprescribing of statins, such that often patients who are most likely to benefit from statins are not prescribed statins, whereas patients who may incur only marginal benefits are prescribed statins.[11–13]

Whether or not to initiate statin treatment is an important societal decision, considering the 2006 total spending on statins was estimated at over $20 billion in the United States alone.[14] Because patients with type 2 diabetes are at greater risk of macrovascular complications, the importance of statin treatment is amplified for this portion of the population. In this article, we use the above referenced risk models to estimate the optimal treatment decision: if and when to initiate statins for the treatment of lipid abnormalities. Our study has two main purposes: first, to investigate how the choice of cardiovascular risk model affects treatment decisions and, second, to contrast the optimal treatment decision among patient attributes, including age, gender, and metabolic state.

METHODS

We use a finite-horizon Markov decision process (MDP) to find the optimal statin start time based on a patient's health state over the course of his or her lifetime. Such models have applications in other contexts related to medical treatment decisions (see Schaefer and others[15] for a review). Our model considers 2 important and competing criteria to select the start time: 1) expected future quality-adjusted time spent in a healthy state relative to 3 competing terminal states (death from coronary heart disease, death from stroke, and death from other causes) and 2) the annual cost of statin treatment and the cost associated with the treatment of cardiovascular events. With regard to the latter, we conduct our analysis from the perspective of a third-party payer.

In our model, patients are defined by major risk factors for diabetes-related complications, including gender, height, weight, smoking status, blood pressure, cholesterol, HbA1c, and history of stroke and CHD. We assume all patients are nonsmokers and that their height and weight do not change as they age. For the purpose of our model, we define a patient's *metabolic state* at a given age as his or her systolic blood pressure, HbA1c, total cholesterol, and high-density lipoprotein (HDL). We assume that a patient's metabolic state changes over time as he or she ages. Systolic blood pressure (SBP) and HbA1c are modeled as a function of age based on fitting observational data using *cubic splines* for a cohort of diabetes patients treated at the Mayo Clinic (see Appendix A for details of the spline fitting). Total cholesterol and HDL are the most significant factors in our model because the action in our MDP model (initiating statin treatment) directly affects total cholesterol and HDL levels. To account for uncertainty in how a patient's cholesterol will change over time, we assume that total cholesterol and HDL follow a Markov process. A patient's cholesterol state is defined by whether he or she is in a high, medium, or low total cholesterol and HDL state, and patients transition through these states probabilistically as they age (see Appendix B for the definition of total cholesterol and HDL states and complete details on estimating transition probabilities).

We make a number of assumptions about the decision whether to initiate statin treatment. First, our model assumes that this decision is revisited periodically, and the current state information is used to determine whether to initiate statin treatment or to wait for the next decision epoch. We assume that once initiated, statin treatment is not reversed (i.e., it is a onetime decision, and the patient will remain on statins with perfect adherence). Furthermore, we assume patients having a stroke or CHD event in a decision epoch who are not on statins automatically go on statins independent of their risk of future events. This latter assumption is reasonable based on current clinical guidelines. In our model, we assume that the effects of treatment are to lower total cholesterol and increase HDL, and these effects are known in advance of initiating therapy and immediately alter the patients' total cholesterol and HDL state. The change is represented by a percentage change (i.e., the changes are proportional to the patient's current total cholesterol and HDL measurement).

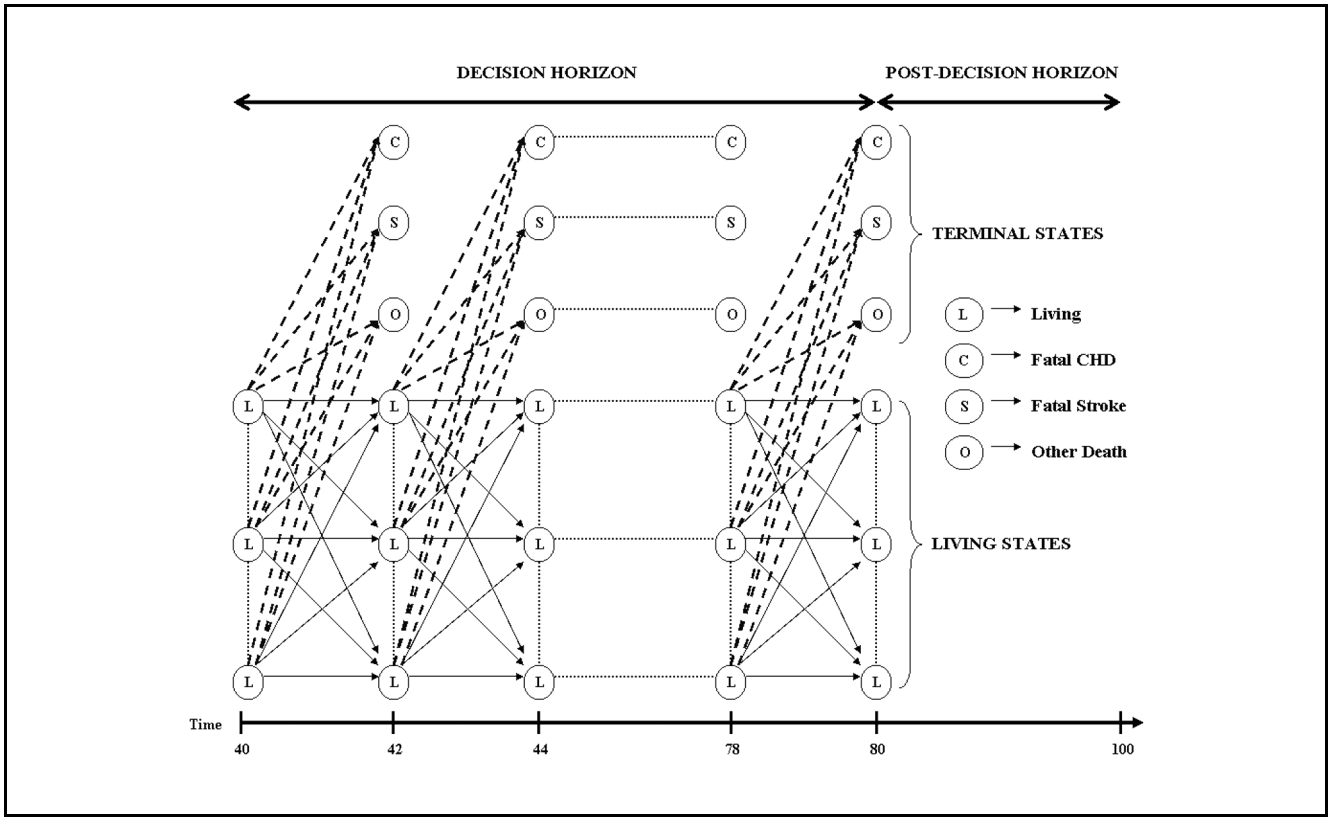

Figure 1 Illustration of state transitions within living states and from living states to terminal states in the Markov decision process (MDP) model.

Based on the above definition of states and actions, our Markov decision process defines the optimal actions (i.e., whether to initiate statins for a patient in a given metabolic state at a given age) as those actions that maximize discounted expected rewards minus treatment costs for all future life years. The decision-making process is defined as follows. Over time, patients transition with certain probabilities through living states and eventually end in a terminal state corresponding to a fatal stroke or CHD event or some other cause of death. Figure 1 is a schematic example of this Markov process. We assume the patient begins in a living state at age 40 and at each period transitions to a new state with probabilities governed by 2 sources. The first, terminal states, is defined by dashed lines in the figure. The probability of entering a terminal state is based on one of the cardiovascular risk models (UKPDS, Archimedes, or Framingham). The probability of transitioning to different living states, denoted by solid lines, is based on clinical data (see ''Data and Study Population'' for a description of the study population) describing longitudinal changes in a patient's metabolic states.

Figure 1 is a simplification of the complete problem that includes 324 living states corresponding to different metabolic states and stroke and CHD history. The number 324 is derived from the product of 3 total cholesterol states (high, medium, and low), 3 HDL states, 6 stroke states (no stroke and 1–5 nonfatal strokes), and 6 CHD states (i.e., $3 \times 3 \times 6 \times 6 = 324$).

At a given living state, if the patient has not initiated statin treatment, then the decision maker may choose between 2 options: 1) initiate statin therapy and 2) delay the decision for one more period. If the decision maker chooses to initiate therapy, then the discounted value of expected rewards minus costs associated with all future quality-adjusted life years is obtained, and no further decisions are available. On the other hand, if the decision maker elects to delay the decision, then the patient progresses to a new metabolic state in the next period from which the same decision is made—that is, initiate statins or delay the decision (provided they do no not enter

a terminal state). The transition probabilities between living states and the cost and reward model (described below) both influence the optimal decision. For instance, high rewards for future years of life may encourage initiating statin therapy at an early age, even though the risk of stroke and CHD may be relatively low. On the other hand, high costs of statin treatment discourage starting statins at an early age because the high costs offset the potential future rewards gained.

Cost and Reward Model

Each state has an associated cost and reward. We define the notation we use in Table 1. In each period t, the current state of the patient is indexed by s_t, which maps to a defined set of patient attributes: total cholesterol, HDL, number of strokes, and CHD events in the patient's medical history. The objective function consists of rewards, $R(s_t)$, based on quality-adjusted life years (QALYs) and the costs that are shown in Table 1.

The cost parameters in Table 1 fall into 3 categories: 1) costs directly associated with a stroke or CHD event, 2) annual costs of long-term follow-up care for patients who have had a stroke or CHD event, and 3) pharmacy cost of statin treatment. Costs of type (1) are incurred in the period in which the stroke or CHD event occurs. Costs of type (2) are incurred throughout the remainder of the model horizon. Costs (3) are incurred starting at the point at which statin treatment is initiated. In our model, we assume that patients may have multiple stroke and CHD events. To account for this, we reduce the expected benefits from future years. For instance, when a patient has a CHD event, his or her future years of life are reduced from 1.0 (for a year of perfect health) to 0.93. Thus, the utility decrement factor reflects the reduced quality of future years of life after a stroke or CHD event. For patients incurring multiple stroke or CHD events, we assume that the utility factor decreases by one half for each future event (i.e., the impact of multiple events on quality of life is highest for the first event and then lower for future events).

Detailed Model Formulation

Given that there is uncertainty in a patient's future health state, the goal of our MDP model is to use available information to make the optimal decision at each decision epoch and state. The optimal decision is the one that maximizes the expected long-run future rewards minus costs averaged over all possible future states. The action in our model, denoted by $a(s_t)$, represents the decision to either initiate statin treatment or to delay the decision until the next decision epoch at the beginning of period $t+1$ and can be represented as the following binary decision variable.

$$a(s_t) = \begin{cases} 1 & \text{if statin treatment is initiated} \\ 0 & \text{if statin treatment is delayed} \end{cases} \quad (1)$$

Because the action is a onetime irreversible decision, it may be taken only once throughout the planning horizon. Thus, if $a_{t'} = 1$, then $a(s_t) = 1, \forall t > t'$. The state s_t indexes the possible health state of the patient at period t, including both living and terminal states. The reward function at each period t depends on the state s_t and can be written as follows:

$$r(s_t, a(s_t)) = N^D\left[R(s_t) - \left(CF^S(s_t) + CF^{CHD}(s_t)\right) - a(s_t)C^{ST}\right] - \left[C^S(s_t, a(s_t)) + C^{CHD}(s_t, a(s_t))\right]$$

for $t = 1, \ldots, T-1$, where N^D denotes the number of years in a decision epoch (e.g., if decision epochs occur every 2 years, then $N^D = 2$). The rewards for the final period in the decision horizon, T, can be written as:

Table 1 Definition of Parameters Used in the Markov Decision Process Model, Including State Parameters, Actions, Costs, and Rewards

Notation	Definition
t	Time index for discrete decision epochs
s_t	Index for states s_t at time period $t = 1,\ldots,T$
$a(s_t)$	Statin treatment decision (action) at period $t = 1,\ldots,T$
$p(s_{t+1}\|s_t, a(s_t))$	State transition probability at time period t, given the state s_t and action $a(s_t)$
$N^s(s_t)$	Number of strokes in a patient's medical history in state s_t
$N^{CHD}(s_t)$	Number of CHD events in a patient's medical history in state s_t
$C^s(s_t)$	Onetime treatment cost of stroke occurring in period t
$C^{CHD}(s_t)$	Onetime treatment cost of coronary heart disease (CHD) event occurring in period t
$CF^s(s_t)$	Annual follow-up care cost of stroke in period t
$CF^{CHD}(s_t)$	Annual follow-up care cost of CHD event in period t
$C(s_t)$	Annual cost of statin treatment in period t
$R(s_t)$	Monetary value of quality-adjusted life years

$$r(s_T, a(s_T)) = N^D\big[R(s_T) - \big(CF^S(s_T) + CF^{CHD}(s_T)\big) - a(s_T)C^{ST}\big] - \big[C^S(s_T, a(s_T)) + C^{CHD}(s_T, a(s_T))\big] + E[PDHR|s_T, a(s_T)]. \quad (2)$$

The last term in (2), $E[PDHR|s_T, a(s_T)]$, is the post–decision horizon expected reward (see Appendix C for a detailed description of how this is estimated). The time horizon is assumed to be finite in length and composed of 2 parts: a decision horizon, and a post–decision horizon. We assume that the statin treatment decision may be made at any decision epoch in the decision horizon; however, the costs and rewards for living beyond the decision horizon continue to accumulate beyond the end of the decision horizon. This offers the advantage of reducing the number of decision points without ignoring the rewards from additional years of life. For example, from the perspective of statin choice decisions, it is reasonable to assume that the choice to initiate statin treatment would be made prior to age 80 or not at all.

Given the above definition of rewards, the goal is to determine the action, a_t, at each state, s_t, to maximize the following value function.

$$v(s_t) = E_{\vec{s}}\Big[\sum_{t=1}^{T}(\lambda^{N^D t})r(s_t, a(s_t))\Big]. \quad (3)$$

The objective function at each future period is discounted by $\lambda \in [0, 1]$ to reflect the reduced value of rewards for future years of life and treatment costs. Based on (3), the recursive optimality equations can be written as follows:

$$v(s_t) = \lambda^{N^D} \max\Big[r(s_t, a(s_t)) + \sum_{\forall s_{t+1}} p(s_{t+1}|s_t, a(s_t))v(s_{t+1})\Big]. \quad (4)$$

Using backward induction, the optimal treatment action can be computed efficiently at each state, s_t. The optimal action is selected by choosing between the expected discounted future rewards of a) the patient initiating statin treatment and b) the patient waiting until the next decision epoch. Starting at the last decision epoch $t = T$ and moving backwards through time (from the end of the horizon to the beginning), the optimal future actions are known at each decision epoch, leaving only the current decision to be made. (See Puterman[16] for a detailed discussion of finite horizon MDPs.)

Data and Study Population

The data used to estimate the transition probabilities and other patient-level inputs are based on a longitudinal medical record for patients at the Mayo Clinic. The medical record, the Diabetes Electronic Management System (DEMS), was specifically designed to track diabetes patients at the Mayo Clinic,[17] permitting direct entry of patient information by the provider during the patient encounter without intermediate forms or paper records. The Mayo Clinic DEMS data are available for the years 1993 to 2005 and include detailed results of laboratory measurements during the period, including blood pressure, HbA1c, and cholesterol. The population for this study was identified as those age 40 years and older and with at least 10 years of follow-up after the initial encounter. Only participants who provided research authorization are included in the study. Baseline characteristics for the study population are presented in Table 2. Samples are well distributed for most ages, with an average sample of 140/year for total cholesterol and HDL (for white male and female patients). At the earliest and latest ages (40–44 and 76–80), the sample size is lower, with an average of 50 samples for women and 80 for men, respectively.

Table 2 Baseline Characteristics for the Study Population, Including Mean and Variance

Patient Attribute	Study Cohort (N = 663)
Age	52.46 (8.83)
Years with diabetes	3.24 (5.33)
% Female	39.67
High-density lipoprotein	43.65 (11.58)
Low-density lipoprotein	126.98 (37.31)
Total cholesterol	216.27 (51.61)
Systolic blood pressure	139.11 (19.75)
HbA1c	8.01 (2.38)

In the next section, we compute results for 2 patients: a white man and woman. The base case assumptions for the 2 cases are provided in Table 3. The patients are assumed to be nonsmokers with no CHD or stroke history and newly diagnosed with type 2 diabetes at age 40. Death from other causes, $P(FO|s_t, a(s_t))$, is based on mortality rate tables[18] and computed as the aggregate probability of death from all causes minus probabilities of death due to stroke and CHD. The time horizon ranges from 40 to 100 years of age, with the decision horizon from 40 to 80. The decision to initiate statin treatment may be made at 2-year increments, resulting in 20 decision epochs. We assume that the effects of statins are to reduce total cholesterol by 24% and HDL by 8%.[19,20]

Table 3 Base Case Assumptions Regarding Model Parameters for Male and Female Test Patients

Parameter Type	Parameter Definition	Value	Source
Patient attributes	Male (height, weight)	(5′ 9″, 196 lb)	Centers for Disease Control and Prevention[23]
	Female (height, weight)	(5′ 4″, 163 lb)	Davis and others[3]
	$P(FO\|s_t, a_t)$	Age and gender dependent	National Center for Health Statistics[18]
Clinical attributes	Blood pressure	Spline fit	Appendix A
	HbA1c	Spline fit	Appendix A
	Total cholesterol	Markov process	Appendix B
	High-density lipoprotein (HDL)	Markov process	Appendix B
Cost inputs	C^S	$11,161	Thom and others[24]
	C^{CHD}	$16,085	Thom and others[24]
	C^{FS}	$1664	Thom and others[24]
	C^{FCHD}	$2576	Thom and others[24]; Russell and others[25]
	C^{ST}	$713	Red Book[26]
	R	$50,000	
	$1-\lambda$	3%	
Utility decrements	$d^{CHD}(1)$	0.07	Clarke and others[27]; Tsevat and others[28]
	$d^{s}(1)$	0.21	Clarke and others[27]; Tengs and others[29,30]; Gage and others[31]

Unless stated, parameters are the same for men and women.

We use each of the cardiovascular risk models referenced earlier for the transition probabilities from living states to stroke and CHD event states, including both the occurrence of fatal and nonfatal stroke and CHD. Predicted probabilities for the Framingham and UKPDS models were calculated by programming the published equations.[4,21,22] For the case of Archimedes, the Archimedes Diabetes PHD (Personal Health Decisions) Web-based risk engine was used (www.diabetes.org/diabetesphd). The same risk parameters used for UKPDS and Framingham were used for Archimedes (i.e., we assume all models have access to the same amount of information about the patient). As a consequence, we ignore the following optional information that may be used by Archimedes.

- Patient's family history of cardiovascular diseases
- Diastolic blood pressure
- Low-density lipoprotein (LDL) cholesterol
- How many times a year a patient visits a doctor for checkups

In some cases, additional (nonoptional) information had to be provided to Archimedes. In these instances, we made the following assumptions:

- Patient engages in moderate levels of physical activity several times a week and/or exercises vigorously at least once a week
- Patient is not an aspirin user currently
- Patient's fasting plasma glucose (FPG) value at the time of diagnosis is unknown
- We do not know whether the patient was experiencing any of the following symptoms when diagnosed: frequent urination, excessive thirst, extreme hunger, unusual weight loss, increased fatigue, or blurry vision
- We do not know whether the patient was having a foot exam at each office visit
- We do not know whether the patient was having a dilated eye exam every year

RESULTS

Results for the optimal decision as a function of age and health state are illustrated in Figures 2 and 3 for the base case in Table 3. The *y*-axis of the figures represents the living states, in which the patient has no history of stroke or CHD, corresponding to the 9 cholesterol states (3 total cholesterol × 3 HDL) representing high (H), medium (M), or low

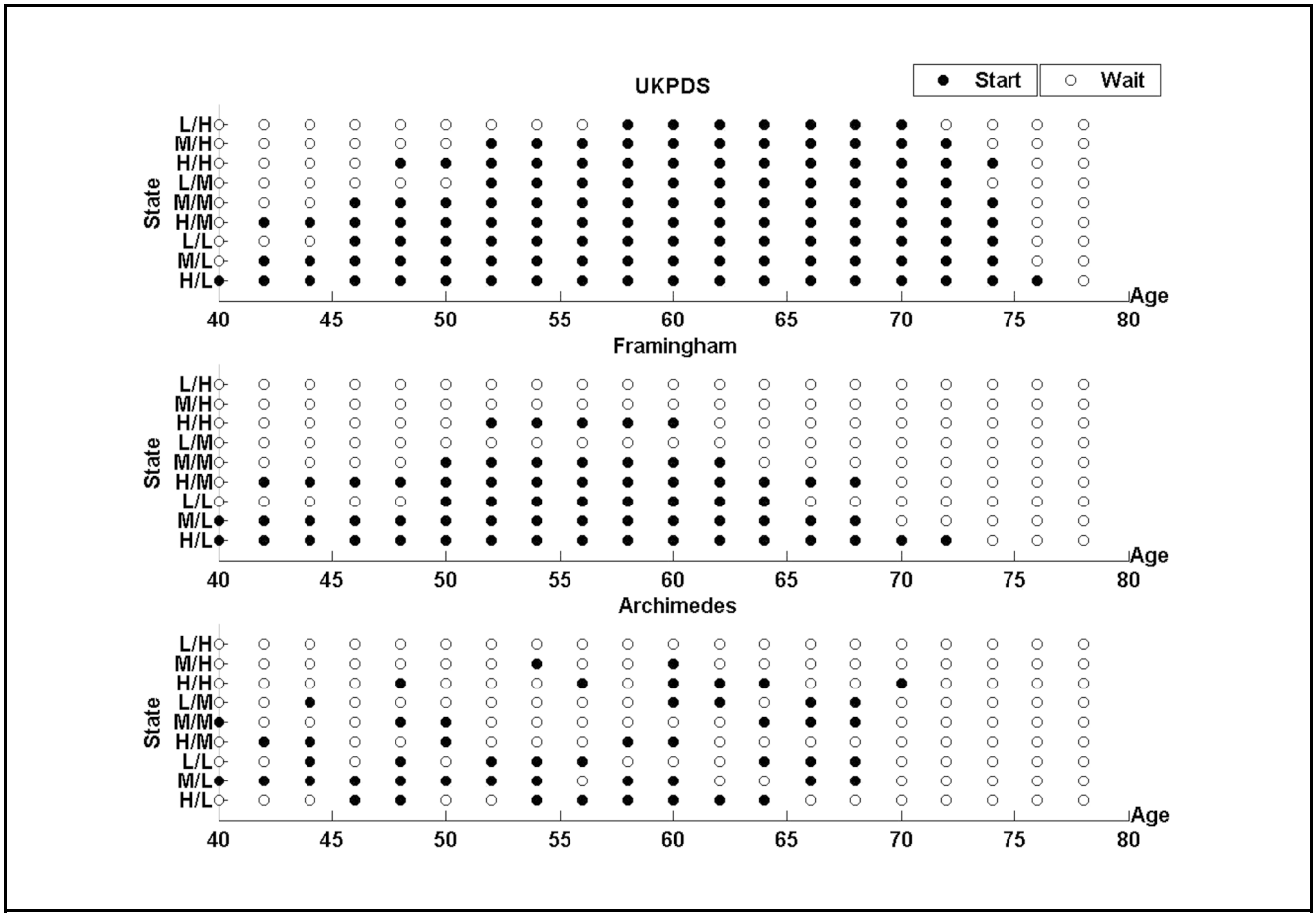

Figure 2 Illustration of optimal statin start time for each state at each age for a base case white male test subject. Solid circles denote the decision to start statins, whereas open circles denote the decision to defer the decision until the following period. The age at which statins are started (x-axis) depends on the total cholesterol/high-density lipoprotein (HDL) state (y-axis).

(L) values for each measure (e.g., H/L denotes high total cholesterol and low HDL).

Comparing the results based on the UKPDS and Framingham models for the male patient in Figure 2, we find that the UKPDS results generally recommend an earlier statin start time than the Framingham results. In fact, the Framingham results recommend that statins should never be initiated for 3 of the 9 metabolic states. These results are consistent with the reduced probability of complications associated with the Framingham model.[32]

The results for Archimedes have a less smooth structure and appear to compare better to Framingham than to UKPDS because the model does not recommend initiating statin treatment for all metabolic states and tends to recommend later start times for some states. The less smooth structure can be attributed to at least 2 factors. First, Archimedes estimates the probability of events through statistical sampling, and there is some statistical error associated with each sample. Although such error is common to all models, it is less apparent for UKPDS and Framingham because they are fit to a smooth (Weibull) distribution. A second potential reason may be that the Archimedes model combines results from several clinical trials. Therefore, presumably there is greater genetic and societal diversity leading to additional variation in the aggregate estimate of probabilities of complications.

Figure 3 illustrates that statins tend to be recommended at later ages for women than for men under all risk models. For UKPDS, 4 of the 9 states do not initiate statins at any age. The results for the woman under the Framingham model tend to be earlier and more common starts than for UKPDS, which is in contrast to the results for the man, in whom the

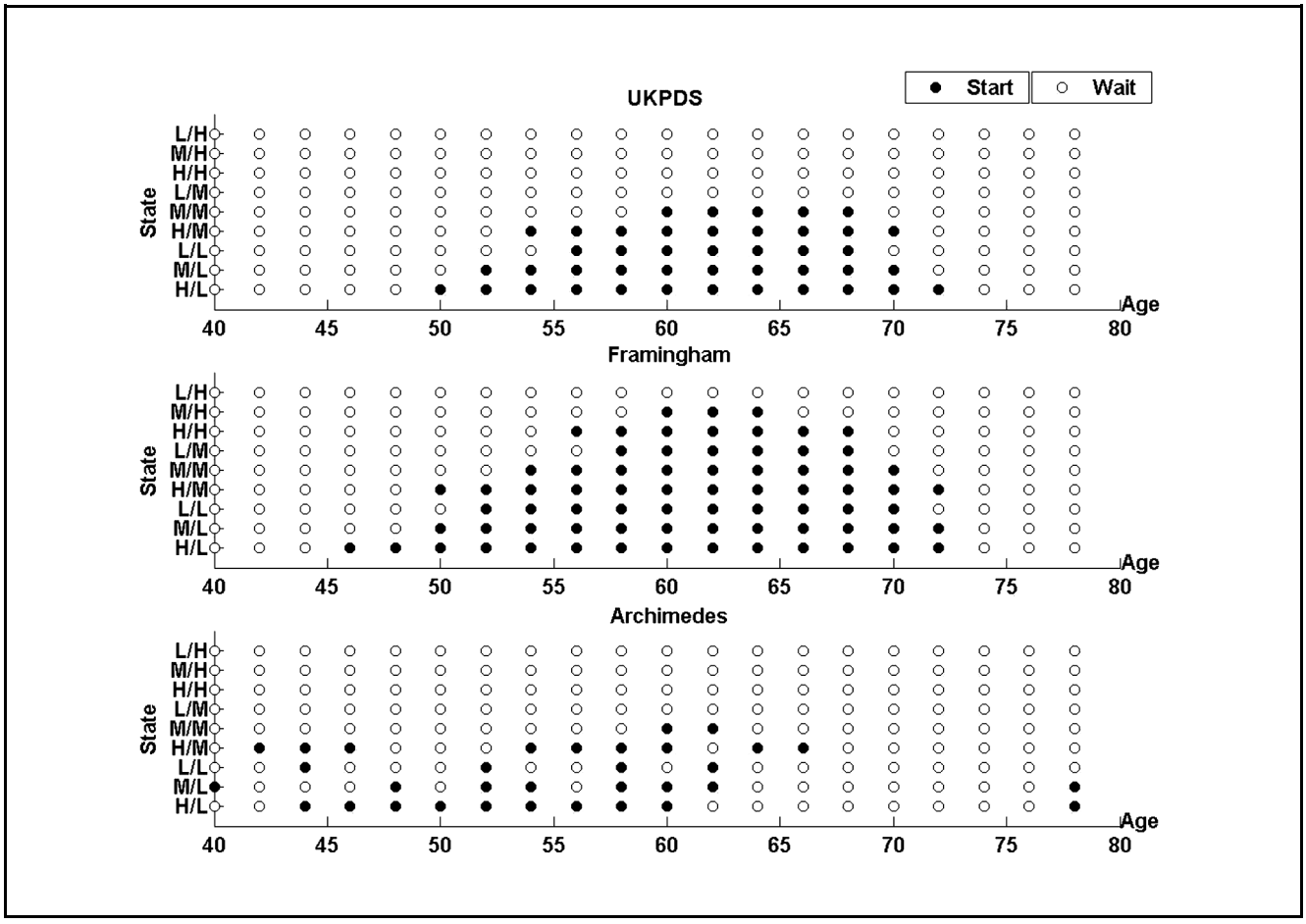

Figure 3 Illustration of optimal statin start time for each state at each age for a base case white female test subject. Solid circles denote the decision to start statins, whereas open circles denote the decision to defer the decision until the following period. The age at which statins are started (x-axis) depends on the total cholesterol/high-density lipoprotein (HDL) state (y-axis).

opposite was true. Again, the results based on the Archimedes model are more sporadic. Two states have an unexpected start time of 78 years of age, which is presumably an artifact of the uncertainty in point estimates due to Monte Carlo sampling.

Sensitivity analysis was done with respect to annual statin costs and future annual rewards. For statin cost, we consider annual costs of $360, $713, and $1435 (see Red Book[26] for the lowest and highest costs and Thom and others[24] for the medium cost example). For annual rewards, we assume $25,000, $50,000, $75,000, and $100,000. The results in Tables 4 and 5 illustrate that these cost and reward parameters significantly affect start time decisions. Comparing Tables 4 and 5, we find that men generally initiate statin therapy at earlier ages, if at all. The optimal age for men and women to start statin therapy in any given metabolic state is generally decreasing as the annual cost of treatment decreases and as the annual reward (i.e., benefit of future life years) increases. In Table 4, the earliest start time for UKPDS for women in the H/L state ranges from 40 years to never starting. At an annual cost of $1435 and reward of $25,000, it is almost never optimal for any patient to initiate treatment (except for men in the highest risk states under the UKPDS model). Alternatively, at an annual cost of $360 and a reward of $100,000, it is optimal under all risk models to initiate statins at some point and immediately at age 40 for the majority of states (for men, it is always optimal to initiate statins at age 40 under this cost and reward assumption). However, for women, the start time may be as late as age 58.

Table 4 Sensitivity of the Optimal Start Times to the Cost of Statins and Nominal Annual Reward for Future Years of Life for Female Patients

	Total Cholesterol		H			M			L		
	HDL		H	M	L	H	M	L	H	M	L
State Model	Statin Cost per Year ($)	Reward (in 1000s of US Dollars)	Earliest Age to Initiate Statin Treatment for Female Patients								
UKPDS	360	25	58	52	48	*	56	50	*	60	54
		50	48	42	40	52	46	42	58	50	46
		75	44	40	40	46	42	40	52	46	40
		100	40	40	40	44	40	40	46	42	40
	713	25	*	*	62	*	*	*	*	*	*
		50	*	54	50	*	60	52	*	*	56
		75	54	48	44	58	52	46	*	56	52
		100	50	44	40	54	48	42	58	52	46
	1435	25	*	*	*	*	*	*	*	*	*
		50	*	*	*	*	*	*	*	*	*
		75	*	*	56	*	*	62	*	*	*
		100	*	56	52	*	*	54	*	*	58
Framingham	360	25	54	48	44	58	52	48	62	56	50
		50	46	42	40	50	44	40	54	48	44
		75	42	40	40	44	40	40	50	44	40
		100	40	40	40	42	40	40	44	40	40
	713	25	*	60	54	*	*	58	*	*	*
		50	56	50	46	60	54	50	*	58	52
		75	50	44	42	54	48	44	58	52	48
		100	46	42	40	50	44	42	56	48	44
	1435	25	*	*	*	*	*	*	*	*	*
		50	*	*	60	*	*	*	*	*	*
		75	*	56	52	*	62	54	*	*	58
		100	58	52	48	*	56	50	*	60	54
Archimedes	360	25	52	42	44	*	60	40	*	*	42
		50	50	42	44	52	40	40	58	56	42
		75	42	42	44	52	40	40	58	46	42
		100	42	42	44	52	40	40	58	46	42
	713	25	*	*	*	*	*	*	*	*	*
		50	*	42	44	*	60	40	*	*	44
		75	50	42	44	52	56	40	*	56	42
		100	50	42	44	52	40	40	*	56	42
	1435	25	*	*	*	*	*	*	*	*	*
		50	*	*	*	*	*	*	*	*	*
		75	*	*	50	*	*	52	*	*	*
		100	*	42	44	*	*	52	*	*	44

The asterisk indicates that it is never optimal to initiate statin treatment. United Kingdom Prospective Diabetes Study (UKPDS), Framingham, and Archimedes represent the cardiovascular risk models, and H, M, L, denote high, medium, and low cholesterol states, respectively.

Sensitivity to Statin Safety

The long-term effects of statins are not yet fully understood. There is evidence from randomized control trials of both positive and negative effects of statins beyond their influence on cardiovascular disease.[33–38] To investigate the hypothetical influence of safety factors related to long-term statin use, we have performed sensitivity analysis for the specific case of the UKPDS risk model, with annual reward $R = \$50,000$ and statin cost $C^{ST} = \$360$, for both male and female test participants. Our sensitivity analysis is based on a proportional increase in the probability of death from other causes. The results are presented in Tables 8 and 9 in Appendix D. In general, we find that the optimal start time is quite

Table 5 Sensitivity of the Optimal Start Times to the Cost of Statins and Nominal Annual Reward for Future Years of Life for Male Patients

	Total Cholesterol		H			M			L		
	HDL		H	M	L	H	M	L	H	M	L
State Model	Statin Cost per Year ($)	Reward (in 1000s of US Dollars)	Earliest Age to Initiate Statin Treatment for Male Patients								
UKPDS	360	25	44	40	40	50	44	40	54	48	44
		50	40	40	40	40	40	40	44	40	40
		75	40	40	40	40	40	40	40	40	40
		100	40	40	40	40	40	40	40	40	40
	713	25	58	52	48	62	56	52	*	62	56
		50	48	42	40	52	46	42	58	52	46
		75	40	40	40	46	40	40	50	44	40
		100	40	40	40	42	40	40	46	42	40
	1435	25	*	*	64	*	*	*	*	*	*
		50	62	56	50	*	60	54	*	*	60
		75	52	48	44	58	52	48	64	58	52
		100	48	44	40	54	48	42	60	54	48
Framingham	360	25	48	40	40	58	46	40	*	54	46
		50	40	40	40	40	40	40	48	40	40
		75	40	40	40	40	40	40	42	40	40
		100	40	40	40	40	40	40	40	40	40
	713	25	*	*	*	*	*	*	*	*	*
		50	52	42	40	*	50	40	*	*	50
		75	40	40	40	50	40	40	*	46	40
		100	40	40	40	42	40	40	50	42	40
	1435	25	*	*	*	*	*	*	*	*	*
		50	*	*	*	*	*	*	*	*	*
		75	*	*	52	*	*	*	*	*	*
		100	*	46	40	*	*	46	*	*	54
Archimedes	360	25	48	42	46	48	40	40	44	40	44
		50	44	42	40	40	40	40	44	40	40
		75	44	40	40	40	40	40	40	40	40
		100	40	40	40	40	40	40	40	40	40
	713	25	*	*	56	*	*	*	*	*	*
		50	48	42	46	54	40	40	*	44	44
		75	46	42	46	48	40	40	44	40	40
		100	46	42	40	48	40	40	44	40	40
	1435	25	*	*	*	*	*	*	*	*	*
		50	*	*	*	*	*	*	*	*	*
		75	64	42	46	54	64	40	*	60	*
		100	56	42	46	54	40	40	*	44	44

The asterisk indicates that it is never optimal to initiate statin treatment. United Kingdom Prospective Diabetes Study (UKPDS), Framingham, and Archimedes represent the cardiovascular risk models, and H, M, L, denote high, medium, and low cholesterol states, respectively.

sensitive to changes in probability of death from other causes. Small changes of 1% have a minor effect on optimal start time, causing changes of 2 years in only a few states. Larger increases of 10% cause changes of as much as 6 years in a number of states, whereas large changes of 30% to 55% result in the optimal decision changing to one of not initiating statins for any states.

DISCUSSION

Our study provides insight into 2 factors that may be contributing to the disagreement in statin treatment guidelines: 1) differences in cardiovascular risk models and 2) differences in gender and metabolic factors. We found that differences in cardiovascular risk models translated into substantial

differences in optimal start times. In fact, for some metabolic states, the results differed in whether a patient should start statins at all during his or her lifetime. For men, except for a small number of instances, the UKPDS results indicate that statins should be initiated earlier than for Framingham or Archimedes. The opposite is largely true for women, for whom UKPDS results tend to be more conservative about initiating statin treatment. We found that the optimal start times for statins follow a smooth pattern for the UKPDS and Framingham models, whereas the start times based on the Archimedes model do not. This is likely attributable to the fact that Archimedes provides estimates with some degree of statistical error.

The optimal time to initiate statin treatment is also quite sensitive to the annual cost of statins and to the reward for future years of life, which is not surprising. Based on our study, it is clear that patient-specific attributes such as gender, age, and metabolic state should play a role in treatment decisions. It is generally true that the optimal time to initiate treatment for the male test participant is earlier than that for the female participant. Assuming a reward of $50,000 and a treatment cost of $360 (consistent with generic statins), the differences between the highest and lowest risk metabolic states for female patients using UKPDS, Framingham, and Archimedes are 18, 14, and 18 years, respectively. For male patients, the differences for UKPDS, Framingham, and Archimedes are 4, 8, and 4 years, respectively. Assuming a reward of $100,000, on the other hand, results in an optimal start time of age 40 for nearly all metabolic states for both men and women.

LIMITATIONS

The model presented in this article has several limitations. First, our model does not incorporate any negative side effects of statins. Although statins are generally well tolerated, the potential outcomes resulting from long-term use of statins are not yet fully understood. Second, although our model is based on the best available clinical information, some of the cost and reward parameters had varying supporting data. We tried to overcome some of these limitations by conducting sensitivity analyses. Another limitation of the clinical information stems from the fact that the study population used to construct the Markov process is from a single medical center and is more likely to be healthy than a typical population, which may not receive continuous access to care. Third, we did not incorporate nonadherence to statin treatment in our model, although this is well known to be an issue with treatments such as statins.[39–41] A limited window of adherence might imply that the optimal time to initiate treatment should be delayed to a point during an individual's lifetime at which maximum benefit could be achieved. Fourth, due to limited supporting data, we modeled CHD and stroke as independent events. Finally, we were only able to model the optimal timing for white race because our clinical data were very limited for minority patients. We plan to conduct a similar analysis for minority patients using other data sources.

CONCLUSIONS

We study a Markov decision process model for optimizing the start time of statin therapy for patients with type 2 diabetes. We have found significant differences in optimal start times depending on the cardiovascular risk models used and the patient's gender and metabolic factors. The optimal time to initiate statin treatment is also quite sensitive to the annual cost of statins and to the reward for future years of life. Based on our study, it is clear that patient-specific attributes such as gender, age, and metabolic state should play an important role in treatment decisions. Our numerical experiments indicate that optimal time to initiate treatment for the male test participant is typically earlier than that for the female participant. Considering all cost parameters and all risk models, the earliest recommended treatment times for the male and female test cases typically have patients initiating statin treatment at age 40. The results of our study further the debate on guidelines for statin treatment, indicating the need for a greater understanding of the role of gender and metabolic factors in treatment decisions and what is causing the differences between the cardiovascular risk models.

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APPENDIX A
Spline Fitting of HbA1c and Systolic Blood Pressure

To model HbA1c and SBP of male and female patients, we use the mean of the observations that are taken at the same age for patients tracked in the DEMS system at the Mayo Clinic (see ''Results'' section for details of the study population). Using these averages, cubic splines were fit, to approximate the variation of patients in the full cohort as a function of age. We have used 5 degrees of freedom in fitting cubic splines, which resulted in the R^2 values in Table 6. The spline fits for blood pressure and HbA1c are illustrated in Figures 4 and 5, respectively.

Table 6 R^2 Values for Cubic Spline Fit of Systolic Blood Pressure and HbA1c

	R^2 Values	
Gender	**Systolic Blood Pressure**	**HbA1c**
Male	0.529	0.669
Female	0.813	0.632

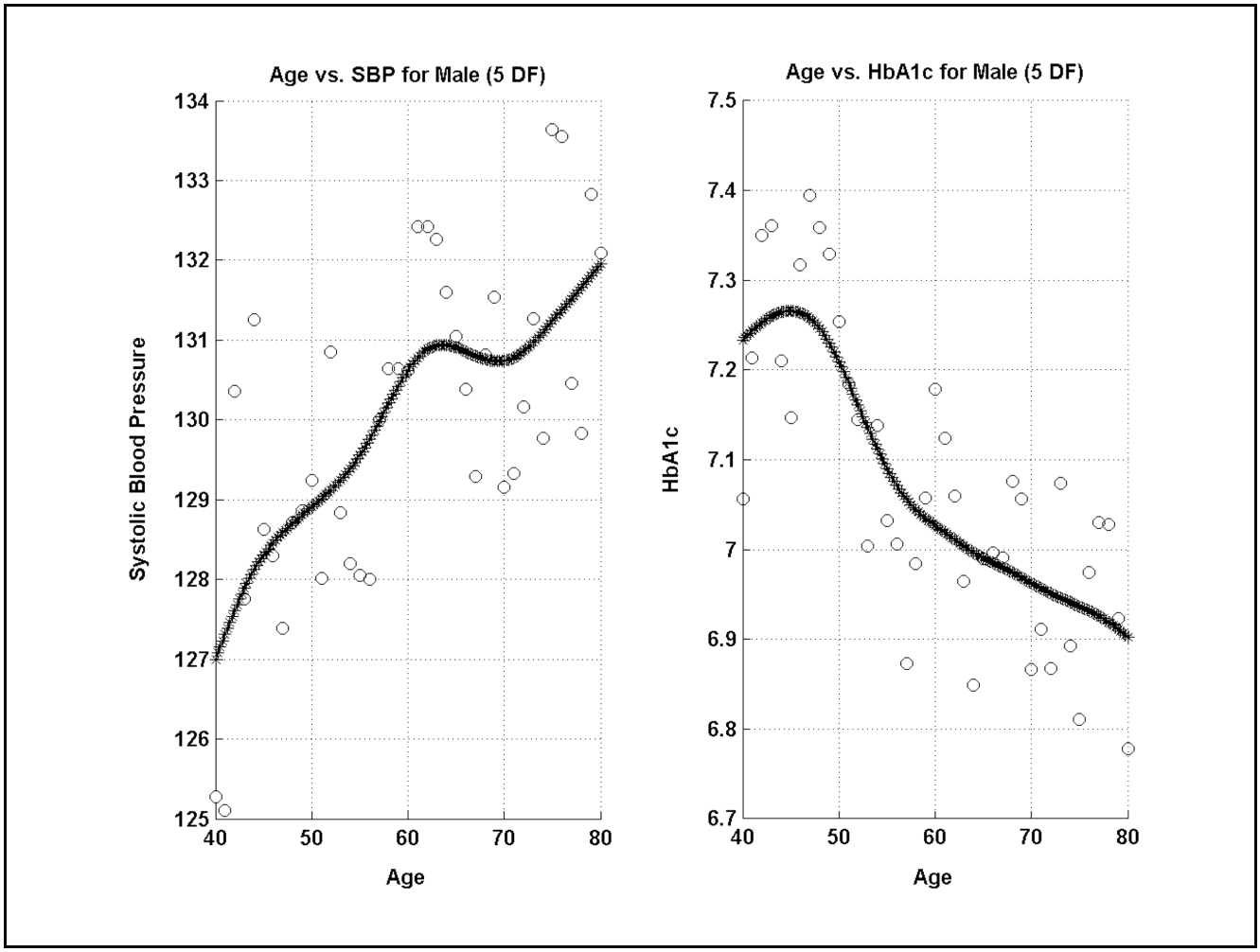

Figure 4 Illustration of spline fitting for SBP and HbA1c as a function of age for male patients.

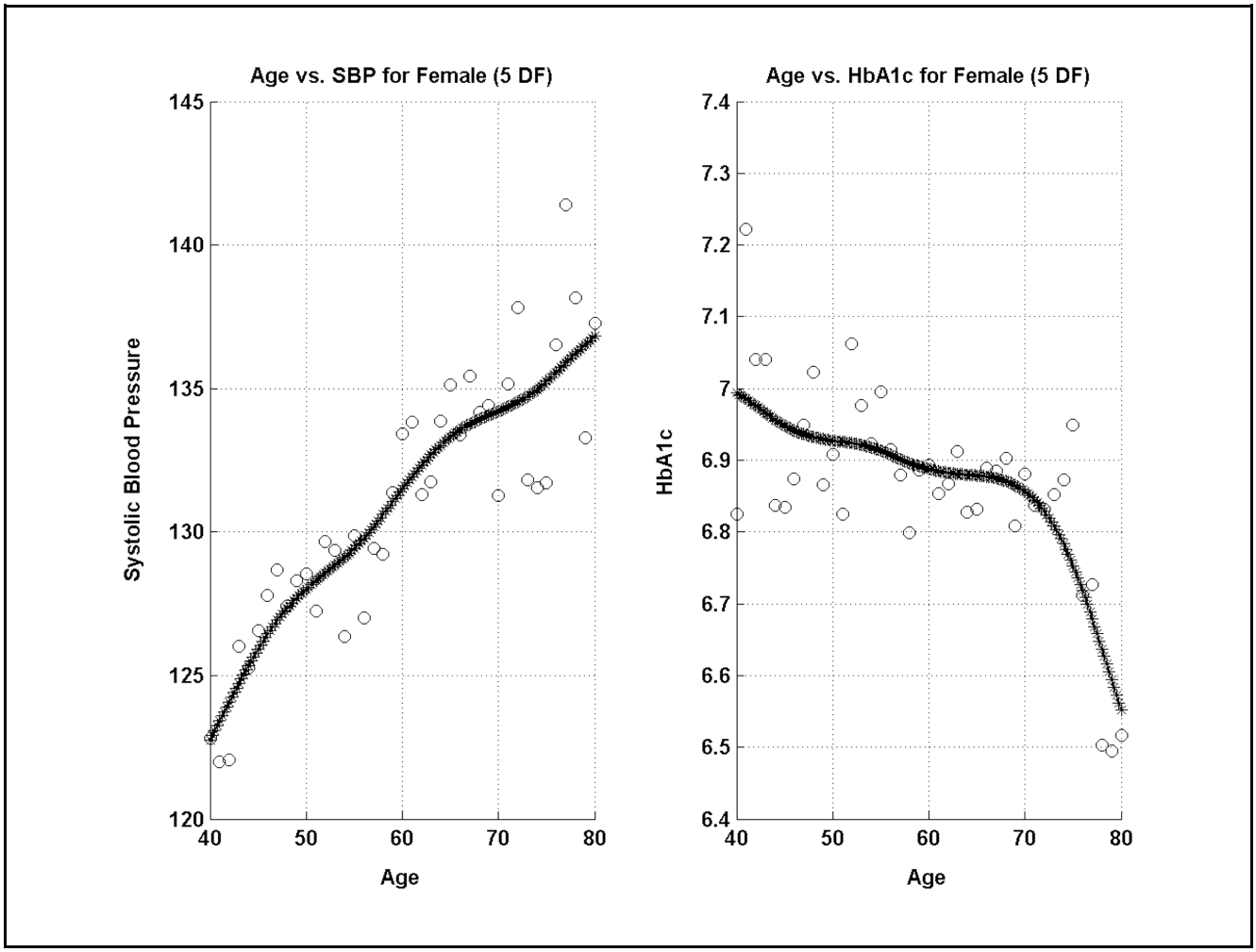

Figure 5 Illustration of spline fitting for HbA1c as a function of age for female patients.

APPENDIX B
Markov Process Transition Probabilities

The Markov process includes 2 types of transition probabilities: 1) transitions from a living state to another living state and 2) transitions from a living to a terminal state. The transition probabilities from living to terminal states are governed by the risk models (Archimedes, Framingham, and UKPDS) and Centers for Disease Control and Prevention (CDC) mortality tables. The transition probabilities to those terminal states are defined as follows (note that the dependence on height, weight, gender, and race is suppressed for notational simplicity):

$P(FS|s_t = \{i, j, k, l\}, a(s_t))$: Probability of fatal stroke in period t given that the patient is at total cholesterol level i and HDL level j, has had k strokes and l CHD events in the past, and is taking action a_t at the beginning of period t.

$P(FCHD|s_t = \{i, j, k, l\}, a(s_t))$: Probability of incurring a fatal CHD event in period t given that the patient is at total cholesterol level i and HDL level j, has had k strokes and l CHD events in the past, and is taking action a_t at the beginning of period t.

$P(FO|s_t = \{i, j, k, l\}, a(s_t))$: Probability of death due to reasons other than CHD and stroke in period t given that the patient is at total cholesterol level i and HDL level j, has had k strokes and l CHD events in the past, and is taking action $a(s_t)$ at the beginning of period t.

The transition probabilities between living states are governed by the cardiovascular risk model that is being used and estimation of transition probabilities between different total cholesterol and HDL states.

(continued)

APPENDIX (continued)

$$
\begin{aligned}
P(s_{t+1} &= \{i', j', k', l'\} | s_t \\
&= \{i, j, k, l\}, a_t) \\
&= P_t^{TC}(i' | i, a_t) P_t^{HDL}(j' | j, a_t) \\
&\quad P_{t,ijkl}^{S}(k' | k, a_t) P_{t,ijkl}^{CHD}(l' | l, a_t). \qquad (5)
\end{aligned}
$$

$$
P_{t,ijkl}^{S}(k' | k, a_t) = \begin{cases} P_{t,ijkl}(NFS | a_t) & \text{if } k' = k+1 \; k \neq S_{Max}, \\ 1 - P_{t,ijkl}(S | a_t) & \text{if } k' = k \; k \neq S_{Max}, \\ 1 - P_{t,ijkl}(S | a_t) & \\ \quad + P_{t,ijkl}(NFS | a_t) & \text{if } k' = k = S_{Max}, \\ 0 & \text{otherwise.} \end{cases} \qquad (6)
$$

$$
P_{t,ijkl}^{CHD}(l' | l, a_t) = \begin{cases} P_{t,ijkl}(NFCHD | a_t) & \text{if } l' = l+1 \; l \neq CHD_{Max}, \\ 1 - P_{t,ijkl}(CHD | a_t) & \text{if } l' = l \; l \neq CHD_{Max}, \\ 1 - P_{t,ijkl}(CHD | a_t) & \\ \quad + P_{t,ijkl}(NFCHD | a_t) & \text{if } l' = l = CHD_{Max}, \\ 0 & \text{otherwise.} \end{cases} \qquad (7)
$$

where

$P_t^{TC}(i' | i, a_t)$: Probability of the patient's total cholesterol being state i' at the beginning of period $t+1$ given that it was at total cholesterol state i and taking action a_t at the beginning of period t.

$P_t^{HDL}(j' | j, a_t)$: Probability of the patient's HDL being state j' at the beginning of period $t+1$ given that it was at HDL state j and taking action a_t at the beginning of period t.

$P_{t,ijkl}(NFS | a_t)$: Probability of incurring a nonfatal stroke in period i given that the patient is at total cholesterol level i and HDL level j, has already incurred k strokes and l CHD events, and is taking action a_t at the beginning of period t.

$P_{t,ijkl}(S | a_t)$: Probability of incurring a stroke in period t given that the patient is at total cholesterol level i and HDL level j, has already incurred k strokes and l CHD events, and is taking action a_t at the beginning of period t.

$P_{t,ijkl}(NFCHD | a_t)$: Probability of incurring a nonfatal CHD event in period t given that the patient is at total cholesterol level i and HDL level j, has already incurred k strokes and l CHD events, and is taking action a_t at the beginning of period t.

$P_{t,ijkl}(CHD | a_t)$: Probability of incurring a CHD in period t given that the patient is at total cholesterol level i and HDL level j, has already incurred k strokes and l CHD events, and is taking action a_t at the beginning of period t.

S_{Max}: Assumed maximum number of strokes a patient can incur.

Table 7 Calculated Quantiles for Separating High, Medium, and Low Total Cholesterol and High-Density Lipoprotein (HDL) Levels for White Men and Women

Gender	Cut Point, %	Total Cholesterol (mg/dL)	HDL (mg/dL)
Male	25	167	35
	75	227	47
Female	25	179	41
	75	237	59

CHD_{Max}: Assumed maximum number of CHDs a patient can incur.

The Framingham and Archimedes models do not predict whether an event (CHD or stroke) is fatal or nonfatal. Therefore, the individual probabilities of fatal and nonfatal CHD and stroke are estimated by using the UKPDS model as follows:

$$P(FS \mid s_t, a_t) = P(Death \mid S, s_t, a_t) P(S \mid s_t, a_t), \qquad (8)$$

$$P(FCHD \mid s_t, a_t) = P(Death \mid CHD, s_t, a_t) P(CHD \mid s_t, a_t), \qquad (9)$$

where the conditional probabilities are based on UKPDS risk model, and $P(Death \mid S, a_t)$, $P(S \mid s_t, a_t)$ denote the conditional probabilities of death given a stroke event, and stroke event, respectively. Similarly, $P(Death \mid CHD, a_t)$, $P(CHD \mid s_t, a_t)$ denote probabilities of death given a CHD event and a CHD event, respectively.

To estimate total cholesterol and HDL state transition probabilities, we assume that at each decision epoch, each attribute is observed in 1 of 3 states: high (H), medium (M), or low (L). Cut points for these 3 states are assumed to be static (i.e., they do not depend on the age of the individual). They were selected based on the 25 and 75 percentiles across all ages (see Table 7). Total cholesterol and HDL cut points were selected independently. The latter assumption is based on our observation that the 2 measurements are nearly uncorrelated in the clinical data set we used (we found a correlation coefficient of –.02 and .05 for men and women, respectively).

Combining the total cholesterol and HDL states yields 9 states in total (H/H, H/M, H/L, M/H, M/M, M/L, L/H, L/M, L/L). The first indicator represents total cholesterol, and the second one represents HDL (i.e., H/L means high total cholesterol and low HDL). To compute transition probabilities, first we normalize the data so that all patients are assumed not to be on statins. Total cholesterol and HDL of any patient who is on statins are corrected based on the assumed effect of statin use. Using the

(continued)

APPENDIX (continued)

corrected data, the computation of transition probabilities that is based on the sample of patients moving between states is as follows. Let $n_{i,i'}(t)$ denote the number of patients moving from state i to state i' at time period t. Then the transition probabilities are estimated as

$$P_t^{TC}(i'|i) = \frac{n_{i,i'}(t)}{\sum_{\forall i'} n_{i,i'}(t)}, P_t^{HDL}(j'|j) = \frac{n_{j,j'}}{\sum_{\forall j'} n_{j,j'}(t)}. \quad (10)$$

APPENDIX C
End-of-Horizon Approximation

Given that a patient reaches the end of the decision horizon in a living state, the expected rewards of future years of life are computed as follows. We let N^D denote the length of the period, in years, between successive decision epochs, and Y^B and Y^E denote the end of the decision horizon and the end of the post–decision horizon, respectively. Similar to the MDP formulation, λ is the annual discount factor. We define $P(L \mid s_T, a_T)$ as the probability of living for one decision epoch beyond Y^B given the state and the action that is being taken at the last decision epoch.

$$P(L|s_T, a_T) = 1 - [P(FS|s_T,a_T) + P(FCHD|s_T,a_T) + P(FO|s_T,a_T)]. \quad (11)$$

The probability of living i periods past Y^B is $[1 - P(L|s_T,a_T)]P(L|s_T,a_T)^{i-1}$. Thus, the expected future reward conditional on reaching the end of the decision horizon can be written as

$$E[PDHR|s_T, a_T] = N^D\left[R(s_T) - \left(CF^S(s_T) + CF^{CHD}(s_T)\right) - a_T C^{ST}\right] \quad (12)$$

$$\times \sum_{i=1}^{\frac{Y^E - Y^B}{N^D}} i[1 - P(L|s_T, a_T)]P(L|s_t, a_T)^{i-1}\lambda^{(i+1)N^D}. \quad (13)$$

At the beginning of period T, the patient decides to initiate statin treatment for the remaining $Y^E - Y^B$ years or not at all by selecting a_T that maximizes $v(s_T)$.

APPENDIX D
Sensitivity Results for Stating Safety

Tables 8 and 9 contain the results of a sensitivity analysis for increases in the probability of death from other causes.

Table 8 Numerical Results for the Hypothetical Influence of Safety Factors Related to Long-Term Statin Use for the Case of the UKPDS Risk Model with Annual Reward R = $50,000 and Statin Cost C^{ST} = $360 for the Base Case Female Patient

	Earliest Age to Initiate Statin Treatment for Female Patients								
	State (Total Cholesterol/HDL)								
f	H/L	M/L	L/L	H/M	M/M	L/M	H/H	M/H	L/H
1.01	40	42	46	42	46	52	50	52	58
1.03	40	42	46	44	48	52	50	56	60
1.05	40	44	48	46	48	56	50	56	*
1.1	42	46	50	48	52	60	56	*	*
1.15	46	50	56	52	*	*	*	*	*
1.2	50	56	*	*	*	*	*	*	*
1.25	56	*	*	*	*	*	*	*	*
1.3	*	*	*	*	*	*	*	*	*
1.35	*	*	*	*	*	*	*	*	*
1.4	*	*	*	*	*	*	*	*	*
1.45	*	*	*	*	*	*	*	*	*
1.5	*	*	*	*	*	*	*	*	*
1.55	*	*	*	*	*	*	*	*	*
1.6	*	*	*	*	*	*	*	*	*

The asterisk indicates that it is never optimal to initiate statin treatment; f denotes the proportional increase factor from probability of death from other causes. H, high; M, medium; L, low; HDL, high-density lipoprotein; UKPDS, United Kingdom Prospective Diabetes Study.

(continued)

APPENDIX (continued)

Table 9 Numerical Results for the Hypothetical Influence of Safety Factors Related to Long-Term Statin Use for the Case of the UKPDS Risk Model with Annual Reward R = \$50,000 and Statin Cost C^{ST} = \$360 for the Base Case Male Patient

	Earliest Age to Initiate Statin Treatment for Male Patients								
	State (Total Cholesterol/HDL)								
f	H/L	M/L	L/L	H/M	M/M	L/M	H/H	M/H	L/H
1.01	40	40	40	40	40	40	40	40	46
1.03	40	40	40	40	40	42	40	42	48
1.05	40	40	40	40	40	42	40	42	48
1.1	40	40	40	40	40	46	40	46	52
1.15	40	40	42	40	42	48	42	50	60
1.2	40	40	46	40	46	58	48	58	*
1.25	40	40	48	42	50	60	50	*	*
1.3	40	46	58	48	58	*	*	*	*
1.35	42	50	*	56	*	*	*	*	*
1.4	48	58	*	68	*	*	*	*	*
1.45	56	*	*	*	*	*	*	*	*
1.5	60	*	*	*	*	*	*	*	*
1.55	70	*	*	*	*	*	*	*	*
1.6	*	*	*	*	*	*	*	*	*

The asterisk indicates that it is never optimal to initiate statin treatment; f denotes the proportional increase factor from probability of death from other causes. H, high; M, medium; L, low; HDL, high-density lipoprotein; UKPDS, United Kingdom Prospective Diabetes Study.

REFERENCES

1. All About Diabetes. American Diabetes Association; 2006. Available from: http://www.diabetes.org/about-diabetes.jsp

2. Turner RC. The UK Prospective Diabetes Study: a review. Diabetes Care. 1998;21:C35–8.

3. Davis TME, Millns H, Stratton IM, Holman RR, Turner RC. Risk factors for stroke in type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 29. Arch Intern Med. 1999; 159:1097–1103.

4. Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). Clin Sci. 2001;101:671–9.

5. Anderson KA, Odel PM, Wilson PWF, Kannel WB. Cardiovascular disease risk profiles. Am Heart J. 1991;121:293–8.

6. Eddy DM, Schlessinger L. Archimedes: a trial-validated model of diabetes. Diabetes Care. 2003;26:3093–101.

7. Eddy DM, Schlessinger L. Validation of the Archimedes diabetes model. Diabetes Care. 2003;26:3102–110.

8. Snow V, Aronson MD, Hornbake ER, Mottur-Pilson C, Weiss KB. Lipid control in the management of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2004;140:644–9.

9. Garg A. Statins for all patients with type 2 diabetes: not so soon. Lancet. 2004;364:641–2.

10. Hayward RA, Hofer TP, Vijan S. Lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem. Ann Intern Med. 2006;145:520–30.

11. Ko DT, Newman AM, Lee DS, Austin PC, Donovan LR, Tu JV. Underutilization of effective treatment in diabetic patients admitted with acute myocardial infarction. J Am Coll Cardiol. 2004;43: 405A–6A.

12. Smith MA, Cox ED, Bartell JM. Overprescribing of lipid lowering agents. Qual Safety Health Care. 2006;15:251–7.

13. Abookire SA, Karson AS, Fiskio J, Bates DW. Use and monitoring of ''statin'' lipid-lowering drugs compared with guidelines. Arch Intern Med. 2001;161:53–8.

14. Health I. Press release: top 10 therapeutic classes by U.S. sales. IMS; 2006. Available from: http://imshealth.com/ims/portal/front/articleC/0,2777,6599_80408854_80411855,00.html

15. Schaefer AJ, Bailey MD, Shechter SM, Roberts MS. Modeling medical treatment using Markov decision processes. In: Brandeau M, Sainfort F, Pierskalla W, eds. Handbook of Operations Re-search/Management Science Applications in Health Care. New York: Kluwer; 2004. p 597–616.

16. Puterman ML. Markov Decision Processes: Discrete Stochastic Dynamic Programming. New York: Wiley-Interscience; 1994.

17. Gorman CA, Zimmerman BR, Smith SA, et al. DEMS: a second generation diabetes electronic management system. Comput Methods Programs Biomed. 2000;62:127–40.

18. National Center for Health Statistics. National Vital Statistics Reports. Hyattsville, MD: National Center for Health Statistics; 2005.

19. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality: an overview of randomized trials. JAMA. 1997;278:313–21.

20. Maron DJ, Fazio S, Linton MF. Current perspectives on statins. Circulation. 2000;101:207–13.

21. D'Agostino RB, Russell MW, Huse DM, et al. Primary and subsequent coronary risk appraisal: new results from the Framingham Study. Am Heart J. 2000;139:272–81.

22. Kothari V, Stevens RJ, Adler AI, et al. UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. Stroke. 2002;33:1776–81.

23. Centers for Disease Control and Prevention (CDC). Advance Data from Vital and Health Statistics. Available from: http://www.cdc.gov/nchs/data/ad/ad347.pdf

24. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2006;113:E85–151.

25. Russell MW, Huse DM, Drowns S, Hamel EC, Hartz SC. Direct medical costs of coronary artery disease in the United States. Am J Cardiol. 1998;81:1110–5.

26. Red Book: 2006 Edition. Ann Arbor, MI: Thomson Healthcare; 2006.

27. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Med Decis Making. 2002;22:340–9.

28. Tsevat J, Goldman L, Soukup JR, et al. Stability of time-tradeoff utilities in survivors of myocardial-infarction. Med Decis Making. 1993;13:161–5.

29. Tengs TO, Yu M, Luistro E. Health-related quality of life after stroke: a comprehensive review. Stroke. 2001;32:964–71.

30. Tengs TO, Lin TH. A meta-analysis of quality-of-life estimates for stroke. Pharmacoeconomics. 2003;21:191–200.

31. Gage BF, Cardinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial-fibrillation. JAMA. 1995;274:1839–45.

32. Zgibor JC, Piatt GA, Ruppert K, Orchard TJ, Roberts MS. Deficiencies of cardiovascular risk prediction models for type 1 diabetes. Diabetes Care. 2006;29:1860–5.

33. Poynter JN, Gruber SB, Higgins PDR. Statins and the risk of colorectal cancer. N Engl J Med. 2005;1352:2184–92.

34. Young-Xu Y, Chan KA, Liao JK, Ravid S, Blatt CM. Long-term statin use and psychological well-being. J Am Coll Cardiol. 2003;42:690–7.

35. Guyton JR. Benefit versus risk in statin treatment. Am J Cardiol. 2006;97:95C–7C.

36. Wang PS, Solomon DH, Mogun H, Avorn J. HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. JAMA. 2000;283:3211–6.

37. Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. Circulation. 2006;114:2788–97.

38. Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. Lancet. 2000;356:1627–31.

39. Jackevicius CA, Mamdami M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA. 2002;288:462–7.

40. Avorn J, Monette J, Lacour A, et al. Persistence of use of lipid-lowering medications: a cross-national study. JAMA. 1998;279:1458–62.

41. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. JAMA. 2002;288:455–61.