

Designing Risk-Adjusted Therapy for Patients with Hypertension

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Limited guidance is available for providing patient-specific care to hypertensive patients, although this chronic condition is the leading risk factor for cardiovascular diseases. To address this issue, we develop an analytical model that takes into account the most relevant risk factors including age, sex, blood pressure, diabetes status, smoking habits, and blood cholesterol. Using the Markov Decision Process framework, we develop a model to maximize expected quality-adjusted life years, as well as characterize the optimal sequence and combination of antihypertensive medications. Assuming the physician uses the standard medication dose for each drug, and the patient fully adheres to the prescribed treatment regimen, we prove that optimal treatment policies exhibit a threshold structure. Our findings indicate that our recommended thresholds vary by age and other patient characteristics, for example (1) the optimal thresholds for all medication prescription are nonincreasing in age, and (2) the medications need to be prescribed at lower thresholds for males who smoke than for males who have diabetes. The improvements in quality-adjusted life years associated with our model compare favorably with those obtained by following the British Hypertension Society's guideline, and the gains increase with the severity of risk factors. For instance, in both genders (although at different rates), diabetic patients gain more than non-diabetic patients. Our sensitivity analysis results indicate that the optimal thresholds decrease if the medications have lower side-effects and vice versa.

Key words: hypertension treatment; personalized healthcare; medical decision making; Markov Decision Processes; threshold policy

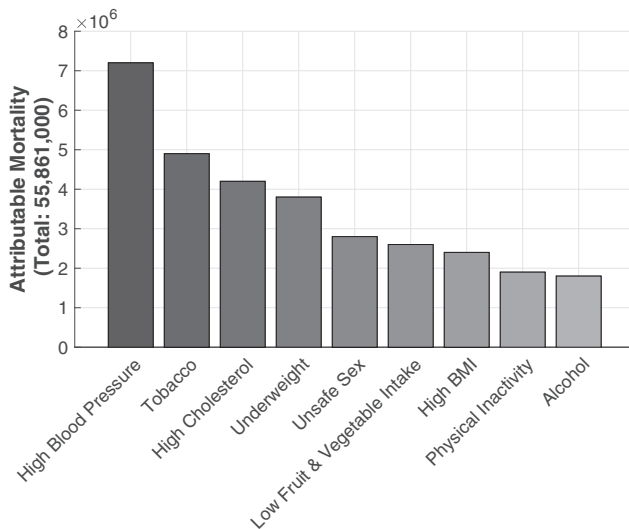
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1. Introduction

Hypertension is a chronic medical condition in which blood pressure in the arteries elevates to a level that may eventually cause serious cardiovascular problems, such as coronary heart disease and stroke, the two leading causes of death and serious long-term disability (Mozaffarian et al. 2016, Yoon et al. 2015). For example, 77% of first stroke events occur among patients with hypertension (Go et al. 2014). Hypertension is also a major risk factor for other chronic diseases, including myocardial infarction, renal failure, and retinopathy (Jones et al. 2009). In a study commissioned by the World Health Organization, Ezzati et al. (2002) identified hypertension as the leading risk for fatalities (see Figure 1, which is adapted from Figure 1 in the

referenced article). From a different perspective, Kontis et al. (2017) attributed South Korea's increased life expectancy to the country's investments in achieving low blood pressure at the population level, among other things.¹

More than 1 billion people in the world suffer from hypertension, and its prevalence is on the rise. In the US, alone, nearly one in three adults aged 40–59 and two in three in older adults suffer from the condition, while only half of these patients have their blood pressure under control (World Health Organization 2013). Although lifestyle changes (including healthy diet, exercise, smoking cessation) can improve blood pressure control, in most cases, the use of medications (i.e., antihypertensive therapy) is necessary for patients for whom lifestyle changes fail to control hypertension.

Figure 1 Mortality Due to Leading Global Risk Factors

Multiple guidelines exist for hypertension management in the US, Canada, Britain, and mainland Europe.² It is important to note that there is no consensus among these guidelines pertaining to blood pressure targets and treatment strategies. In a recent conference focusing on hypertension,³ Dr. Schiffrin, one of the keynote speakers, emphasized that “recommendations for when to use or start different classes of drugs” differ between guidelines. Additionally, these guidelines mostly provide non-personalized (i.e., one-size-fits-all) recommendations that do not take into account differences in the risk profiles of individuals (Steimle and Denton 2017). These two issues have led to gaps at the translational level in clinical practice, and these gaps have resulted in physicians relying primarily on their own clinical judgment to determine the best course of action.

The need for personalized therapy is undeniable and constitutes an open research challenge in the medical decision-making domain (Denton et al. 2011). As such, it should come as no surprise that personalized medicine is central to the medical community at large and identified as the “future of medicine” (Liebman 2007, Williams et al. 2003). Even though the role of personalized therapy for patients with hypertension has been emphasized in the medical literature (Floras 2013, National Institute for Health and Clinical Excellence 2011, Savoia et al. 2017), there are some differences in its interpretation. At one extreme, it entails “the use of genomic, epigenomic, exposure and other data to define individual patterns of disease, potentially leading to better individual treatment” (US Food and Drug Administration 2013) and at the other, it involves the tailoring of medical treatment (such as choosing the most suitable drug) to the specific characteristics of each patient

group (Redekop and Mladsi 2013, Savoia et al. 2017). In the context of our study, we adopt the latter, and explore the value of customizing medical treatments to individual characteristics pertaining to Cardiovascular Disease (CVD) risks, that is, age, sex, diabetes status, blood cholesterol, smoking habits, in addition to the patient’s blood pressure.

The Operations Management/Operations Research (OM/OR) literature is silent pertaining to clinical decision support for hypertension management. The inherent complexity of the hypertension treatment process, which comprises a set of sequential decisions under uncertainty, lends itself naturally to a Markov Decision Process (MDP) representation. Indeed, this has been recognized in the seminal 1990 paper by Schechter (1990a,b). In this study, we develop an MDP model, which takes into account key patient characteristics in order to determine the optimal sequence and combination of antihypertensive medications. To this end, our model aims to minimize the likelihood of coronary heart disease and stroke as well as drug-related side-effects. We accomplish this goal through identifying the optimal combination of medications that maximizes the patient’s total expected quality-adjusted life years (QALYs), which serves as the common index to measure the effectiveness of medical interventions. It also accounts for both the quality and quantity of life. QALY is normalized to 1 for a patient with perfect health (for a full year) and 0 for death (Drummond et al. 2015). In this study, we consider the global cardiovascular risk which is influenced, according to the Framingham Heart Study, by a set of key comorbidities and risk factors including diabetes, blood cholesterol, smoking habits, age, and sex, in addition to the patient’s blood pressure (D’Agostino et al. 2008). Our research, hence, is a key step toward the personalization of antihypertensive treatment by providing insights to help clinicians enhance care tailored to their patients. Using the proposed framework, we explore the following research questions:

1. Does the optimal hypertension treatment policy depend on patient characteristics, and, if so, how?
2. Does the optimal hypertension treatment policy have structural properties that can provide insights to the clinicians?
3. What is the value of a personalized hypertension treatment policy for the patient?

This study contributes to the literature on personalized healthcare in three ways. To the best of our knowledge, this is the first analytical study on hypertension treatment that takes a patient-oriented perspective on medical decision-making. Arguably, this would assist clinicians in customizing their treatment

strategy based on the characteristics of the patient, as opposed to the traditional one-size-fits-all approach. Secondly, we show that threshold-type policies are optimal, and this is good news from the clinician's perspective, since such policies are intuitive and easy to implement. Note that all current medical guidelines for hypertension treatment are also stated in a threshold-type structure. Finally, we characterize the personalization-related and optimization-related components of the QALY improvements associated with our approach. This solidifies our understanding of the value of personalization in hypertension treatment.

The remainder of the study is organized as follows. We provide a brief medical background about hypertension and an overview of the most relevant literature in section 2. In section 3, we explain the medical decision-making process for hypertension management and present the MDP modeling framework. Section 4 details the analytical properties of the optimal solutions. In section 5, we conduct an extensive numerical analysis through a case study and discuss the value of treatment personalization and care optimization for patients. In this section, we also present a set of sensitivity analyses based on variations in the model parameters. Finally, section 6 concludes the study.

2. Background

We begin this section by providing a brief medical background on hypertension. The subsequent two subsections provide an overview of the two streams of literature directly relevant to our work. These are the rather sparse OM/OR literature about hypertension control, and the MDP applications in traditional and personalized medical decision-making. Finally, at the end of this section, the link between this study and existing OM/OR literature is explored.

2.1. Medical Background on Hypertension

Blood pressure (BP) is conventionally measured in millimeters of mercury unit (denoted by mmHg) and is usually expressed using two terms: systolic blood pressure (SBP) and diastolic blood pressure (DBP). SBP is the arterial blood pressure during a heartbeat, while DBP is the blood pressure between heartbeats. Hypertension is commonly associated with SBP higher than 140 mmHg or DBP higher than 90 mmHg, but the diagnosis also heavily depends on the risk profile of the patient. There is substantial evidence that SBP is a more important indicator for hypertension than DBP, hence a stronger predictor for CVD (D'Agostino et al. 2008). Conventionally, the diagnosis of hypertension is based on several in-clinic and out-of-clinic measurements after an elevated initial

reading (Mozaffarian et al. 2016). Hypertension is classified as either primary or secondary. In the primary (or essential) hypertension, which accounts for 90–95% of the cases, no medical condition can be found as the major cause. Secondary hypertension, however, can be attributed to medical conditions associated with the heart, endocrine system and arteries. In this study, we focus on primary hypertension.

Unfortunately, around two-thirds of hypertensive patients do not achieve optimal blood pressure levels with a single drug; hence, most of them are required to take multiple antihypertensive medications simultaneously (clinically known as combination therapy), on a daily basis for the rest of their lives (Saito et al. 2005). There are five generic classes of medications to treat hypertension: β -Blockers (BB), Angiotensin-Converting-Enzyme Inhibitor (ACEI), Angiotensin II Receptor Blockers (ARB), Diuretic (DU, with the Thiazide as the most common type), and Calcium Channel Blockers (CCB). These classes differ both in their side-effects and in their effectiveness to reduce blood pressure.

2.2. OM/OR Literature on Hypertension Control

The OM/OR literature concerning hypertension management is quite sparse and dated. Schechter (1988, 1990a,b) studies a series of hypertension management problems to identify the time when blood pressure readings should be stopped before prescribing a medication. These studies, however, do not address key hypertension management issues such as medication effectiveness and side-effects, the risk of CVD, patient characteristics, and combination therapy. The author acknowledges these limitations and particularly calls for a more sophisticated dynamic framework as a suitable model for optimizing antihypertensive prescriptions. Optimal antihypertensive therapy was also studied by Moyé and Roberts (1982) to investigate the economically optimal protocol of antihypertensives. The data in this study is based on interviews with physicians, and no patient characteristics are taken into account. Also, the study considers only DBP, which is of less clinical value in comparison to SBP. Moskowitz et al. (1993) examine hypertension diagnosis with the objective of minimizing the risk of misclassification error (i.e., the incorrect diagnosis of a healthy person as hypertensive and vice versa). In this study, a multistage statistical procedure is developed for the design and evaluation of a screening program that leads to a lower risk of misclassification error, while maintaining a lower participation effort. Bonifonte et al. (2017) use stochastic optimization and jointly consider SBP and DBP to determine the optimal dosage of the prescribed antihypertensives. Their study, which is conducted at the population level, considers the blood pressure-induced risk of

mortality quantified by the so-called J-curve function (Tsika et al. 2014).

2.3. MDP Applications in Medical Decision-Making

A sizeable body of literature has explored the use of MDP in medical decision-making. The most recent papers in this stream of literature include screening, prevention or treatment of chronic diseases such as liver disease (Alagoz et al. 2004, 2007a,b, Sandıkçı et al. 2008), kidney disease (Lee et al. 2008, Skandari et al. 2015), HIV (Shechter et al. 2008), ovarian hyperstimulation (He et al. 2010), breast cancer (Ayvaci et al. 2012, Chhatwal et al. 2010), prostate cancer (Zhang et al. 2012), colorectal cancer (Erenay et al. 2014, Güneş et al. 2015), and diabetes (Denton et al. 2009, Honeycutt et al. 2003, Kurt et al. 2011, Mason et al. 2014). It is important to note that all these papers tackle the problem at the population level, thereby not offering personalized recommendations. In an effort to address this gap, an increased interest in the application of MDP models in personalized medical decision-making has recently emerged in the OM/OR community. The studies in this stream primarily use Partially Observable Markov Decision Processes (POMDP), a variant of MDP, in which the state variable is not perfectly known. Using a two-stage POMDP-MDP modeling framework, Ibrahim et al. (2016) provide a personalized anticoagulation therapy for patients at risk of stroke. With the objective of maximizing total quality-adjusted life years, both Ayer et al. (2012) and Erenay et al. (2014) developed POMDP models to characterize optimal personalized mammography and colonoscopy screening, based on the individual risk of breast and colorectal cancers, respectively. Finally, Ayer et al. (2015) proposed the same modeling framework to optimize breast cancer screening strategies, while considering heterogeneity in women's adherence to their screening appointments. Our study differs from these papers from the perspective of the definition and application of personalized medical decision-making. While we define personalization as the heterogeneity in patient risk profile, and focus on hypertension management, Ayer et al. (2012) and Erenay et al. (2014) have a similar risk-profile-based definition of personalization, but their focus is on breast cancer and colorectal cancer, respectively. Ibrahim et al. (2016) and Ayer et al. (2015), on the other hand, formulate personalization as the sensitivity to atrial fibrillation medication and cancer screening program adherence, respectively.

2.4. Other Related Literature in OM/OR

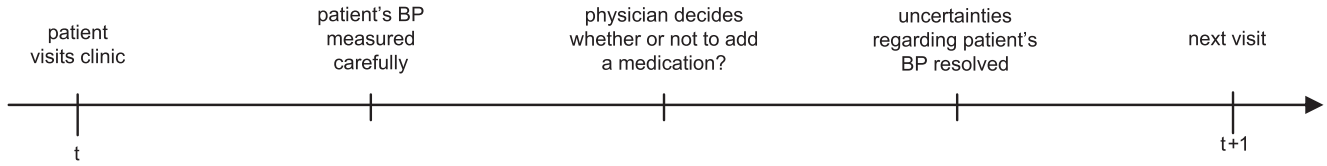
Our research is also related to the extant stream of dynamic capacity investment models in OM/OR that deal with the timing of capacity expansion

(Rajagopalan 1998), switching to a new technology (Li and Tirupati 1994), and launching new product development (Loch and Kavadias 2002), etc. Van Mieghem (2003) provides an excellent review of this stream. The common theme in this literature is characterized by the irreversibility of resource allocation decisions, and the uncertainty over the future rewards from these decisions (Dixit and Pindyck 1994, Trigeorgis 1996). Similar to our model, the optimal allocation decisions follow the so-called “control-limit policy,” which is characterized by a simple threshold: when the expected demand/reward exceeds the threshold, then it is optimal to invest; otherwise, it is optimal to stay out. An important observation is that a majority of papers in this literature deal with investment settings in which the capacities can be adjusted in continuous units (Eberly and Van Mieghem 1997, and the references in Van Mieghem 2003) or discrete units (Angelus and Porteus 2002, Cakanyildirim and Roundy 2002, and the references in Narongwanich et al. 2002). Our work builds on the second case, in which resources are indivisible (i.e., lumpy), and can be adjusted only in a number of feasible discrete sizes. Since the integrality constraints give rise to combinatorial nature, the results under this setting are quite limited under general conditions. Therefore, further restrictions, such as considering binary decisions (Chao and Kavadias 2008) and binary types (Kavadias and Loch 2003) in dynamic R&D project selection, are added to the model to make its analysis tractable. Finally, thanks to their ease of interpretation and practicality, control-limit type policies have found applications in other sequential irreversible decision problems in OM that deal with “when to enter a market” (Özer and Uncu 2013, 2015), “when to stop searching” (Atkinson et al. 2016, Harrison and Sunar 2015, Palley and Kremer 2014), “when to stop acquiring new/advanced demand information” (Boyacı and Özer 2010, Ding et al. 2014, Rahmani et al. 2017), etc. We refer readers to Oh and Özer (2016) for a recent treatment of optimal stopping problems.

3. Problem Statement and Modeling Framework

In this section, we present our model after describing the salient features of the hypertension management problem (HTNMP). Due to the chronic nature of hypertension, patients suffering from this condition need to visit their physicians on a regular basis. Figure 2 illustrates the timeline of decisions and events faced by patients and physicians in a typical hypertension management process. Note that there are three main steps between any two consecutive epochs t and $t + 1$. In the first step, the patient's blood pressure is measured using validated equipment

Figure 2 Timeline of Decisions and Events in a Typical Hypertension Management Process



(such as BpTRU). To minimize the effect of outliers and randomness in the measurements, a rigorous protocol is followed. The protocol comprises several in-clinic – and, if necessary, out-of-clinic – BP measurements (e.g., 24-hour ambulatory BP monitoring or home BP monitoring). During the in-clinic measurements, the blood pressure levels are measured multiple times (usually six), then averaged out after discarding the first observation while the patient is left alone in the room. For details of blood measurement protocols, refer to Daskalopoulou et al. (2015). After carefully measuring the patient's blood pressure, the physician decides (a) whether or not to prescribe a new antihypertensive medication, and (b) if so, which drug to prescribe among the set of available medication types (step 2). Two restrictions are imposed on these decisions based on common clinical practice. First, at each visit, one new medication at most can be prescribed in addition to the drugs the patient is already taking (National Institute for Health and Clinical Excellence 2011). Second, when a new medication is prescribed, it cannot be removed afterward, because of adverse consequences of such withdrawal, for example, rebound hypertension, increased risk of cardiovascular events, and even death (Reidenberg 2011). Finally, in the last step, the blood pressure evolves stochastically according to the patient characteristics and his/her medication status.

Hypertensive patients comprise a non-homogenous sub-population with regards to their demographic backgrounds, lifestyle choices, and comorbidities. Thus, the information we use to determine optimal treatment decisions includes systolic blood pressure, age, sex, diabetes status, blood cholesterol measures, and smoking habits. These are the main risk factors leading to cardiovascular events, including coronary heart disease (CHD) and stroke (ST) (D'Agostino et al. 2008). In this study, we primarily focus on the prevention of the first cardiovascular event, after which the patient would need alterations in therapy (Lovibond et al. 2011). As mentioned earlier, our objective is to maximize a patient's total expected QALYs, taking into account the likelihood of a cardiovascular event (or death) and medication side-effects. This is achieved through the stabilization of the patient's blood pressure so that the total benefits of

reducing the risk of serious CHD and ST outweigh the life-long disutility of medication side-effects. The antihypertensive medications are selected based on their effectiveness (i.e., reducing blood pressure) and side-effects (i.e., reducing the quality of life). In this study, we focus on the most common antihypertensive classes introduced in section 2.1, that is, BB, ACEI, ARB, DU, and CCB. For model tractability, we assume the physician would prescribe a standard medication dosage suggested by Law et al. (2009), and the patient fully adheres to the prescribed medication. Next, we formulate the various MDP elements, which leads us to present the Bellman optimality equations.

3.1. Decision Epochs

The decision epochs in our problem are denoted by $t = 0, 1, 2, \dots, T$; $T < \infty$, where t represents the number of quarter years above the age of 40 (Lovibond et al. 2011). Therefore, t is linked to the patient's age, as for instance $t = 0$ and $t = T$ represent the minimum and maximum age in our study, respectively.

3.2. State Space

The state space at period t , denoted by x_t , contains all patient's necessary information for the decision-making at the visit. The state space consists of two elements: patient's health state and her medication status denoted by b_t and m_t , respectively. Therefore:

$$\begin{aligned} x_t &= (b_t, m_t) \\ \text{where} \\ b_t &\in \mathcal{B} \text{ and } m_t = (m_{1t}, m_{2t}, \dots, m_{Mt}) \end{aligned} \quad (1)$$

In what follows, we explain the construction of the feasible set \mathcal{B} and vector m_t .

Patient's Health State: In our model, we represent the stages before and after the first cardiovascular event, which we consider differently as a terminal event from the perspective of preventive care. To this end, we divide the state space into two parts: $\tilde{\mathcal{B}}$ and $\tilde{\tilde{\mathcal{B}}}$, where the former corresponds to blood pressure levels, given that the patient has not faced any terminal event, and the latter corresponds to terminal states. We represent the patient's health state at each period by $b_t \in \mathcal{B}$. Hence, $\mathcal{B} = \tilde{\mathcal{B}} \cup \tilde{\tilde{\mathcal{B}}}$, where $\tilde{\mathcal{B}} = \{\underline{B}, \underline{B} + 1, \dots, \bar{B}\}$ and $\tilde{\tilde{\mathcal{B}}} = \{\bar{B} + 1, \bar{B} + 2, \bar{B} + 3\}$. The

subset \tilde{B} , with elements \tilde{b}_t , contains discrete blood pressure points between minimum \underline{B} and maximum \bar{B} levels, whereas subset \bar{B} , with elements \bar{b}_t , contains three terminal states as follows. States $\{\bar{B} + 1\}$ and $\{\bar{B} + 2\}$ represent CHD and ST, respectively, as the most serious consequences of hypertension. Finally, $\{\bar{B} + 3\}$ represents non-CVD mortality. A patient who faces a terminal event exits the process and accrues a lump-sum reward equal to the quality-adjusted life expectancy associated with the terminal event (for more details, see Section 3.4). From a modeling perspective, the two subsets differ from each other regarding their recurring characteristics. In summary, \tilde{B} captures the recurring non-terminal health states, that is, event-free blood pressure levels, whereas \bar{B} corresponds to the non-recurring terminal states. In our model, $\{\bar{B} + 1\}$ and $\{\bar{B} + 2\}$ are semi-transient states that virtually transition, with certainty, to the absorbing state $\{\bar{B} + 3\}$, which has a zero reward.

Patient's Medication Status: The vector \mathbf{m}_t contains the list of antihypertensive medications prescribed by period t . We represent the patient's medication status by $\mathbf{m}_t = (m_{1t}, m_{2t}, \dots, m_{Mt})$, where $m_{it} \in \{0, 1\}$ indicates whether the patient is taking medication i in period t , and M is the total number of medications in the problem.

3.3. Action Space

At each decision epoch t , the physician decides which medication (if any) should be added to the patient's existing list of prescribed medications. Note that for $M = 1$, which entails a binary decision, the problem boils down to the classical stopping time problem, where the stopping time corresponds to the time when the medication is initiated (Powell and Ryzhov 2012). For $M \geq 2$, the problem turns into M nested stopping time problems, one for each medication. The action space $\mathcal{A}_t(x_t)$, with element $a_t(x_t)$, therefore, is defined as follows:

$$\mathcal{A}_t(x_t) = \mathcal{A}_t(b_t, \mathbf{m}_t) = \{0, \mathcal{I}_t\}, \quad (2)$$

where \mathcal{I}_t represents the set of eligible medications that have not been prescribed before period t , that is, $\mathcal{I}_t = \{i : m_{it} = 0\}$. Hence, the feasible action at each decision epoch is either to prescribe one of the eligible medications from the action space (i.e., $a_t(x_t) = i$), or to do nothing (i.e., $a_t(x_t) = 0$). For notational convenience, we suppress the dependency of the action on the state, and simply use a_t in the remainder of the study.

3.4. Transition Probabilities Between States

For the state variables b_t and \mathbf{m}_t , we need to characterize the transition functions which determine the state

space in the next period as a function of the current state and decision. The transition between medication states is simply characterized by a deterministic function, as we only need to keep track of the medications the patient is taking at any period, and the decision made at that period. The transition between health states, however, is stochastic and governed by a Markov chain $P_t[b_{t+1}|b_t, a_t]$ with elements $p_t[b_{t+1}|b_t, a_t]$. In the following lines, we describe the formulation of the transition function. The transition function for the non-terminal health states \tilde{b}_t is governed by a Markov chain $\tilde{P}_t[\tilde{b}_{t+1}|\tilde{b}_t, a_t]$ that depends on the health state and action in period t . Let $\tilde{p}_t[\tilde{b}_{t+1}|\tilde{b}_t, a_t]$ denote the elements of this transition matrix. We model this transition function in three stages. First, an individual's blood pressure in the next stage is approximately Normally distributed with mean $\tilde{\beta}_{t+1}$ and variance σ^2 (O'Sullivan et al. 1999, Whelton et al. 2002). The mean $\tilde{\beta}_{t+1}$ is influenced by both the medication decision and aging of the patient, while variance σ^2 captures all the fluctuations in blood pressure levels due to uncontrolled factors (Mancia 2012). Second, to incorporate the unavoidable effect of aging on blood pressure, we consider an upward linear trend on the mean blood pressure level with respect to time (Robitaille et al. 2012, Wilkins et al. 2010). Namely, the mean blood pressure level in the next stage increases by $\gamma\Delta t$, where γ is the slope of the blood pressure change with one year of aging, and Δt is the length of time (measured in years) between two successive decision epochs, hence $\Delta = 0.25$ years in our problem. Finally, in order to capture the role of medication prescription in the transition, we formulate the medication effectiveness as the reduction in the blood pressure mean (Chobanian et al. 2003, James et al. 2014). We assume that medication i shifts the mean of blood pressure downward by ε_i mmHg. To summarize, the mean of the blood pressure distribution in the next period, when medication i is prescribed to the patient whose current blood pressure is \tilde{b}_t , can be expressed as follows:

$$\tilde{\beta}_{t+1} = \tilde{b}_t - \sum_i \varepsilon_i \mathbb{I}_{(a_t=i)} + \gamma\Delta t, \quad (3)$$

where $\mathbb{I}_{(a_t=i)}$ is the indicator function for the decision at period t ; and equal to 1 if the decision at t is to prescribe medication i , otherwise it is set to 0. To fully characterize the transition functions for all health states, we need three other elements which account for the three terminal events in our model. Let, $\alpha_{1t}(\tilde{b}_t, a_t)$, $\alpha_{2t}(\tilde{b}_t, a_t)$ and $\alpha_{3t}(\tilde{b}_t, a_t)$ denote the conditional probabilities of transitioning, under decision a_t , from \tilde{b}_t to the three terminal states $\{\bar{B} + 1\}$, $\{\bar{B} + 2\}$, and $\{\bar{B} + 3\}$ in the next period, respectively.

Given the probability of death $\alpha_{3t}(\tilde{b}_t, a_t)$, the probabilities of facing $\{\bar{B} + j\}$ (with $j = 1$ corresponding to CHD, and $j = 2$ corresponding to ST) can be formulated as $\alpha'_{jt}(\tilde{b}_t, a_t) = (1 - \alpha_{3t}(\tilde{b}_t, a_t))\alpha_{jt}(\tilde{b}_t, a_t)$, $j = \{1, 2\}$. We can now fully characterize the transition probability function as follows:

$$p_t(b_{t+1}|b_t, a_t) = \begin{cases} \left(1 - \sum_{j=1}^3 \alpha'_{jt}(b_t, a_t)\right) \tilde{p}_t(b_{t+1}|b_t, a_t), & b_t, \text{ and } b_{t+1} \in \tilde{B} \\ \alpha'_{jt}(b_t, a_t), & b_t \in \tilde{B}, b_{t+1} = \{\bar{B} + j\} : j = \{1, 2, 3\} \\ 1, & b_t \in \tilde{B}, b_{t+1} = \{\bar{B} + 3\} \\ 0, & \text{otherwise} \end{cases} \quad (4)$$

with $\alpha'_{3t}(\tilde{b}_t, a_t) = \alpha_{3t}(\tilde{b}_t, a_t)$.

3.5. Reward Functions

Our model includes two reward functions for the resulting MDP: one for the immediate rewards of the non-terminal states, and one for the terminal rewards. In the following paragraphs, we describe the construction of these functions.

Immediate Reward Function: The immediate reward function $r_t(x_t, a_t)$ captures the one-period QALY of a patient who is in non-terminal state $x_t = (\tilde{b}_t, \mathbf{m}_t)$ and follows decision a_t . To incorporate the burden (i.e., the side-effects) of medication i , we decrease the QALYs of a patient by δ_i , which captures the decrements in the quality of life due to the use of the medication. If the patient does not face any terminal event, her event-free immediate reward function can be expressed as:

$$\hat{r}_t(\tilde{b}_t, \mathbf{m}_t, a_t) = \Delta t \left(1 - \sum_i \delta_i m_{i(t+1)}\right), \quad (5)$$

where $m_{i(t+1)}$ is the i^{th} element of the updated medication state \mathbf{m}_{t+1} . We need, however, to account for the possibility of encountering terminal events by the next period. To do so, we prorate the above QALYs according to when the patient might face a terminal event. We assume the events will occur in the middle of the period (Sonnenberg and Beck 1993). In other words, if the event occurs, the patient lives without the event for half interval length, and with the event for the remaining half. Otherwise, the patient lives event-free for the entire period. Let ω_j be the QALY of a patient who experiences event $\{\bar{B} + j\}$ during period t , where $j \in \{1, 2, 3\}$ and $\omega_3 = 0$, as $j = 3$ corresponds to death. Then, the expected QALY for the entire period can be computed as follows:

$$Q(\bar{B} + j) = \frac{1}{2} \left(\hat{r}_t(\tilde{b}_t, \mathbf{m}_t, a_t) + \omega_j \right). \quad (6)$$

We can now present the expected immediate reward function as follows:

$$r_t(\tilde{b}_t, \mathbf{m}_t, a_t) = \left(1 - \sum_{j=1}^3 \alpha'_{jt}(\tilde{b}_t, a_t)\right) \hat{r}_t(\tilde{b}_t, \mathbf{m}_t, a_t) + \sum_{j=1}^3 \alpha'_{jt}(\tilde{b}_t, a_t) Q(\bar{B} + j). \quad (7)$$

The above expression implies that $r_t(\tilde{b}_t, \mathbf{m}_t, a_t) = \hat{r}_t(\tilde{b}_t, \mathbf{m}_t, a_t)$ in the absence of any terminal event (i.e., when $\alpha'_{1t} = \alpha'_{2t} = \alpha'_{3t} = 0$).

Lump-Sum Terminal Reward Function: We denote by R_{jt} , the total expected terminal reward for a patient who is in the terminal state $\{\bar{B} + j\}$ in period t . In other words:

$$r_t(\{\bar{B} + j\}, \mathbf{m}_t, a_t) = R_{jt}, \quad (8)$$

where R_{jt} is the quality-adjusted life expectancy (QALE) of a patient who experiences his first non-fatal event or death in period t . In other words, R_{jt} captures both the quality and quantity of the expected life after facing event j , hence $R_{3t} = 0$.

3.6. The MDP Formulation

Putting all the above pieces together, we can now formulate the value function for HTNMP. Let $v_t(b_t, \mathbf{m}_t)$ be the maximum total discounted expected QALYs earned by a patient given health state b_t and medication state \mathbf{m}_t in period t . The Bellman optimality equations for the non-terminal health states can be written as:

$$v_t(\tilde{b}_t, \mathbf{m}_t) = \max_{a_t \in \mathcal{A}_t(\tilde{b}_t, \mathbf{m}_t)} \left\{ r_t(\tilde{b}_t, \mathbf{m}_t, a_t) + \lambda \Delta t \sum_{\tilde{b}_{t+1}} p_t(\tilde{b}_{t+1}|\tilde{b}_t, a_t) v_{t+1}(\tilde{b}_{t+1}, \mathbf{m}_{t+1}) \right\}, \quad \forall t = 0, 1, \dots, T-1 \quad (9)$$

where $\lambda \in [0, 1]$ denotes the annual discount factor. For terminal states $\tilde{b}_t \in \{\bar{B} + j\}$, and terminal decision period T , we define the terminal value functions as follows:

$$v_t(\{\bar{B} + j\}, \mathbf{m}_t) = R_{jt}, j = \{1, 2, 3\}, \forall t = 0, 1, \dots, T-1 \quad \text{and} \quad v_T(b_t, \mathbf{m}_t) = R_T, \quad (10)$$

where R_T is the remaining quality-adjusted life expectancy of a patient at the end of the decision

horizon T . We assume $R_T = 0$ when a patient passes the age of 100 in our decision process, as hypertensive patients rarely reach this age (Franco et al. 2005).

The notations used for the key model parameters, as well as all abbreviations in this study, are summarized in Appendix A. Also, note that all the parameters, decision variables, and the value function in Equation (9) contain an index ψ to indicate the characteristics of the patient for whom the model is solved. However, for the sake of notational simplicity, we drop the patient-specific index throughout. Ideally, one would want to consider the variations between individual patients regarding their response to different medications. In particular, the extent of reduction in the mean and variability in blood pressure of each patient would be of interest. To date, however, medical decisions are informed by studies at the population level (i.e., pooled responses to medical treatment, rather than individual responses based on specific patient characteristics). In this context, the largest scale study in the BMJ (through meta-analysis of 147 trials) provides estimates of the average response to medications (Law et al. 2009).

4. Structural Properties

In this section, we show that a threshold type (also known as control-limit) policy is an optimal solution to HTNMP. In order to do this, we need to prove the monotonicity of optimal policy with respect to health states. The proofs are provided in Appendix S1. Throughout the study, we assume that medications can be ordered, in the sense that the higher the effectiveness of a medication, the higher its side-effects. Given this assumption, we can rank all the medications in ascending order with respect to their effectiveness (or equivalently side-effects), which together can also be interpreted as the medication *strength*. Hence, a stronger medication implies that the medication is more effective and has greater side-effects. Let $\{1, 2, \dots, M\}$ be the set of medications ordered accordingly. Before we present our main result, we need to provide a few technical definitions and assumptions that will be used in the characterization of the optimal policy.

Definition [Increasing Failure Rate]: A transition probability matrix P (and the resulting Markov chain) is called IFR (increasing failure rate) if its rows are in increasing stochastic order. In other words:

$$\rho(b) = \sum_{k=b'} P(k|b, a), \quad (11)$$

is nondecreasing in b for all $b' \in B$. This definition is equivalent to the well-known notion of first-order stochastic dominance. IFR property has an intuitive

interpretation in the context of this study and other chronic diseases (see e.g., Alagoz et al. (2004) and Shechter et al. (2008)). In our problem, it means the higher the level of blood pressure, the more likely it transitions to even higher blood pressure levels or terminal events.

Definition [Superadditivity]: A function $g(x, a)$ is *superadditive* if for $x^+ \geq x^-$ and $a^+ \geq a^-$, the following holds:

$$g(x^+, a^+) + g(x^-, a^-) \geq g(x^+, a^-) + g(x^-, a^+). \quad (12)$$

If the reverse inequality holds, then $g(x, a)$ is said to be *subadditive*. An equivalent definition of a superadditive function is commonly stated as follows:

$$g(x^+, a^+) - g(x^-, a^+) \geq g(x^+, a^-) - g(x^-, a^-). \quad (13)$$

This condition implies that the incremental change in a superadditive function with respect to x is greater for a larger value of a than for a smaller value of a . We use these definitions to introduce our technical assumptions that are needed to establish the structural properties of the HTNMP optimal policies.

ASSUMPTION 1. $\alpha_{jt}(b_t, a_t), \forall j$ are (i) non-decreasing in b_t and (ii) subadditive in b_t and a_t .

ASSUMPTION 2. (i) $r_t(b_t, \mathbf{m}_t, a_t)$ and (ii) $r_T(b_t, \mathbf{m}_t)$ are nonincreasing in b_t .

ASSUMPTION 3. The reverse cumulative distribution function for the transition matrix, that is, $q(k|b_t, a_t) = \sum_{b'=k}^{\infty} p(b'_t|b_t, a_t)$ is (i) IFR and (ii) non-decreasing in b_t .

ASSUMPTION 4. $r_t(b_t, \mathbf{m}_t, a_t)$ is superadditive in b_t and a_t .

ASSUMPTION 5. $q(k|b_t, a_t)$ is subadditive in b_t and a_t .

Although similar assumptions are commonly employed in the literature to characterize structural properties of the optimal policies for MDPs (Puterman 2005), in our context, the above assumptions yield intuitive interpretations. To start with, Assumption 1(i) implies that as blood pressure increases, the risk of encountering terminal events does not decrease. Assumption 1(ii) means that the risk of encountering terminal events under weaker action (i.e., weaker medication or do-nothing) vs. a stronger action, weakly increases with blood pressure level. This is intuitive, considering the higher effectiveness of stronger medications in blood pressure reduction. Assumption 2 imposes monotonicity on both the immediate and terminal reward functions, in the sense that none of them increases with blood pressure level. This means that the quality of

life and life expectancy do not increase with blood pressure. Recall that we previously discussed the intuitive implications of the IFR property of $q(k|b_t, a_t)$ in Assumption 3(i). Along similar lines, Assumption 3(ii) implies that as blood pressure increases, the risk of reaching a certain level of blood pressure and higher (including terminal events) does not decrease. The superadditivity of the reward function $r_t(b_t, \mathbf{m}_t, a_t)$ imposed by Assumption 4 implies that increase in quality of life due to prescription of a new medication (i.e., $a_t = i$) weakly increases with blood pressure level. In other words, blood pressure reduction has a greater benefit at higher blood pressure levels, which implies that $r_t(b_t, \mathbf{m}_t, i_t^+) - r_t(b_t, \mathbf{m}_t, i_t^-)$ is nondecreasing in b_t . Note that i_t^- and i_t^+ indicate lower rank (including do-nothing) and higher rank (or stronger) medications, respectively. Finally, the subadditive property imposed by Assumption 5, means the difference between the risks of transitioning to a certain blood pressure level or higher - including terminal events - under weaker medication vs. stronger medication increases with blood pressure level. This follows intuitively because of the greater importance of blood pressure lowering at higher blood pressure levels.

We are now ready to present the optimality of threshold policy in the HTNMP, given the set of definitions and assumptions discussed earlier. To characterize the structure of optimal policy, we first show some preliminary results on the value function. Note that the value function satisfies the Bellman equation provided in Equation 9, and can be written as follows:

$$v_t(b_t, \mathbf{m}_t) = \max_{a_t} [H_t(b_t, \mathbf{m}_t, a_t)], \quad (14)$$

where $H_t(b_t, \mathbf{m}_t, a_t)$ is defined as the value-to-go function for a patient whose non-terminal health state and the list of prescribed medications are b_t and \mathbf{m}_t , respectively, and when the medication decision is set to a_t . In other words:

$$H_t(b_t, \mathbf{m}_t, a_t) = r_t(b_t, \mathbf{m}_t, a_t) + \lambda^{\Delta t} \sum_{b_{t+1}} p_t(b_{t+1}|b_t, a_t) v_{t+1}(b_{t+1}, \mathbf{m}_{t+1}). \quad (15)$$

Using the above definitions, we first show that the monotonicity of $v_t(b_t, \mathbf{m}_t)$ and the superadditivity of $H_t(b_t, \mathbf{m}_t, a_t)$ are preserved recursively for all periods.

PROPOSITION 1. *Suppose that Assumptions 1–5 hold. Then the following are true:*

1. $v_t(b_t, \mathbf{m}_t)$ is nonincreasing in b_t , $\forall t = 0, \dots, T$.
2. $H_t(b_t, \mathbf{m}_t, a_t)$ is superadditive in b_t and a_t , $\forall t = 0, \dots, T$.

Given the preservation of the monotonicity and superadditivity properties, we can now prove the monotonicity of optimal policy $a_t^*(b_t, \mathbf{m}_t)$ with respect to health state b_t .

PROPOSITION 2. *Suppose Assumptions 1–5 hold, $\forall t = 0, \dots, T$. Then, at each period t and medication state \mathbf{m}_t , there exists a threshold b_t^* such that*

$$a_t^*(b_t, \mathbf{m}_t) = \begin{cases} i_t^- & b_t < b_t^* \\ i_t^+ & b_t \geq b_t^* \end{cases} \quad (16)$$

Proposition 2 simply indicates that the optimal policy for HTNMP is a threshold type of policy under the stated assumptions.

5. Case Study: Hypertension Management at the Montreal General Hospital Clinic

To estimate our model parameters, we used data collected from 109 hypertension patients at Montreal General Hospital as the primary source of data. We consulted the medical literature as the secondary source. A complete account of the data sources and the parameter estimation procedure are provided in Appendix S2.

The goal of this section is threefold: first, we numerically solve the optimal MDP based on the estimated parameters and illustrate several characteristics of the resulting optimal policies, such as their behavior concerning blood pressure level, age, and other risk factors. Second, we compare the value, regarding QALYs, accrued from our optimal policy with that obtained by following the British Hypertension Society's guidelines. This comparison enables us to evaluate the value of personalized treatment for various risk factors. We also decompose such value into two elements: *personalization* and *optimization*. This decomposition helps us evaluate the role of optimized treatments after adjusting for the role of personalization. Third, we analyze the sensitivity of our results to the variation in some of our model's key parameters. This provides useful insights about the impact of change in these parameters on optimal policies.

To solve the MDP model, we used the monotone backward induction algorithm, designed for solving the finite horizon MDPs which admit threshold policies (Puterman 2005). We solved our problem for various patient characteristics between 40 and 100 years of age.

5.1. Illustration of Optimal Policies

Assuming the set of intuitive properties for the components of our MDP model (listed in Section 4), we

characterize the structure of optimal prescription policy. Accordingly, the optimal policy consists of a series of threshold levels for each medication and each set of patient characteristics. Furthermore, the thresholds are nested within each other, which in turn imply an optimal sequence in which medications are prescribed. Also, since the thresholds are patient-specific, both the optimal sequence and timing of prescriptions are tailored to the individual characteristics of the patient.

As a numerical illustration, we present the optimal medication policies for a risk-free male patient (i.e., non-smoker, non-diabetic with healthy blood cholesterol levels). Figure 3 depicts the optimal policy for the patient mentioned above, given that he has not been prescribed any medication yet (hence the figure represents the optimal *first-line* treatment policy).

The key insights from the optimal policy are as follows:

- First of all, as proven in Section 4, the optimal policy has a threshold structure. For example, if the patient is 40 years old, the optimal decision is not to prescribe any medication if his blood pressure is less than 152 mmHg. If his blood pressure is between 152 and 158, then we need to prescribe ACEI, and so on. As shown in Figure 3, these threshold-type policies provide informative insights about the optimal timing and sequence of medication prescriptions. Such policies are intuitive and easy to implement, particularly in the context of our study, where all the relevant guidelines are also stated in a threshold-type structure.
- Given the optimal threshold levels associated with each medication, we can observe that medications are prescribed based on their order of effectiveness (or side-effects), namely their rank of strength. In other words, the lower the blood pressure, the weaker the

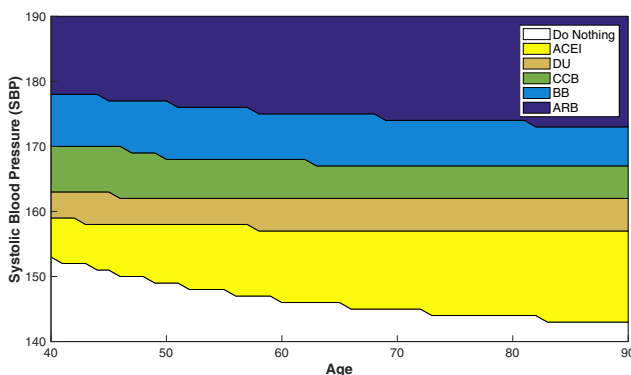
choice of medication should be. This implies that with everything kept the same, for $SBP_1 \leq SBP_2$ it is never optimal to prescribe a stronger medication at SBP_1 while prescribing a weaker medication at SBP_2 . This does not imply that it is not optimal to start with a stronger medication. Indeed, as Figure 3 depicts, for a patient with the above-mentioned characteristics, the optimal policy is indeed to start with the strongest medication if the patient's initial blood pressure exceeds 180 mmHg. This prescription strategy, hence, suggests various optimal sequence and combinations of medications based on the patient characteristics.

- The optimal threshold levels for all medications are non-increasing in age. This implies that as patients get older, the blood pressure level at which medications should be prescribed decreases (weakly). The rationale behind this is that age is a primary risk factor for CVD events (D'Agostino et al. 2008). Ashley and Niebauer (2003) argue that the benefit from treatment of hypertension increases with age as the absolute risk of CVD increases with age. This key observation is also consistent with a recent empirical study, based on the observations of 8.8 million patients in the United States, which indicates that older adults should maintain a lower SBP than younger adults (Fletcher et al. 2017).

Note that Figure 3 provides the optimal policy only for a patient who has not started taking any medication. In a problem with M medications, the full plan of optimal policies (i.e., the optimal sequence of medications along with the corresponding optimal prescription thresholds) consists of $2^M - 1$ optimal recommendations. This means we need to update the patient's medication state at each visit and find the optimal prescription from a graph that corresponds to the updated state. For instance, consider a risk-free male patient with 160 mmHg of systolic blood pressure. The optimal decision for this patient is taking ACEI as the first-line treatment. The optimal decision for the same patient one year later should be found from Figure 4 which pertains to a patient who is taking ACEI. Figure 4 depicts the optimal policies for a patient whose medication status is {ACEI}, {ACEI, DU}, {ACEI, DU, CCB}, and {ACEI, DU, CCB, BB}, respectively.

As can be seen in Figure 4d, the only alternative for patients taking the first four medications is either waiting (i.e., doing nothing) or taking the last medication which has not yet been prescribed (i.e., ARB in this case). Another remarkable observation is that as the number of medications taken by the patient increases, the overall threshold levels also increase

Figure 3 Optimal Medication Prescription for a Risk-Free Male Taking No Medication [Color figure can be viewed at wileyonlinelibrary.com]



(i.e., the blood pressure threshold for adding medication shifts upward). Therefore, the value of adding a new medication decreases with the number of previously-added medications. This result is consistent with the medical literature which postulates a diminishing marginal effectiveness of medications (Timbie et al. 2010). Our results are also consistent with other medical evidence. For example, (i) medications need to be prescribed at a lower threshold for a male than for a female (*ceteris paribus*). This is consistent with medical findings that being male alone increases the risk of CVD events. Also, (ii) medications need to be prescribed at a lower threshold for a male who smokes than for a male with diabetes. This suggests that for men, smoking is a more severe risk factor than diabetes. We have observed the opposite results for females, inferring that for women, having diabetes is

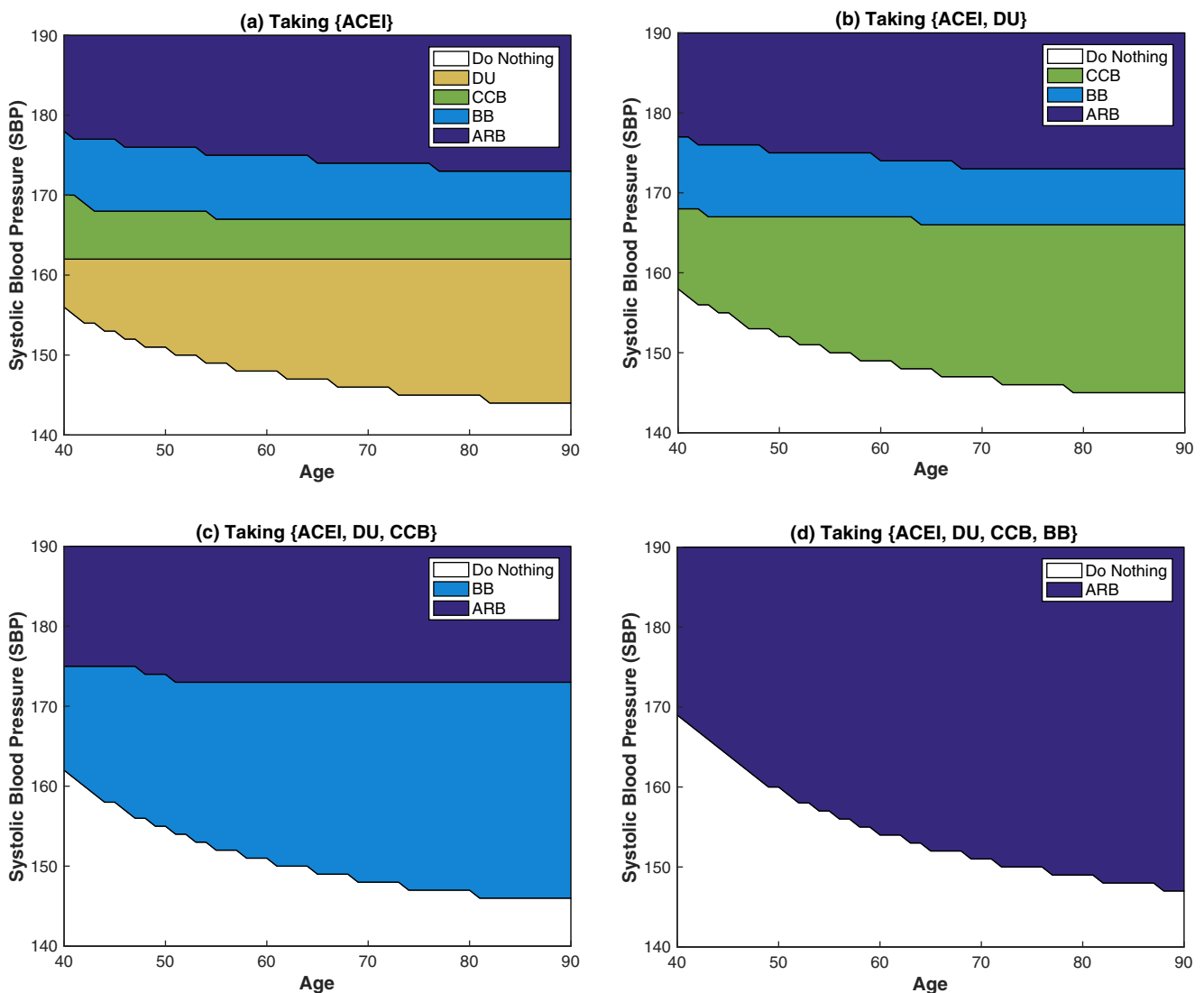
a more severe risk than smoking (D’Agostino et al. 2008).

5.2. Comparison with British Hypertension

Society’s Guidelines: The Value of Personalization

Among several prevailing guidelines, our optimal policies are more similar, in nature, to the British Hypertension Society’s (BHS) guidelines (National Institute for Health and Clinical Excellence 2011). Figure 5 summarizes the BHS guidelines for hypertension diagnosis and treatment. Despite the similarities between BHS and our model regarding (a) medication ranking, (b) the threshold nature of treatment policy, and (c) the fact that only one new medication can be prescribed at each stage, they differ in several other ways. First, the sequence of medications for treatment of hypertension is fixed

Figure 4 Optimal Medication Prescription for a Risk-Free Male [Color figure can be viewed at wileyonlinelibrary.com]



in BHS (see the right panel of Figure 5), while we suggest a flexible sequence of medications, as discussed earlier. Particularly, our model suggests that, depending on the patient's blood pressure level, any of the five medications can be used as a first-line treatment. Second, the treatment policy in BHS is not very much customized to the patient characteristics (except for a limited consideration of age). We provide different treatment policies based on the patient's key characteristics. For instance, our optimal recommendations are different for males than for females, or for males who smoke than for males who do not smoke. Third, the principle in BHS is *treatment by target* through keeping blood pressure below certain (mostly fixed) targets. Our optimal policy, however, aims for a *treatment by benefit* principle, through balancing the total benefits of reducing CVD risk with the long-term discomfort of medication side-effects. Finally, the optimal thresholds in BHS are fixed at 135 (for patients younger than 80) or 145 (for older patients), while our recommended thresholds vary by age and the patient's other characteristics.

To quantify the difference between BHS and our optimal policies, we compared the patients' QALYs under these two treatment regimens. Figure 6 illustrates, for different patients, the percentage improvements in QALYs, as a result of following our optimal procedure compared to the BHS recommendations.

Evidently, the improvements in QALYs increase when the patient has an additional or more severe risk factor. For example, the benefit of following our recommendations vs. BHS' is more prominent among males than females, and a patient who smokes or has diabetes benefits more, as compared to when he is a non-smoker or non-diabetic, respectively. Also, smoking males benefit from our recommendations more than males who have diabetes. Conversely, the benefit is larger for females who have diabetes than for females who smoke.

5.3. Identifying the Value of Treatment Optimization

Adjusting for the effect of medication personalization enables us to investigate the role of treatment optimization. To do so, we developed three models that decompose the optimization component of our original model. In the first optimization model (called **Policy 1** or *restricted policy*), we only optimize the fixed threshold induced by BHS. In other words, we fix the sequence and age to those imposed by BHS. In the second optimization model (called **Policy 2** or *sequence-dependent policy*), we let the model select a flexible sequence (and the associated thresholds) for medication prescriptions in an optimal fashion. In the third optimization model (called **Policy 3** or *age-dependent policy*), we let the model choose a flexible threshold in accordance with aging. In this model, the

Figure 5 BHS Guidelines for Diagnosis (Left) and Treatment (Right) of Hypertension [Color figure can be viewed at wileyonlinelibrary.com]

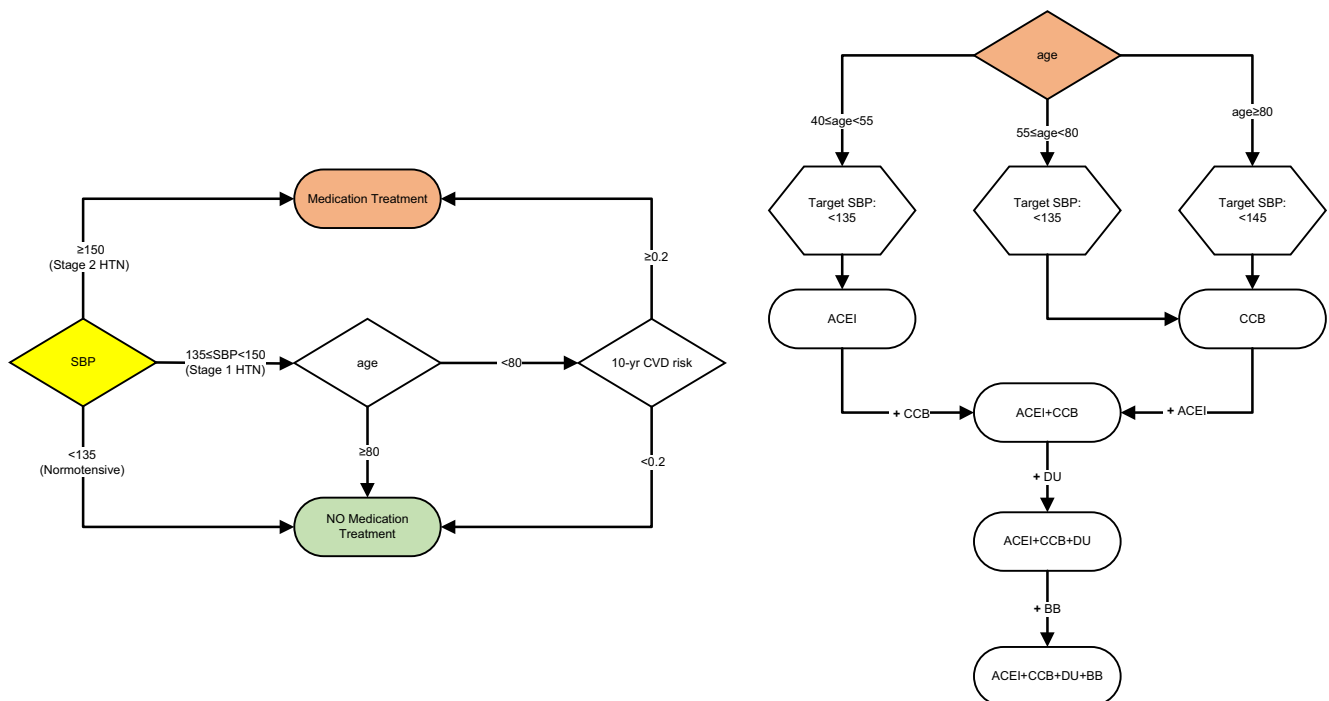
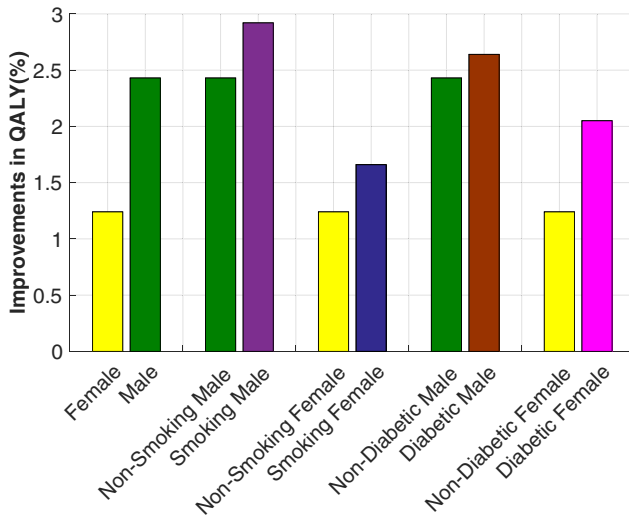


Figure 6 Percentage Improvement in QALYs: HTNMP vs. BHS [Color figure can be viewed at wileyonlinelibrary.com]



sequence is fixed to the one induced by BHS. The HTNMP, therefore, can be seen as a combination of the above three models. Table 1 summarizes the components of all optimization models in this study.

We employed the same MDP formulation for all the above optimization problems, which differ only on the assumption of how the medication prescription is carried out. Table 2 summarizes the four ways in which the medication state and decision variable can be defined depending on the assumption regarding the prescription procedure.

Therefore, the formulation of the MDP model corresponding to any of the above optimization scenarios can be expressed based on the corresponding definition of the states and decision, as per the summary in Table 3, in the following way:

$$v_n(s_n) = \max_{d \in \mathcal{D}_n(s_n)} \left\{ r_n(s_n, d_n) + \lambda \sum_{s_{n+1}} p_n(s_{n+1} | s, d) v_{n+1}(s_{n+1}) \right\}, \quad (17)$$

where s_n and d_n are general notations for the state and decision variables, respectively, and n is the stage number, which does not necessarily coincide with age (as in the case of **Policy 1** and **Policy 2**).

Figure 7 illustrates an example of the first-line treatment policies for a risk-free female induced by BHS

Table 1 The Flexibility of Elements of All Optimization Models in This Study

	Sequence	Age
Policy 1	✗	✗
Policy 2	✓	✗
Policy 3	✗	✓
HTNMP	✓	✓

Table 2 State and Decision Variables Depending on the Flexibility of Medication Sequence

	Medication state	Decision
Sequence		
Fixed	$l \in \{0, 1, \dots, M\}$: the number of medications the patient is taking	$u \in \{0, 1\}$: should we prescribe the next medication on the [fixed] list?
Not fixed	$m = (m_1, m_2, \dots, m_M)$, $m_i \in \{0, 1\}$: the medications the patient is taking	$a \in \{0, 1, \dots, M\}$: which medication to be prescribed from the list of [remaining] medications?

and each of the four optimization models introduced in this section. Note that the treatment policies in Figure 7a, b, and d are similar because of their fixed sequence of medications, which dictates no choice but ACEI as the first-line treatments. The threshold policies in Figure 7c and e are similar, since under their corresponding treatment policies the physician is allowed to choose between all medications as the first-line treatment.

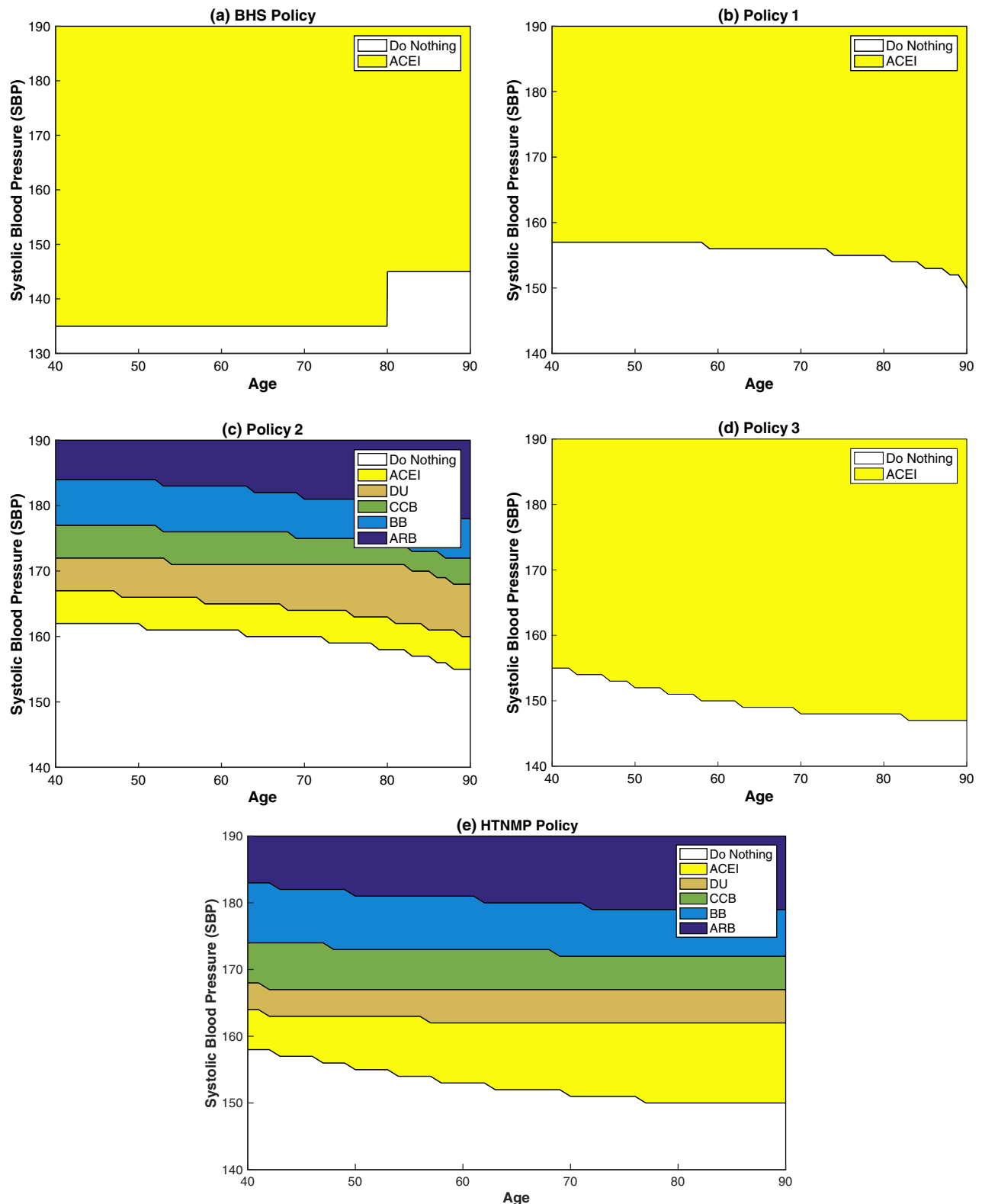
The key observations from this analysis can be summarized as follows:

- As discussed before, the treatment-by-target policy in BHS (Figure 7a) suggests a fixed threshold for the first-line medication prescription for patients older than 80.
- **Policy 1** (Figure 7b), which allows neither for a flexible choice of the first medication nor for an explicit consideration of age, suggests an optimal threshold that is initially constant but gradually decreases afterward, due to the end-of-horizon effect in the finite-time dynamic programming (Puterman 2005).
- **Policy 2** (Figure 7c), which is flexible in the choice of the first-line medication, but does not explicitly account for age, provides different thresholds for the different first-line medications. However, similar to **Policy 1**, the thresholds are initially constant, then gradually decrease due to the end-of-horizon effect.
- **Policy 3** (Figure 7d), which explicitly takes age into consideration but not a flexible choice of the first-line medications, suggests a first-line prescription threshold which decreases with age more quickly.

Table 3 State and Decision Variables for the Four Policies in Section 5.3

	State (s_n)	Decision (d_n)	Form of optimal threshold
Policy 1	$s_n = (b_n, l_n)$	$d_n = u_n \in \{0, 1\}$	b^*
Policy 2	$s_n = (b_n, \mathbf{m}_n)$	$d_n = a_n \in \{0, 1, \dots, M\}$	$b^*(\mathbf{m})$
Policy 3	$s_n = (b_n, l_n, t_n)$	$d_n = u_n \in \{0, 1\}$	$b^*(t)$
HTNMP	$s_n = (b_n, \mathbf{m}_n, t_n)$	$d_n = a_n \in \{0, 1, \dots, M\}$	$b^*(\mathbf{m}, t)$

Figure 7 Medication Initiation for a Risk-Free Female [Color figure can be viewed at wileyonlinelibrary.com]



- Finally, **HTNMP** (Figure 7e), which takes into account both a flexible medication choice and age, yields optimal age-dependent threshold levels for each medication.

Next, we compare each of the above procedures with BHS (as the baseline) in terms of the accrued QALYs. Figure 8 summarizes the results. While all the optimization policies outperform BHS, **Policy 1** has the

lowest improvement, compared to BHS. This is because the sequence of medications under this policy does not vary with respect to the realization of blood pressure over time. This suggests that the value of the optimal policy in HTNMP, to a large extent, stems from its flexibility with respect to sequencing and the patient's age. For females, **Policy 2** (i.e., sequence-dependent) is slightly better than **Policy 3** (i.e., age-dependent). For males, however, it is **Policy 3** that becomes slightly better than **Policy 2**. This is intuitive because age is a more prominent risk factor in men. Finally, the HTNMP, which combines sequence- and age-dependent optimizations, becomes more valuable as the patient risk profile exacerbates (either due to the increased number of risk factors or because they become more severe).

Fixing the set of patient characteristics under all of the above optimization models, we can adjust for the value of personalization in HTNMP. A natural question that may arise is whether there is a *synergy* that can be achieved by simultaneous optimizations with respect to sequence and age. To address this question, we compared the joint improvements of **Policy 2** and **Policy 3** (called **Policy 2+3**) with that of HTNMP (after subtracting the effect of **Policy 1**, which is a common effect in the treatment policies). Figure 9 depicts the results of this comparison. The difference (illustrated in Figure 10) measures the synergistic effect of the simultaneous consideration of sequence and age in HTNMP, vs. their separate combinations in **Policy 2+3**. As can be seen, there is a fairly constant synergy for all risk profiles. Part of the improvements in HTNMP should therefore be attributed to this synergy. In summary, the improvement in our optimal policies vs. BHS can be attributed to three main effects:

1. *Personalization* of optimal recommendations to the patient risk profile.
2. *Optimization* of the medication policies with respect to the sequence and age.
3. *Synergy* in HTNMP as a result of simultaneous sequence- and age-dependent optimizations.

5.4. Sensitivity Analysis

To assess the robustness of our optimal policies with respect to the variation in the input parameters, we conducted sensitivity analyses for some of these

Figure 9 Comparison of Collective Improvement in Policy 2 And Policy 3 vs. HTNMP [Color figure can be viewed at wileyonlinelibrary.com]

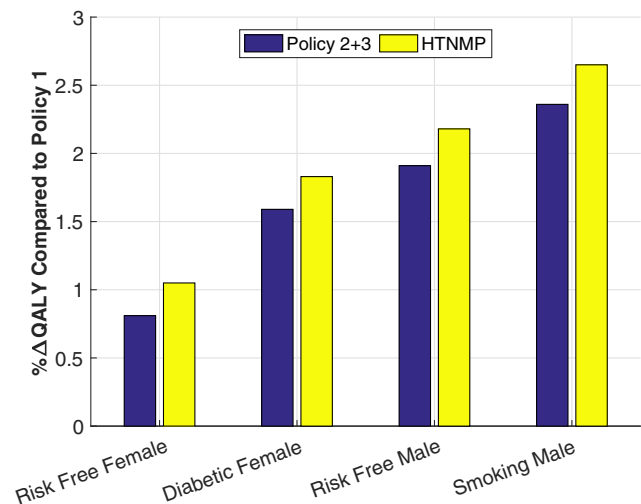


Figure 8 Comparison of %Improvements in QALYs With Respect to BHS [Color figure can be viewed at wileyonlinelibrary.com]

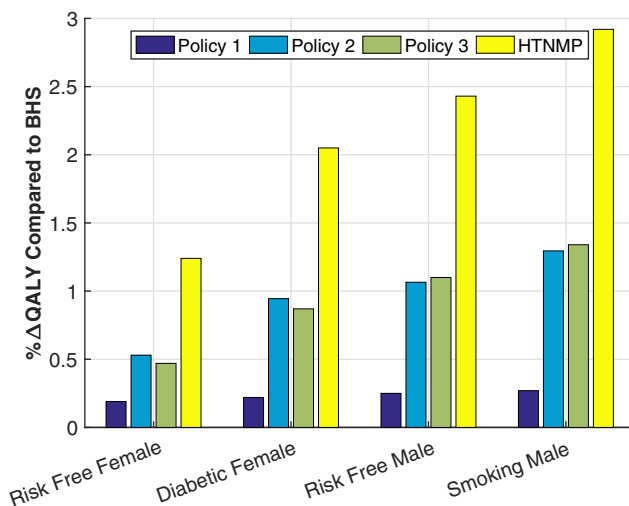
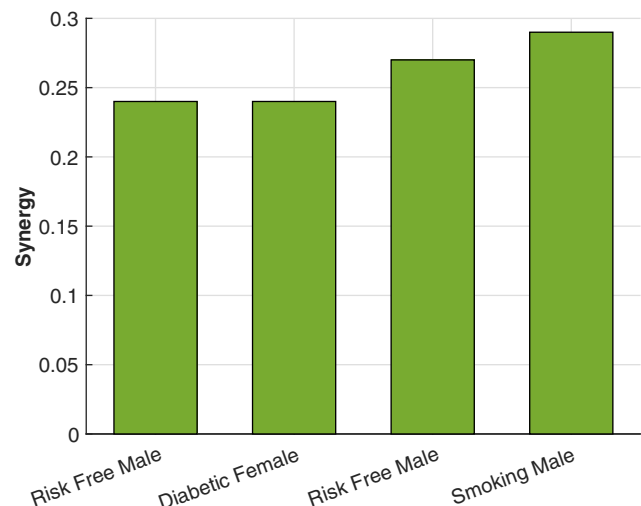


Figure 10 Synergy of Simultaneous Optimization and Personalization in HTNMP [Color figure can be viewed at wileyonlinelibrary.com]



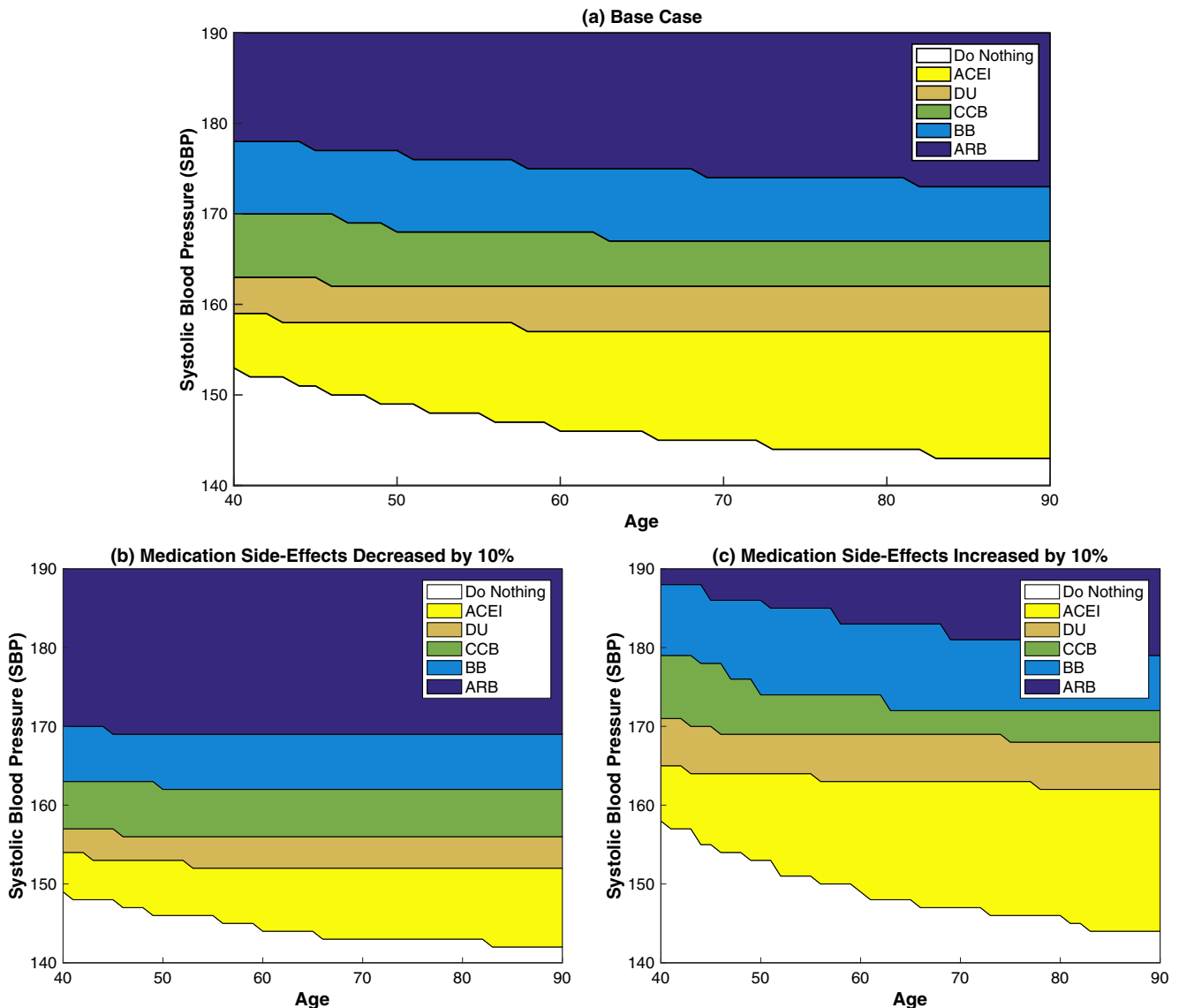
parameters. For the sake of brevity, we present the results with respect to (1) medication side-effects (i.e., δ_i), (2) the removal of the strongest medication, and (3) the number of medications (i.e., M). For the first part, we vary δ_i by $\pm 10\%$ from the baseline values used in the study. Figure 11 illustrates the results of this analysis. As can be seen in the figure, the optimal thresholds are affected by changes in the medication side-effects. Specifically, a decrease in δ_i would result in a decrease in the optimal thresholds, indicating an earlier prescription. This is quite intuitive because, keeping all else equal, when medications have lower side-effects, they lead to higher QALYs, hence can be prescribed at lower blood pressure thresholds. Also, the total expected QALYs is more sensitive to the increase in medication

side-effects, compared to a decrease in the same magnitude. Therefore, medications with higher side-effects are prescribed at increasingly higher blood pressure levels.

The results of sensitivity analysis with respect to changes in the utilities of the nonfatal events ω_j (not shown here) are similar to those with respect to side-effects. In other words, keeping all else equal, optimal thresholds increase in ω_j , implying that medications are prescribed at higher blood pressure levels as the nonfatal events become less severe.

We also investigated the impact of removing the strongest medication (i.e., ARB or $i = 5$) from the specialist's toolkit. This may be necessary for some patients who have allergies, intolerable side effects, or comorbidities. We denote this new case by $M = 4'$.

Figure 11 Medication Initiation for a Risk-Free Male [Color figure can be viewed at wileyonlinelibrary.com]



The optimal thresholds for this scenario are illustrated in Figure 12, which can be compared against the original thresholds in Figure 3. Figure 13 depicts the comparison for each medication, separately.

We note that, after removing ARB from the specialist's toolkit, the optimal thresholds for all remaining four medications increase. This means that the blood pressure level at which the removed medication was prescribed is now substituted by remaining medications, recognizing the increased importance of treatment at older ages. However, the level of increase in optimal thresholds for all remaining medications decreases with age, as a reflection of the end of horizon.

Finally, we analyzed the effect of removing access to each of the medications in both genders for three groups of patients; risk-free, smoking, and diabetic. Figure 14 depicts the percentage loss in QALYs as a result of the removal, compared to the baseline case (i.e., $M = 5$).

As can be expected, the accrued QALYs always decrease when there are fewer medications. That said, the %loss in QALYs depends both on the patient characteristics and the strength of medications as follows. First, the loss is directly related to the severity of the patient's risk profile. For example, when losing access to a medication, diabetic females lose more QALYs than females who smoke, while vice versa for males. Second, while the loss in QALYs is higher for risk-free males than for risk-free females (recall that being male alone is a risk factor for CVD), the relative increase in the loss, as a result of increased severity of risk factor, is much higher for females than it is for males (Sesso et al. 2003). Third, for all patient groups, the loss increases with the strength of medication to be removed from the list. This implies that, if all else remains unchanged, and if a medication is to be removed, the least effective of all potential medications should be chosen.

6. Concluding Remarks

In this paper, we study the problem of identifying optimal combination therapy for treatment of hypertension, taking into account the patient risk profile. The latter is a response to the need for a personalized hypertension treatment that seeks to find optimal treatment policies for individual patients according to their characteristics. Such a treatment plan, which is the end-goal of the hypertension treatment community (Floras 2013), not only leads to better treatment strategies but also improves overall adherence among patients, as is often the case with other chronic diseases (Yuan et al. 2012, Zapka et al. 2011).

To assess the value of personalization in hypertension treatment, we develop an MDP model and characterize optimal timing and sequencing of new prescriptions available in the physician's toolkit. By studying the proposed MDP, we show that the optimal treatment policies exhibit a threshold structure, and that these thresholds vary for different patient characteristics. For patients with a more severe CVD risk profile (e.g., male, smoker, or diabetic) the thresholds for adding new medications are lower, indicating a lower tolerance for high blood pressure. Our personalized treatment recommendations outperform BHS guidelines, and the QALY benefits associated with our framework are greater among patients with higher CVD risks. We also show that treatment optimizations, in addition to treatment personalization, result in net QALY benefits to patients. We note that our results are sensitive to key model parameters in an intuitive way. For instance, the optimal thresholds decrease if medications have lower side-effects and vice versa. Also, when we remove a medication from the specialist's toolkit, we observe that the optimal thresholds for the remaining four medications increase.

The results mentioned above have important implications for health-care providers from both patient and resource vantage points. From the patient's perspective, our analyses suggest that both medication initiation and sequencing policies need to be customized for patient characteristics. From the resource perspective, customizing treatment policies based on patient characteristics may lead to better resource utilization for healthcare providers. For example, the optimization of medication decisions with respect to age and sequence provides the highest benefit for patient groups that are diabetic female and males who smoke. Given the costs associated with implementing optimized medication decisions, it would be more effective to launch implementation starting with these two patient groups, and expand it gradually to risk-free male

Figure 12 Optimal Policies for a Risk-Free Male without Access to ARB [Color figure can be viewed at wileyonlinelibrary.com]

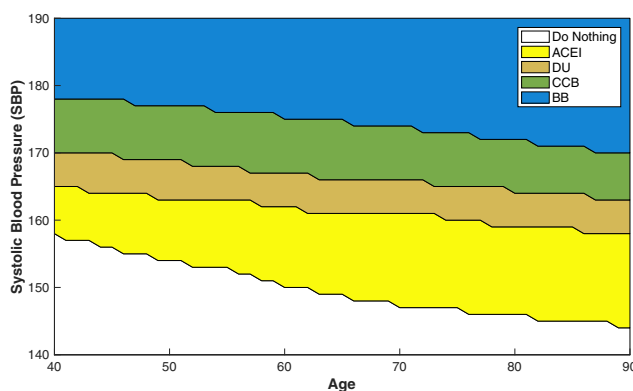
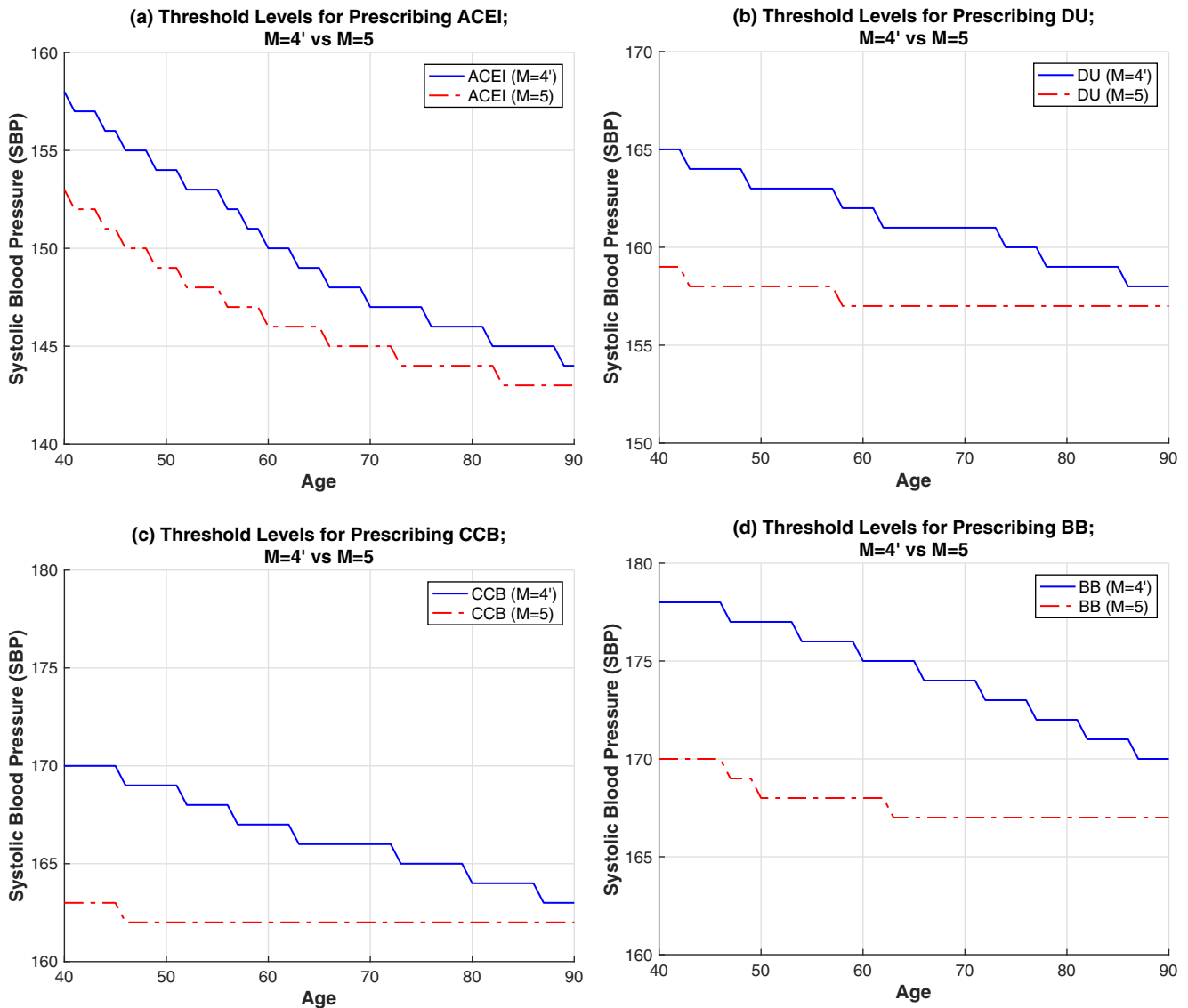


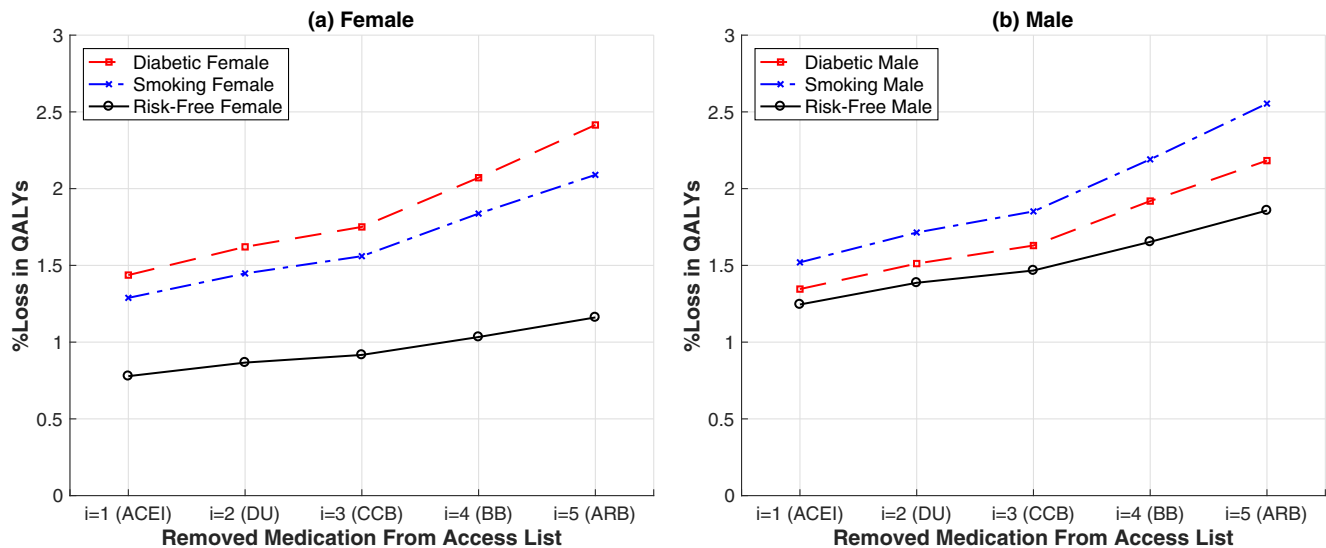
Figure 13 Comparing Optimal Threshold Levels With and Without Access to ARB [Color figure can be viewed at wileyonlinelibrary.com]

and female groups, respectively. Similarly, our problem can be seen as a preventive care model in which the risk associated with the first serious CVD events is minimized. The prevention of cardiovascular events, particularly based on Framingham risk estimation, is becoming increasingly common as the basis for making treatment decisions (Martin et al. 2004). As such, implementing optimal recommendations proposed in this study could lead to a reduced number of CVD events (most importantly CHD and ST), which would, in turn, free some resources (e.g., hospital beds, staff, ambulances, etc.) reserved for dealing with these events. Our model can be also used in conjunction with forecasting and planning limited resources needed for vascular services. For example, our results show that the risk of

hypertension, hence CVD events, increases with age. These results imply that communities with higher percentages of older adults would have a greater need for vascular services.

There are a number of ways this study could be extended. In the interests of space, we highlight some of the possible and most promising future research avenues in terms of improving impact on patient care. First, additional effort is warranted for relaxing the standard dose assumption we adopted in this study. In practice, a physician's common options include half or twice standard doses, in addition to the recommended standard dose. The incorporation of dosage decisions in this study's framework increases its chances of being implemented in practice. The second extension involves

Figure 14 Loss in QALYs Due to Lack of Access to One [Color figure can be viewed at wileyonlinelibrary.com]



relaxation of the assumption that blood pressure readings are accurate. Indeed, it is well-known that traditional measurements from the patient's arm constitute a proxy to the actual blood pressure at heart. There are alternative measurement techniques, such as applanation tonometry, which can provide more accurate measurements. Along these lines, comparative analyses under noise-free and noisy measurement scenarios in a personalized setting would enable us to gauge the *Value of Information* (VOI) achieved from more accurate blood pressure measurements. Given the cost associated with obtaining accurate blood pressure measurements, and the fact that not all patients equally need greater accuracy, this extension would potentially identify how to optimally distribute a limited budget across different patient groups, based on cost-benefit analysis. Even though analysis under a noisy measurement scenario would be considerably more complicated, we expect that patients with more severe risk profiles would benefit more than others from greater blood pressure measurement accuracy, as our results suggest that the value of optimization improves with a patient's risk profile.

In this study, we assumed that patients fully adhere to their treatment regimen. Therefore, a third way of extending this study is to account for imperfect patient adherence behavior. It is anticipated that implementation of this extension, along with the first proposed extension, would be very interesting, given that there might be a relationship between dosage decision and a patient's adherence behavior. For example, for patients

with weaker adherence, it might be optimal to compensate by increasing the prescribed dosage to offset the reduced medication effectiveness. Last but not least, our study provides a necessary foundation for developing practical decision support systems to help physicians make more individualized decisions about antihypertensive medications. However, we would like to acknowledge that before implementing such systems, further research is essential to assess the performance of our model with larger datasets. In particular, more research would be valuable for estimating the heterogeneity in patients' response to medications at different dosage levels. Also, implementing a decision support system would require developing efficient algorithms and an IT infrastructure to tackle large-scale patient datasets in the real-life clinical environments. We hope that our study acts as a stepping stone for these extensions so that we can better design personalized therapies for patients with hypertension.

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Appendix A. Notations and Abbreviations

Table A1 List of Model Parameters Used in Defining Transitions and Rewards

β_t	Blood Pressure Mean (BPM) at period t
σ^2	The variance with which blood pressure changes: index for Blood Pressure Variability (BPV)
γ	Slope of the blood pressure change with one year of aging
ε_i	Decrease in BPM as a result of taking medication i : index for medication effectiveness
δ_i	Decrement in QALYs due to medication i : index for medication side-effects
$\alpha_{jt}(\tilde{b}_t, a_t)$	Conditional probability of facing event j under blood pressure level \tilde{b}_t and medication decision a_t
ω_j	QALY under terminal event $\{\bar{B} + j\}$
M	Total number of medications in the toolkit of the specialist
R_{jt}	Total expected terminal reward after facing terminal event $\{\bar{B} + j\}$
R_T	Total expected terminal reward after reaching period T

Table A2 List of Abbreviations Used Throughout the Study

ACEI	Angiotensin-converting-Enzyme Inhibitor
ARB	Angiotensin II Receptor Blockers
BB	Beta Blocker
BHS	British Hypertension Society
BP	Blood Pressure
BMJ	British Medical Journal
CCB	Calcium Channel Blockers
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DU	Diuretic
ESH	European Society of Hypertension
HTNMP	Hypertension Management Problem
ISH	International Society of Hypertension
MDP	Markov Decision Process
OM	Operations Management
OR	Operations Research
POMDP	Partially Observable Markov Decision Process
QALE	Quality Adjusted Life Expectancy
QALY	Quality Adjusted Life Year
SBP	Systolic Blood Pressure
ST	Stroke
VOI	Value of Information

Notes

¹The study was on the popular media on February 22, 2017. See <http://www.cnn.com/2017/02/21/health/life-expectancy-increase-globally-by-2030/>

²JNC8/JAMA Guidelines for the Management of Hypertension in Adults, American Society of Hypertension/International Society of Hypertension Guidelines, Hypertension Canada Guidelines, British Hypertension Society's Guidelines, National Institute for Health and Care Excellence Guidelines, and European Society of Hypertension/European Society of Cardiology Guidelines.

³HYPERTENSION 2014: Joint Meeting of the European Society of Hypertension (ESH) and International Society of Hypertension (ISH); June 13–16, 2014; Athens, Greece.

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Supporting Information

Additional supporting information may be found online in the supporting information tab for this article:

Appendix S1: Proofs of Propositions.

Appendix S2: Data Sources and Parameter Estimation.