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Innovative Applications of O.R.

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

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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.

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-

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