Monitoring policy in the context of preventive treatment of cardiovascular disease.

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Abstract

Preventing chronic diseases is an essential aspect of medical care. To prevent chronic diseases, physicians focus on monitoring their risk factors and prescribing the necessary medication. The optimal monitoring policy depends on the patient's risk factors and demographics. Monitoring too frequently may be unnecessary and costly; on the other hand, monitoring the patient infrequently means the patient may forgo needed treatment and experience adverse events related to the disease. We propose a finite horizon and finite-state Markov decision process to define monitoring policies. To build our Markov decision process, we estimate stochastic models based on longitudinal observational data from electronic health records for a large cohort of patients seen in the national U.S. Veterans Affairs health system. We use our model to study policies for whether or when to assess the need for cholesterol-lowering medications. We further use our model to investigate the role of gender and race on optimal monitoring policies.

Keywords: Cardiovascular diseases, Cholesterol, Healthcare, Markov decision process

1 Introduction

Cardiovascular disease (CVD) is one of the leading causes of death in the United States (Pool, Ning, Wilkins, Lloyd-Jones, & Allen, 2018). On average, cardiovascular disease causes 33% of all deaths, and 48% of the US population is living with some form of CVD, including hypertension. Two of the most common causes of death related to CVD are strokes and coronary heart diseases (CHD). It is estimated that managing CVD costs $351.2 billion dollars a year to Medicare in the United States (Benjamin et al., 2019). As part of preventing cardiovascular diseases, physicians treat patients with cholesterol and blood pressure lowering medications to manage two of the main risk factors for CVD. This is done based on the American College of Cardiology (ACC) guidelines for cholesterol (Grundy et al., 2018) and for high blood pressure in adults (Whelton, Carey, Aronow, Casey, & Collins, 2017). However, the guidelines do not define how frequently physicians should monitor the evolution of the risk factors. Let alone how monitoring should change with respect to age, gender, and race, all of which are established predictors of CVD outcomes (Sussman et al., 2017).

Current monitoring guidelines consider treatment and patient age to recommend the intervals between cholesterol and blood pressure observations. Nonetheless, information such as demographic and historic health-related factors are not used to define a monitoring policy. Nowadays, healthcare providers have access to electronic health records (EHRs), which consist of longitudinal healthcare information for patients. The availability of longitudinal information makes it possible to build stochastic models that describe uncertainty in risk factors to optimize individualized monitoring guidelines for patients based on societal benefits. For CVD, the societal benefits are estimated by the reward for increased quality adjusted lifespan and direct and indirect costs, such as the cost of appointments, testing, treatment, and the cost of having a CVD event (Caleyachetty et al., 2015).

The primary goals of this article are as follows:

1. Propose and validate stochastic models that learn from EHRs to define a cholesterol monitoring policy by maximizing the expected societal benefits.
2. Study how patients' gender and race influence the optimal Markov decision process (MDP)-based monitoring policy and compare this policy to current guidelines.

To achieve these goals, we first describe the existing guidelines. First and foremost, current guidelines recommend prescribing medications to patients depending on the patient's 10-year risk of having a CVD event (heart attack or stroke). The patient's CVD risk is estimated using a published risk model with factors including blood pressure (BP), cholesterol low-density lipoproteins (LDL, also known as "bad cholesterol"), current treatment, and patient demographics (Moran, Bibbins-Domingo, Pletcher, Vittinghoff, & Thanataveerat, 2016). The patient 10-year risk is categorized as low-risk if the value is below 5%, borderline-risk between 5% to 7.5%, intermediate-risk between 7.5% to

20%, and high-risk over 20% (Grundy et al., 2018). In the case of managing cholesterol, prescribing statins are often the next course of action if diet and exercise alone are not sufficient.

Statins are a once a day pill that patients take indefinitely, assuming they can tolerate the side effects (Grundy et al., 2018). They are generally considered safe for most people but they can have some minor side effects, and they come at a cost to the patient and/or health system. Physicians may also prescribe one of several medications for blood pressure, often starting with Angiotensin-converting enzyme (ACE) inhibitors or Angiotensin II Receptor Blockers (ARBs). The physician decides the type of treatment, cholesterol or blood pressure, based on the 10-year risk of CVD events, and the current cholesterol and blood pressure levels. Nevertheless, the patient's health behavior is stochastic, and the time between each appointment varies, according to observational data, from a couple of months to years, which implies that the physicians should consider this randomness into their monitoring decisions. Regular monitoring is important, but there are pros and cons of frequent vs. infrequent monitoring. Monitoring very frequently may be unnecessary and costly for certain patients; on the other hand, monitoring infrequently means the patient may forgo needed treatment and experience adverse events related to the disease.

From the physician's point of view, each appointment is an opportunity to collect observational data. During an appointment, physicians often gather the patient's current and past available information in the EHR. With this information, the physician can estimate the 10-year risk, and prescribe treatment to lower CVD risk if necessary. Finally, physicians recommend when to have patients have follow-up tests and appointments for continued monitoring of risk factors.

In the United States, the ACC guidelines recommend monitoring cholesterol every 4 to 6 years if the patient is healthy and every 1 to 2 years if the patient is 75 years old or older and is healthy. For patients on treatment, the guideline suggests to monitor cholesterol every 3 to 12 months, so that physicians check the medication efficacy and change the treatment if needed (Grundy et al., 2018). This policy is a one-size-fits-all policy, as it does not consider the patient's demographics. For blood pressure, the ACC guidelines recommend annual measurements if the patient is healthy, every 3 to 6 months if the patient has an elevated BP, and every 1 to 3 months for patients on treatment (Whelton et al., 2017). In contrast to cholesterol monitoring, which requires a blood test, measuring blood pressure is done regularly as part of standard clinical practice. For this reason, we focus on cholesterol monitoring policies as the primary decision of importance to CVD prevention. For blood pressure, we will assume the physicians will follow the monitoring and treatment guidelines, where for patient with high blood pressure or high risk will receive blood pressure-lowering treatment (Whelton et al., 2017).

In our approach to studying optimal cholesterol monitoring policies we consider cost and benefits from a societal perspective. Each year that the patient is

healthy, there is a reward for the additional life year gained, which we convert to a monetary measure using a *willingness-to-pay* (WTP) estimate that is common to public health studies. We also consider costs to societal stakeholders, including the patient, the physician, and third-party payers, including health insurers and health organizations (Pandya, Sy, Cho, Weinstein, & Gaziano, 2015). Collectively, these considerations reflect the societal perspective when determining optimal monitoring policies.

To test our MDP model, we used longitudinal data for cholesterol and blood pressure in a cohort of 10,000 randomly selected patients seen in the Veteran Affairs (VA) system. All patients had at least two outpatient visits to clinics. The data follows the patients from 2003 until 2018. The data is divided in three primary data sets: Demographics, treatments, and health factors. For demographics, we have information on the patient's race, gender, age, and smoking habits. For treatments, we have the prescription date, the type of treatment, and the number of pills. Finally, for health factors, we count the measurements for total cholesterol, high-density lipoproteins cholesterol (HDL), low-density lipoproteins cholesterol (LDL), systolic blood pressure, and diastolic blood pressure.

The rest of the paper is organized as follows. In Section 2, we present the literature review related to our problem and highlight the differences between our approach and the ones presented in the literature. In Section 3, we propose a finite horizon and finite state MDP model which adds new factors such as cholesterol, blood pressure, age, and the 10-year risk of having a major cardiovascular event (heart attack or stroke). Also, we present the EM-algorithm that we use to estimate each of the cholesterol LDL and systolic blood pressure probability distributions from observational data. In Section 4, we present our case study with longitudinal data in a large cohort of patients seen in the national Veterans Affairs health system. We test our model for cholesterol using the data in our case study and discussed how the model is applied. Finally we compare our model versus current cholesterol monitoring guidelines and summarize our main conclusions.

2 Literature review

The most relevant research related to our work falls into the following fields: (1) dynamic monitoring prevention and treatment models; (2) parameter estimation using longitudinal sparse data; and (3) cholesterol monitoring policies to prevent cardiovascular diseases. In this section, we highlight papers related to our work and briefly describe how our proposed methodology differs.

Literature in dynamic monitoring is divided into prevention and treatment. Within the are of prevention, we focus on monitoring policies after a disease has occurred, or intervention has been done to prevent the disease (Akhavan-Tabatabaei, Sánchez, & Yeung, 2016; Ayer, Alagoz, Stout, & Burnside, 2016; Helm, Lavieri, Van Oyen, Stein, & Musch, 2015; Mason, Denton, Shah, &

Smith, 2014). Among the most common applications, models define monitoring policies to prevent deaths after cancer was diagnosed. To accomplish this, the literature focuses on maximizing QALYs by applying different methodologies such as MDPs and partially observable MDPs (POMDPs). Models have also been created for patients who need constant surveillance. such as mental health care, liver cancer, HIV, and diabetes (Chen, Ayer, & Chhatwal, 2017; Deo, Rajaram, Rath, Karmarkar, & Goetz, 2013; Mason et al., 2014; Nazir, Anggraini, Octavia, & Syafria, 2016). These models then focus on identifying when should surveillance should take place.

For dynamic monitoring for treatment, the literature has applied MDP to define the optimal treatment policies for chronic diseases. Some of these applications focus on cancer, transplant, among others (Campbell, Blake, Kephart, Grunfeld, & Macintosh, 2016; Otten, Timmer, & Witteveen, 2020; Petousis et al., 2019; Sabouri, Huh, & Shechter, 2017). In particular, for CVD, the literature has focused on cholesterol-lowering medications (Sandikci, Maillart, Schaefer, & Roberts, 2011; Schell, Marrero, Lavieri, Sussman, & Hayward, 2016; Steimle & Denton, 2017). Depending on the patient's health state, the models select the type of medication to prescribe assuming patients have 100% adherence and regularly attend appointments (e.g. fixed annual visits). Our work focuses on monitoring models and we assume that physicians will follow current treatment guidelines. Our model tackles diseases with less constant surveillance adds a layer of complexity by modeling disease progression outside of surveillance. Additionally we incorporate patients' age, gender, race, and societal rewards.

Within the field of parameter estimation, we reviewed OR literature in cardiovascular diseases. Previous models assume that risk factors such as cholesterol and blood pressure follow a stochastic process. Past studies have assumed a Markovian behavior for these risk factors while calculating the transition probabilities by estimating the frequency that a transition appears in the data (Basu & Meltzer, 2018; Negoescu, Bimpikis, Brandeau, & Iancu, 2017; Thompson, Guthrie, & Payne, 2017). Normally, the models assume that the data is enough to correctly fit these frequencies (Yeh, Chan, Symanski, & Davis, 2010). Additionally, depending on the application, the Markov chains vary depending on demographics and the patient's health state (Basu & Meltzer, 2018). In our study we consider the effects of gender, race, and age on the Markov chains, so we can study how these factor influence optimal policies.

Because data about risk factors is collected sporadically according to the pattern of patients visits, EM algorithms (Sherlaw-johnson, Gallivan, & Burridge, 1995), and maximum likelihood estimation methods (Yeh et al., 2010), are used to estimate stochastic behaviors from incomplete data. To our knowledge, these methods have not yet been applied to cholesterol or blood pressure data.

Finally, to estimate cholesterol monitoring frequencies, the US guidelines suggest testing healthy patients every 4 to 6 years (Grundy et al., 2018).

Nonetheless, other countries, such as United Kingdom, Australia, and New Zealand, have different policies. Some even recommend testing healthy patients every year (Dansinger, Williams, Superko, & Schaefer, 2019). Most of these policies propose various recommendations depending on whether the patient is on treatments or not. Nonetheless, some studies suggest that a detailed monitoring policy may reduce the risk of having a CVD event by having a better knowledge of the patient (Kenik, Jean-Jacques, & Feinglass, 2014) (Thomson et al., 2019). Given these conflicting expert opinions, there is a need to better understand optimal monitoring policies using data-driven models.

In summary, our paper differs from previous studies for three reasons. First, we propose an MDP model to define cholesterol monitoring policies by optimizing societal rewards and considering the effects of gender and race. Second, less frequent surveillance is needed to prevent cardiovascular diseases compared to other diseases; therefore, our models consider long periods when the patient is not measured. We model the effects of events between two cholesterol tests. Third, we apply EM algorithms to estimate the transition probabilities due to the long periods between tests. To the best of our knowledge, this is the first study to consider these three aspects. We show these algorithms can fit well-validated Markov chains for cholesterol and blood pressure using non-uniformly collected data observations in EHRs. Considering each of these improvements, we believe that we will improve the current ACC cholesterol monitoring guidelines, having precise guidelines for gender and race.

3 Model Formulation and Validation

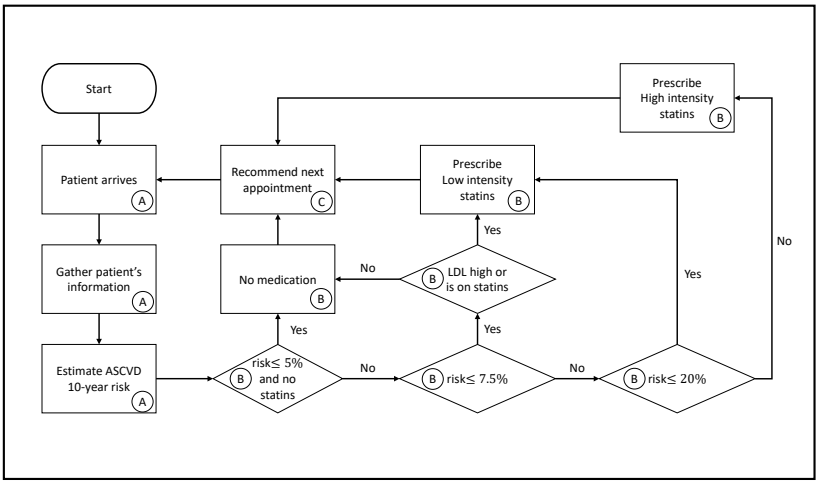
In this section, we will present our decision model to estimate a cholesterol monitoring policy that maximizes societal benefits. We divide this model into three parts: the MDP for optimizing cholesterol monitoring policies, the estimation of transition probabilities by using EM-algorithms, and the simulation model to test and validate our model. To evaluate the patients, we model the patient's risk factors between appointments. In Figure 1, we present the flow of a particular appointment.

We start by stating definitions and mathematical notation (see Table 1) that we will use throughout this section.

3.1 Definitions and model assumptions

In this section, we introduce the concepts and the main assumptions of the model. Since we are focused on the prevention of CVD, we focus on healthy patients, with no evidence previous chronic diseases in their medical records. Therefore, we define $H := \{N, C, D\}$ as the set of the possible living states of the patient where N represents that the patient is in normal health conditions, C represents that the patient had a CVD event, and D represents that the patient died for any unrelated CVD causes, also known as *all other causes of mortality* (Grundy et al., 2018). We assume that the model stops as soon as the patient's living state is C or D. Similar to prior literature, a patient with

Fig. 1 During a particular appointment, the physician gathers information ((A) boxes). Based on this information, the physician defines the treatment (Grundy et al., 2018) ((B) boxes) and considers when the patient should come back ((C) box). This process will continue until the patient gets to a certain age, dies, or has a cardiovascular event. Our research question will focus on optimizing the green process



no previous CVD events, will have either a CHD event or a stroke, but both are assumed no to happen simultaneously in the same time period (Pandya et al., 2015). Additionally, we estimate the probability of a CVD event and death based on age. We also assume that the proportion of CVD events that are strokes will not change with age.

During an appointment, the physician gathers the patient's medical information and prescribes medication if necessary. The physician also considers when the next cholesterol testing should take place. We assume the physician does not have access to observations between appointments. The first risk factor collected is the LDL cholesterol level. Therefore, when the patient arrives, the physician is assumed to know the relevant factors that define the patient's health (living) state and cholesterol level (i.e. we assume the test was completed prior to the arrival for an appointment). We define $Ch := \{\text{Low, Normal, Acceptable, Borderline High, High, Severe}\}$ as the different cholesterol LDL levels, as shown in Table 2 (Grundy et al., 2018).

Also, the physician gathers the patient's blood pressure. Similar to LDL, we divide the blood pressure into established clinical groups (Whelton et al., 2017). We define $B := \{\text{Normal, Elevated, Hypertension I, Hypertension II, Hypertensive Crisis}\}$ as the different blood pressure levels, which are shown in Table 2.

We focus on optimizing monitoring policies, and thus the time between appointments, and we assume the physician prescribes the treatment following recommended guidelines at the schedule appointments. Treatment decisions

Table 1 List of notation for MDP model

Notation	Description
E	Set of patient's appointments index by t, where $E := \{1, ..., T\}$.
H	Set of possible living states of the patient index by h_t in appointment t.
Ch	Set of cholesterol LDL levels index by θ_t in appointment t.
BP	Set of blood pressure levels index by γ_t in appointment t.
A	Set of decisions index by a.
Tr_t	Treatment prescribed to the patient in appointment t.
age_t	Age of the patient in appointment t.
s_t	State of the patient in appointment t defined as $s_t = (\theta_t, \gamma_t, h_t, Tr_t, age_t)$.
$Pr_{Ch}(age_t, Tr_t)$	Transition probability matrix for cholesterol levels at age age_t and treatment Tr_t after appointment t.
$p_{Ch_t}(\theta_{t+1} \mid s_t, a)$	Probability that in appointment $t+1$, the patient has LDL θ_{t+1} when decision a is taken.
$Pr_{Ch}^{(k)}(Tr)$	Matrix that represents the $k-th$ iteration of the EM-algorithm at treatment Tr.
$Pr_{BP}(age_t)$	Transition probability matrix for blood pressure levels at age age_t.
$p_{BP_t}(\gamma_{t+1} \mid s_t, a)$	Probability that in appointment $t+1$, the patient has BP γ_{t+1} when decision a is taken.
$pr_{H_h}(s_t)$	Probability that in an interval the living state is h given state s_t.
$p_{H_t}(h_{t+1} \mid s_t, a)$	Probability that in appointment $t+1$, the patient is in living state h_{t+1} when decision a is taken.
$r_t(s_t, a)$	Rewards when the patient is in state s_t and decision a is taken in appointment t.
$v_t(s_t)$	Optimal value function at appointment t and state s_t.
cA	Cost of going to an appointment.
$cT(Tr_t)$	Cost of a month of in treatment Tr_t.
$cC1_{CHD}$	Cost of first year of a CHD event.
$cC2_{CHD}$	Cost of subsequent years after CHD event.
$cC1_{St}$	Cost of first year of a stroke event.
$cC2_{St}$	Cost of subsequent years after stroke event.
WTP	Benefit of being healthy per year.
$WTP(a)$	Benefit received for a periods.
$LY(age)$	Expected remaining life years at age.
δ_{CHD}	CHD event QALY decrement per year.
δ_{St}	Stroke event QALY decrement per year.
δ_{Tr_t}	QALY decrement per year on treatment Tr_t.
β	Discount factor.
d_{CHD}	Probability a patient suffers a CHD event given that a patient had a CVD event.
d_{St}	Probability a patient suffers a stroke given that a patient had a CVD event.

are assumed to be based on the patient's 10-year risk of having CVD per the recommended treatment plan from the ACC Guideline on the Management of Blood Cholesterol (Grundy et al., 2018), shown in Figure 1. Between any two appointments, the patient's cholesterol and blood pressure change depending on the treatments and how long is the time between appointments, which determines the number of transitions in the Markov chain.

We focus on statins, because they are the most common medication used to treat high cholesterol. Statins are commonly divided into two intensities: low and high. Between these two groups, physicians consider which statin dose is

Table 2 Risk factors levels: The discrete sets of published clinically relevant cholesterol LDL ranges used to define cholesterol LDL states (Grundy et al., 2018) and systolic blood pressure ranges used to define blood pressure states (Benjamin et al., 2019)

Risk factor and level	Range
Cholesterol LDL	
Low (L)	$<$ 70 mg/dL
Normal (N)	$\geq$ 70 mg/dL and $<$ 100 mg/dl
Acceptable (A)	$\geq$ 100 mg/dL and $<$ 130 mg/dl
Borderline High (B)	$\geq$ 130 mg/dL and $<$ 160 mg/dl
High (H)	$\geq$ 160 mg/dL and $<$ 190 mg/dl
Severe (S)	$\geq$ 190 mg/dL
Systolic blood pressure	
Normal (N)	$<$ 120 mm Hg
Elevated (E)	$\geq$ 120 mm Hg and $<$ 130 mm Hg
Hypertension I (H1)	$\geq$ 130 mm Hg and $<$ 140 mm Hg
Hypertension II (H2)	$\geq$ 140 mm Hg and $<$ 180 mm Hg
Hypertensive Crisis (HC)	$\geq$ 180 mm Hg

the best depending on the patient's 10-year risk of having a CVD event. This 10-year risk is estimated based on LDL, SBP, age of the patient, sex, race, and currently prescribed treatment. For BP, we assume that the physician will prescribe medication also based on the ACC guidelines (Whelton et al., 2017). The physician will prescribe BP lowering medications when the patient has an H1 or higher BP level. For cholesterol and BP, we assume that the patient will have perfect adherence to the medications. Finally, we assume that patients comply with the physician's recommendation on when the next cholesterol test should take place.

To model the stochastic process for LDL assume that it satisfies a Markov assumption, similar to previously motivated studies. As treatment and patient age affect the LDL behavior, we estimated the conditional probability based on these factors. Moreover, we assumed that the cholesterol treatment does not affect the patient's SBP due to the lack of correlation observed in prior studies (Mason et al., 2014).

Given that the current ACC guidelines recommend that the maximum time between cholesterol tests is 6 years, for our model the possible decisions are between 3 to 72 months, with intervals of 3 months representing the shortest time between appointments. We also assume that the patient follows the physician recommendation to get a cholesterol test prior to their appointment. While such adherence is not perfect in practice, making this assumption leads to a easier to interpret the model results by focusing on the most likely and intended expectation.

Finally, our model focuses on maximizing the total societal benefits of the monitoring policy. We consider the costs of treatment, going to an appointment, and having a CVD event and rewards for each life year, taking into account the decrements when the patient is on treatment or has CVD. We will explain these benefits and costs in detail in the next section.

3.2 Markov decision process model formulation

We model our problem with a finite state and finite time MDP. We present each of the components that belong to these type of models.

Epochs: Let $E := \{1, ..., T\}$ be the set of decision epochs for possible appointments with cholesterol tests. Each epoch is indexed by t.

States: During each appointment $t \in E$, the physician gathers the LDL level $\theta_t \in Ch$, the SBP level $\gamma_t \in B$, the living state of a patient $h_t \in H$, the age of the patient age_t, and defines the treatment Tr_t. To simplify, we define s_t as the overall health state of the patient in appointment t, which includes the previous information. Hence, $s_t := (\theta_t, \gamma_t, h_t, Tr_t, age_t)$.

Decisions: Because the physician will recommend when to check cholesterol next, we define A as the set of decisions where $A := \{1, ..., m\}$. If $a \in A$, then the patient is advised to come back in a months. Notice that the physician takes action at the end of the appointment, and s_t represents the state of the patient after measuring blood pressure, cholesterol, and the prescription of any new treatment.

Transition probabilities: Between appointments, the patient LDL and blood pressure vary. Furthermore, a patient may suffer from cardiovascular diseases or die of other causes. Therefore, first, we define $Pr_{Ch_{ij}}(age_t, Tr_t)$ as the probability that if the patient has a LDL state i and is following treatment Tr_t at appointment t, then on the next period the patient will have LDL state j. Since, the physician learns the patient's new LDL level during appointments, we define $p_{Ch_t}(\theta_{t+1} = j \mid s_t, a)$ as the probability that the patient will have an LDL state of j in appointment $t + 1$, if the patient is in state s_t and the physician recommends to monitor cholesterol in a periods. If we assume that $\theta_t = i$, then we estimate the probability that in the appointment $t + 1$ the patient has LDL state j as follows.

$$p_{Ch_t}(\theta_{t+1} = j \mid s_t, a) = \sum_{k_1 \in Ch} \sum_{k_2 \in Ch} \cdots \sum_{k_{a-1} \in Ch} \Big(Pr_{Ch_{ik_1}}(age_t, Tr_t) \; Pr_{Ch_{k_1 k_2}}(age_t + 1, Tr_t) \ldots Pr_{Ch_{k_{a-1} j}}(age_t + a - 1, Tr_t) \Big) \tag{1}$$

Equation 1 reflects the Markovian assumption about LDL. Similarly, we define $Pr_{BP_{ij}}(age_t)$ as the probability that if the patient has a blood pressure state i and is age_t years old in appointment t, then on the next period the patient will be in blood pressure state j . Also, we define $p_{BP_t}(\gamma_{t+1} = j \mid s_t, a)$ as the probability that if the patient is in state s_t and the physician recommends to monitor cholesterol in a periods, then the patient will have a blood pressure state of j in appointment $t + 1$. Assuming that $\gamma_t = i$, we estimate the probability that in appointment $t + 1$ the patient has a blood pressure state j as follows.

$$p_{BP_t}(\gamma_{t+1} = j \mid s_t, a) = \sum_{k_1 \in B} \sum_{k_2 \in B} \cdots \sum_{k_{a-1} \in B} \Big(Pr_{BP_{ik_1}}(age_t) \\ Pr_{BP_{k_1 k_2}}(age_t + 1) \ldots Pr_{BP_{k_{a-1} j}}(age_t + a - 1) \Big) \tag{2}$$

Between appointments, the patient may suffer a CVD event or die because of other causes. We define $pr_{H_h}(s_t)$ as the probability that if the patient is in state s_t, the patient is at living state h at period t. Therefore, we can estimate, as shown in Equation 3, the probability that the patient is healthy at the next appointment. This probability is defined as $p_{H_t}(h_{t+1} = N \mid s_t, a)$ which is the probability that in appointment $t + 1$ the patient is healthy, given that the patient was in state s_t at period t, and the physician recommended to test cholesterol again in a periods.

$$p_{H_t}(h_{t+1} = N \mid s_t, a) = \prod_{l=1}^{a} \sum_{j \in Ch} \sum_{k \in B} p_{Ch_t}(j \mid s_t, l) p_{BP_t}(k \mid s_t, l) \\ pr_{H_N}(\theta_l = j, \gamma_l = k, Tr_t, age_t + l) \tag{3}$$

We consider that a patient reaches the next appointment with a normal health condition state, only if the patient does not suffer a CVD event or dies between appointments. Therefore, in Equation 3, $\sum_{j \in Ch} \sum_{k \in B} p_{Ch_t}(j \mid s_t, l) p_{BP_t}(k \mid s_t, l) pr_{H_N}(\theta_l = j, \gamma_l = k, Tr_t, age_t + l)$ represents the expected probability that the patient has a normal living state in period $t + l$. Because the patient goes through a period of time between each appointment, then Equation 3 also represents that the patient is healthy in all periods.

As the probability of dying from other causes is neither related to the cholesterol level nor the blood pressure level of the patient, we estimate the probability of dying in a periods, as follows.

$$p_{H_t}(h_{t+1} = D \mid s_t, a) = 1 - \prod_{l=1}^{a} \big(1 - pr_{H_D}(age_t + l)\big) \tag{4}$$

Finally, in Equation 5, we present the probability that the patient has a cardiovascular event.

$$p_{H_t}(h_{t+1} = C \mid s_t, a) = 1 - p_{H_t}(h_{t+1} = N \mid s_t, a) - p_{H_t}(h_{t+1} = D \mid s_t, a) \tag{5}$$

Rewards: At each appointment, the physician's decision may result in costs during and after the appointment. First, depending on the treatment, there is a cost per period when the patient is taking a particular treatment, defined as $cT(Tr_t)$. Also, when going to an appointment, the patient and the insurer are assumed to incur a cost cA, including a cholesterol test, time

spent in the appointment and traveling, and the appointment cost. Finally, depending on the patient's age, the patient has a probability of having a CVD event, which also incurs a cost $cC(age_t)$, payed by the health insurer.

We consider two types of CVD events: stroke and heart attack. For each of these events, we estimate the cost of the first year of having a CVD event ($cC1_S$ and $cC1_C$ respectively), which consists of hospitalization, interventions, and treatments, and the cost of subsequent years ($cC2_S$ and $cC2_C$). Also, we include the willingness-to-pay (WTP) per year that the patient is healthy. We define $WTP(a)$ as the benefits received from a societal perspective, per patient, for a periods. If the patient had a CVD event, we multiply the WTP by a decrement δ per year. Finally, depending on the age of the patient, we estimate the average expected years of life $LY(age_t)$ and multiply it by a decrement rate given the type of CVD event τ_C or τ_S. In Equations 6 and 7 we estimate the cost of having a CHD event $cC_C(age_t)$ or a stroke $cC_S(age_t)$ respectively, given that the CVD event was diagnosed at age age_t.

$$cC_C(age_t) = cC1_C + cC2_C(LY(age_t)\tau_C - 1)(1-\delta_C) - WTP(LY(age_t)\tau_C)(1-\delta_C) \tag{6}$$

$$cC_{St}(age_t) = cC1_S + cC2_S(LY(age_t)\tau_S - 1)(1-\delta_S) - WTP(LY(age_t)\tau_S)(1-\delta_S) \tag{7}$$

The patient may suffer either a CHD event or a stroke. We define as d_{CHD} as the probability that a patient suffers a CHD event given that the patient suffered a CVD event, and d_{St} as the probability that a patient suffers a stroke given that the patient suffered a CVD event. It is worth noting that the probability that a healthy patient has a CHD event is $p_{H_t}(h_{t+1} = C \mid s_t, a)d_{CHD}$ and a stroke is $p_{H_t}(h_{t+1} = C \mid s_t, a)d_{St}$, where $d_{CHD} + d_{St} = 1$. Therefore, $cC(age_t) = cC_{CHD}(age_t)d_{CHD} + cC_{St}(age_t)d_{St}$.

Between two appointments, we consider the cost of going to the 2^{nd} appointment, the cost of the treatment, and the cost of having a CVD event. Therefore, in Equation 8 we estimate $r_t(s_t, h_t = N, a)$, defined as the rewards when the patient is on state s_t, the patient is healthy, and the physician recommends to monitor cholesterol in a periods of time. We also consider a utility decrement over the benefits received if the patient is on treatment Tr_t, defined as δ_{Tr_t}. The complete reward function can be written as follows.

$$r_t(s_t, h_t = N, a) = -cA + \sum_{l=0}^{a-1} p_{H_t}(N \mid s_t, l)\Big(WTP(1)(1-\delta_{Tr_t}) - cT(Tr_t) - \sum_{j\in Ch}\sum_{k\in B} p_{Ch_t}(j \mid s_t, l)p_{BP_t}(k \mid s_t, l)pr_{H_C}(age_t + l, j, k) cC(age_t + l + 1)\Big) \tag{8}$$

Bellman equations: We define the optimal value function $v_t(s_t)$ as the maximum expected benefits the patient receives from appointment t in state s_t until appointment T or until the patient suffers any cardiovascular event (death or disease). We construct the Bellman equations, for all s_t and $t \in E$, associated with this model, as follows.

$$V_t(s_t) = max_{a\in A}\Big\{r_t(s_t, a) + \beta \sum_{j\in Ch}\sum_{k\in B}\sum_{h\in H}\Big(p_{Ch_t}(j \mid s_t, a)p_{BP_t}(k \mid s_t, a) p_{H_t}(h \mid s_t, a)V_{t+1}(s_{t+1})\Big)\Big\}, \forall t, s_t \tag{9}$$

As we mentioned before, the physician knows the patient's health state and cholesterol level when the appointment starts. Also, the physician recommends treatment Tr_t, following the treatment plan before deciding when the next cholesterol test should occur. In Equation 10, we present the boundary conditions of the model, depending on whether the process ends because the patient has a CVD event, the patient gets to the final epoch T being healthy, or the patient dies from other causes. If the patient is healthy at the last appointment, then no more decisions are taken, and the expected benefits for subsequent years represent the immediate reward. If the patient dies from other causes, then no additional costs or benefits are considered.

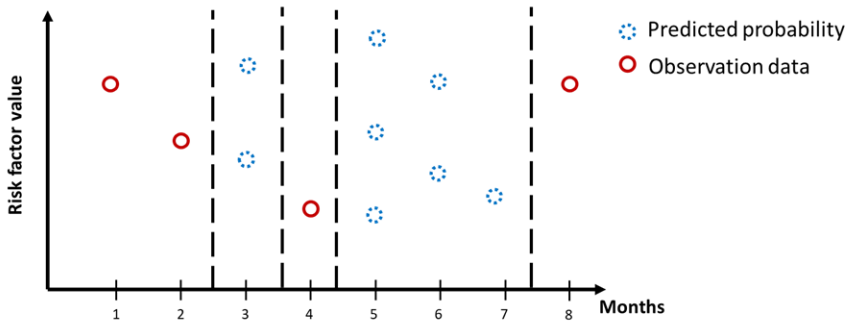
$$V_t(s_t) = \begin{cases} 0 & \text{if } h_t \in \{C, D\} \\ WTP(LY(age_T))(1-\delta_{Tr_T}) & \text{if } h_t = N \text{ and } t = T \end{cases}, \forall t, s_t \tag{10}$$

3.3 Estimation of the risk factor stochastic behavior

In parametrizing our models, the time between data collection may vary due to different factors, such as health state, demographics, and undergoing treatment. Yeh et al. (2010), study these types of problems and compare different methodologies to estimate probabilities for ignorable intermittent missing data (Yeh et al., 2010). After testing various methods, they recommend using Sherlaw-Johnson et al. (1995) EM algorithm to calculate these probabilities (Sherlaw-johnson et al., 1995).

We previously redefined the model presented by the Sherlaw-Johnson et al. (1995) and follow the same structure to estimate $Pr_{Ch}(age_t, Tr_t)$ and $Pr_{BP}(age_t)$ (Otero-Leon et al., 2021). As the cholesterol and blood pressure stochastic behavior may vary by age, we run the algorithm for different age ranges with a size of r years. We define the age range, denoted by z, based on the number of data points available.

Fig. 2 Based on the available observational data, the EM algorithm predicts possible values for each risk factor for each time period and estimates the Markov chain which minimizes the error between steps



As shown in Figure 2, the algorithm uses the observational data to estimate a Markov chain. To apply the algorithm, we first define $O_{uvw}(Tr)$ as the number of observed transitions from LDL level u to LDL level v in w periods when on treatment Tr in the age range of z years. For simplicity, let the age range go from ages 1 to z. For the E-step, we define $Pr_{Ch}^{(k)}(Tr)$ as the matrix in the $k-th$ iteration of the algorithm. Now define $Pr_{ijl,uvw}$ as the probability that a transition between LDL levels i and j occurs in l epochs, where the patient was observed to be in LDL level u at epoch $w-l$ and then observed in LDL level v at epoch w and can be estimated as follows.

$$Pr_{ijl,uvw} = \frac{Pr_{Ch_{ui}}^{l}(Tr) Pr_{Ch_{ij}}(Tr) Pr_{Ch_{jv}}^{w-l-1}(Tr)}{Pr_{Ch_{uv}}^{w}(Tr)} \tag{11}$$

Now define $S_{ij}(Pr_{Ch}^{(k)}(Tr))$ as the expected number of transitions from LDL level i to LDL level j occurring if there is complete data in the $k-th$ iteration, which can be estimated as follows.

$$S_{ij}(Pr_{Ch}^{(k)}(Tr)) = \sum_{u \in B} \sum_{v \in B} \sum_{w=1}^{z} O_{uvw}(Tr) \sum_{l=0}^{w-1} Pr_{ijl,uvw} \tag{12}$$

For the M step of the algorithm, $Pr_{Ch}^{(k+1)}(Tr)$ is computed as follows.

$$Pr_{Ch}^{(k+1)}(Tr) = \frac{S_{ij}(Pr_{Ch}^{(k)}(Tr))}{\sum_{w=1}^{z} S_{iw}(Pr_{Ch}^{(k)}(Tr))} \tag{13}$$

Notice that for each type of treatment we need to apply this algorithm. The algorithm stops when the $Pr_{Ch}^{(k)}(Tr)$ converges, i.e. for a small ϵ, $\mid Pr_{Ch_{ij}}^{(k+1)}(Tr) - Pr_{Ch_{ij}}^{(k)}(Tr) \mid < \epsilon$ for all $i, j \in Ch$. Then for all age_t in the age range, $Pr_{Ch}^{(k)}(age_t, Tr) = Pr_{Ch}^{(k)}(Tr)$. Finally,we apply the same algorithm to estimate $Pr_{BP}(age_t)$.

We validate the resulting Markov chains from the EM-algorithm by applying a likelihood ratio test (Besag & Mondal, 2013). To estimate the likelihood ratio test, let us first define $n_{ij}(age, Tr)$ as the number of observed data points where patients go from cholesterol level i to cholesterol level j, on treatment Tr in the selected age range. Let $\hat{p}_{ij}(age, Tr)$ denote the observe ratio of data points between cholesterol levels i and j. Then $\hat{p}_{ij}(age, Tr) = \frac{n_{ij}(age,Tr)}{\sum_j n_{ij}(age,Tr)}$. Now let us define $L_{EM}(age, Tr)$ as the likelihood function after using the EM algorithm and $L_{Data}(age, Tr)$ as the likelihood function of the data. Then we can estimate each likelihood function as:

$$L_{EM}(age, Tr) = \prod_{i,j} Pr_{CH_{i,j}}(age, Tr)^{n_{ij}(age,Tr)} \tag{14}$$

$$L_{Data}(age, Tr) = \prod_{i,j} \hat{p}_{i,j}(age, Tr)^{n_{ij}(age,Tr)} \tag{15}$$

Then we can apply a Chi square test to the following value:

$$-2ln\Big(\frac{L_{EM}(age, Tr)}{L_{Data}(age, Tr)}\Big) \sim \chi^2_{m(m-1)},$$

where m is the number of cases where $n_{ij}(age, Tr) > 0$.

3.4 Estimation of the probability of having a CVD event

For the probability of having a CVD event, the medical literature typically recommends using the CVD 10-year risk. Nevertheless, as this estimation is for 10 years, we assume that we can divide the probability equally through each year, following a linear behavior (Steimle & Denton, 2017). We then estimate the CVD 10 year-risk based on the patient's demographics, age, race, gender, LDL, total cholesterol, blood pressure, treatments, and smoking habits. As we are dealing with VA data, we use the calculator presented by Sussman, et al. (2017) (Sussman et al., 2017). Let $pr_{H_C}(s_t)$ be that probability that the patient has a CVD event given state s_t. Also, let τ be the number of months between epoch $t-1$ and t. Finally, let $pr_{10}(s_t)$ be the 10-year risk given state s_t, therefore, we estimate the probability of having a CVD in τ number of months as:

$$pr_{H_C}(s_t) = 1 - (1 - pr_{10}(s_t))^{\frac{7}{120}} \tag{16}$$

It is worth noting that the estimation presented in Equation 16 assumes a linear increase in the risk of the patient from time 0 to 10 years. This approximation then may underestimate or overestimate the real risk depending on the patient's risk factors; however, the estimate is reasonable in the aggregate and a very common assumption in public health modeling. Finally, we estimate the probability of dying from other causes with the CDC tables of life years, depending on the patient's age (Arias & Xu, 2019).

4 Results

In this section we present the results of our case study based on the VA health system. We present the results of our model parameter estimation and validation of the input data and the model. We estimate the optimal cholesterol monitoring policy by applying the finite state and finite time MDP to the VA database. We test our model for patients between the ages of 40 and 80. Finally, we compare the policy obtained from our MDP model to the ACC guidelines and to actual decisions made by physicians in practice at the VA.

We define the length of decision epoch to be 3 months, as this is the minimum suggested time period between two cholesterol blood tests (Grundy et al., 2018), giving us a total of 160 epochs over the 40 year time horizon from age 40 to 80. As mentioned in the assumptions, in each epoch, the patient has 6 possible cholesterol levels, 5 possible blood pressure levels, 3 living states, and 3 different treatments, for a total of $43,200$ states. We use the backward induction algorithm to solve this problem (Puterman, 1994).

4.1 Case study

We tested our model with longitudinal data for cholesterol and blood pressure in a cohort of 10,000 randomly selected patients seen in the national Veterans Affairs health system. All patients had at least two outpatient visits to the clinics, without diabetes, and without preexisting CVD. We include in our study patients with statins or blood pressure medication. The data follows the patients from 2003 until 2018, and Table 3 shows an overview of the population studied.

We structured the data in three primary data sets: demographics, treatments, and health factors. For demographics, we have information on the patient's race, gender, age, and smoking habits. For treatments, we have the prescription date, the type of treatment, and the number of pills. Finally, we count the measurements for cholesterol and blood pressure. As cholesterol and blood pressure are measured on different frequencies, we structured the data by date and health factor measured. It is worth noting that blood pressure is measured more frequently than cholesterol because of the ease of measurement in a clinical setting that was noted previously.

Table 3 Baseline characteristics of the population. We divide the variables into categorical (demographics) and numeric variables (risk factors). We estimate the mean value and standard deviation for the risk factors and count the number of patients in each demographic variable. We then performed a univariate test for each variable to test if there is a difference between patients with and without CVD events and we provide the resulting p-values

	Mean (± SD) or No.(%)		
Characteristic	Patients without CVD Events	Patients with CVD events	P
n	9675	325	
Gender			
male	8751 (90.4)	318(97.8)	<0.001
Female	924 (9.6)	7 (2.2)	<0.001
Ethnicity			
White	7254 (75.0)	266 (81.8)	0.006
African american	1806 (18.7)	50 (15.4)	0.154
Other	354 (3.7)	6 (1.8)	0.115
Smoker	1951 (20.2)	72 (22.2)	0.419
Diabetes	2458 (25.4)	123 (37.8)	<0.001
Blood Pressure			
sbp	129.30 (9.40)	132.32 (10.46)	<0.001
dbp	76.59 (6.62)	74.43 (7.16)	<0.001
Time between visits (months)	4.49 (3.31)	4.12 (2.92)	0.045
Cholesterol			
HDL	47.11 (13.21)	44.88 (13.56)	0.003
LDL	108.73 (26.01)	100.36 (26.23)	<0.001
Time between visits (months)	10.46 (6.52)	9.66 (5.81)	0.032

As exclusion criteria, we do not consider patients who had a prior CVD event or had diabetes due to the fact our model focuses on prevention. Since diabetes is a major risk factor for cardiovascular disease, patients in this group typically following different treatment policies. The ACC guidelines recommend treating patients differently depending on the age group, which are divided into children and teenagers (younger than 20 years old), young adults (20 to 39 years old), adults (40 to 70 years old), and older adults (older than 70 years old). Additionally, for prevention, the ACC guideline recommends focusing on adults and young adults' age groups because older adults usually need more customized care (often by a cardiologist). Our data set mostly consists of the adults age group.

4.1.1 Model Parameters

We gathered some of the model parameters for the reward function of our MDP from the literature to parameterize our model. We divide these parameters into two groups: costs and benefits and disutilities. We show their values and their sources in Table 4.

The cost of going to an appointment (cA) is estimated considering the cost of traveling and waiting, the price of a general physician visit, and the cost of a cholesterol laboratory test. In the United States, the patient's traveling time to an appointment is around 25 minutes, and the time waiting and spent in the appointment is about 42 minutes (Pandya et al., 2015). Using the Bureau of Labor Statistics' average hourly wage in the United States of $24.98, the cost of traveling and waiting is around $32.06 (Bureau of Labor Statistics, 2018). As the physician orders a cholesterol test on each appointment, we add $35 for

Table 4 Reward function parameters and sources used in the model. All the values shown in this table are adjusted for inflation to 2020 USD (U.S. Bureau of Labor and Statistics, 2021)

Parameter Type	Parameter	Value	Source
Costs and Benefits			
	Going to an appointment (cA)	\$142	(Pandya et al., 2015)
	A month of Low intensity statin ($cT(L)$)	\$8	(GoodRx, 2019a)
	A month of High intensity statin ($cT(H)$)	\$16	(GoodRx, 2019b)
	First year CHD event ($cC1_{CHD}$)	\$68,677	(O'Sullivan et al., 2011)
	Subsequent years after CHD event ($cC2_{CHD}$)	\$4,588	(O'Sullivan et al., 2011)
	First year stroke event ($cC1_{St}$)	\$22,645	(O'Sullivan et al., 2011)
	Subsequent years after stroke event ($cC1_{St}$)	\$7,240	(O'Sullivan et al., 2011)
	Benefit of being healthy per year (WTP)	\$100,000	(Rascati, 2006)
	Expected remaining Life years (LY(age))	CDC LY tables	(Arias & Xu, 2019)
	Discount factor	0.97	(Pandya et al., 2015)
Disutilities			
	CHD event QALY decrement per year (δ_{CHD})	0.07	(Mason et al., 2014)
	Stroke event QALY decrement per year (δ_{St})	0.21	(Mason et al., 2014)
	Statins decrement (δ_{Tr_t})	0.003	(Mason et al., 2014)

this test (Pandya et al., 2015). Finally, we set as \$75 as the cost of the visit with a general practitioner (Pandya et al., 2015).

We consider two categories of statin treatment, low and high intensity. For the costs of treatments, we consider the Statin Atorvastatin 40mg for the price of the Low-intensity statin ($cT(L)$), and we use the Statin Rosuvastatin 20mg for the cost of the High-intensity statin ($cT(H)$). For each of these, we check the Good Rx website and choose the average of the lowest prices.

When a CVD event happens, there are costs associated with the initial hospitalization, intervention, and subsequent cholesterol test and treatments. For our analysis, we consider the costs of two CVD events, CHD and strokes. Based on O'Sullivan et al. (2011) and estimating the values for 2019, the cost of the first year with CHD is approximately \$68,677, and the cost of the first year after a stroke is \$22,645. For subsequent years, accounting for medications, follow-ups, and control screenings, the cost with CHD is \$4,588, and the cost with a stroke is \$7,240.

For the benefits, we use a willingness-to-pay for a QALY of \$100,000, as is common in literature (Rascati, 2006) as our baseline. We also vary this to investigate sensitivity of our results to WTP. We consider the CDC life year tables for the expected life years given that the patient is healthy (Arias & Xu, 2019). Finally, we use 0.07 for the QALY decrement if the patient has a CHD event, 0.21 if the patient has a stroke and 0.003 when the patient is on statins (Tengs & Wallace, 2000).

4.2 Model validation

As mentioned in Section 3, we first validated the Markov chains we estimated for cholesterol and blood pressure by dividing the available data into training and test sets. Then, we validated the MDP model by comparing the percentage of patients with a CVD event and the expected life years versus the current available CDC life tables.

4.2.1 Transition probability matrices

We divided the data set into different groups, depending on sex and race, because these factors are important predictors of 10-year risk (Sussman et al., 2017). In our data, 69.1% of the patients identified as white male, 20.4% African-American male, 6.7% as white female, and 3.8% as African-American female. Due to the lack of data for African-American female patients we were unable to conduct numerical experiments on that sub-population.

Additionally, between each of these groups, we divided the data depending on the treatment plan and age range of the patients to estimate the stochastic behaviors. We estimated the discrete time Markov chains for each of these patient groups. To validate the model we divided the data between training and test sets. Randomly, we chose 2/3 of the data set as training data and 1/3 as test data. Finally, as mentioned in Section 3. we used a likelihood ratio test to validate the Markov chains and show the results in Table 5.

Table 5 For each patient group we compare the observations with the estimated Markov chain and estimate the p-value of the likelihood ratio test. We define the null hypothesis as the Markov chain fits the data behavior. If the p-value is lower to 0.05 (in bold) the null hypothesis is rejected

		P-Value		
Patient Group (% of Total)	**Age Range**	**No Medication**	**Low intensity Statins**	**High intensity Statins**
White female (6.7%)	40	0.894	0.597	0.239
	45	1.000	0.987	0.827
	50	1.000	1.000	0.618
	55	1.000	0.974	0.253
	60	0.995	0.669	1.000
	65	1.000	0.954	1.000
	70	1.000	0.864	0.615
	75	0.589	0.246	**0.000**
African-American male (20.4%)	40	0.241	0.847	0.080
	45	0.890	0.997	**0.019**
	50	1.000	0.830	**0.000**
	55	0.980	1.000	**0.031**
	60	0.355	0.744	0.158
	65	0.989	0.982	**0.001**
	70	1.000	0.662	0.534
	75	1.000	0.221	**0.003**
White male (69.1%)	40	1.000	1.000	0.997
	45	1.000	1.000	0.183
	50	0.999	0.998	0.703
	55	0.747	0.871	0.601
	60	0.228	0.188	0.969
	65	0.491	0.128	0.145
	70	0.962	0.116	**0.021**
	75	0.841	0.156	0.408

For the patient groups with more data, such as white male, the likelihood ratio test does not reject the null hypothesis. Otherwise when less data is available, the test tends to reject the null hypothesis. Moreover, cases which are rare, such as younger people (ages between 40 to 60) with high-intensity statins, the test tends to also reject the null hypothesis. Nonetheless, as we will show in the model's output, the 10-year risk for younger patients is not high enough to receive high intensity statins. Therefore we can safely trust

the EM-algorithm outputs. We apply the same test for blood pressure, with the difference that we do not divide the data by treatments. Because we count with more blood pressure information, the test did not reject any of the cases.

4.2.2 Markov decision process model validation

We validated the MDP model by comparing the expected life years versus the American population's CDC reports. We ran our model for each of the three patients groups mentioned in the last section, using a sample of 1/3 of the VA population in each group. Table 6 presents the results of the model compared to the CDC life tables.

Table 6 The validation shows that our model increases the average life years for African-American males and is not statically different for the other two groups

Patient Group	Model's Avg life years	CDC life years
White male	77.3 ± 0.71	76.4
African-American male	74.5 ± 0.72	71.9
White female	80.9 ± 0.61	81.2

As we estimate our data with the VA population, we expected the life years to be higher than the average American population, as they tend to have better access to healthcare (NCVAS, 2018). It is worth noting that the highest difference is between our model and the CDC life tables for African-American males. One of the possible reasons this happens is the regular access to healthcare for the VA population which are more likely to have a combination of public and private health insurance,ue to Medicare, VA health care, and a second career after retirement. This access to healthcare is not uniformly true for the general population that is the basis of the CDC statistics. For example, it's estimated that 13.3 % of non-veterans do not have access to healthcare (NCVAS, 2018). A second possible reason is that our model does not attempt to directly consider racial disparities that be the cause of lower life expectancy for African-American males compared to white males in the CDC life tables.

4.3 MDP model's recommended cholesterol monitoring policy

We estimate the optimal policy for three demographic groups: white male, African-American male, and white female. As we focus on prevention, we analyze the policy only for healthy patients, as CVD and Death are absorbing states. As age affects the policy, estimating the 10-year risk will give us more insights into the policy. In Figure 3 we present the optimal policy by age range, treatment, and 10-year risk for the white male group. As mentioned before, we divided the 10-year risk into low, borderline, intermediate, and high risk.

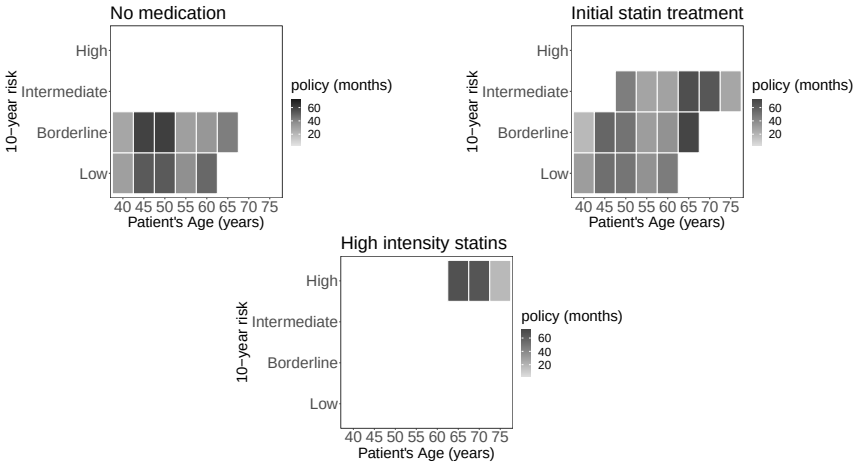
For younger white male patients who are not on preventive treatment, age 45 to 55, the MDP policy falls into the range of the current ACC guidelines. It differs for white male patients between 40 and 45, where the policy recommends

that cholesterol tests be taken on average every 30 months, lower than what the ACC guidelines recommend. For a white male patient on treatment between the ages of 40 to 55, the model recommends more time between appointments than ACC guidelines (3 to 12 months).

When a white male patient not on preventive medication gets older, the time between tests decreases below what the ACC guidelines suggest. On the other hand, for those white male patients who are on treatment, the time between tests varies depending on age and CVD risks. For example, for patients 55-years old and older, the time between appointments decreases when the risk increases. Also, for white male patients on statins between 60 to 70 years old, the model suggests a higher time between appointments than the current ACC guidelines. This behavior is a response to the natural increase in risk when the patients get older. Nonetheless, age 75, the time between appointments decreases, similar to the current ACC guidelines. Finally, the policy suggests to continue monitoring white male patients with high intensity statins. If the patient's risk decreases, then it is possible that the physician also decreases the statin intensity level.

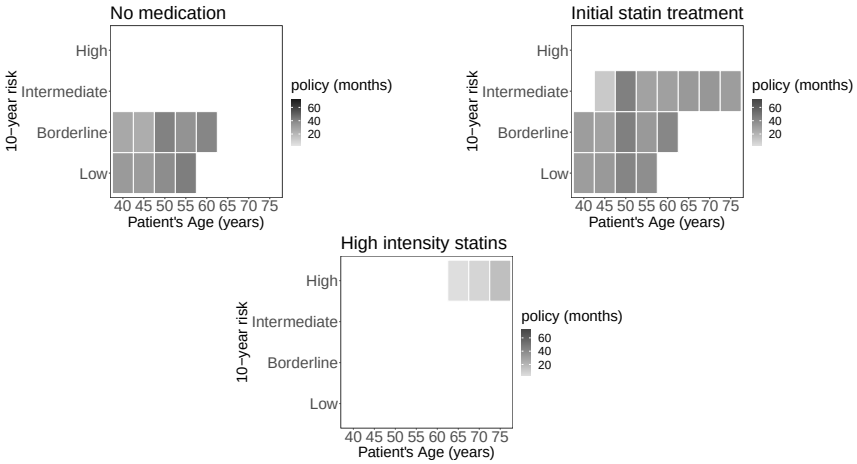
We analyzed the policy for white males, divided by age ranges, cholesterol level, blood pressure level, and treatment. We noticed that the policy does not change significantly with respect to cholesterol levels and blood pressure levels when they are varied independently. On the other hand, when both risk factors change, the effect is seen in the 10-year risk and the policy changes as well. The results are shown in Figure 8, in the Appendix.

Fig. 3 White male optimal policy by 10-year risk. The optimal policy varies depending on the patient's age, treatment, and 10-year risk. The color represents the time between appointments where lighter is less time between appointments and darker is more time between appointments. The optimal policy ranges from 3 months to 72 months between appointments. As we are following the ACC cholesterol treatment guideline, there are spaces in white that represent unreachable states



Similar to previous results, the MDP policy for African-American males is affected by the patient's age, the 10-year risk, and the treatment. In Figure 4, we present the optimal policy. This policy suggests that African-American male patients should have shorter time between cholesterol tests than white male patients, where none of the cases exceeds 40 months between visits. Similarly, the recommended time between visits decrease for African-American male patients 55-years old and older.

Fig. 4 African-American male optimal policy by 10-year risk. The optimal policy varies depending on the patient's age, treatment, and 10-year risk. The color represents the time between appointments where lighter is less time between appointments and darker is more time between appointments. The optimal policy ranges from 3 months to 72 months between appointments. As we are following the ACC cholesterol treatment guideline, there are spaces in white that represent unreachable states

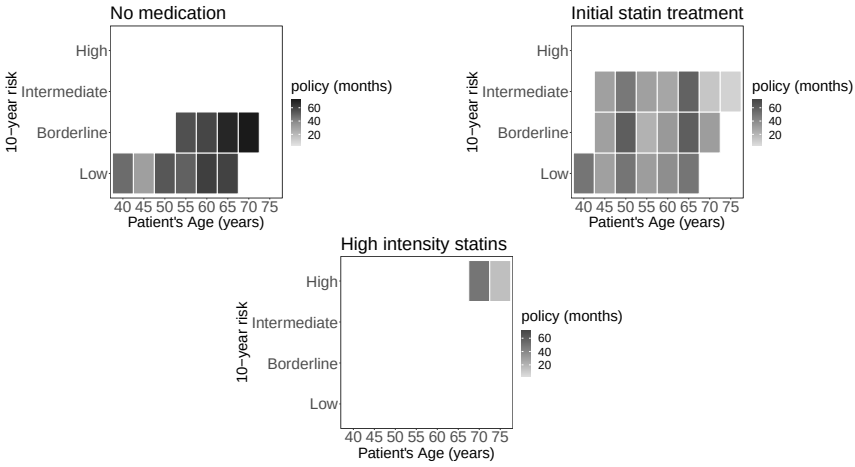


Finally, the policy for white female patients suggests having more time between cholesterol tests for patients who have not started preventive treatment, compared to white male patients, as shown in Figure 5. For those patients on treatment, the MDP policy recommends for less time between appointments for this demographic group than for white males but more time between appointments than African-American males. These results are consisted with the lower 10-year risk that women have according to the VA risk models (Sussman et al., 2017). Nonetheless, this policy also shows that gender is essential for cholesterol testing policies.

4.4 Comparison of MDP policies to ACC guidelines and VA practice

We compare our MDP-based policy versus three other types of recommended policies used in practice. First, we divide the ACC guideline into two cases.

Fig. 5 White female optimal policy by 10-year risk. The optimal policy varies depending on the patient's age, treatment, and 10-year risk. The color represents the time between appointments where lighter is less time between appointments and darker is more time between appointments. The optimal policy ranges from 3 months to 72 months between appointments. As we are following the ACC cholesterol treatment guideline, there are spaces in white that represent unreachable states



(1) The minimum values for the range recommended by the ACC guideline (ACC Min), testing every four years when the patient is not on treatment, and three months when the patient is on treatment; (2) The maximum values for the range recommended by the ACC guideline (ACC Max), testing every six years when the patient is not on treatment, and testing every year when the patient is on treatment. The third policy that we tested is an empirical estimate of the current VA practice based on observational data (VA Data). We use the data set to estimate the mean frequency of cholesterol tests by age group, cholesterol level, blood pressure level, and treatment.

We compare the policies by evaluating them using the MDP model and compare the patients' average discounted rewards, average discounted costs, and the probability of having a CVD event. Additionally, we evaluate these policies assuming that patients start without a previous CVD event and cholesterol-lowering treatment. Finally, we evaluate the policies for patients beginning at the age of 40 who are not on treatment.

We notice in Figure 6 that, on average, the MDP policy slightly increases total expected rewards compared to other policies. Nonetheless, when we analyze the costs, we notice that the MDP policy decreases all patient groups' costs. Additionally, the patient's percentage of CVD events is also smaller when applying the MDP policy.

As shown before, our policy tends to monitor untreated patients more frequently than ACC Min and less frequently than ACC Max for patients on statins. This behavior affects the costs of the appointments. Also, for all

groups, the MDP policy decreases total costs. Finally, the policy recommends more frequent monitoring when the patient is not on medication, therefore prescribing low-intensity statins as quickly as needed. This outcome reduces the time that the patient is on high-intensity statins, hence reducing the overall treatment cost.

For white men, the MDP policy increases the total discounted rewards on average $\$2,516$ (0.11%) per patient, compared to the ACC Max policy, which is the second-best policy. Additionally, compared to ACC Max, our policy will decrease the total discounted costs on average \$623 (5.16%). These discounted rewards and costs are measure, on average, over 37 years. We observed similar results for the other patient groups, where we compare the results versus the following best policy, ACC Max. For African-American men, the MDP policy increases the total discounted rewards on average $\$5,822$ (0.29%) and decreases the total discounted costs by $\$1,599$ (9.56%), on average, over 35 years. For white women, the MDP policy increases the total discounted rewards on average $\$2,265$ (0.10%) and decreases the total discounted costs by \$479 (5.47%), on average, over 41 years.

The latest Veteran Affairs census has approximately 8 million white male patients over the age of 40, 1.2 million African-American male patients over the age of 40, and 0.6 million white female patients over the age of 40 (NCVAS, 2018). The estimated changes fue to the MDP policy suggest the potential for increasing VA population's societal rewards by approximately \$28.5 billion dollars. Furthermore, the societal costs will decrease by around \$7.2 billion dollars.

We further tested this behavior by varying the WTP value, remaining the costs constant. Additionally, our policy is robust with changes of WTP unless a value of $\$10,000$ or less is used. When the WTP is decreased to $\$10,000$, the policy focuses on minimizing costs, increasing the time between appointments for patients without medication, and decreasing the time between appointments for patients with High-intensity statins. The latest behavior results from lowering the statin intensity as soon the risk decreases, as the cost of a patient in high-intensity statins is double that of low-intensity statins. We show these results for White male patients in Figure 7.

5 Conclusions

When dealing with cardiovascular diseases, one of the critical decisions is how often a patient gets a cholesterol test. Measuring too frequently may be inconvenient and costly; on the other hand, measuring too infrequently mean the patient may forgo needed treatment and experience adverse events related to the disease. The American College of Cardiology recommends that healthy patients take cholesterol tests every 4 to 6 years, and patients receiving cholesterol treatment should take cholesterol tests every 3 to 12 months. Our study

Fig. 6 Policies evaluation. We present the rewards, appointments costs, CVD costs, and treatment costs, which are discounted until the patient's first appointment. For the CVD event graph, we present the probability that at some point the patient has a CVD event. On the x-axis, we have each of the patient's groups. On the y-axis, we present the average value per patient

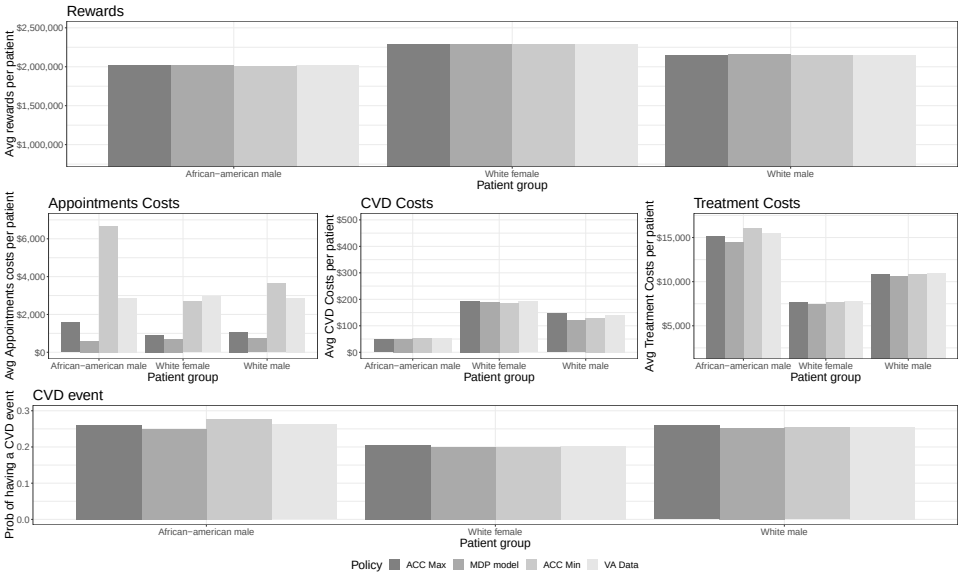
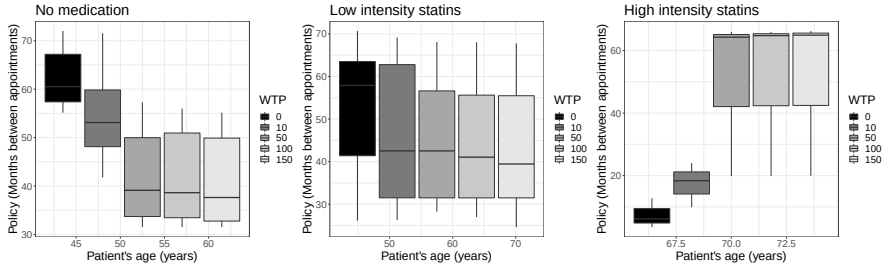


Fig. 7 Sensitivity analysis of the policy by varying the WTP value per year. We present in the boxplots the median and each of the quartiles



shows that MDP-based policies can increase rewards and decrease costs; moreover, the changes depend on age, gender, and race, suggesting a one-size-fits-all policy may not be ideal.

In our framework, we proposed and validated multiple statistical models that learn from EHRs. First, we used an EM algorithm to fit the cholesterol and blood pressure behaviors. The EM algorithm outputs non-stationary discrete-time Markov chains that vary by gender, race, treatment, and age. We validated the Markov chains by applying likelihood ratio tests for three demographic groups: White male patients, African-American male patients,

and white female patients. We found that EM algorithms help fit cholesterol and blood pressure behaviors when using longitudinal data gathered unevenly. Also, we found that with a lack of sufficient information, the EM algorithms have a less accurate performance when fitting Markov chains to cholesterol behaviors. Fortunately, this case only happens for young patients with high-intensity statins, which rarely occurs as the 10-year risk for younger patients usually is low. We believe these algorithms will help estimate patients' risk factors for other healthcare applications, as healthcare data is only gathered when the patients go to healthcare providers.

After estimating each patient group's risk factor probability distributions, we presented a finite-time and finite-state MDP that considers cholesterol LDL, systolic blood pressure, age, and patient's treatment. We showed that the monitoring policy must consider the ASCVD 10-year risk, the patient's age, and the treatment to maximize the benefits. The policy varied between 3 months to 6 years, recommending on average to decrease the time between appointments when the risk, age, or treatment intensity increases. Finally, we evaluated our policy and compared it with current guidelines.

We also studied how the patient demographics affect the MDP policy. We showed that race and gender influence the optimal frequency of monitoring cholesterol. For example, the model suggests that African-American males may benefit from more frequent surveillance than white males. On the other hand, for white females the MDP model recommended less frequent monitoring to lower the CVD event risk when they are not on treatment. On treatment, the model recommends more frequent surveillance for white female patients compared to white male patients but less than African-American male patients.When the model recommends less frequent surveillance, the patient's health is not negatively affected. For these particular cases, the model decreases the appointments costs and treatment costs without reducing the patients' QALYs or increasing the associated CVD costs.

The nature of these results is a response to the increased 10-year CVD risks that male patients have over female patients and the increased risk that African-American patients have over white patients. Studies suggest that differences in risk among patients are associated with access to healthcare and racial inequalities (Rajkomar, Hardt, Howell, Corrado, & Chin, 2018). Unfortunately, the difficulty in measuring the patients' risk factors, may delay treatment to the patients, hence increasing their CVD risk (Phelan & Link, 2015). Learning from the available data, the model maximizes rewards by scheduling appointments when needed, optimizing the patient's treatment intake, and reducing the risk of having a CVD event.

We presented the model's recommended policy by race, gender, and treatment. The time between cholesterol tests for African-American male patients is, on average, 34 months without treatment and 20 months with treatment. For white male patients, the time between tests was 43 months without treatment and 46 months on treatment. Finally, the time between tests for white female patients was 55 months without treatment and 34 months with treatment.

Compared to a one-size-fits-all policy, such as the ACC guidelines, our model suggests that considering patients' demographics could increase the societal rewards by approximately $28.5 billion dollars for the VA health system. This increase was associated with an MDP policy that decreased unnecessary appointments and setting appointments when the probability of starting treatment increases. Starting low-intensity statins sooner reduces the probability of taking high-intensity statins, hence reducing the overall treatment cost. Additionally, our policy reduces the probability of having a CVD event, resulting in a reduction of approximately $7.2 billion dollars for the VA health system.

Like all model-based studies ours has some limitations. First, our MDP model does not capture all the realities of treatment in practice and thus the benefits of using an MDP based policy for different demographic groups is subject to error; nevertheless, we tried to consider the most important clinical factors in creating our models. Furthermore, we acknowledge that our model is based on the VA population, which predominantly comprises white male patients. Additionally, we recognize that underlining causes affect each demographic group's risk of cardiovascular disease. Unfortunately, we did not have access to this data, and it was not feasible to gather. Nevertheless, our results suggest that patients' demographics may be a key risk factors for healthcare and one-size-fits-all policies may be associated with a combination of higher cost and lower quality adjusted lifespan. Additionally, the MDP model structure serves as a prototype to help physicians and public health experts improve cholesterol control. Finally, this model could be adapted to other chronic diseases that require monitoring to make medical treatment decisions (e.g., blood sugar control for diabetes).

Future work might consider adding the probability distributions of how the patient responds to recommendations. Given that patients do not always follow physicians' recommendations, future enhancements may be worth considering. The first one is adherence to medications, where studies suggest that the frequency of appointments may increase adherence. This behavior affects the estimation of the 10-year risk, increasing it if the adherence is low. Second, the patient will not necessarily come back to an appointment, as the physician recommends. Therefore the time between appointments could also be considered stochastic. Our research provides a starting point to further investigate some of these questions. Finally, our approach to building a model for CVD using longitudinal EHR data, and other sources of data, could find application to other diseases that involve periodic monitoring of risk factors.

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6 Appendix

Fig. 8 White male optimal policy. The optimal policy varies depending on the patient's age, cholesterol levels, and blood pressure levels. The color represents the time between appointments where lighter is less time between appointments and darker is more time between appointments. The optimal policy ranges from 3 months to 72 months between appointments. The spaces in white represent invalid cases, e.g. where patients should be in a specific type of treatment base on the patient's 10-year risk. For example a 70-year old white male patient should be on statin treatment, therefore there is no optimal policy for patients without treatment