



Innovative Applications of O.R.

Optimizing the simultaneous management of blood pressure and cholesterol for type 2 diabetes patients

J.E. Mason^{a,*}, B.T. Denton^{a,1}, N.D. Shah^b, S.A. Smith^c^a Edward P. Fitts Department of Industrial & Systems Engineering, North Carolina State University, 111 Lampe Drive, Raleigh, NC 27613, USA^b Division of Health Care Policy & Research, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA^c Division of Endocrinology, Diabetes, Nutrition, & Metabolism, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA

ARTICLE INFO

Article history:

Received 16 November 2012

Accepted 14 September 2013

Available online 25 September 2013

Keywords:

OR in medicine

Markov decision process

Type 2 diabetes

Blood pressure treatment

Cholesterol treatment

ABSTRACT

We present a Markov decision process (MDP) model to determine the optimal timing of blood pressure and cholesterol medications. We study the use of our model for a high-risk population of patients with type 2 diabetes; however, the model and methods we present are applicable to the general population. We compare the optimal policies based on our MDP to published guidelines for initiation of blood pressure and cholesterol medications over the course of a patient's lifetime. We also present a bicriteria analysis that illustrates the trade off between quality-adjusted life years and costs of treatment.

© 2013 Elsevier B.V. All rights reserved.

1. Introduction

Currently over 25 million people in the United States have diabetes. In 2010, approximately 1.9 million people aged 20 or older were newly diagnosed with diabetes (CDC, 2011). Treatment of the diabetes population can be costly: it is estimated that \$153 billion per year in direct medical costs is spent on diabetes-related treatment in the United States (Dall et al., 2010), and this yearly cost is expected to triple in the next 25 years. Two ways to control costs are to (1) manage medication costs through reduced medication use and (2) prevent or delay the occurrence of stroke and coronary heart disease (CHD) events for which diabetes patients are particularly at risk, thereby reducing the hospitalization and other significant follow-up costs associated with these events. Optimizing medication treatment decisions poses a challenge because reduced medication use may cause an increase in events.

In addition to cost, important criteria to consider from the patient perspective include life expectancy and quality of life. Expected quality-adjusted life years (QALYs) are a commonly used criteria in the health policy literature associated with both quality of life and mortality (Gold, Stevenson, & Fryback, 2002). They are

defined as a measure of a life year on a 0 (dead) to 1 (perfect health) scale, where decrements from 1 represent the burden of treatment, minor illnesses, and debilitating diseases or events. QALYs can measure the trade-off between the burden of medication and the benefits of prevention of stroke and CHD events.

Several risk models have been developed to predict the probability of complications of type 2 diabetes over the course of an individual's lifetime (Kothari et al., 2002; Stevens, Kothari, Adler, Stratton, & Holman, 2001; Stevens et al., 2004; Eastman et al., 1997; Eddy & Schlessinger, 2003). These models serve as a guide to clinicians for establishing the importance of treatment; however, there has been little investigation of how to effectively use these risk models to design optimal treatment policies for blood pressure and cholesterol management. The research presented in this article seeks to bridge this gap by furthering the basic knowledge of how to optimally treat cardiovascular risk in patients with diabetes over the course of their lifetime.

We present an MDP to determine the optimal timing of medical treatment decisions for blood pressure and cholesterol control in patients with type 2 diabetes. We consider two different bi-criteria MDP formulations. First, we use our model to find the optimal treatment decision that trades off the expected time to first event and the cost of medication. Second, we use our model to find the optimal treatment decisions that trade off expected QALYs and total costs of treatment (medication costs plus one-time and follow-up treatment costs for adverse events). In both cases we combined the two criteria using a willingness-to-pay factor to balance life years (LYs) and QALYs against the costs of medication and treat-

* Corresponding author. Present address: Department of Public Health Sciences, University of Virginia, 1300 Jefferson Park Avenue, Charlottesville, VA 22908, USA. Tel.: +1 434 924 2813.

E-mail addresses: jem4yb@virginia.edu (J.E. Mason), btdenton@umich.edu (B.T. Denton), shah.nilay@mayo.edu (N.D. Shah), smith.steven@mayo.edu (S.A. Smith).

¹ Present address: Department of Industrial and Operations Engineering, University of Michigan, 1205 Beal Avenue, Ann Arbor, MI 48109, USA.

ment, respectively. We vary the willingness-to-pay factor to estimate the efficient frontier of treatment policies. We also evaluate the most common treatment guidelines in the United States and other countries applied to U.S. patients and compare them to the Pareto-optimal policies from our model.

Our model considers control of coexisting stochastic risk factors, which is a problem that arises in the context of many chronic diseases. There is a significant literature on treatment optimization. However, to our knowledge ours is the first to examine simultaneous control of multiple risk factors. We highlight the benefits of coordinated treatment over the myopic nature of current guidelines by comparing costs, QALYs, and event-free LYs for the different policies.

We address several specific research questions in this article including the following: How much can coordinated management of coexisting risk factors improve patient outcomes (e.g., QALYs, LYs before an adverse health event) over current guidelines? What effect does treatment coordination have on costs? How should treatment plans differ for males and females? How dependent is the optimal treatment regimen on an individual patient's metabolic risk profile? To help answer these questions, we present patient-specific treatment plans based on our model. We also compare expected LYs and medication costs, and expected QALYs and total costs for optimal treatment plans and current practice guidelines.

The remainder of this article is organized as follows: In Section 2 we provide background on diabetes treatment and a review of the relevant literature. In Section 3 we give a detailed description of the MDP model. In Section 4 we present numerical results. Finally, in Section 5 we highlight main conclusions and directions for future work.

2. Diabetes treatment background and literature review

We focus on the prevention of stroke and CHD events since they are the leading causes of death for patients with type 2 diabetes. Most patients with diabetes use medication to manage blood pressure and cholesterol since they are the most significant controllable risk factors for stroke and CHD. Glucose control is also important, particularly for the prevention of microvascular events (such as blindness and nerve damage); however, it has not been shown that tight control of glucose in individuals with diabetes has significant risk reduction for cardiovascular events (Action to Control Cardiovascular Risk in Diabetes Study Group, 2008; ADVANCE Collaborative Group, 2008; Duckworth et al., 2009).

There are many published recommendations in the United States and other countries for initiation of blood pressure and cholesterol medications. Table 1 provides a summary of U.S. and international guidelines for initiation of these medications based on well-established risk factors. We evaluated the current U.S. guideline for diabetes patients, which we refer to as U.S. 1. This guideline

uses the same treatment thresholds for all patients with diabetes. For comparison we also evaluated a U.S. guideline for patients without diabetes, which we refer to as U.S. 2. This guideline defines a different risk-based treatment threshold, depending on risk level defined by factors including gender and age, as defined in Table 1. In the United States, guidelines for initiation of blood pressure and cholesterol medications for all types of patients have been developed by two independent committees, the seventh Joint National Committee (JNC 7) (Antonopoulos et al., 2002) for blood pressure guidelines and the Adult Treatment Panel III (ATP III) (Chobanian, Bakris, Black, Cushman, & Green, 2003) for cholesterol guidelines. For diabetes patients these guidelines are “one size fits all”; all diabetes patients are treated to the same threshold, regardless of risk of events, gender, age, or any other factors. The uncoordinated treatment of these risk factors is questionable since blood pressure and cholesterol both affect the overall health of a patient and his or her risk of complications (Stevens et al., 2001; Stevens et al., 2004).

U.S. and other international guidelines are typically defined by clinical thresholds for stroke and CHD risk factors (other events which are less common such as kidney failure and neuropathy also influence guidelines). The most common risk factors considered by the guidelines are cholesterol and systolic blood pressure (SBP). There are several measures associated with cholesterol including low-density lipoprotein (LDL), high-density lipoprotein (HDL), lipid ratio (LR), and total cholesterol (TC). A patient's TC is a combination of LDL, HDL, and triglycerides, a relationship estimated by the Friedewald equation (Friedewald, Levy, & Fredrickson, 1972). A patient's LR is TC divided by HDL. If any of these risk factors are outside of the specified threshold the guideline recommends the patient should begin an additional medication for cholesterol or blood pressure treatment, as appropriate. Note, for ATP III* in Table 1, patients with increased risk are treated at lower LDL thresholds than low risk patients.

Risk models that use risk factors as inputs, including the United Kingdom Prospective Diabetes Study (UKPDS) risk engine (Stevens et al., 2001; Stevens et al., 2004; Kothari et al., 2002), make it possible to build models in which initiation of medications affects probabilities of complications for patients with diabetes. The UKPDS model is a set of risk equations based on a large cohort of diabetes patients in the United Kingdom; inputs for the risk equations include time since diagnosis of diabetes, age, SBP, LR, and gender. We use the UKPDS model to estimate probabilities of fatal and nonfatal stroke and CHD events in our MDP.

Several models related to our MDP model have been studied. In the context of type 1 diabetes, Parker, Doyle, and Peppas (2001) provide an overview of control algorithms for real-time monitoring and management of blood glucose. Algorithms are presented to determine appropriate insulin delivery. Other models focus on treatment decisions for patients with type 2 diabetes. Denton, Kurt, Shah, Bryant, and Smith (2009) proposed a non-stationary MDP model to study the optimal timing of statin initiation for cholesterol management, providing optimal control for a single risk fac-

Table 1
International guideline thresholds for initiation of cholesterol and blood pressure medications. Guidelines that assume diabetes patients are not considered CHD risk equivalent are represented with *. LDL is measured in mg/dL for the U.S. guidelines, and LDL, HDL, and TC are measured in mmol/L for all other guidelines. LR is unitless, and SBP is measured in mmHg.

Guideline	Cholesterol	Blood pressure
U.S. 1 (Antonopoulos et al. (2002) & Chobanian et al. (2003))	ATP III: LDL \geq 100	JNC 7: SBP > 130
U.S. 2 (Antonopoulos et al. (2002) & Chobanian et al. (2003))	ATP III* $\begin{cases} \text{High Risk: LDL} \geq 100, \\ \text{Medium Risk: LDL} \geq 130, \\ \text{Low Risk: LDL} \geq 190 \end{cases}$	JNC 7*: SBP > 140
Australia (Harris et al. (2009))	LDL \geq 2.5 or TC \geq 4.0 or HDL < 1.0	SBP > 130
Canada (Bhattacharyya et al. (2008))	LDL \geq 2.5 or LR \geq 4.0	SBP > 130
European Union (Graham (2007))	LDL \geq 2.5 or TC \geq 4.5	SBP > 130
Great Britain (Joint British Societies 2 (2005))	LDL \geq 2.0 or TC \geq 4.0	SBP > 130

tor. Kurt, Denton, Schaefer, Shah, and Smith (2011) provide structural properties of the optimal statin initiation policy. Timbie, Hayward, and Vijan (2010) simulated initiation of blood pressure and cholesterol medications in order to treat to the U.S. guideline targets. However, this simulation model was only used at one point in the patient’s life rather than simulating the use of guidelines over a patient’s lifetime. Shah et al. (2011) also studied the impact of managing blood pressure and cholesterol according to guidelines for treatment (U.S. and international) over the course of a patient’s lifetime.

MDP models have also been used to determine the optimal timing of one-time medical interventions for a number of diseases other than diabetes. Alagoz, Maillart, Schaefer, and Roberts (2004), Alagoz et al. (2007) provide a discrete-time, infinite-horizon, stationary MDP model to determine the optimal timing of liver transplantation based on a patient’s MELD score. They also present structural results, proving sufficient conditions for the existence of a control-limit policy for transplantations. Shechter, Bailey, Schaefer, and Roberts (2008) present an MDP model for the optimal initiation of HIV treatment according to a patient’s CD4 count with the goal of maximizing a patient’s quality-adjusted lifetime. They assume a stationary, infinite-horizon model and prove that a control-limit policy exists in terms of the patient’s CD4 count.

This article contributes to the existing literature in two main ways. First, we present a novel model formulation to determine optimal treatment policies for management of a chronic disease over the course of a patient’s lifetime. Our model involves the use of multiple medications for simultaneous control of multiple risk factors. To our knowledge, we are the first to model simultaneous optimal control of multiple risk factors. Most related research concentrates on optimal treatment decisions for a single risk factor. Previously proposed diabetes models are descriptive in nature (e.g., simulation models, or Markov chains) and do not provide dynamic, prescriptive policies over time as our work does. Second, we use our model to answer important policy questions regarding the benefits of coordinating treatment guidelines for cholesterol and blood pressure control. We anticipate our findings will provide insights into the ordering of treatment decisions in other contexts.

3. Model

Our MDP model defines the patient’s health status (including SBP, TC, and HDL), current medications, number of stroke and CHD events that have occurred in the past, and risk of future stroke and CHD events based on a discrete set of health states, also described with the term metabolic states. A discrete set of actions represent the initiation of various treatment options. The objective of our model is to find the optimal sequence and timing of medications to manage stroke and CHD risk. Fig. 1 provides a simplified state transition diagram of our model for the purpose of illustrating the problem. In the diagram, solid lines illustrate the actions of initiating one or both of the most common medications (statins (ST), ACE inhibitors (AI)), and dashed lines represent the occurrence of an adverse event (stroke or CHD event) or death from other causes. In each medication state, including the no medication state (\emptyset), patients probabilistically move between health states, here represented by L (low), M (medium), H (high), and V (very high). For patients on one or both medications, improvements in patient risk factors (blood pressure, cholesterol, or both) reduce the probability of adverse events.

In our model treatment decisions are assumed to be irreversible. Once a patient begins a blood pressure or cholesterol medicine, it is assumed that he or she remains on the medication for

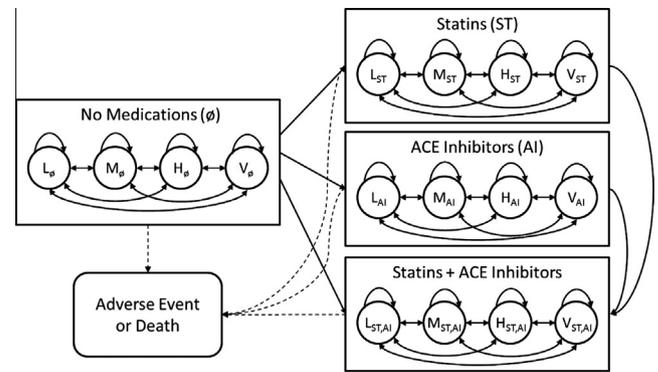


Fig. 1. Simplified state transition diagram for the case of two medications. When medications are initiated (actions denoted by the solid lines), the risk factors are improved and the probability of the occurrence of an adverse event (denoted by the dashed lines) is reduced.

the remainder of his or her life. This is consistent with clinical recommendations for these medications (Snow, Aronson, Hornbake, Mottur-Pilson, & Weiss, 2004; Vijan & Hayward, 2004; Chobanian et al., 2003). In some cases, major side effects may cause patients to discontinue treatment (e.g., statins can cause liver problems or severe muscle pain). However, this occurs in a small proportion of patients.

The problem we explore in this article is a generalization of the above two-medication problem, depicted in Fig. 1, in which the patient may elect to initiate one or more of a set of available treatments at each decision epoch. This optimal treatment problem can be viewed as a nested stopping time problem. After the first medication is initiated (the first stopping time is chosen), there is a subsequent stopping time problem for the next medication to be initiated, and so on. A brief description of the MDP model is presented below.

Actions are taken at a discrete set of decision epochs indexed by $t = 1, \dots, T$, where epoch t represents the year $[t, t + 1)$. This range constitutes the finite decision horizon. Similar to other studies (Denton et al., 2009; Kurt et al., 2011; Shah et al., 2011), yearly decision epochs are used to represent annual visits to a clinician. Ages above T are represented by an infinite post-decision horizon, assuming no new medications are initiated, allowing for accrual of rewards for patients living past the end of the decision horizon.

States are composed of living states and absorbing states. Each living state is defined by the factors that influence a patient’s cardiovascular risk: the patient’s TC, HDL, and SBP levels, medication status, and history of stroke and CHD events. We denote the set of the TC states by $\mathcal{L}_{TC} = \{L, M, H, V\}$, with similar definitions for HDL, $\mathcal{L}_{HDL} = \{L, M, H, V\}$, and SBP, $\mathcal{L}_{SBP} = \{L, M, H, V\}$. The thresholds for these ranges are based on clinically-relevant cut points for treatment found in Table 2 (Cleeman et al., 2001). The history of stroke and CHD events is defined by the current number of events the patient has had up to some maximum number, k : $\mathcal{L}_S = \{0, 1, \dots, k\}$ and $\mathcal{L}_{CHD} = \{0, 1, \dots, k\}$. Elements of these sets are indexed by ℓ_{TC} , ℓ_{HDL} , ℓ_{SBP} , ℓ_S , and ℓ_{CHD} , respectively. The set of health states is given by $\mathcal{L} = \mathcal{L}_{TC} \times \mathcal{L}_{HDL} \times \mathcal{L}_{SBP} \times \mathcal{L}_S \times \mathcal{L}_{CHD}$. Elements of \mathcal{L} are indexed by ℓ .

The set of medication states is denoted by $\mathcal{M} = \{\mathbf{m} = (m_1, m_2, \dots, m_n) : m_i \in \{0, 1\}, \forall i = 1, 2, \dots, n\}$, where n denotes the number of medications. If $m_i = 0$, the patient is not currently on medication i , and if $m_i = 1$, the patient is currently on the medication. When a patient begins treatment i , the medication effects are denoted by $\omega^{TC}(i)$, representing the proportional change in TC, $\omega^{HDL}(i)$, representing the proportional change in HDL, and $\omega^{SBP}(i)$, representing the proportional change in SBP. Note, in general cholesterol medications result in decreased TC and increased

Table 2
Ranges for TC, HDL, and SBP states based on Cleeman et al. (2001).

	L	M	H	V
TC (mg/dL)	<160	[160,200)	[200,240)	≥240
HDL (mg/dL)	<40	[40,50)	[50,60)	≥60
SBP (mmHg)	<120	[120,140)	[140,160)	≥160

HDL, while blood pressure medications result in decreased SBP. The medications we consider are targeted specifically at either cholesterol or blood pressure and each has negligible effect on the other risk factor. For example, if medication i is a blood pressure medication, then $\omega^{\text{TC}}(i) = \omega^{\text{HDL}}(i) = 0$.

The living states in the model are denoted by $(\ell, \mathbf{m}) \in \mathcal{L} \times \mathcal{M}$. The absorbing states are represented by the death states: $\mathcal{D} = \{\mathcal{D}_S, \mathcal{D}_{\text{CHD}}, \mathcal{D}_O\}$. The three types of death states represent dying from a stroke, \mathcal{D}_S , a CHD event, \mathcal{D}_{CHD} , or other causes, \mathcal{D}_O . The absorbing states will be denoted by $d \in \mathcal{D}$. Including living and absorbing states, there are a total of $4^3 \times 2^n \times (k+1)^2 + 3$ states in our model.

At each decision epoch, it must be determined which medications to initiate (if any). The action space is dependent on the history of medications that have been initiated in previous epochs. For each medication, at each epoch, medication i can be initiated (I) or initiation can be delayed (W). These actions are defined for medication i as follows:

$$A_{(\ell, m_i)} = \begin{cases} \{I_i, W_i\} & \text{if } m_i = 0, \\ \{W_i\} & \text{if } m_i = 1, \end{cases} \quad (1)$$

where $\mathbf{A}_{(\ell, \mathbf{m})} = \{A_{(\ell, m_1)} \times A_{(\ell, m_2)} \times \dots \times A_{(\ell, m_n)}\}$. Action $\mathbf{a} \in \mathbf{A}_{(\ell, \mathbf{m})}$ denotes the action taken in state (ℓ, \mathbf{m}) . If a patient is in living state (ℓ, \mathbf{m}) and takes action \mathbf{a} , the medication state is then denoted by \mathbf{m}' , where m'_i is set to 1 for any medications i that are newly initiated by action \mathbf{a} ; $m'_i = m_i$ for all medications i which are not newly initiated. Once medication i is initiated, the patient's blood pressure and cholesterol are modified by the medication effects denoted by $\omega^{\text{TC}}(i)$, $\omega^{\text{HDL}}(i)$, and $\omega^{\text{SBP}}(i)$, resulting in a reduction in the probability of having a stroke or CHD event.

Three types of probabilities are incorporated into the model: probabilities among health states, probability of events (both fatal and nonfatal), and probability of death from other causes. At epoch $t \in 1, \dots, T$, death from other causes occurs with probability π_t^O . If the patient is in state $(\ell, \mathbf{m}) \in \mathcal{L} \times \mathcal{M}$, a nonfatal stroke or CHD event occurs with probability $\pi_t^S(\ell, \mathbf{m})$ and $\pi_t^{\text{CHD}}(\ell, \mathbf{m})$, respectively, which depend on the patient's age, health state, medication status, and other risk factors such as race and gender. Fatal stroke and CHD events occur with probability $\tilde{\pi}_t^S(\ell, \mathbf{m})$ and $\tilde{\pi}_t^{\text{CHD}}(\ell, \mathbf{m})$, respectively. Given that the patient is in state (ℓ, \mathbf{m}) at epoch t , the probability of moving into one of the absorbing states $d \in \mathcal{D}$ at epoch $t+1$ is denoted by $\bar{p}_t^m(d|\ell)$, where

$$\bar{p}_t^m(d|\ell) = \begin{cases} \pi_t^O & \text{if } d = \mathcal{D}_O, \\ \tilde{\pi}_t^{\text{CHD}}(\ell, \mathbf{m}) & \text{if } d = \mathcal{D}_{\text{CHD}}, \\ \tilde{\pi}_t^S(\ell, \mathbf{m}) & \text{if } d = \mathcal{D}_S, \end{cases} \quad (2)$$

for $(\ell, \mathbf{m}) \in \mathcal{L} \times \mathcal{M}$, and $\bar{p}_t^m(d|d) = 1$ for all $t \in 1, \dots, T$. The probability of having a nonfatal event or dying (from an event or other causes) is denoted by $\pi_t^*(\ell, \mathbf{m})$, where

$$\begin{aligned} \pi_t^*(\ell, \mathbf{m}) &= (1 - \pi_t^{\text{CHD}}(\ell, \mathbf{m}) - \tilde{\pi}_t^{\text{CHD}}(\ell, \mathbf{m}))\pi_t^S(\ell, \mathbf{m}) \\ &+ (1 - \pi_t^S(\ell, \mathbf{m}) - \tilde{\pi}_t^S(\ell, \mathbf{m}))\pi_t^{\text{CHD}}(\ell, \mathbf{m}) + \tilde{\pi}_t^S(\ell, \mathbf{m}) \\ &+ \tilde{\pi}_t^{\text{CHD}}(\ell, \mathbf{m}) + \pi_t^O. \end{aligned} \quad (3)$$

Given that the patient is in health state $\ell \in \mathcal{L}$, the probability of being in health state ℓ' in the next epoch following is denoted by $q_t(\ell'|\ell)$. The transition probabilities between health states do not de-

pend on the medication state since the transition probabilities $q_t(\ell'|\ell)$ are computed from the natural progression of blood pressure and cholesterol in the absence of medication; however, the medication state does alter the associated thresholds for each TC, HDL, and SBP state, defined in Table 2, based on medication effects. Thus, medication use reduces probabilities of events. We define $p_t^m(j|\ell)$ to be the probability of a patient being in state $j \in \mathcal{L} \cup \mathcal{D}$ at epoch $t+1$, given the patient is in living state (ℓ, \mathbf{m}) at epoch t , where \mathbf{m} incorporates the action \mathbf{a} taken at time t . The probability $p_t^m(j|\ell)$ is defined by the following:

$$p_t^m(j|\ell) = \begin{cases} \left[1 - \sum_{d \in \mathcal{D}} \bar{p}_t^m(d|\ell) \right] q_t(j|\ell) & \text{if } \ell, j \in \mathcal{L}, \\ \bar{p}_t^m(j|\ell) & \text{if } \ell \in \mathcal{L}, j \in \mathcal{D}, \\ 1 & \text{if } \ell = j \in \mathcal{D}, \\ 0 & \text{otherwise.} \end{cases} \quad (4)$$

The reward $r_t(\ell, \mathbf{m})$ is the dollar reward for QALYs minus treatment and medication costs accrued in decision epoch t in living state (ℓ, \mathbf{m}) as described in the following equation:

$$\begin{aligned} r_t(\ell, \mathbf{m}) &= R(\ell, \mathbf{m}) - C^O - (C^S(\ell) + C^{\text{CHD}}(\ell)) - (CF^S(\ell) \\ &+ CF^{\text{CHD}}(\ell)) - C^{\text{MED}}(\mathbf{m}), \end{aligned} \quad (5)$$

for $t = 1, \dots, T$, where $R(\ell, \mathbf{m}) = R_0(1 - d^S(\ell))(1 - d^{\text{CHD}}(\ell))(1 - d^{\text{MED}}(\mathbf{m}))$ is the dollar reward for one QALY. The quantity R_0 is the dollar reward per QALY, which is analogous to the willingness-to-pay threshold in health economics studies. When a patient has an event or initiates a medication, her quality of life is decreased. The decrement factors $d^S(\ell)$, $d^{\text{CHD}}(\ell)$, and $d^{\text{MED}}(\mathbf{m})$ represent the decrease in quality of life from a stroke, a CHD event, or medication initiation, respectively. Event decrement factors are used in the year the event occurs and every year thereafter. Medication decrement factors are used in every year that the patient is using the medication. If the patient is on multiple medications, $d^{\text{MED}}(\mathbf{m})$ is the sum of the individual medication decrements. The costs C^O , $C^{\text{MED}}(\mathbf{m})$, $C^S(\ell)$ and $C^{\text{CHD}}(\ell)$, and $CF^S(\ell)$ and $CF^{\text{CHD}}(\ell)$ represent cost of other health care for diabetes patients, cost of medications, cost of initial hospitalization for stroke and CHD events, and cost of follow-up treatment for stroke and CHD events, respectively.

For a patient in living state (ℓ, \mathbf{m}) in epoch t , let $v_t(\ell, \mathbf{m})$ denote the patient's maximum total expected discounted rewards prior to her first event or death. The following recursion defines the optimal action in each state for $t = 1, \dots, T-1$:

$$v_t(\ell, \mathbf{m}) = \max_{\mathbf{a} \in \mathbf{A}_{(\ell, \mathbf{m})}} \left\{ r_t(\ell, \mathbf{m}'(\mathbf{a})) + \lambda \sum_{j \in \mathcal{L} \cup \mathcal{D}} p_t^{m'(\mathbf{a})}(j|\ell) v_{t+1}(j, \mathbf{m}'(\mathbf{a})) \right\}, \quad (6)$$

where j indexes states in $\mathcal{L} \cup \mathcal{D}$, $\mathbf{m}'(\mathbf{a})$ is defined as the medication state \mathbf{m} with action \mathbf{a} taken into account, and $\lambda \in [0, 1)$ is the discount factor per decision epoch, which is commonly set to 97% in health economic evaluations (see Chapter 7 of Gold, Siegel, Russell, & Weinstein (1996) for a discussion of this). The boundary condition is given by $v_T(\ell, \mathbf{m}) = r_T(\ell, \mathbf{m}) + E[\text{PDHR}|\ell, \mathbf{m}]$, where $E[\text{PDHR}|\ell, \mathbf{m}]$ is the expected post-decision horizon reward (PDHR). This represents expected rewards for a patient living past the decision horizon (e.g., past age 100). The PDHR depends on the state and treatment status of the patient in the last year of the decision horizon and the number of years into the post-decision horizon that the patient lives. This approximation of rewards is needed because of the limited samples in the data set for older patients.

Various criteria can be expressed using the general reward function in Eq. (5). For example, letting $R(\ell, \mathbf{m}) = 1$ for all patients with $\ell_S = \ell_{\text{CHD}} = 0$ and all cost parameters set to zero represents the objective of primary prevention (i.e., the value function for a gi-

Table 3

Baseline characteristics for the study population ($N = 663$), including mean and variance.

Patient attribute	Study cohort
Age	52.46 (8.83)
Years with diabetes	3.24 (5.33)
% Female	39.67
HDL	43.65 (11.58)
LDL	126.98 (37.31)
TC	216.98 (37.31)
SBP	139.11 (19.75)
HbA1c	8.01 (2.38)

ven state at a given decision epoch is the expected LYs to first event). Another primary prevention model criterion that can be expressed using the reward function is to let $R(\ell, \mathbf{m}) = 1 - d^{\text{MED}}(\mathbf{m})$ for patients with $\ell_S = \ell_{\text{CHD}} = 0$. This primary prevention model takes into account the downside of treatment by incorporating the disutility of treatment before a patient's first event. A third primary prevention model would incorporate both the disutility and cost of medications before the patient has any events. Thus, $R(\ell, \mathbf{m}) = R_0$ and all costs other than $C^{\text{MED}}(\mathbf{m})$ are set to zero. In all of these cases, patients with $\ell_S \neq 0$ or $\ell_{\text{CHD}} \neq 0$ have $R(\ell, \mathbf{m}) = 0$. As we discuss in Section 4, inclusion or removal of different parts of the general reward function (e.g., costs of other medical care for diabetes patients) can greatly affect optimal policies.

4. Results

In this section we present numerical results illustrating optimal treatment policies for two bicriteria perspectives: (a) expected time to first event versus medication costs, and (b) expected QALYs versus medication and treatment costs. Backward induction was used to compute the optimal treatment decisions over the patient's lifetime. The model and solution method was coded in C/C++. Model instances were solved in under 40 minutes using a 2.83 gigahertz PC with 8 gigabytes of RAM. We provide results for each perspective for a population of 40-year-old patients newly diagnosed with type 2 diabetes. The proportion of patients in each of the health states at age 40 is estimated using the Mayo cohort described in Section 4.1.

The remainder of this section is organized as follows: In Section 4.1 we define the specific parameters for our problem, the model inputs, and their sources. In Section 4.2 we present a comparison of outputs from our model to those found in the literature for validation purposes. In Section 4.3 we present a model for primary prevention with results for maximization of LYs before an event. In Section 4.4, we provide results from the population level for maximizing QALYs over the patient's lifetime (i.e., average results for patients with diabetes). For the results presented Sections 4.3 and 4.4, we compare the optimal treatment outcomes to the outcomes from applying U.S. and international guidelines. We also highlight the main differences in the policies for individual patients. In Section 4.5, we present sensitivity analysis for our model.

4.1. Data and study population

We used 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 Mayo Clinic, Rochester, MN (Gorman et al., 2000). The DEMS dataset included 663 patients with cholesterol, HbA1c, blood pressure, and other laboratory values. Population statistics are provided in Table 3. The patients in this dataset are hereafter referred to as the Mayo

Table 4

Percentage change in risk factors for given medications as computed from Mayo Electronic Medical Records and Diabetes Electronic Management System.

Medication (i)	Affected risk factor		
	Cholesterol		Blood pressure
	$\omega^{\text{TC}}(i)$	$\omega^{\text{HDL}}(i)$	$\omega^{\text{SBP}}(i)$
Statins	-14.0	+7.3	-
Fibrates	-3.9	+4.7	-
ACE/ARBs	-	-	-3.7
Thiazides	-	-	-5.0
Beta blockers	-	-	-4.6
Calcium channel blockers	-	-	-2.5

Clinic cohort. Changes in TC, HDL, and SBP values from medications are found in Table 4. These values were estimated by computing the percent change in metabolic values before and after initiation of the given treatments using methods reported in Denton et al. (2009). These changes are assumed to be independent and additive for patients on multiple medications. The percentage change in the appropriate metabolic value(s) was calculated regardless of what other medication the patient was on. For example, the effect of statins was assumed to be independent of whether the patient had initiated ACE inhibitors for blood pressure reduction. A limitation of this approach is that the medication effects may be different depending on what other medications the patient is taking, particularly from the same class (e.g., the combined effect of statins and fibrates may be less than the sum of their individual benefits); however, the optimal order of cholesterol medication initiation based on our model was the same as the order observed in the Mayo Clinic cohort for 89% of the patients. For blood pressure medications, 77.7% of patients started medications in the optimal order with at most one medication out of order.

The descriptions and values of utility and cost parameters can be found in Table 5. In our numerical experiments we chose $R_0 = \$100,000$ as the base-case willingness-to-pay factor since this is the most commonly used value in U.S. studies (Rascati, 2006); however, we will use a range of willingness-to-pay values for R_0 for the population results. Costs and utility decrements for each cholesterol and blood pressure medication are found in Table 6. The costs are the lower bound values based on U.S. pharmaceutical cost estimates (Red Book, 2009), and the utility decrements are based on estimates from the literature (Tengs & Wallace, 2000; Pignone, Earnshaw, Tice, & Pletcher, 2006; Greving, Visseran, de Wit, & Algra, 2011) and author judgement in cases where estimates are not available in the literature. We perform sensitivity analysis on the medication utility decrements in the interval $[0, 0.01]$, due to the uncertainty in the appropriate values that should be used. For all the numerical experiments, we consider a decision horizon from age 40 to age 100 with an infinite horizon estimate of rewards accrued after the end of the decision horizon.

The transition probabilities among health states were also computed from the DEMS dataset. A spline fit was used to interpolate missing laboratory values for cholesterol values to obtain an estimate of yearly levels for these risk factors (Denton et al., 2009). Each risk factor was divided into L , M , H , and V categories (as defined in Section 3). The transition probabilities among metabolic states were estimated from the percentages of patients that moved between each state at time t to each state at time $t + 1$.

Transition probabilities to event and death states were drawn from the literature. The UKPDS risk equations (Kothari et al., 2002; Stevens et al., 2001; Stevens et al., 2004) were used to compute probabilities of incurring a CHD event or stroke, both fatal and nonfatal, based on patient risk factors including age, gender, TC, SBP, and HbA1c. The Centers for Disease Control and Prevention (CDC) mortality tables (CDC, 2007) were used to estimate the probability of death from other causes.

Table 5
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	Nationwide Inpatient Sample (2006)
	Initial hospitalization for CHD (C^{CHD})	\$18,590	Nationwide Inpatient Sample (2006)
	Follow-up for stroke (CF^S)	\$1664	Thom et al. (2006)
	Follow-up for CHD (CF^{CHD})	\$2576	Russell et al. (1998) and Thom et al. (2006)
	Willingness-to-pay factor (R_0)	\$100,000	Rascati (2006)
	Discount factor (λ)	0.97	Gold et al. (1996)
Utility inputs	CHD decrement (d^{CHD})	0.07	Clarke et al. (2002) and Tsevat et al. (1993)
	Stroke decrement (d^S)	0.21	Clarke et al. (2002), Tengs et al. (2001), and Tengs and Lin (2003)

Table 6
Costs and utility decrements for each medication used in the model.

Medication	Cost	Utility decrement
Statins	\$212	0.003
Fibrates	\$652	0.003
ACE/ARBs	\$48	0.005
Thiazides	\$48	0.005
Beta blockers	\$48	0.005
Calcium channel blockers	\$866	0.005

4.2. Model validation

In order to validate the results from our MDP, we compared outputs from our model to life expectancy estimates from the Framingham Heart Study (FHS) for diabetes patients with and without cardiovascular disease (Franco, Steyerberg, Hu, Mackenbach, & Nusselder, 2007). The FHS recruited 5209 study participants living in Framingham, Massachusetts between 1948 and 1951. Franco et al. (2007) chose three separate 12-year follow-up periods to include in their study. The beginning years of the three periods were 1956, 1969, and 1985. A total of 9033 patient observation periods were included once patients with incomplete data or patients having cardiovascular disease were removed. The two estimates compared from the FHS and our model were the expected LYs before a stroke or CHD event from age 50 and the expected LYs before death from age 50.

The FHS reported three sets of estimates for LYs before an event, LYs after an event, and total LYs from age 50: no diabetes, diabetes, and overall (including patients with and without diabetes). Our MDP assumes patients have diabetes, so the estimates for patients with diabetes at age 50 should provide a good lower bound for the estimates from the MDP model. Since patients without diabetes at

age 50 may develop diabetes in the future, the overall estimates should provide an upper bound on the estimates for patients with diabetes at age 50. Tables 7 and 8 present the comparison of expected LYs before death, expected LYs before a stroke or CHD event, and expected LYs after an event from age 50 for our MDP model and the FHS. We present MDP results for two policies: the current U.S. guidelines (U.S. 1) and no treatment. Although no data are available on the actual treatment policy for the patients in the FHS, it is likely that most patients would have followed a policy that would result in expected LYs between the estimates for the two policies given. As expected, the LYs before an event from the MDP model fall between the FHS diabetes estimate and the FHS overall estimate for males and females. This is also true for female life expectancy estimates; however, the life expectancy from age 50 estimate for males using U.S. 1 falls outside of the corresponding FHS range. It is important to note that the additional LYs after an event for the FHS diabetes estimate is very close to the estimate for additional LYs for the MDP results. For males and females, the estimates for the additional LYs after an event from the MDP are within the 95% confidence intervals for the FHS diabetes patients.

Unfortunately there is no perfect way to validate medical decision making models such as ours. There are many possible reasons why our estimates for event-free years and life expectancy would differ from the estimates from the FHS. First, our model uses 2007 estimates of probabilities of death from other causes; life expectancies have increased significantly since the 1950s when the FHS study began. Second, we use the UKPDS risk equations to estimate the risk of stroke and CHD events; while these equations are widely believed to provide valid estimates of risk, they are based on observed events from a population of diabetes patients from the United Kingdom. Finally, it is impossible to know what medication policy was used by the patients in the FHS, and available medications and U.S. treatment guidelines have changed significantly since the 1950s.

Table 7
Male comparison of expected LYs before death, expected LYs before a stroke or CHD event, and expected LYs after an event from age 50 for our MDP model and the Framingham Heart Study (FHS). The 95% confidence intervals are provided for the FHS estimates.

	FHS: Diabetes Patients	FHS: Overall	MDP: U.S. 1	MDP: No Treatment
Life expectancy	21.3 (19.4–23.1)	27.9 (27.3–28.6)	28.8	26.9
LYs before event	14.2 (12.3–16.1)	21.2 (20.5–22.0)	21.2	18.9
LYs after event	7.1 (6.0–8.3)	6.7 (6.2–7.1)	7.6	8.0

Table 8
Female comparison of expected LYs before death, expected LYs before a stroke or CHD event, and expected LYs after an event from age 50 for our MDP model and the Framingham Heart Study (FHS). The 95% confidence intervals are provided for the FHS estimates.

	FHS: Diabetes Patients	FHS: Overall	MDP: U.S. 1	MDP: No Treatment
Life expectancy	26.5 (24.4–28.5)	33.8 (33.2–34.4)	32.1	29.4
LYs before event	19.6 (17.5–21.9)	27.3 (26.7–28.0)	25.3	23.1
LYs after event	6.8 (5.5–8.2)	6.4 (6.0–6.9)	6.8	6.3

4.3. Primary prevention treatment policies

In this section we consider primary prevention of stroke and CHD events. The yearly rewards for primary prevention are defined as follows:

$$r(\ell, \mathbf{m}) = \begin{cases} R_0 - C^O - C^{MED}(\mathbf{m}) & \forall \ell : \ell_S = \ell_{CHD} = 0, \\ 0 & \text{otherwise.} \end{cases} \quad (7)$$

Patients receive rewards for LYs (R_0) minus costs of medication and other healthcare costs up until the occurrence of a first event including CHD or stroke (fatal or nonfatal) or death from other causes. We set all costs other than the other costs and medication costs equal to zero: $C^S(\ell) = C^{CHD}(\ell) = C^{FS}(\ell) = C^{FCHD}(\ell) = 0$. In addition, no costs are incurred in this model after a patient has an event. With this reward structure, the objective is to maximize the reward for LYs minus costs incurred prior to an event or death. In other words, the goal of this reward structure is to delay the patient's first event. This goal is consistent with the U.S. guideline's goal of primary prevention (Antonopoulos et al., 2002; Chobanian et al., 2003), and expected time to first event (e.g., stroke, CHD event, or death) is often used as a measure of primary prevention to evaluate the benefits of treatment (Colhoun et al., 2004; Ridker et al., 2008; Okada et al., 2011).

Figs. 2 and 3 compare the primary prevention optimal treatment policies and published guideline results for males and females, respectively. These graphs present the expected LYs versus the expected discounted costs of medication before an event has occurred (the other costs have not been included in the graph). The results for the optimal treatment policies are displayed using the optimal tradeoff curves where the reward for LYs, R_0 , is varied from \$25,000 to very large values of R_0 where LYs are maximized ($R_0 > \$1,000,000,000$). The base case of $R_0 = \$100,000$ is shown on the curves. There is great similarity in costs and LYs between the U.S. and international guideline results. While the LYs achieved with the guidelines are very near the optimal policy curves for both the males and females, we see that the costs of the guidelines could be greatly reduced by implementing the optimal policies due to the flatness of the optimal policy curve as the LYs increase.

The main difference between the male and female results for LYs versus medication costs is seen on the vertical axis. According

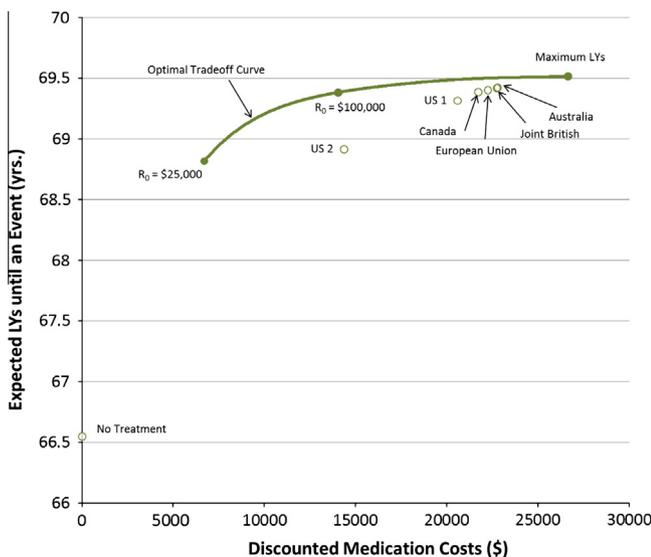


Fig. 2. Comparison of optimal treatment policies for male patients to treatment by U.S. and international guidelines.

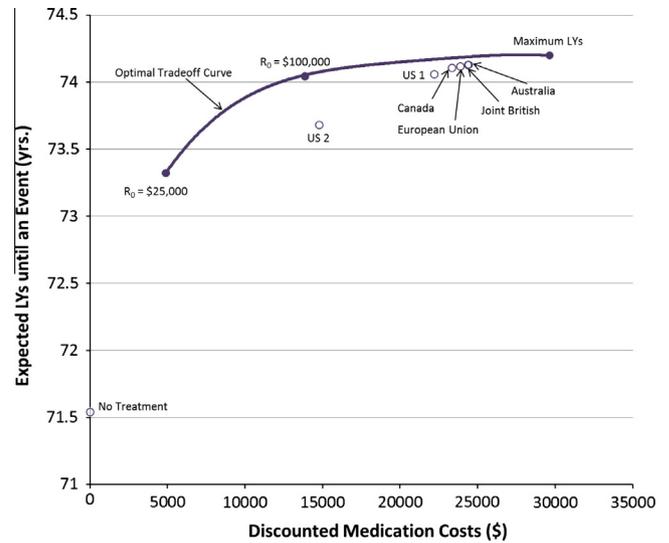


Fig. 3. Comparison of optimal treatment policies for female patients to treatment by U.S. and other international guidelines.

to our results, on average females can expect approximately five additional years before an event than males. Furthermore, relative to no treatment, males can increase their expected time to an event by as much as 2.97 years, while females can only increase their expected time to first event by up to 2.66 years from no treatment by following the optimal guidelines. In addition, following U.S. 1 provides males an additional 2.76 event-free LYs over no treatment while females can only achieve an additional 2.52 event-free LYs. Thus, we see that male patients can receive a greater benefit than females from medication as seen from the primary prevention perspective. In both cases, as the value of R_0 increases, the optimal guidelines result in increased event-free LYs over U.S. 1 for all male and female patients.

The results presented in Figs. 2 and 3 are the expected LYs and medication costs for the average male and female patient, respectively. However, not every patient receives the same benefit from treatment. Figs. 4 and 5 provide histograms for the difference in event-free LYs and medication costs between the optimal guidelines, for the $R_0 = \$100,000$ case, and U.S. 1. While the expected cost for all males is lower for the optimal guideline than U.S. 1, only 55% of the patients would increase event-free LYs (by up to 0.398 LYs) using the optimal guideline. For the other 45% of the patients, LYs could be decreased by as much as 0.084 LYs. As with male patients, for female patients the optimal guidelines result in lower expected cost. However, only 27% of females would increase event-free LYs (by up to 0.202 LYs) using optimal guidelines over U.S. 1. The remaining 73% of patients would see a decrease in LYs with the use of the optimal guidelines. The reduction in LYs for these patients could be as much as 0.101 LYs.

For more insight into how the policies differ, we provide general descriptions of the policies for the optimal guidelines ($R_0 = \$100,000$) and U.S. 1. According to the optimal guidelines ($R_0 = \$100,000$), all patients start statins first. The second line treatment is fibrates or thiazides depending on the health status of the patient. The third line treatment is another blood pressure medication (thiazides for those that started fibrates second and beta blockers for those that started thiazides second). The optimal time of initiation of the first four medications varies according to the health status of the patient, but they are started by the time the patient is 45, with the fifth medication being started as late as age 63. In all cases, the final medication to be added for all patients is calcium channel blockers. It is started very late in life (age 70 or later)

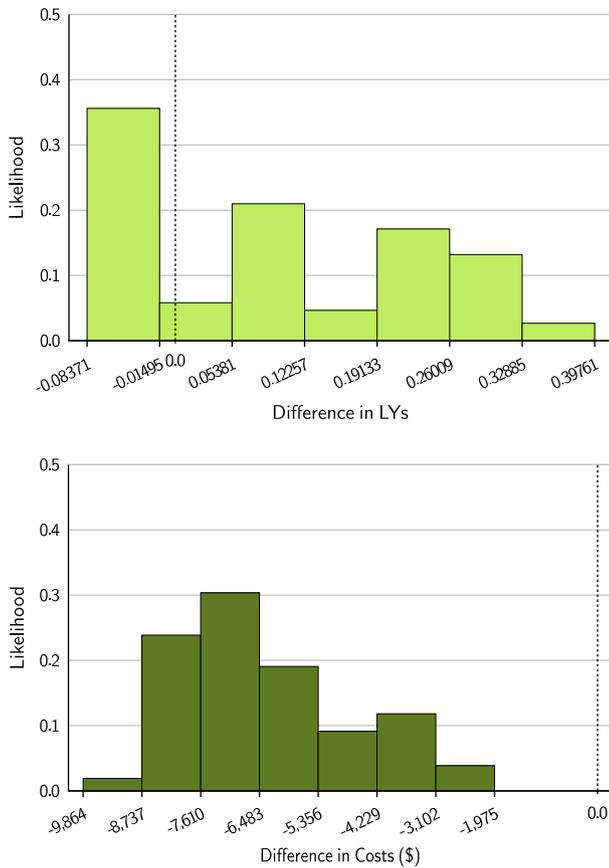


Fig. 4. Histograms to provide the difference in LYs and medication costs for males between the optimal guidelines ($R_0 = \$100,000$) and U.S. 1.

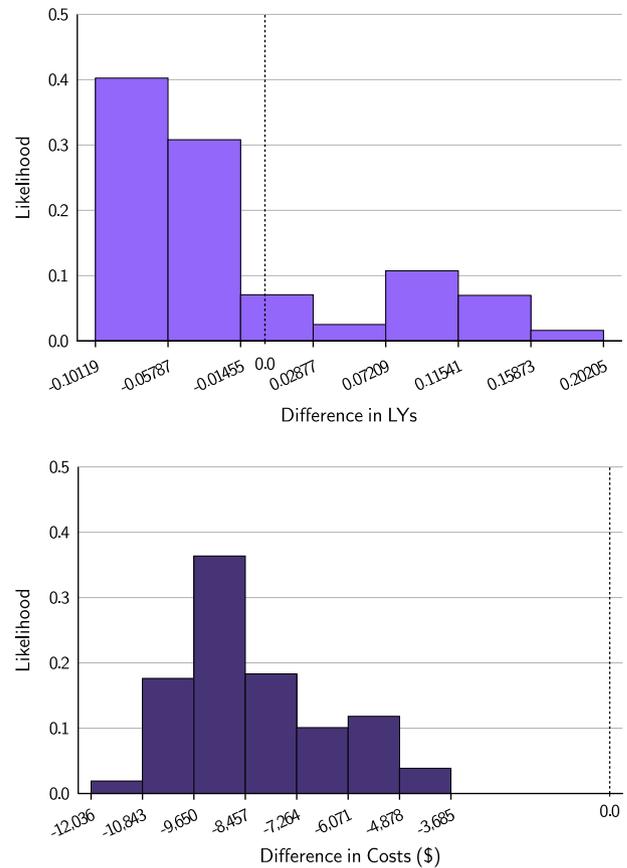


Fig. 5. Histograms to provide the difference in LYs and medication costs for females between the optimal guidelines ($R_0 = \$100,000$) and U.S. 1.

or not at all, depending on the patient's gender and health status. When applying U.S. 1, the policies range from starting all six available medications by age 43 for patients in the sickest health state to starting no medications for patients in the healthiest state. For patients that do start medications, the order is to initiate statins and thiazides, then fibrates and ACE inhibitors/ARBs, followed by beta blockers, and finally calcium channel blockers. These descriptions are true for both males and females. The optimal treatment policy could be applied in practice by using a look-up table containing the optimal actions that are dependent on patient factors including gender, age, current medications, and metabolic values.

4.4. Primary and secondary prevention treatment policies

In this section we consider primary and secondary prevention: QALYs are accrued before and after the first stroke and CHD event. We estimate expected QALYs and expected discounted costs over each patient's lifetime using the reward function defined in Eq. (5). This provides another perspective on the effectiveness of the current guidelines to the optimal guidelines.

Fig. 6 presents the optimal tradeoff curve of QALYs versus costs of medication and hospitalization for events for all male patients by varying the reward for QALYs, R_0 . Each point on the optimal trade off curve, the no treatment point, and each of the points for the current guidelines represent the expected QALYs and expected costs for the average male. The curve represents the outcomes from optimal treatment with $R_0 = \$25,000$ to optimal treatment with very large values for R_0 for which QALYs are maximized ($R_0 > \$1,000,000$). The base case value of R_0 ($R_0 = \$100,000$) is shown on the curve. We compare this curve to the U.S. and other

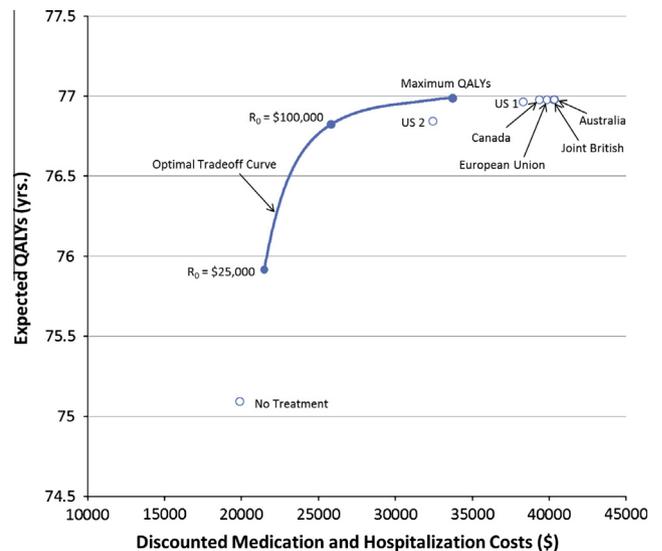


Fig. 6. Comparison of optimal treatment policies for male patients to treatment by U.S. and international guidelines.

international guidelines and no treatment. All of the guidelines besides U.S. 2—the current guideline for patients without diabetes and the previous guideline for patients with diabetes—are similar with respect to expected QALYs and costs. U.S. 2 does not result in QALYs that are as high, but costs are lower. This suggests that treatment based on risk levels and patient risk factors could reduce expected costs with small reduction in expected QALYs.

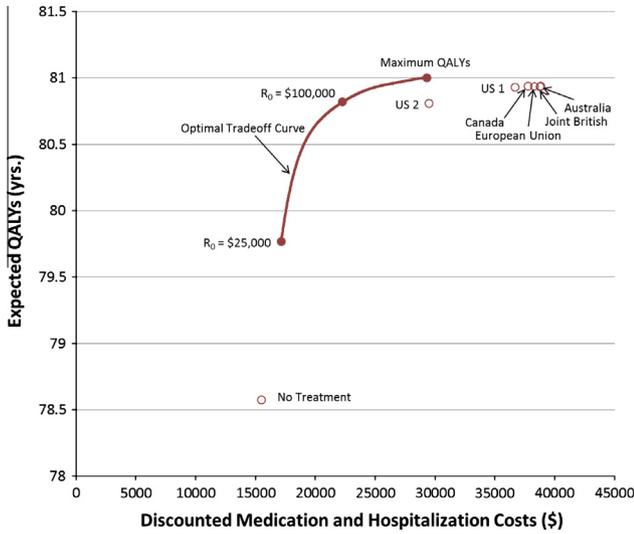


Fig. 7. Comparison of optimal treatment policies for female patients to treatment by U.S. and international guidelines.

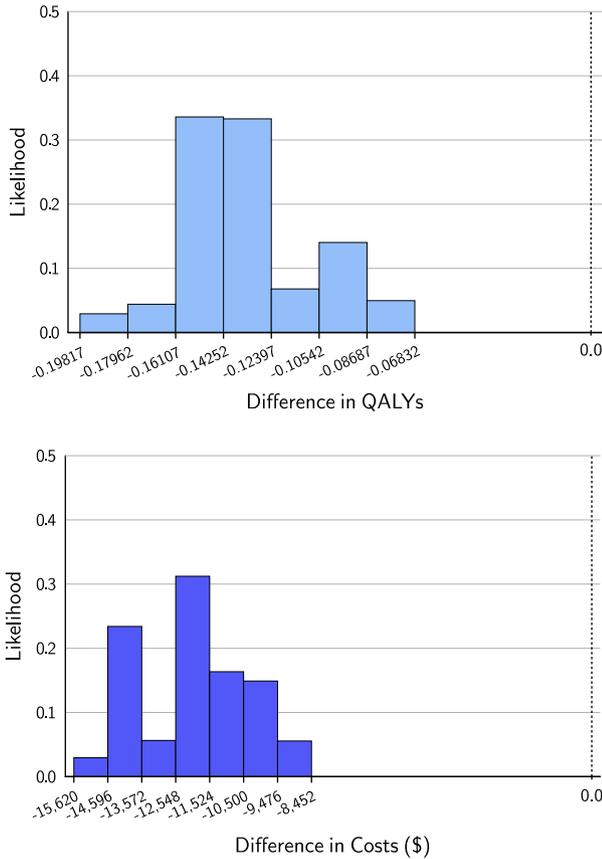


Fig. 8. Histograms to provide the difference in QALYs and medication and hospitalization costs for males between the optimal guidelines ($R_0 = \$100,000$) and U.S. 1.

We also see from the Fig. 6 that the same expected QALYs can be achieved with the optimal policies as U.S. 1 and the international guidelines when a very high R_0 value is used. This given quality adjusted lifespan can be achieved with the optimal treatment policies at a much lower expected discounted cost of medication and hospitalization for events than the guidelines. We see a savings of at least \$4573 (the difference in costs between Maxi-

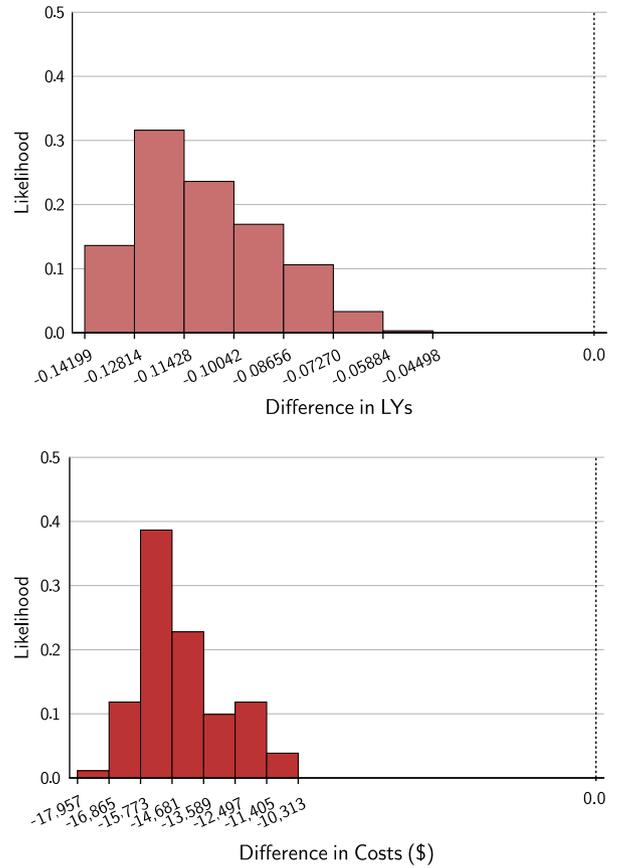


Fig. 9. Histograms to provide the difference in QALYs and medication and hospitalization costs for females between the optimal guidelines ($R_0 = \$100,000$) and U.S. 1.

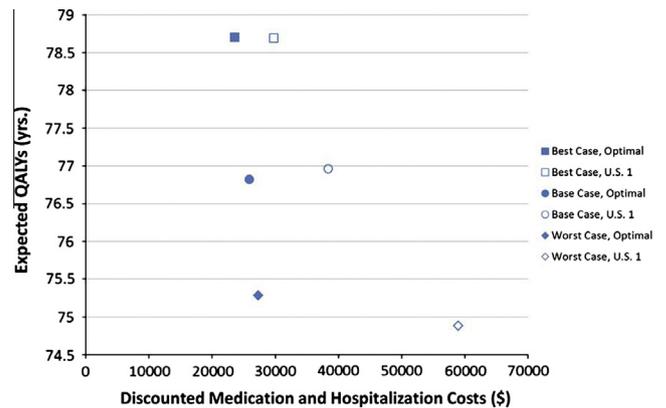


Fig. 10. Comparison of QALYs versus costs for best, worst, and best case parameters for disabilities, medication effectiveness, medication cost, and hospitalization cost. Results are presented for male patients with the optimal guidelines ($R_0 = \$100,000$) and U.S. 1.

imum QALYs and U.S. 1) per male patient on average with the optimal policies compared with the U.S. and international guidelines.

Fig. 7 presents the same optimal tradeoff curve for female patients by varying R_0 . We again observe the similarity of U.S. 1 and the international guidelines. For female patients, the increase in QALYs for using U.S. 1 over the previous U.S. guidelines (U.S. 2) costs \$60,221/QALY; in comparison to the cost of the male increase in QALYs of \$49,349/QALY. These \$/QALY estimates are found by calculating the difference in costs over the difference in

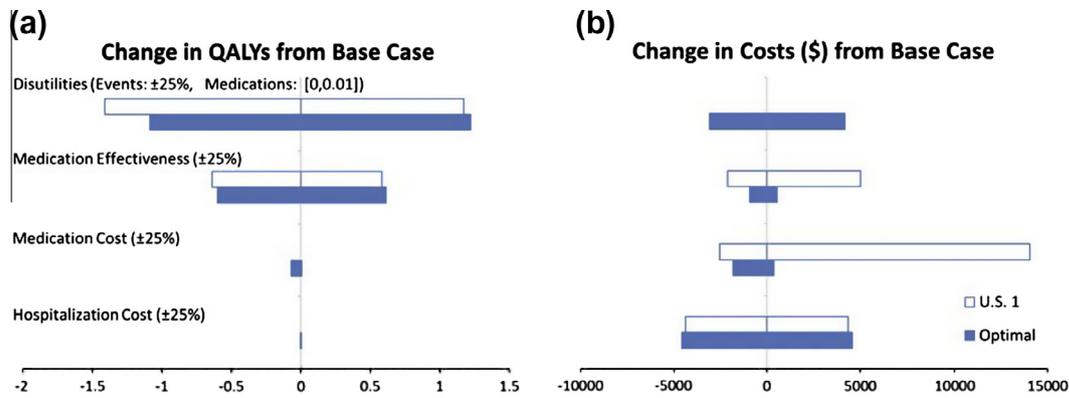


Fig. 11. Diagrams illustrating the difference in QALYs and medication and hospitalization costs relative to the base case when one-way sensitivity analysis is performed on disutilities, medication effectiveness, medication cost, and hospitalization cost. Results are presented for male patients with the optimal guidelines ($R_0 = \$100,000$) and U.S. 1.

QALYs between the two guidelines considered. This is likely due to the fact that U.S. 2 takes into account gender, risk of events, and age. Also, the risk of stroke and CHD events is in general lower for females than for males.

We also see from Fig. 7 that we can simultaneously improve expected QALYs and reduce costs for female patients with the optimal treatment policies over the U.S. and international guidelines. This is likely due to the fact that the guidelines treat male and female patients the same, not adjusting for differences in gender when determining medication initiation decisions. The optimal policies take into account the lower probabilities of events for females earlier in life, resulting in initiation of fewer medications, higher expected QALYs, and lower expected discounted costs of treatment. According to our model, with the optimal treatment policies, a savings of at least \$7378 coupled with an increase of 0.072 QALYs per female patient could be realized compared to the U.S. and international guidelines.

There are a few notable differences between the QALY results for males and females. Females can expect 3.48 QALYs more than males with no treatment. Males can expect to improve their QALYs with optimal treatment by as much as 1.90 QALYs while females can improve by up to 2.43 QALYs. As a final observation, we see that optimal treatment policies would have more effect on improving QALY and cost outcomes over U.S. 1 for females than for males.

As with the primary prevention results of Section 4.3, we provide histograms for the difference in QALYs and costs for males and females. Fig. 8 shows the difference in QALYs and costs between the optimal guidelines ($R_0 = \$100,000$) and U.S. 1 for males. Fig. 9 provides the same histograms for females. All males and females simultaneously have lower QALYs and lower costs using the optimal guidelines ($R_0 = \$100,000$) over U.S. 1. As R_0 is increased, costs for the optimal guidelines remain lower than cost for U.S. 1 for males and females but QALYs are higher for all females and nearly all males.

While the U.S. 1 policies for males and females are the same as described in Section 4.3 since they do not depend on the reward function, the optimal guidelines are quite different. For the base case of $R_0 = \$100,000$, patients begin medications later in life than with the primary prevention objective guidelines. All males and females should begin statins as the first treatment. According to the optimal policies, intensification should occur in the following order: thiazides, beta blockers, ACE inhibitors/ARBs, fibrates, and calcium channel blockers. The optimal timings of the initial treatment and intensification depend on the patient's health status and gender. For example, the time to start statins ranges from age 40 to age 66, with the start time being most affected by health status. Patients begin the last medication as late as age 98.

4.5. Sensitivity analysis

In Sections 4.3 and 4.4 we included results that showed how sensitive the optimal results were to the willingness-to-pay factor R_0 . In this section we present best case, worst case, and one-way sensitivity analysis results for other important model inputs: utility decrements for medications and events, medication effectiveness, medication costs, and hospitalization and follow-up costs for events. Medication disutilities are varied over the interval $[0,0.01]$, and all other model inputs are varied by $\pm 25\%$. Fig. 10 compares the base case QALYs versus costs for male patients to the results when all perturbed parameters are set at the most favorable values (best case) or the least favorable values (worst case). For example, in the best case, medications have 0 disutility, event disutilities are 25% smaller, medication effectiveness is 25% greater, and costs are 25% lower. We see from Fig. 10 that the optimal guidelines ($R_0 = \$100,000$) are always less costly than U.S. 1, and as the parameters change from worst case to best case, the cost difference between the optimal results and U.S. 1 reduces. While the base case optimal QALYs are less than those for U.S. 1, the optimal QALYs are greater than the U.S. 1 QALYs in the best case by 0.007 and in the worst case by 0.404.

Fig. 11 presents the results of one-way sensitivity analysis. The diagrams for QALYs and costs show how sensitive the optimal ($R_0 = \$100,000$) and U.S. 1 guidelines are to changes in each set of parameters by comparing the QALYs and costs to the base case results for each guideline. Overall the optimal guideline ($R_0 = \$100,000$) is more robust than U.S. 1 because the optimal policy is able to adjust to account for changes in parameters. This is particularly noticeable in the diagram in Fig. 11(b) where medication effectiveness and medication cost are varied. The U.S. 1 QALYs do not change when costs are varied, and the U.S. 1 costs do not change when disutilities are varied. This is due to the fact that the U.S. 1 policy does not change based on model inputs. The sensitivity analysis results for female patients are very similar to the results presented for the male patients.

5. Conclusions

Our findings suggest the use of coordinated treatment of blood pressure and cholesterol can reduce the costs of treatment and hospitalization while improving length and quality of life. For primary prevention, the same event-free LYs from U.S. 1 could be achieved with optimal guidelines at a reduced cost. Using the optimal guidelines with large values of R_0 allows for additional LYs before an event or death over U.S. 1, though costs can be higher.

For the combined primary and secondary prevention, the model-based optimal treatment policies result in medications being initiated over a longer time period than with U.S. 1, producing a reduction in costs and in some cases improvement in expected QALYs. Since female patients have a later onset of stroke and CHD risk, compared to males, the delayed initiation of drugs from the optimal treatment policies is sufficient to manage risk of events while improving quality of life and reducing costs. Female patients can save at least \$7378 per patient on average over a lifetime compared to the U.S. and international guidelines. The main impact of the optimal policies for male patients is seen on the cost side. Male patients can save at least \$4573 per patient on average in lifetime costs compared to the U.S. and international guidelines. Implementation of the optimal policies could produce approximately the same expected QALYs as with the implementation of U.S. 1 while greatly reducing the overall cost of treatment.

We have quantified the benefits of coordinated treatment and highlighted the need for the U.S. treatment guidelines to coordinate treatment for blood pressure and cholesterol medications. The coordination of these types of medications is particularly beneficial since both blood pressure and cholesterol medications are used to prevent the stroke and CHD events. While we have presented the benefits of coordinated treatment for the management of blood pressure and cholesterol in diabetes patients, there are general insights that can be gained from the management of multiple risk factors for other types of patients.

In the future we could extend our model to include additional medications and treatment for other related risk factors. For example, aspirin could be added to the model since aspirin helps reduce the risk of stroke and CHD events in high risk individuals, albeit with the low probability of significant side effects such as gastrointestinal bleeding. In addition, the model could be extended to manage HbA1c with the use of glucose control medications. It is possibly a limitation in our current model that we use modification of surrogate markers (blood pressure and cholesterol) to reflect the benefits of medication rather than modified risk of events (stroke and CHD). In the future, the model could be altered to allow for modified risk of events to reflect the benefits of medication.

Our model has some limitations. While the medication effectiveness parameters are estimated from observational data, we do not explicitly model treatment effectiveness based on adherence to medication, and we do not account for changes in medication adherence over time. Similarly, we do not explicitly model treatment effectiveness based on medication dosage. The parameters used to calibrate our model are for patients who have health insurance and therefore may not perfectly reflect the general population. Our results are for a typical patient represented by the general trends we observe in the observational data used to calibrate our model and the all other cause mortality based on average population estimates. Our model could be calibrated to reflect individual risk factors for specific types of patients.

Acknowledgements

This material is based in part upon work supported by the National Science Foundation under Grant No. CMMI 0969885 (Denton). Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the National Science Foundation. This project was also funded in part by the Agency for Healthcare Research and Quality (AHRQ) under Grant No. 1R36HS020878-01 (Mason). The authors are grateful for the helpful comments from two anonymous reviewers that helped to improve this manuscript.

References

- CDC (2011). *National diabetes fact sheet*. <<http://www.cdc.gov/diabetes/pubs/factsheet11.htm>>.
- Dall, T., Zhang, Y., Chen, Y., Quick, W., Yang, W., & Fogli, J. (2010). The economic burden of diabetes. *Health Affairs*, 29(2), 297–303.
- Gold, M., Stevenson, D., & Fryback, D. (2002). HALYs and QALYs and DALYs, oh my: similarities and differences in summary measures of population health. *Annual Review of Public Health*, 23, 115–134.
- Kothari, V., Stevens, R., Adler, A., Stratton, I., Manley, S., Neil, H., et al. (2002). UKPDS 60 – Risk of stroke in type 2 diabetes estimated by the United Kingdom prospective diabetes study risk engine. *Stroke*, 33(7), 1776–1781.
- Stevens, R., Kothari, V., Adler, A., Stratton, I., & Holman, R. (2001). The UKPDS risk engine: A model for the risk of coronary heart disease in type 2 diabetes (UKPDS 56). *Clinical Science*, 101(6), 671–679.
- Stevens, R., Coleman, R., Adler, A., Stratton, I., Matthews, D., & Holman, R. (2004). Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes (UKPDS 66). *Diabetes Care*, 27(1), 201–207.
- Eastman, R., Javitt, J., Herman, W., Dasbach, E., Zbrozek, A., Dong, F., et al. (1997). Model of complications of NIDDM: I. Model construction and assumptions. *Diabetes Care*, 20(5), 725–734.
- Eddy, D. M., & Schlessinger, L. (2003). Archimedes – A trial-validated model of diabetes. *Diabetes Care*, 26(11), 3093–3101.
- The Action to Control Cardiovascular Risk in Diabetes Study Group (2008). Effects of intensive glucose lowering in type 2 diabetes. *The New England Journal of Medicine* 358, 2545–2559.
- The ADVANCE Collaborative Group (2008). Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *The New England Journal of Medicine* 358, 2560–2572.
- Duckworth, W., Abraira, C., Moritz, T., Reda, D., Emanuele, N., Reaven, P., et al. (2009). Glucose control and vascular complications in veterans with type 2 diabetes. *The New England Journal of Medicine*, 360, 129–139.
- Antonopoulos, S. (2002). Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. *Circulation* 106, 3143–3421.
- Chobanian, A., Bakris, G., Black, H., Cushman, W., Green, L., et al. (2003). The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension: American Heart Association*, 42, 1206–1252.
- Friedewald, W., Levy, R., & Fredrickson, D. (1972). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clinical Chemistry*, 18, 499–502.
- Harris, P., Joyner, B., Phillips, P., & Webster, C. (2009). *Diabetes management in general practice*. Diabetes Australia Publication NP.
- Bhattacharyya, O., Shah, B., & Booth, G. (2008). Management of cardiovascular disease in patients with diabetes: The 2008 Canadian diabetes association guidelines. *Canadian Medical Association Journal*, 179(9), 920–926.
- Graham, I. (2007). European guidelines on cardiovascular disease prevention in clinical practice: Executive summary. *Atherosclerosis*, 194, 1–45.
- Joint British Societies 2 (2005). JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 91, 1–52.
- Parker, R., Doyle, F., & Peppas, N. (2001). The intravenous route to blood glucose control. *IEEE Engineering in Medicine and Biology*, 20(1), 65–73.
- Denton, B., Kurt, M., Shah, N., Bryant, S., & Smith, S. (2009). Optimizing the start time of statin therapy for patients with diabetes. *Medical Decision Making*, 29, 351–367.
- Kurt, M., Denton, B., Schaefer, A., Shah, N., & Smith, S. (2011). The structure of optimal statin initiation policies for patients with type 2 diabetes. *III Transactions on Healthcare*, 1(1), 49–65.
- Timbie, J., Hayward, R., & Vijan, S. (2010). Diminishing efficacy of combination therapy, response-heterogeneity, and treatment intolerance limit the attainability of tight risk factor control in patients with diabetes. *Health Services Research*, 45(2), 437–456.
- Shah, N., Mason, J., Kurt, M., Denton, B., Schaefer, A., Montori, V., et al. (2011). Comparative effectiveness of guidelines for the management of hyperlipidemia and hypertension for type 2 diabetes patients. *PLoS ONE*, 6(1), e16170.
- Alagoz, O., Maillart, L., Schaefer, A., & Roberts, M. (2004). The optimal timing of living-donor liver transplantation. *Management Science*, 50(10), 1420–1430.
- Alagoz, O., Maillart, L., Schaefer, A., & Roberts, M. (2007). Choosing among living-donor and cadaveric livers. *Management Science*, 53(11), 1702–1715.
- Shechter, S., Bailey, M., Schaefer, A., & Roberts, M. (2008). The optimal time to initiate HIV therapy under ordered health states. *Operations Research*, 56(1), 20–33.
- Snow, V., Aronson, M., Hornbake, E., Mottur-Pilson, C., & Weiss, K. (2004). Lipid control in the management of type 2 diabetes mellitus: A clinical practice guideline from the American college of physicians. *Annals of Internal Medicine*, 140(8), 644–649.
- Vijan, S., & Hayward, R. (2004). Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: Background paper for the American college of physicians. *Annals of Internal Medicine*, 140, 650–658.
- Cleeman, J., Grundy, S., Becker, D., Clark, L., Cooper, R., & Denke, M. A., et al. (2001). Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high

- blood cholesterol in adults (Adult Treatment Panel III). *JAMA – Journal of the American Medical Association* 285(19), 2486–2497.
- Gold, M., Siegel, J., Russell, L., & Weinstein, M. (Eds.). (1996). *Cost-effectiveness in health and medicine*. Oxford University Press.
- Gorman, C. A., Zimmerman, B. R., Smith, S. A., Dinneen, S. F., Knudsen, J. B., Holm, D., et al. (2000). DEMS – A second generation diabetes electronic management system. *Computer Methods and Programs in Biomedicine*, 62(2), 127–140.
- Rascati, K. (2006). The \$64,000 question – What is a quality-adjusted life-year worth? *Clinical Therapeutics*, 28(7), 1042–1043.
- Red Book (2009). Tech. Rep., Thomson Healthcare, Inc.
- Tengs, T., & Wallace, A. (2000). One thousand health-related quality-of-life estimates. *Med Care*, 38(6), 583–637.
- Pignone, M., Earnshaw, S., Tice, J., & Pletcher, M. (2006). Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: A cost-utility analysis. *Annals of Internal Medicine*, 144, 326–336.
- Greving, J., Visseran, F., de Wit, G., & Algra, A. (2011). Statin treatment for primary prevention of vascular disease: Whom to treat? Cost-effectiveness analysis. *BMJ*, 342, d1672.
- Nationwide Inpatient Sample (2006). Tech. Rep., Healthcare Cost and Utilization Project.
- Thom, T., Haase, N., Rosamond, W., Howard, V., Rumsfeld, J., Manolio, T., et al. (2006). Heart disease and stroke statistics – 2006 Update – A report from the American heart association statistics committee and stroke statistics subcommittee. *Circulation*, 113(6), E85–E151.
- Russell, M., Huse, D., Drowns, S., Hamel, E., & Hartz, S. (1998). Direct medical costs of coronary artery disease in the United States. *American Journal of Cardiology*, 81(9), 1110–1115.
- Clarke, P., Gray, A., & Holman, R. (2002). Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). *Medical Decision Making*, 22(4), 340–349.
- Tsevat, J., Goldman, L., Soukup, J., Lamas, G., Connors, K., Chapin, C., et al. (1993). Stability of time-tradeoff utilities in survivors of myocardial infarction. *Medical Decision Making*, 13(2), 161–165.
- Tengs, T., Yu, M., & Luistro, E. (2001). Health-related quality of life after stroke – A comprehensive review. *Stroke*, 32(4), 964–971.
- Tengs, T., & Lin, T. (2003). A meta-analysis of quality-of-life estimates for stroke. *Pharmacoeconomics*, 21(3), 191–200.
- CDC (2007). *National vital statistics reports*.
- Franco, O., Steyerberg, E., Hu, F., Mackenbach, J., & Nusselder, W. (2007). Associations of diabetes mellitus with total life expectancy and life expectancy with and without cardiovascular disease. *Annals of Internal Medicine*, 167, 1145–1151.
- Colhoun, H., Betteridge, D., Durrington, P., Hitman, G., Neil, H., Livingstone, S., et al. (2004). Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the collaborative atorvastatin diabetes study (CARDS): Multicentre randomised placebo-controlled trial. *Lancet*, 364(9435), 685–696.
- Ridker, P., Danielson, E., Fonseca, F., Genest, J., Gotto, A., Kastelein, J., et al. (2008). Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *New England Journal of Medicine*, 359, 2195–2207.
- Okada, S., Morimoto, T., Ogawa, H., Kanauchi, M., Nakayama, M., Uemura, S., et al. (2011). Differential effect of low-dose aspirin for primary prevention of atherosclerotic events in diabetes management. *Diabetes Care*, 34(6), 1277–1283.