

**Medical Policies in the Context of Primary Prevention for Cardiovascular Disease**

by

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## **ABSTRACT**

Access to electronic health records creates an opportunity to build stochastic models that support healthcare providers' decisions to prevent chronic diseases. As the patient's health conditions vary, decision-makers must apply optimal medical policies that learn from patients' health behaviors and consider their needs. In this dissertation, we present new models that address the following key challenges: (1) understanding how the patient demographics influence the disease progression, (2) developing sequential decision-making models under uncertainty that pursue the best health outcomes for individual patients, and (3) developing sequential decision-making models with limited resources to prevent chronic diseases for a population.

We propose operations research methods to develop policies to prevent cardiovascular diseases. We applied our models to longitudinal data for cardiovascular diseases in a large cohort of patients seen in the national Veterans Affairs health system. The contributions of this work include: (1) Developing an EM algorithm to model patient's health progression, (2) creating a simulation framework to test and analyze different treatment guidelines, (3) developing a sequential decision-making model to define cholesterol monitoring policies that maximize societal benefits, and (4) developing an algorithm for identifying and selecting high-risk patients into adherence-improving interventions. Finally, our modeling framework establishes the analytical and theoretical foundation to build stochastic models that address multiple healthcare opportunities for improvement.

# CHAPTER 1

## Introduction

Over the last couple of decades, electronic health records (EHRs) have emerged as a standard for tracking important medical data for patients seen in health systems. As a result, health systems are gathering large amounts of longitudinal data that can be used to create a deeper understanding of how patients' health conditions change over time. Additionally, EHRs help illustrate the differences between disease progression and medication effects across patients. This resource creates opportunities for health systems to extend beyond just the patients' current health status by predicting the long-term impact of healthcare policies over a patient's lifetime and developing new policies to prevent the patients' disease progression. These policies are particularly relevant for chronic diseases and other permanent conditions that patients may live with for many years.

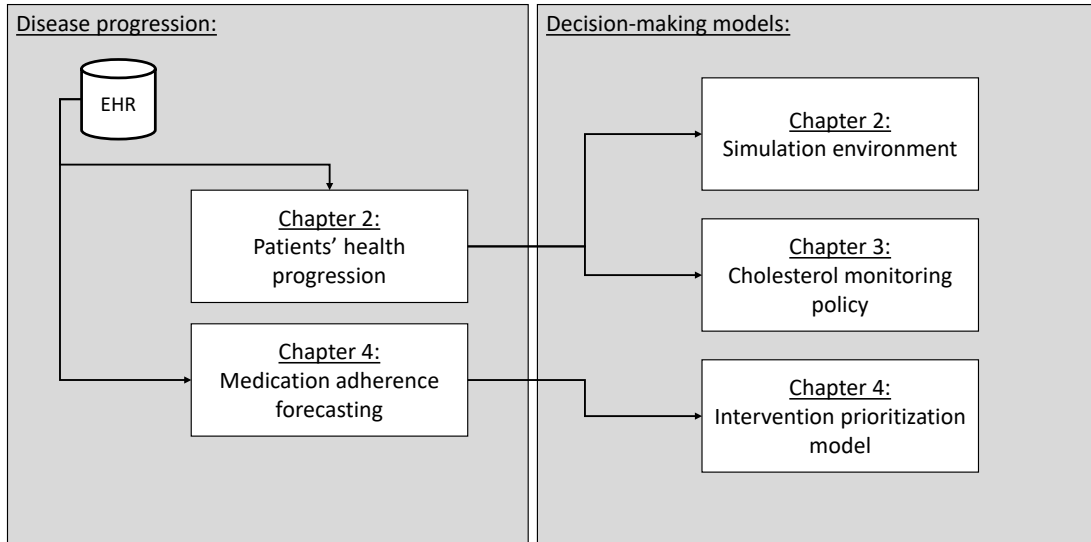
This dissertation focuses on cardiovascular disease (CVD) prevention as an important example of how longitudinal EHR data can improve care. We chose CVD prevention because it is a common condition requiring multiple decisions over time. Moreover, it is one of the leading causes of death worldwide [6]. In 2021, cardiovascular diseases caused 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 disease (CHD). It is estimated that managing CVD costs \$351.2 billion annually to Medicare in the United States [7].

In this context, physicians monitor and treat patients based on recommended policies created based on clinical trials and clinical judgment [1, 8], which are usually one-size-fits-all as they do not consider the patient's sex, race, and age. Furthermore, information on historic health-related factors is not used. The availability of longitudinal information makes it possible to model the uncertainty in risk factors generated by the differences in patients' health behavior. Therefore, there is a need to build stochastic models that can include this uncertainty and help define optimal policies to improve patients' health. Within this framework, this dissertation seeks to develop policies by addressing the following key challenges:

1. Understanding how the patient demographics influence the disease progression.

2. Developing sequential decision-making models under uncertainty that pursue the best health outcomes for individual patients.
3. Developing sequential decision-making models with limited resources to prevent chronic diseases for a population.

Figure 1.1: Overview of dissertation chapters.



In Figure 1.1, we present an overview of the components to answer these key challenges and how the dissertation is organized. In Chapter 2, we present a methodology to fit the patient’s health progression using an Expectation Maximization (EM) algorithm [9]. Additionally, we develop a Monte-Carlo simulation model to test and analyze different treatment guidelines. These treatment guidelines define which blood pressure and cholesterol-lowering medications are prescribed to lower the risk of heart attack and strokes. These guidelines are applied sequentially over time based on monitoring the patient’s risk factors. Finally, they vary depending on the type and value of risk factor-associated thresholds used for starting medication. In Chapter 3, we provide a sequential decision-making model to define cholesterol monitoring policies that maximize societal benefits. In Chapter 4, we develop a dynamic logistic regression model (DLR) to predict the patient’s future medication adherence. We also present a binary integer programming model (BIP) to decide which patients to prioritize for adherence-improving interventions. Finally, we conclude with remarks and future work in Chapter 5. We now proceed to describe each chapter and its contributions briefly.

## 1.1 Chapter 2 Summary: Using longitudinal health records to simulate the impact of national treatment guidelines for cardiovascular disease

Health history is gathered irregularly for many chronic diseases and conditions. For cardiovascular diseases, physicians typically measure healthy patients' risk factors, such as cholesterol and blood pressure ranging from every 1 to 6 years. In Chapter 2, we develop an EM algorithm that fits unevenly sparse data to estimate transition probabilities for a discrete-time finite state Markov chain. Furthermore, we use the Markov chain to create a discrete-time Monte-Carlo simulation model to test multiple treatment guidelines for CVD prevention. We use our model to estimate treatment benefits in terms of CVD risk reduction and treatment harms due to side effects, based on when and how much medication the patients are exposed to over time. The main contributions of Chapter 2 are as follows:

- We develop an EM algorithm that can fit patients' sparse medical data to Markov chains. These Markov chains are then used to simulate the patient's disease progression.
- We show that, to decrease the error between the Markov chains versus the patient's real disease progression, it is necessary to consider patients' demographics, in particular, sex, age, and race. Additionally, EM algorithms are an effective tool for characterizing stochastic processes from longitudinal observational data.
- We develop a Monte-Carlo simulation model to easily test multiple treatment guidelines for cholesterol and blood pressure. Additionally, the simulation model facilitates testing guidelines that follow patients for long periods of time.
- To parameterize our model, we use a longitudinal dataset for cholesterol and blood pressure in a cohort of 10,000 randomly sampled patients seen in the national Veterans Affairs health system.
- We are able to conclude that among published guidelines, those focusing on reducing CVD risk can reduce treatment without significantly increasing the risk of severe health outcomes.
- This work is published in the *2021 Winter Simulation Conference Proceedings* [10].

## **1.2 Chapter 3 Summary: Cholesterol monitoring policies for cardiovascular disease prevention**

To prevent cardiovascular 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. In Chapter 3, we propose a finite horizon and finite-state Markov decision process (MDP) to define monitoring policies. We study policies for whether or when to assess the need for cholesterol-lowering medications. Additionally, we investigate the role of the patient's demographics in optimal monitoring policies. We use longitudinal data from the Veteran Affairs health system to analyze the differences in policies between men and women and white and black patients. The main contributions of Chapter 3 are as follows:

- We develop a framework to prevent CVD that accounts for patients' demographics.
- We develop an MDP model that includes societal costs and rewards, such as appointment costs, treatment costs, costs associated with cardiovascular diseases, and the patient's willingness-to-pay for being healthy. Moreover, the model estimates the total costs and rewards during the patient's lifetime.
- We show that MDP-based policies increase benefits by \$28.5 billion compared to the current American College of Cardiology policies. The MDP-based policy decreases the number of unnecessary appointments, starts treatment sooner, and decreases the number of CVD events. Moreover, the changes depend on age, gender, and race, suggesting that a one-size-fits-all guideline may not be ideal.
- This work is published in *Health Care Management Science* [9].

## **1.3 Chapter 4 Summary: Prediction of long-term medication adherence and its potential benefits for intervention**

Long-term adherence to medication helps prevent chronic diseases. However, after the first year of prescription, only 50% of the patients will eventually continue taking their medication [11]. In recent years several adherence-improving interventions have become available to help mitigate adherence decay [12]. Nevertheless, in many contexts, providing all patients with interventions is not feasible due to the high cost of such programs [12]. In Chapter 4, we propose a new approach



to optimize the selection of patients to assign interventions subject to a budget constraint. We present a model that employs a dynamic logistic regression model that uses patients' claim data, medical health factors, demographics, and monitoring frequencies to predict the risk of future non-adherence. Additionally, we present a binary integer program that utilizes the adherence forecast and selects which patients should be included in adherence-improving interventions. The main contributions of Chapter 4 are as follows:

- We develop a dynamic forecasting model that helps identify when patients will stop adhering to medications. Identifying at-risk patients and those patients that would most benefit from adherence support helps facilitate clinical interventions.
- Solving the Binary integer program (BIP) model is NP-hard in general, but we prove that prioritizing patients with the highest marginal avoid CVD risk between two epochs is optimal under certain conditions.
- We show that applying the BIP policy reduces 22.9% the number of cardiovascular events in the population. Moreover, combining the DLR model and the BIP policy, this percentage increases to 36.5%.

## 1.4 Concluding remarks

This research develops operations research methods that use electronic health records to define chronic disease prevention policies. Thanks to these models, healthcare providers can rely on additional tools to understand disease progression, identify high-risk patients, and manage chronic diseases accurately across demographic subgroups. While the models were created and motivated by the need to manage CVD, the analytical and theoretical foundation established in this dissertation may be applicable to guide monitoring and resource allocation decisions faced by a variety of other chronic conditions. Chapter 5 summarizes the contributions and presents opportunities for future research.

## CHAPTER 2

# Using Longitudinal Health Records to Simulate the Impact of National Treatment Guidelines for Cardiovascular Disease

### 2.1 Introduction

The EHRs availability provides an opportunity to understand patients' disease progression, hence creating the possibility to build simulation models that support healthcare providers' decisions. In particular, simulation-based approaches are useful as an additional tool (besides randomized clinical trials) to guide screening and treatment decisions. They are especially valuable in guiding chronic disease management, given the long time frame over which guidelines are applied. In some cases, traditional long-term randomized control trials (RCTs) may not be possible at all. The conduct of long-term RCTs are often hindered by their cost, "lost-to-follow-up" and "treatment /protocol contamination" [13]. Simulation-based approaches can hence be used to explore a range of possible interventions, using the RCT-derived average treatment effects for causal estimates while also assessing the effects over the population's lifetime [14].

Most clinical trials have a short duration for cardiovascular diseases (CVD), and patients enrolled in trials could differ from those seen in any health system. Therefore, physicians and policymakers may benefit from using simulation models (created using clinical trial data and EHR data) to compare and contrast healthcare policies. More specifically, treatment guidelines, before applying them to patients they see in their practices.

The objective of this chapter is threefold. First, we develop an Expectation Maximization (EM) algorithm to model disease progression in patients. Second, we provide a case study of the development of a simulation model from longitudinal EHR data in the context of CVD prevention. Third, we use the model to evaluate the impact of drug treatment guidelines for prevention of CVD. More specifically, for each of the guidelines we consider, we evaluate the trade-off between two important considerations: 1) CVD risk reduction caused by treatment and 2) treatment burden from

the perspective of the number of medications patients are exposed to over time. The former is a measure of the benefits of treatment, and the latter is a surrogate measure of the harm of medication (e.g., cost, side effects). We use a discrete-time Monte-Carlo simulation model using longitudinal EHR data from the Veteran Affairs (VA) health system to evaluate the most well-known U.S. treatment guidelines.

The rest of this chapter is organized as follows: Section 2.2 provides background on CVD and a brief review of some of the most related prior studies. In Section 2.3, we describe our model inputs and assumptions. In Section 2.4, we describe our EM algorithm and present the simulation model. In Section 2.5, we apply our model to a longitudinal database of the Veteran Affairs department and present the results. Finally, in Section 2.6, we discuss the results and propose the next steps.

## **2.2 Background on cardiovascular disease and relevant literature**

CVD is responsible for roughly a third of all deaths in the U.S. population per year. It is especially prevalent in patients between 40 and 80 years old [6]. To prevent deaths and CVD events, physicians treat patients with medications to lower cholesterol and blood pressure, two of the most well-known and controllable risk factors for CVD. For our study’s purpose, we will focus on CVD prevention, acknowledging that medications are essential to reduce the risk of a CVD event.

In the United States, multiple guidelines exist to treat high cholesterol and high blood pressure, yet there are open questions about which guideline is “best”. The two most often used guidelines are those developed by the American College of Cardiology (ACC) [1, 8] and the Joint National Committee (JNC) [15]. These guidelines prescribe treatment decisions that depend on health risk factors, which affect the relative benefits of treatment for patients [16, 17]. The ACC guidelines focus on reducing overall 10-year risk, while the JNC guidelines focus on reducing blood pressure. These variations lead to differences in whether and when patients start the treatment and their risk of having a CVD event. The specific CVD events we consider in this study include heart attacks and strokes.

Physicians usually rely on the estimates of the CVD event risk to prescribe treatments. There are multiple studies on estimating the CVD event risk. The most widely used risk assessment guideline is given by the American College of Cardiology/American Heart Association (ACC/AHA) [18]. Their study used a Cox proportional hazards model to estimate the 10-year risk of heart disease or stroke using patients’ information such as age, gender, race, smoking habits, cholesterol, blood pressure, and treatment. Another study by [19] recalibrated the ACC calculator using the observation data in the Veterans’ Affairs system, which provides more accurate estimates of risk for the

population considered.

Risk factors such as blood pressure and cholesterol for CVD can have highly stochastic behaviors and may be sparsely collected. Sparse and missing data are common in real-world data sources, from poverty measurements to marketing strategies for new products. The two most common approaches for dealing with missing data in this context are imputation and maximum likelihood methods. 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 [20, 21, 22, 23]. Usually, the models assume that the data are enough to fit these frequencies correctly [24]. Other approaches include statistics techniques to estimate the transition probabilities, such as Poisson regressions with linear-mixed-effects for blood pressure [25] and generalized linear regression models for CVD risk [26]. Additionally, depending on the application, the Markov chains vary depending on demographics and the patient’s health state [20, 27, 28, 23]. Our study considers the effects of gender, race, and age on the Markov chains.

Because data about risk factors are collected sporadically according to the pattern of patients’ visits, data-augmentation techniques show excellent results when fitting these sparse data to Markov chains [29]. Data-augmentation techniques refer to applying iterative optimization algorithms where non-observed data are introduced to the data set to estimate the stochastic behaviors [29]. Within these techniques, EM algorithms [30] and maximum likelihood estimation methods [24] are commonly used. We believe EM algorithms benefit from the structure of longitudinal patient data, as it is a data-augmentation method that learns from the observations to impute a possible value to complete the patient’s health behavior [30]. Furthermore, EM algorithms have been applied to CVD by estimating clusters of patients with hypertension [31], estimating the probability of CVD mortality [32], and estimating CVD events [33]. Additionally, they have been applied in many healthcare settings, for example, mental health [24], patient flow in a hospital [34], prostate cancer active surveillance [35], and emergency medical services [36], among other applications. We extend the scope of applications by applying EM algorithms presented in the literature [24] to estimate cholesterol and blood pressure stochastic processes from EHRs.

CVD have been studied extensively in the literature, focusing on risk factor estimation, survival models, and cost-effectiveness of disease prevention and treatment. For example, [37] estimated a time series model to predict high-risk cholesterol levels. [38] estimated the incidence, survival, and lifetime risk of stroke in a Rotterdam population. [39] and [40] presented the cost-effective analysis for treatment in CVD prevention. As a variant to previous studies, we propose a framework that feeds from sparse longitudinal data to simulate the patient’s behavior through their lifetime.

## **2.3 Input and assumptions for the simulation model**

In this section, we describe the U.S. Department of Veterans Affairs database that we used to develop and test our simulation model. Then, we discuss the assumptions that we made when estimating model parameters. Finally, we explain how we estimated the stochastic behaviors that served as input to our simulation model.

### **2.3.1 Data set description**

Our simulation model was developed from a longitudinal dataset for cholesterol and blood pressure in a cohort of 10,000 randomly sampled patients seen in the national Veterans Affairs health system. VA-trained analysts randomly sampled, validated, and prepared an anonymized dataset [19] that was used as input to our model. Patients were eligible to be included in the cohort if they had at least two outpatient visits with a cholesterol and blood pressure screening. The data follows the patients from 2003 until 2018, with information on demographics, treatments, and health factors. More precisely, the dataset has information on the patients' race, gender, age, smoking habits, prescription dates, the type of treatment, and the number of pills for treatments. The data includes laboratory measurements such as low-density lipoprotein (LDL) cholesterol, total cholesterol, and systolic blood pressure (SBP). It is worth noting that blood pressure is measured more frequently than cholesterol because of the ease of measurement in a clinical setting. Thus patterns of data availability can vary.

Since our study focuses on CVD prevention, we excluded patients with a CVD event or diabetes (a major risk factor for CVD) prior to their earliest EHR data entry. These patients will have very different needs and treatment patterns than those who are candidates for primary prevention, our study's focus. 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 80 years old), and older adults (older than 80 years old). Because of the nature of our data set, it mainly consists of the adult age group. Therefore, we only selected patients between the ages of 40 to 80. Finally, we considered patients with at least two cholesterol tests, given our focus on estimating a stochastic model from longitudinal data. After pruning the original data set based on the exclusion criteria, 6658 patients remained.

### **2.3.2 Definitions and assumptions**

We assume the physician does not have access to observations between appointments. The physician also acknowledges any CVD event, even if it happens between appointments and patients exit the CVD prevention process. According to the guidelines, each of the risk factors, LDL, SBP, and

Total Cholesterol, are divided between different levels, as shown in Table 2.1 [1, 2].

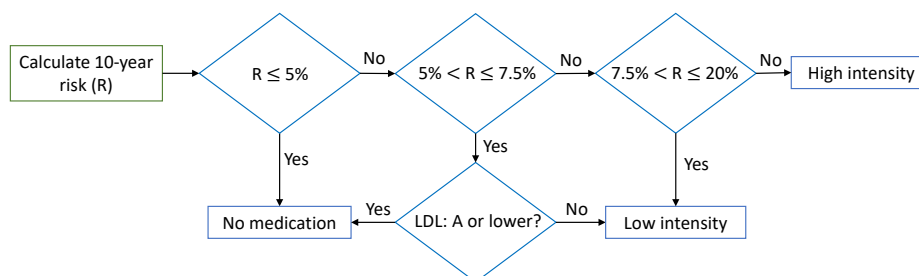
Table 2.1: Risk factors levels. The discrete sets of published clinically relevant cholesterol ranges used to define cholesterol states [1] and systolic blood pressure ranges used to define blood pressure states [2].

Risk factor and level		
Cholesterol LDL (mg/dL)	Total cholesterol (mg/dL)	Systolic blood pressure (mm Hg)
Low (L): < 70	Normal (N): < 200	Normal (N): < 120
Normal (N): $\geq 70$ and < 100	Borderline High (B): $\geq 200$ and < 240	Elevated (E): $\geq 120$ and < 130
Acceptable (A): $\geq 100$ and < 130	High (H): $\geq 240$	Hypertension I (H1): $\geq 130$ and < 140
Borderline High (B): $\geq 130$ and < 160		Hypertension II (H2): $\geq 140$ and < 180
High (H): $\geq 160$ and < 190		Hypertensive Crisis (HC): $\geq 180$
Severe (S): $\geq 190$		

For both cholesterol and blood pressure, physicians may prescribe a variety of medications. For cholesterol, we focus on statins, which are by far the most common medication used to treat high cholesterol. Statins are divided into two intensities: low and high. Between these two groups, physicians consider which intensity of statins is the best depending on the patient’s 10-year risk of having a CVD event (most patients will receive the low (nominal) dose). The 10-year risk is estimated based on LDL, SBP, patient age, sex, race, and currently prescribed treatment using the ACC risk model. For blood pressure, we will focus on the five primary types of medications: Angiotensin-receptor blockers (ARBs), Angiotensin-converting enzyme (ACE) inhibitors, Thyazides, Calcium Channel Blockers, and Beta-Blockers. For cholesterol and SBP, we assume risk reduction factors are consistent with normal adherence to medications, as observed in clinical trials.

We tested the ACC guideline for cholesterol-lowering medications, which we present in Figure 2.1. Prior studies have proposal risk thresholds ranging from 5% to 7.5% [41]. A lower threshold means that patients will begin treatment sooner, while a higher threshold will defer treatment.

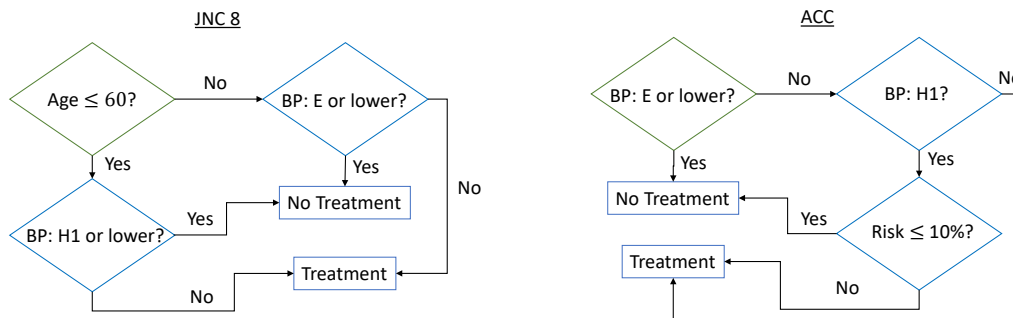
Figure 2.1: The ACC guideline for cholesterol treatment. The treatment is defined depending on the patient’s current 10-year CVD risk (R) and the current cholesterol level.



For blood pressure medications, we focus on the JNC8 guideline [15] (which we refer to as

simply the JNC guideline) and the ACC guideline [1]. The main difference between these two is that the ACC guideline suggests that the 10-year risk should be measured first before prescribing treatment. In contrast, the JNC guideline bases blood pressure treatments based on the patient’s blood pressure level. In Figure 2.2 we present both guidelines.

Figure 2.2: Blood pressure treatment guidelines. Both guidelines suggest that a blood pressure of Hypertension 1 (H1) should be the first threshold to assess if the patient needs medication. JNC increases the threshold for older patients since blood pressure tends to increase naturally with age. On the other hand, ACC guidelines use the estimate of the 10-year risk, which is also affected by the patient’s age and other risk factors.



To model the stochastic behavior of blood pressure and cholesterol, as previous literature has done, we assume that they are independent and satisfy a Markov assumption [42]. We validate this assumption in Section 2.5. The ACC guidelines suggest that patients on either cholesterol-lowering or blood pressure-lowering treatment should go to the doctor every 3 to 12 months. For this reason, we assume that patients will have at least one appointment per year.

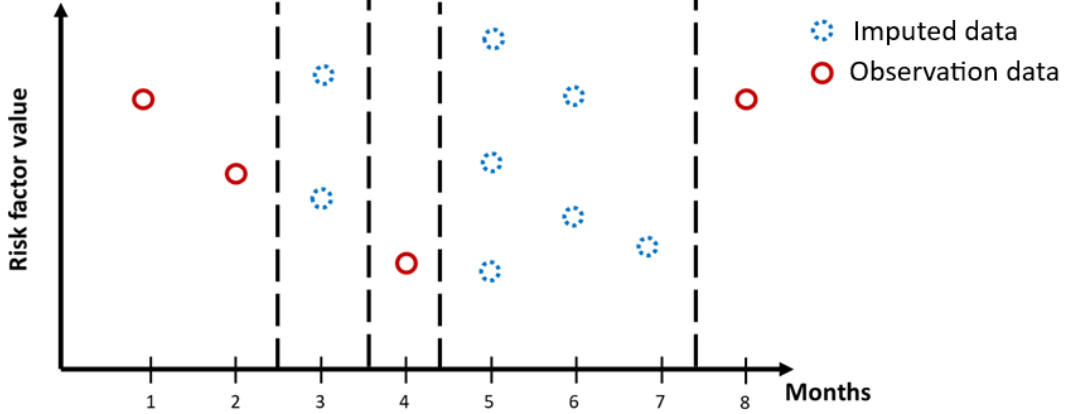
### 2.3.3 Estimation of Markov Chain Parameters for Blood Pressure and Cholesterol

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 [24]. After testing various methods, they recommend using Sherlaw-Johnson et al. (1995) EM algorithm to calculate these probabilities [30].

We redefined the model presented by Sherlaw-Johnson et al. (1995) and followed the same structure to estimate the patient’s cholesterol and blood pressure behavior. We define as  $P_{Ch}(age, \tau)$  as the cholesterol transition probability matrix for  $age$  and treatment  $\tau$ , and we define  $P_{BP}(age)$  as the blood pressure transition probability matrix for  $age$  and treatment  $\tau$ . As the cholest-

terol and blood pressure stochastic behavior may vary by age, we run the algorithm for different age ranges with a size of 5 years. We define the age range, denoted by  $z$ , based on the number of data points available.

Figure 2.3: EM algorithm data imputation. 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 2.3, the algorithm uses the observational data to estimate a Markov chain. To apply the algorithm, we first define  $O_{uvw}(\tau)$  as the number of observed transitions from LDL level  $u$  to LDL level  $v$  in  $w$  periods when on treatment  $\tau$  in the age range of  $z$  years. For simplicity, let the age range go from 1 to  $z$ . For the E-step, we define  $P_{\text{Ch}}^{(k)}(\tau)$  as the matrix in the  $k$ -th iteration of the algorithm. Now define  $P_{ijl,uvw}$  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.

$$P_{ijl,uvw} = \frac{P_{\text{Ch}ui}^l(\tau)P_{\text{Ch}ij}(\tau)P_{\text{Ch}jv}^{w-l-1}(\tau)}{P_{\text{Ch}uv}^w(\tau)} \quad (2.1)$$

Now define  $S_{ij}(P_{\text{Ch}}^{(k)}(\tau))$  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.

$$S_{ij}(P_{\text{Ch}}^{(k)}(\tau)) = \sum_{u \in \text{Ch}} \sum_{v \in \text{Ch}} \sum_{w=1}^z O_{uvw}(\tau) \sum_{l=0}^{w-1} P_{ijl,uvw} \quad (2.2)$$

For the M step of the algorithm,  $P_{\text{Ch}}^{(k+1)}(\tau)$  is computed as follows.



$$P_{\text{Ch}}^{(k+1)}(\tau) = \frac{S_{ij}(P_{\text{Ch}}^{(k)}(\tau))}{\sum_{w=1}^z S_{iw}(P_{\text{Ch}}^{(k)}(\tau))} \quad (2.3)$$

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

There are two main parameters to implement the EM algorithm: 1) the initial transition probability matrix and 2) the stopping criteria. Common approaches use observed data to estimate the initial transition probabilities, but these approaches may result in probabilities equal to 0 due to data sparsity. For this reason, we followed the recommendation of [30] to start with a uniform distribution. We also follow the authors' recommendation for the stopping criteria by defining an error of  $10^{-4}$  for the absolute difference between the same term in matrices from successive iterations.

We validate the resulting Markov chains from the EM algorithm by applying a likelihood ratio test [43]. To estimate the likelihood ratio test, let us first define  $n_{ij}(age, \tau)$  as the number of observed data points where patients go from cholesterol level  $i$  to cholesterol level  $j$ , on treatment  $\tau$  in the selected age range. Let  $\hat{p}_{ij}(age, \tau)$  denote the observed ratio of data points between cholesterol levels  $i$  and  $j$ . Then  $\hat{p}_{ij}(age, \tau) = \frac{n_{ij}(age, \tau)}{\sum_j n_{ij}(age, \tau)}$ . Now let us define  $L_{EM}(age, \tau)$  as the likelihood function after using the EM algorithm and  $L_{Data}(age, \tau)$  as the likelihood function of the data. Then we can estimate each likelihood function as:

$$L_{EM}(age, \tau) = \prod_{i,j} P_{\text{Ch}_{i,j}}(age, \tau)^{n_{ij}(age, \tau)} \quad (2.4)$$

$$L_{Data}(age, \tau) = \prod_{i,j} \hat{p}_{i,j}(age, \tau)^{n_{ij}(age, \tau)} \quad (2.5)$$

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

$$-2 \ln \left( \frac{L_{EM}(age, \tau)}{L_{Data}(age, \tau)} \right) \sim \chi_{m(m-1)}^2,$$

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

### 2.3.4 Estimation of the probability of having a CVD event

For the probability of having a CVD event, the ASCVD model uses the CVD 10-year risk. Given the VA population used for this study, we use a modified risk calculator designed for this population

[19]. The modified calculator, which we refer to as VA-ASCVD, estimates the risk using the patient’s demographics, age, race, gender, LDL, total cholesterol, blood pressure, treatments, and smoking habits. Additionally, we include risk reduction factors when patients are on treatment to estimate risk reduction resulting from treatment. Marrero (2021) presents risk reduction factors depending on the statin intensity when controlling cholesterol [17]. Also, Karmali (2017) presents risk reduction factors depending on blood pressure medication and the 10-year CVD risk [16]. Finally, we estimate the dying probability for other causes with the *CDC* tables of life years [3].

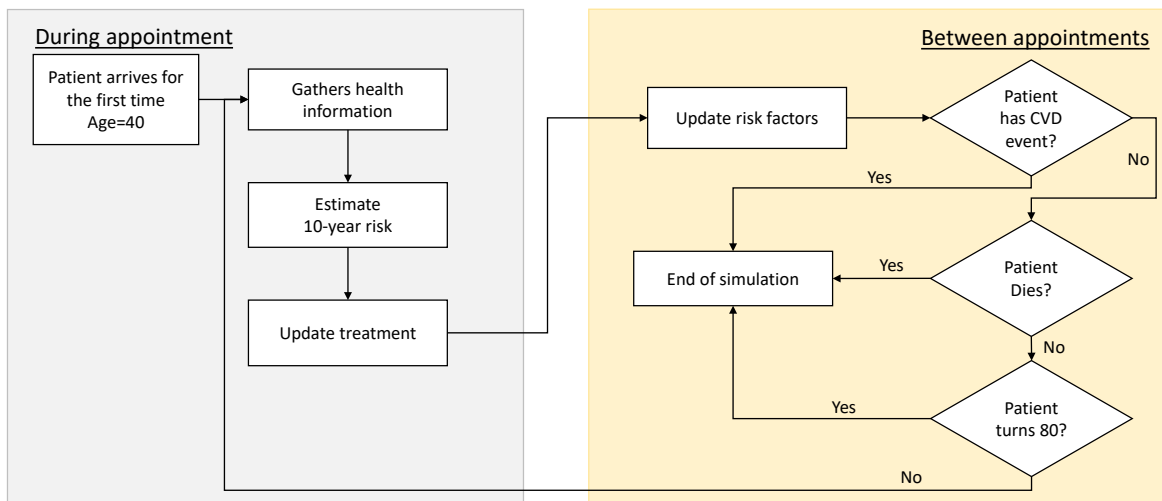
## 2.4 Simulation model

Given inputs and assumptions, we now present the simulation model and the scenarios and performance measures we used to validate the model.

### 2.4.1 Modelling patient flow

The guidelines suggest surveilling patients over 40 years old, prone to increase the chance of CVD. Figure 2.4 presents the simulation flow for each patient, divided into two main time frames: events during an appointment with the physician and events between appointments.

Figure 2.4: Simulation flow. The simulation model focuses on preventing CVD events. We simulated the health factors during and between appointments, assuming that on every epoch the patient has a probability of having a CVD event.



At annual appointments, the physician first gathers the patient’s health information. This health

information consists of LDL cholesterol, total cholesterol, and SBP and assesses the current treatment plan. After gathering the patient's health information, the physician estimates the patient's 10-year risk of having a CVD event. Finally, the physician suggests prescribing treatments if necessary.

The patient follows the current treatment between appointments, and the risk factors will evolve following the stochastic behaviors. As we assess the patient every year, the patient may suffer a CVD event or die from other natural causes between appointments. If the latter occurs, the simulation ends. If the patient has a CVD event, we simulate the remaining years until the patient dies or turns 80, assuming that physicians will immediately prescribe treatments. If the patient is healthy, the simulation ends when the patient turns 80 years old. We assume that the current treatment will continue throughout the patient's life.

### **2.4.2 Treatment scenarios**

As mentioned in the previous section, physicians may follow different guidelines to treat high cholesterol and blood pressure. For this work, we focus on the ACC guidelines for cholesterol. We will test the effects of using a 10-year risk threshold of 5% or 7.5% to start low-intensity statins. For blood pressure treatment, we will test the JNC guidelines and the ACC guidelines. Thus, we considered the following scenarios:

- Scenario 1 - (Base Case) ACC (7.5%): ACC guideline for cholesterol with a (7.5%) threshold and the ACC guideline for blood pressure.
- Scenario 2 - ACC (5%): ACC guideline for cholesterol with a (5%) threshold and the ACC guideline for blood pressure.
- Scenario 3 - ACC (7.5%)/JNC: ACC guideline for cholesterol with a (7.5%) threshold and the JNC guideline for blood pressure.
- Scenario 4 - No treatment: No treatment for cholesterol or blood pressure.

Our reference (base case) scenario is scenario 1. Scenario 2 is used to test different cholesterol guidelines against the reference scenario, and scenario 3 is used to test the effects of varying blood pressure guidelines against the reference scenario. Additionally, scenario 4 assumes no treatment as an additional reference scenario when the patients are not on treatment to prevent a CVD event.

### **2.4.3 Evaluation of scenarios**

We focused on two different metrics to compare the scenarios. First, we estimated the percentage of patients with treatment per epoch. This metric helps determine if a guideline suggests a high

treatment burden. Moreover, this metric also helps estimate the probability that a patient starts sooner or later treatment.

We also estimated the average 10-year risk. We propose this metric to compare the efficacy of different scenarios. Therefore, we can comment on whether increasing the percentage of patients with treatment is beneficial or not (i.e., the 10-year risk lowers).

## **2.5 Results**

In this section, we present the initial model parameterization, model validation, and then describe our main results. The entire analysis was performed in R (version 3.6.2), with the following specifications: Windows Server 2012, Intel Xeon 2.40 GHz with 40 GB Ram. We simulated patients who start at 40 years old with normal cholesterol and blood pressure levels and no treatment. We decided a half-width of 1% was acceptable in this context. We conducted ad hoc experiments using scenario 1 to determine a suitable sample size of 3,000 patients for our numerical experiments.

### **2.5.1 Verification and validation**

We validate the simulation result by comparing it with the published estimate of the death rate by natural causes and the CVD event rate. We also perform a likelihood ratio test to evaluate the Markov chain assumption.

#### **2.5.1.1 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 [19]. In our data, 69.1% of the patients were white males, 20.4% of them were black males, 6.7% as white females, and 3.8% of them were black females. Due to an insufficient number of female patient samples, we cannot get significant estimates from the numerical experiment. We present the results for male patients, as women were not sufficiently represented in our data set at all ages we considered. Additionally, we acknowledge that after applying our exclusion criteria to raw data, the data for other races is insufficient to conduct numerical experiments. Finally, we only had access to the patient's race, therefore, we were not able to study the ethnicity effect on health behavior.

We divided male patients into two different groups, black males and white males because race is an important factor for 10-year risk prediction [19]. Between 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. We divided the data between training and test sets to validate the model. Randomly, we chose 2/3 of the data set as

training data and 1/3 as test data. Finally, as mentioned in Section 2.4. we used a likelihood ratio test to validate the Markov chains and show the results in Table 2.2.

Table 2.2: EM algorithm validation. 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

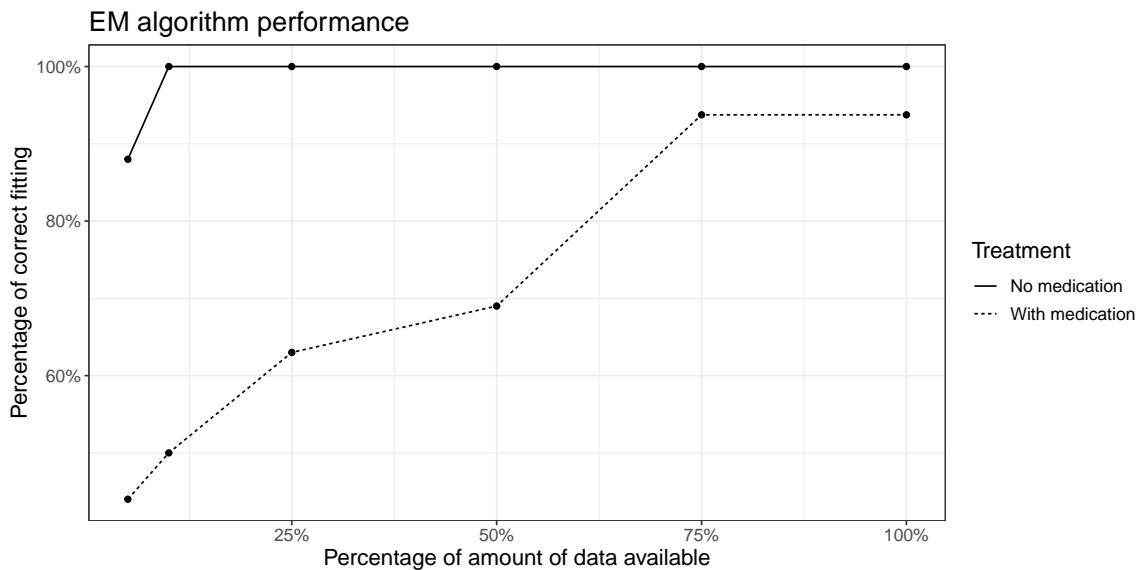
Patient Group (% of Total)	Age Range	P-Value		
		No Medication	Low intensity Statins	High intensity Statins
<b>Black male</b> (20.4%)	40	0.241	0.847	0.080
	45	0.890	0.997	<b>0.019</b>
	50	1.000	0.830	<b>0.000</b>
	55	0.980	1.000	<b>0.031</b>
	60	0.355	0.744	0.158
	65	0.989	0.982	<b>0.001</b>
	70	1.000	0.662	0.534
	75	1.000	0.221	<b>0.003</b>
<b>White male</b> (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	<b>0.021</b>
	75	0.841	0.156	0.408

The likelihood ratio test does not reject the null hypothesis for the patient groups with more data, such as white males. Otherwise, the test rejects the null hypothesis when less data are available. Moreover, in rare cases, such as younger people (ages 40 to 60) with high-intensity statins, the test also tends to reject the null hypothesis. Nonetheless, as shown 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. The test did not reject any cases because we counted with more blood pressure information.

A straightforward question arises about how much data are needed so that the EM algorithm correctly fits the behavior. In Figure 2.5, we analyzed how the fitting of cholesterol is affected according to the data available. The results showcase that the algorithm performance worsens for patients with medication at a higher rate than for patients without medication. This result is likely explained by the smaller number of samples for treated patients in a dataset like ours. Therefore,

we recommend that when gathering data, it is important to look at all patient types and not just the total number of patients to determine the viability of the dataset for estimating a model.

Figure 2.5: EM algorithm performance. We ran the EM algorithm while varying the amount of data available for male patients. We estimated the percentage of cases where the algorithm fitted correctly. We notice that the amount of time the cholesterol behavior was fitted correctly when the patient has medication decreases drastically with fewer data.



Finally, we tested the assumption that cholesterol and blood pressure are independent. We estimated the correlation between LDL, SBP, cholesterol-lowering medication, and blood pressure-lowering medication. We used Pearson’s correlation and applied it to the population data. While statins have been shown to have a minor effect on blood pressure levels [44], based on our data, the correlation between LDL and SBP is  $0.022 \pm 0.008$ . We also estimated the correlation between SBP and cholesterol-lowering medication, where we tested whether the SBP changes when the patient has different medication intensity levels. For this test, the correlation was  $-0.0025 \pm 0.008$ . We did the same analysis between LDL and blood pressure-lowering medication, where we tested if the LDL changes whether the patient is with or without medication. This correlation was  $-0.1452 \pm 0.007$ . Notice that these correlations are close to zero; therefore, we believe our assumption is reasonable.

### 2.5.1.2 Simulation model

To validate the number of deaths by natural causes, we compared our results with the CDC tables [3]. Moreover, to validate the number of CVD events, we compared our results with the 2020

American Heart Association report [4]. We looked at the values at the age range of 75 to 80 using the base case reference scenario for both cases. We present the results in Table 2.3. We got consistent results when validating for the other age ranges.

Table 2.3: Simulation validation. Simulation results versus the CDC life tables [3] and the American Heart Association report [4].

Measurement-patient group	Simulation (Mean value $\pm$ SD)	American population data
<b>Death rate</b>		
White male	48.7% $\pm$ 1.7%	48.92%
Black male	60.5 % $\pm$ 1.5 %	60.28%
<b>Cardiovascular Events</b>		
White male	22.4% $\pm$ 1.49%	25.1%
Black male	22.4% $\pm$ 1.5%	25.1%

The statistical estimate of the death rate based on the simulation model is very close to the CDC tables. In particular, there is no statistical difference for male patients. On the other hand, the CVD event rate’s statistical estimate is similar but lower compared to the AHA. This result is expected given patients in the VA population have excess to continuous care versus the overall U.S. population the CDC estimates are based on.

## 2.5.2 Comparison of scenarios

We present results for a population that follows the same proportion of the VA population of white males (77.2%) and black males (22.8%). We simulated each of the four scenarios referenced above, and we estimated the percentage of patients with cholesterol-lowering treatment, blood pressure-lowering treatment, and 10-year risk as a function of the patient’s age.

In Figure 2.6a we notice that at the age of 50, all the guidelines suggest that more than 50% of the patients should be on cholesterol-lowering medications. Nonetheless, the ACC(5%) guideline increases patients’ percentage on medications after 55 by 14%. Finally, after 60 years old, all three guidelines are close to 100% of patients on treatment. It is worth noticing that the JNC guideline increases cholesterol treatment from ages 40 and 50 by 2.5 % on average. This may be because the ACC blood pressure guidelines are affected by the 10-year risk, which changes depending on whether the patient is on treatment for blood pressure or not. While at the age of 50 onward, the difference is not statistically significant.

Similarly, in Figure 2.6b, different cholesterol guidelines do not affect the number of blood pressure-lowering medications. The JNC guideline tends to start medication much sooner. For example, at age 43, more than 80% of the patients are predicted to be on treatment. On the other hand, the ACC blood pressure guideline reaches 80%, five years later. This result shows a much

higher treatment burden if the JNC guidelines are used; however, according to Figure 2.7 there is no statistical difference in 10-year risk among the three scenarios.

Figure 2.6: Scenario comparison. Percentage of patients on treatment: Recall that patients start treatment when they have a CVD event, for this reason, there can be patients with treatment in the No-Treatment Scenario.

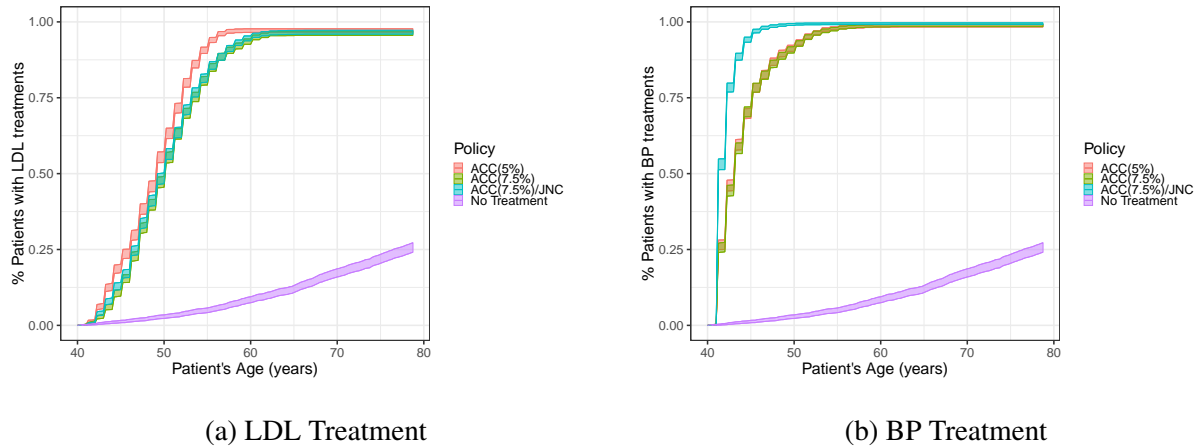
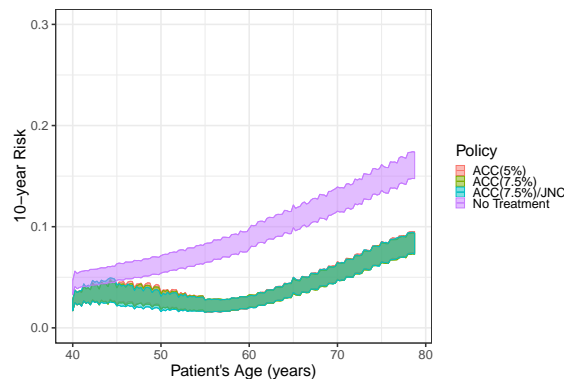


Figure 2.7: 10-year risk comparison. As patients begin treatment, the scenarios with treatment begin to differ from the no treatment scenario. Where at the age of 50, the risk is reduced by 3% on average and after the age of 80, the risk is reduced by 9% on average.



## 2.6 Conclusions and future work

Health systems have improved the tracking of patients' medical data over time to the point where there is ample longitudinal data suitable for simulating health status changes over many years. Still, data may be missing or sparsely populated, which raises questions on how to build validated



simulation models. These simulation models can be excellent resources for physicians and policy-makers to compare and contrast alternative healthcare policies. This article presents a simulation model for patients treated to prevent CVD using a longitudinal data set from the U.S. Veterans Affairs health system. We tested different treatment guidelines for cholesterol and blood pressure to compare the risk reduction of heart attacks and strokes and treatment burden based on the proportion of patients in specific subgroups who were on medication at certain ages.

Our simulation model used the EM algorithm to estimate Markov chains for cholesterol and blood pressure, the most important controllable risk factors for CVD prevention. We simulated patients within two groups: Black men and white men. 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 two demographic groups: White male patients and black male patients. 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 are only gathered when the patients go to healthcare providers.

We tested the ACC guidelines for cholesterol and blood pressure and the JNC guideline for blood pressure. For cholesterol, additionally, we studied the effects of reducing the threshold when patients start treatment. Our results suggest that lowering the risk threshold from 7.5% to 5% does not benefit patients based on risk reduction alone; however, it results in a higher proportion of patients being treated and exposing them to the burden of medication. On the other hand, the JNC guideline also recommends treatment earlier in life as it focuses on reducing the patient's blood pressure. Thus, our results suggest that ACC guidelines that focus on risk reduction also reduce the number of patients with treatment without negatively affecting their health.

As with all studies, ours has some limitations. First, we assume that patients and physicians adhere to standard expectations regarding the frequency of routine physical exams to collect data on risk measures. However, in reality, there may be deviations from these "best practices". Nevertheless, this seems to be the most reasonable standard upon which to estimate the harms and benefits of treatment resulting from the recommended guidelines. Finally, our study is based on a specific population, U.S. Veterans, which may not generalize to the entire U.S. population. As the following steps, we want to study other population groups, such as white women and black women.

Despite the limitations, we believe our study demonstrates a productive use of longitudinal EHR data. We were able to show that using EM algorithms is a suitable approach to deal with

sparse data when building simulation models based on non-stationary Markov chains. Our work focuses on CVD, but there are numerous chronic diseases like cancer, Alzheimer's, and diabetes, where similar approaches could be applied. Lastly, our Markov chain models can be extended to higher-dimensional stochastic processes with more risk factors and correlations across risk factors for more in-depth investigations of CVD and other chronic diseases.

## CHAPTER 3

# Cholesterol Monitoring Policies for Cardiovascular Disease Prevention

### 3.1 Introduction

In Chapter 2, we develop models to understand disease progression and create a controlled simulation environment to test policies. Therefore, the natural next step is to study how to develop policies that help prevent diseases. In particular, to prevent cardiovascular diseases (CVDs), 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 [1] and for high blood pressure in adults [8]. However, the guidelines do not define how frequently physicians should monitor the evolution of the risk factors, let alone how monitoring should change concerning age, gender, and race, all of which are established predictors of CVD outcomes [19].

Current monitoring guidelines are not personalized. The availability of longitudinal information makes it possible to build stochastic models that describe uncertainty in risk factors to optimize individualized patient monitoring guidelines based on societal benefits, which comprise the benefits perceived by the patients and healthcare insurance providers. 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 [45].

The primary goals of this chapter 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 [46]. The patient's 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% [1]. In the case of managing cholesterol, prescribing statins is often the next course of action if diet and exercise alone are insufficient.

Statins are a once-a-day pill that patients take indefinitely, assuming they can tolerate the side effects [1]. They are generally considered safe for most people, but they can have some minor side effects and 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 and/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. According to observational data, the time between each appointment varies from a couple of months to years, implying that the physicians should consider this randomness in their monitoring decisions. Regular monitoring is important, but frequent vs. infrequent monitoring has pros and cons. 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 monitoring cholesterol every 3 to 12 months so that physicians check the medication efficacy and change the treatment if needed [1]. This policy is one-size-fits-all, 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 [8]. 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 a patient with high blood pressure or high risk will receive blood pressure-lowering treatment [8].

Our approach to studying optimal cholesterol monitoring policies considers 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 [47]. 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 follow the patients from 2003 until 2018. The data are divided into 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 (SBP), and diastolic blood pressure (DBP).

The rest of the chapter is organized as follows. In Section 3.2, 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 3.3, 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 CVD event (heart attack or stroke). Also, we use the EM algorithm presented in Section 2.4 to estimate the cholesterol LDL and systolic blood pressure probability distributions from observational data. In Section 3.4, 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 cholesterol model using the data in our case study and discuss how the model is applied. Finally, we compare our model versus current cholesterol monitoring guidelines and summarize our main conclusions.

## 3.2 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 sparse longitudinal data; and (3) cholesterol monitoring policies to prevent CVD. This section highlights papers related to our work and briefly describes how our proposed methodology differs.

Literature in dynamic monitoring is divided into prevention and treatment. Within the area of prevention, the literature focuses on monitoring policies after a disease has occurred or an intervention has been done to prevent the disease [48, 49, 50, 42]. Among the most common applications, some models define monitoring policies to prevent deaths after diagnosed cancer. 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 [51, 52, 42, 53]. These models then focus on identifying when the surveillance should take place.

For treatment, the literature has applied MDPs to define the optimal treatment policies for chronic diseases. Some of these applications focus on cancer and organ transplant, among others [54, 55, 56, 57, 58]. In particular, for CVD, the literature has focused on blood pressure and cholesterol-lowering medications [59, 25, 60, 61]. Depending on the patient's health state, the models select the type of medication to prescribe, assuming patients adhere to medications and regularly attend appointments (e.g., fixed annual visits). Nonetheless, the current cholesterol monitoring guidelines suggest measuring cholesterol every 4 to 6 years when the patient is assumed healthy. Therefore, our work focuses on defining a precise monitoring policy, assuming that physicians follow current treatment guidelines. Our model helps prevent CVD by defining this policy while dynamically monitoring the patient's health. Monitoring these diseases adds a layer of complexity by modeling disease progression outside of surveillance. A correct prevention policy helps physicians treat patients accordingly.

The literature acknowledges the importance of using personalized medicine over one-size-fits-all policies when dealing with healthcare prevention. As new technologies are available, such as wearable monitors, telemedicine, and electronic pill counts, it is possible to have complete electronic health records (EHRs). EHRs make it viable to define policies that better understand the patient's health behavior [62, 63]. On the other hand, personalized policies help ensure health equity within minority groups [64], patient-specific modeling, and bring better-individualized outcomes [65]. Therefore, the literature suggests balancing the individual and societal risk factors [66], which we include in our model by incorporating patients' age, gender, race, and societal rewards.

Finally, to estimate cholesterol monitoring frequencies, the US guidelines suggest testing healthy patients every 4 to 6 years [1]. Nonetheless, countries like the United Kingdom, Australia, and New Zealand, have different policies. Some even recommend testing healthy patients every year [67]. Most of these policies propose various recommendations depending on whether the patient is on treatments. 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 [68] [69]. Given these conflicting expert opinions, there is a need to understand better optimal monitoring

policies using data-driven models.

In summary, our research 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 CVDs than 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. This study is the first to consider these three aspects to the best of our knowledge. We show that 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.

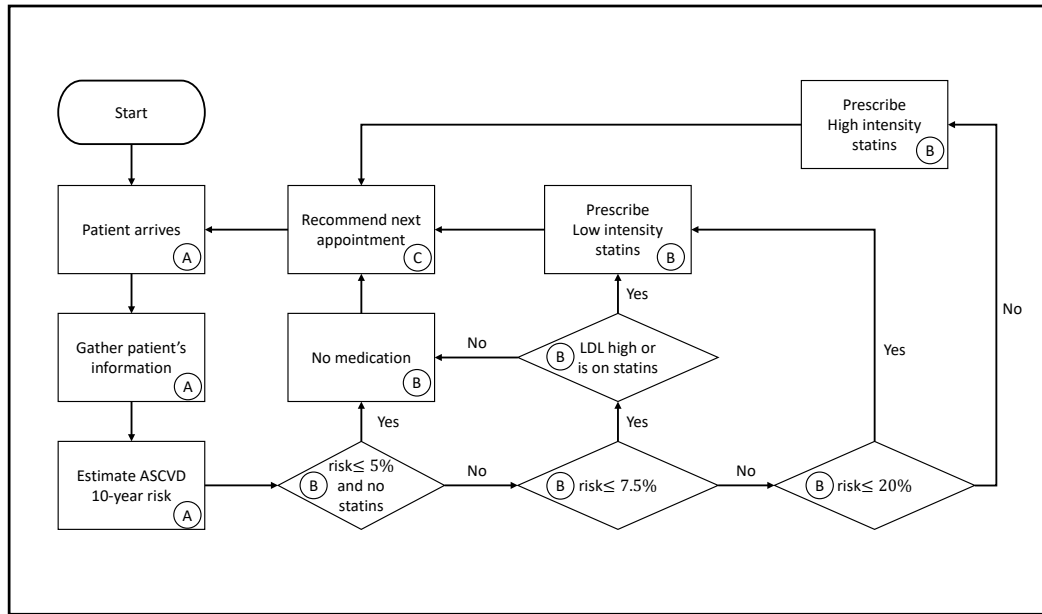
### 3.3 Model Formulation and Validation

In this section, we will present our decision model to estimate a cholesterol monitoring policy that maximizes societal benefits. We divide this model into two parts: the MDP for optimizing cholesterol monitoring policies and the simulation model to test and validate our model. To estimate the transition probabilities, we use the EM algorithms presented in Section 2.4. To evaluate the patients, we model the patient’s risk factors between appointments. In Figure 3.1, we present the flow of a particular appointment. We start by stating definitions and mathematical notation (see Table 3.1) that we will use throughout this section.

#### 3.3.1 Definitions and model assumptions

In this section, we introduce the model’s concepts and main assumptions. Since we are focused on preventing CVD, we focus on healthy patients with no evidence of previous chronic diseases in their medical records. Therefore, we define  $\mathcal{H} := \{N, C, D\}$  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* [1]. We assume the model stops as soon as the patient’s living state is  $C$  or  $D$ . Similar to prior literature, a patient with no previous CVD events will have either a CHD event or a stroke. However, both are assumed not to happen simultaneously in the same time period [47]. As the model stops when the patient suffers a CVD event for the first time, we do not consider the effects of previous CVD events on the likelihood of a CHD event or stroke. Additionally, we estimate the probability of a CVD event and death based on age. Finally, the

Figure 3.1: CVD prevention flowchart. During a particular appointment, the physician gathers information ((A) boxes). Based on this information, the physician defines the treatment [1] ((B) boxes) and considers when the patient should come back ((C) box). This process will continue until the patient reaches a certain age, dies, or has a CVD event. Our research question will focus on optimizing the green process



proportion of CVD events that are strokes will also change based on 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  $Ch := \{Low, Normal, Acceptable, Borderline High, High, Severe\}$  as the different cholesterol LDL levels, as shown in Table 2.1 [1].

Also, the physician gathers the patient’s blood pressure. Similar to LDL, we divide the blood pressure into established clinical groups [8]. We define  $B := \{Normal, Elevated, Hypertension I, Hypertension II, Hypertensive Crisis\}$  as the different blood pressure levels, which are shown in Table 2.1.

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 scheduled appointments. Treatment decisions are assumed to be based on the patient’s 10-year risk of hav-



Table 3.1: List of notation for MDP model part 1.

Notation	Description
$E$	Set of patient's appointments index by $t$ , where $E := \{1, \dots, T\}$ .
$H$	Set of possible living states of the patient index by $h_t$ in appointment $t$ .
$Ch$	Set of cholesterol LDL levels index by $\theta_t$ in appointment $t$ .
$BP$	Set of blood pressure levels index by $\gamma_t$ in appointment $t$ .
$A$	Set of decisions index by $a$ .
$\tau_t$	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 $s_t = (\theta_t, \gamma_t, h_t, \tau_t, age_t)$ .
$P_{Ch}(age_t, \tau_t)$	Transition probability matrix for cholesterol levels at age $age_t$ and treatment $\tau_t$ after appointment $t$ .
$p_{Ch_t}(\theta_{t+1} s_t, a)$	Probability that in appointment $t + 1$ , the patient has LDL $\theta_{t+1}$ when decision $a$ is taken.
$P_{Ch}^{(k)}(\tau)$	Matrix that represents the $k - th$ iteration of the EM algorithm at treatment $\tau$ .
$P_{BP}(age_t)$	Transition probability matrix for blood pressure levels at age $age_t$ .
$p_{BP_t}(\gamma_{t+1} s_t, a)$	Probability that in appointment $t + 1$ , the patient has BP $\gamma_{t+1}$ when decision $a$ is taken.
$P_{H_h}(s_t)$	Probability that in an interval the living state is $h$ given state $s_t$ .
$p_{H_t}(h_{t+1} s_t, a)$	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 $s_t$ .
$c_{APP}$	Cost of going to an appointment.
$c_{\tau_t}$	Cost of a month in treatment $\tau_t$ .
$c_{CHD_1}$	Cost of first year of a CHD event.
$c_{CHD_2}$	Cost of subsequent years after CHD event.
$c_{ST_1}$	Cost of first year of a stroke event.
$c_{ST_2}$	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.
$\delta_{CHD}$	CHD event QALY decrement per year.
$\delta_{ST}$	Stroke event QALY decrement per year.
$\delta_{\tau_t}$	QALY decrement per year on treatment $\tau_t$ .

ing CVD per the recommended treatment plan from the ACC Guideline on the Management of Blood Cholesterol [1], shown in Figure 3.1. 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.

Table 3.2: List of notation for MDP model part 2

Notation	Description
$\eta_{\text{CHD}}$	Life years decrement rate when patient suffers a CHD.
$\eta_{\text{ST}}$	Life years decrement rate when patient suffers a stroke.
$\beta$	Discount factor.
$d_{\text{CHD}}(\text{age})$	Probability a patient suffers a CHD event given that a patient had a CVD event at a determined age.
$d_{\text{ST}}(\text{age})$	Probability a patient suffers a stroke given that a patient had a CVD event at a determined age.

We focus on statins because they are the most common medication to treat high cholesterol. Statins are commonly divided into two intensities: low and high [17]. Between these two groups, physicians consider which statin dose is 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, patient age, sex, race, and currently prescribed treatment. For BP, we assume that the physician will prescribe medication also based on the ACC guidelines [8]. The physician will prescribe BP-lowering medications when the patient has an H1 or higher BP level. We do not consider different BP-lowering medications because as soon as the patient starts medications, their blood pressure tends to decrease [25]. For cholesterol and BP, we assume that the patient will adhere perfectly to the medications. Finally, we assume that patients comply with the physician’s recommendation on when the next cholesterol test should occur.

To model the stochastic process for LDL, we 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 [42].

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’s recommendation to get a cholesterol test prior to their appointment. While such adherence is not perfect in practice, making this assumption leads to an 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, considering the decrements when the patient is on treatment or has CVD. We will explain these benefits and costs in detail in the next section.

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

**States:** During each appointment  $t \in \mathbb{E}$ , the physician gathers the LDL level  $\theta_t \in \text{Ch}$ , the SBP level  $\gamma_t \in \mathbb{B}$ , the living state of a patient  $h_t \in \mathbb{H}$ , the age of the patient  $age_t$ , and defines the treatment  $\tau_t$  based on the ACC guideline presented in Figure 3.1. To simplify, we define  $s_t$  as the overall health state of the patient in appointment  $t$ , which includes the previous information. Hence,  $s_t := (\theta_t, \gamma_t, h_t, \tau_t, age_t)$ .

**Decisions:** Because the physician will recommend when to check cholesterol next, we define  $\mathbb{A}$  as the set of decisions where  $\mathbb{A} := \{1, \dots, m\}$ . If  $a \in \mathbb{A}$ , 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 patient's state after measuring blood pressure, cholesterol, and the prescription of any new treatment.

**Transition probabilities:** Between appointments, the patient's LDL and blood pressure vary. Furthermore, a patient may suffer from CVDs or die of other causes. Therefore, first, we define  $P_{\text{Ch}_{ij}}(age_t, \tau_t)$  as the probability that if the patient has a LDL state  $i$  and is following treatment  $\tau_t$  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  $p_{\text{Ch}_t}(\theta_{t+1} = j | s_t, a)$  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.

$$p_{\text{Ch}_t}(\theta_{t+1} = j | s_t, a) = \sum_{k_1 \in \text{Ch}} \sum_{k_2 \in \text{Ch}} \cdots \sum_{k_{a-1} \in \text{Ch}} \left( P_{\text{Ch}_{ik_1}}(age_t, \tau_t) P_{\text{Ch}_{k_1 k_2}}(age_t + 1, \tau_t) \cdots P_{\text{Ch}_{k_{a-1} j}}(age_t + a - 1, \tau_t) \right) \quad (3.1)$$

Equation 3.1 reflects the Markovian assumption about LDL. Similarly, we define  $P_{\text{BP}_{ij}}(age_t)$  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  $p_{\text{BP}_t}(\gamma_{t+1} = j | s_t, a)$  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.

$$p_{\text{BP}_t}(\gamma_{t+1} = j | s_t, a) = \sum_{k_1 \in \text{BP}} \sum_{k_2 \in \text{BP}} \cdots \sum_{k_{a-1} \in \text{BP}} \left( P_{\text{BP}_{i k_1}}(\text{age}_t) P_{\text{BP}_{k_1 k_2}}(\text{age}_t + 1) \cdots P_{\text{BP}_{k_{a-1} j}}(\text{age}_t + a - 1) \right) \quad (3.2)$$

Between appointments, the patient may suffer a CVD event or die because of other causes. We define  $p_{\text{H}_h}(s_t)$  as the probability that if the patient is in state  $s_t$ , the patient is at living state  $h$  at period  $t$ . Therefore, as shown in Equation 3.3, we can estimate the probability that the patient is healthy at the next appointment. This probability is defined as  $p_{\text{H}_t}(h_{t+1} = N | s_t, a)$  which is the probability that in appointment  $t + 1$  the patient is healthy, given that the patient was at state  $s_t$  at period  $t$ , and the physician recommended to test cholesterol again in  $a$  periods.

$$p_{\text{H}_t}(h_{t+1} = N | s_t, a) = \prod_{l=1}^a \sum_{j \in \text{Ch}} \sum_{k \in \text{BP}} p_{\text{Ch}_t}(j | s_t, l) p_{\text{BP}_t}(k | s_t, l) P_{\text{H}_N}(\theta_l = j, \gamma_l = k, \tau_t, \text{age}_t + l) \quad (3.3)$$

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 3.3,  $\sum_{j \in \text{Ch}} \sum_{k \in \text{BP}} p_{\text{Ch}_t}(j | s_t, l) p_{\text{BP}_t}(k | s_t, l) P_{\text{H}_N}(\theta_l = j, \gamma_l = k, \tau_t, \text{age}_t + l)$  represents the expected probability that the patient has a normal living state in period  $t + l$ . Notice that  $P_{\text{H}_N}(\theta_l = j, \gamma_l = k, \tau_t, \text{age}_t + l)$  depends on how the patient's cholesterol and blood pressure levels change between two appointments. Because the patient goes through  $a$  period of time between each appointment, then Equation 3.3 also represents that the patient is healthy in all periods.

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

$$p_{\text{H}_t}(h_{t+1} = D | s_t, a) = 1 - \prod_{l=1}^a (1 - P_{\text{H}_D}(\text{age}_t + l)) \quad (3.4)$$

Finally, in Equation 3.5, we present the probability that the patient has a CVD event.

$$p_{\text{H}_t}(h_{t+1} = C | s_t, a) = 1 - p_{\text{H}_t}(h_{t+1} = N | s_t, a) - p_{\text{H}_t}(h_{t+1} = D | s_t, a) \quad (3.5)$$

**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 takes a particular treatment, defined as  $c_{\tau_t}$ . Also, when going to an appointment, the patient and the insurer are assumed to incur a cost  $c_{\text{APP}}$ , 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  $c_{\text{CVD}}(\text{age}_t)$ , paid 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 ( $c_{\text{S}_1}$  and  $c_{\text{CHD}_1}$  respectively), which consists of hospitalization, interventions, and treatments, and the cost of subsequent years ( $c_{\text{S}_2}$  and  $c_{\text{CHD}_2}$ ). Also, we include the willingness-to-pay (WTP) per year that the patient is healthy. We define  $\text{WTP}(a)$  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  $\delta$  per year. Finally, depending on the age of the patient, we estimate the average expected years of life  $\text{LY}(\text{age}_t)$  and multiply it by a decrement rate given the type of CVD event  $\eta_{\text{CHD}}$  or  $\eta_{\text{ST}}$ . In Equations 3.6 and 3.7 we estimate the cost of having a CHD event  $c_{\text{CHD}}(\text{age}_t)$  or a stroke  $c_{\text{ST}}(\text{age}_t)$  respectively, given that the CVD event was diagnosed at age  $\text{age}_t$ .

$$c_{\text{CHD}}(\text{age}_t) = c_{\text{CHD}_1} + c_{\text{CHD}_2}(\text{LY}(\text{age}_t)\eta_{\text{CHD}} - 1)(1 - \delta_{\text{CHD}}) - \text{WTP}(\text{LY}(\text{age}_t)\eta_{\text{CHD}})(1 - \delta_{\text{CHD}}) \quad (3.6)$$

$$c_{\text{ST}}(\text{age}_t) = c_{\text{ST}_1} + c_{\text{ST}_2}(\text{LY}(\text{age}_t)\eta_{\text{ST}} - 1)(1 - \delta_{\text{ST}}) - \text{WTP}(\text{LY}(\text{age}_t)\eta_{\text{ST}})(1 - \delta_{\text{ST}}) \quad (3.7)$$

The patient may suffer either a CHD event or a stroke. We define as  $d_{\text{CHD}}(\text{age})$  as the probability, at a given age, that a patient suffers a CHD event given that the patient suffered a CVD event, and  $d_{\text{ST}}(\text{age})$ , at a given age, 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  $p_{\text{H}_t}(h_{t+1} = C | s_t, a)d_{\text{CHD}}(\text{age}_t)$  and a stroke is  $p_{\text{H}_t}(h_{t+1} = C | s_t, a)d_{\text{ST}}(\text{age}_t)$ , where  $d_{\text{CHD}}(\text{age}_t) + d_{\text{ST}}(\text{age}_t) = 1$ . Therefore,  $c_{\text{CVD}}(\text{age}_t) = c_{\text{CHD}}(\text{age}_t)d_{\text{CHD}}(\text{age}_t) + c_{\text{ST}}(\text{age}_t)d_{\text{ST}}(\text{age}_t)$ .

Between two appointments, we consider the cost of going to the  $2^{\text{nd}}$  appointment, the cost of the treatment, and the cost of having a CVD event. Therefore, in Equation 3.8 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  $\tau_t$ , defined as  $\delta_{\tau_t}$ . The complete reward function can be written as follows.

$$\begin{aligned}
r_t(s_t, h_t = N, a) = & -c_{\text{APP}} + \sum_{l=0}^{a-1} p_{\text{Ht}}(N|s_t, l) \left( \text{WTP}(1)(1 - \delta_{\tau_t}) - c_{\tau_t} \right. \\
& \left. - \sum_{j \in \text{Ch}} \sum_{k \in \text{BP}} p_{\text{Ch}_t}(j|s_t, l) p_{\text{BP}_t}(k|s_t, l) P_{\text{HC}}(\text{age}_t + l, j, k) c_{\text{CVD}}(\text{age}_t + l + 1) \right)
\end{aligned} \tag{3.8}$$

**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 CVD event (death or disease). We construct the Bellman equations, for all  $s_t$  and  $t \in \mathbb{E}$ , associated with this model, as follows.

$$\begin{aligned}
V_t(s_t) = & \max_{a \in A} \left\{ r_t(s_t, a) \right. \\
& \left. + \beta \sum_{j \in \text{Ch}} \sum_{k \in \text{BP}} \sum_{h \in \text{H}} \left( p_{\text{Ch}_t}(j|s_t, a) p_{\text{BP}_t}(k|s_t, a) p_{\text{Ht}}(h|s_t, a) V_{t+1}(s_{t+1}) \right) \right\}, \forall t < T, s_t
\end{aligned} \tag{3.9}$$

As we mentioned before, the physician knows the patient's health state and cholesterol level when the appointment starts. Also, the physician recommends treatment  $\tau_t$ , following the treatment plan before deciding when the next cholesterol test should occur. In Equation 3.10, 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, no more decisions are taken, and the expected benefits for subsequent years represent the immediate reward. If the patient dies from other causes, no additional costs or benefits are considered. If the patient had a CVD event between appointments  $t - 1$  and  $t$ , then  $h_t = C$ . As shown in Equation 3.8, the cost associated with the CVD event is considered during  $t - 1$ , as this equation represents the cost between appointment  $t - 1$  and appointment  $t$ . Additionally, as shown in Equations 3.6 and 3.7, the CVD event's cost considers the future costs and benefits until the patient dies. Therefore, the immediate rewards will be 0 for appointment  $t$ .

$$V_t(s_t) = \begin{cases} 0 & \text{if } h_t \in \{C, D\} \\ \text{WTP}(\text{LY}(\text{age}_T))(1 - \delta_{\tau_T}) & \text{if } h_t = N \text{ and } t = T \end{cases}, \forall t, s_t \tag{3.10}$$

### 3.3.3 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 [60]. 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 deal with VA data, we use the calculator presented by Sussman, et al. (2017) [19]. Let  $P_{HC}(s_t)$  be that probability that the patient has a CVD event given state  $s_t$ . Also, let  $a$  be the number of months between epoch  $t - 1$  and  $t$ . Finally, let  $p_{10}(s_t)$  be the 10-year risk given state  $s_t$ . Therefore, we estimate the probability of having a CVD in  $a$  number of months as:

$$p_{HC}(s_t) = 1 - (1 - p_{10}(s_t))^{\frac{a}{120}} \quad (3.11)$$

It is worth noting that the estimation presented in Equation 3.11 assumes a linear increase in the risk of the patient from time 0 to 10 years. This approximation 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 [3].

## 3.4 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 actual decisions made by physicians in practice at the VA. To test our model for different demographic groups, we estimate the transition probabilities, run the MDP model, and analyze the results separately for each group.

We define the minimum length between two decision epochs to be three months, as this is the minimum suggested time period between two cholesterol blood tests [1]. Additionally, we assume that we monitor the patient for a maximum of 40 years from age 40 to 80. If we monitor the patient’s cholesterol every three months, the maximum number of appointments will be 160. 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 maximum of 43,200

states. We use the backward induction algorithm to solve this problem [70].

### 3.4.1 Case study

We tested our model with the VA longitudinal data introduced in Chapter 2. We include in our study patients with statins or blood pressure medication. The data follow the patients from 2003 until 2018, and Table 3.3 shows an overview of the population studied.

Table 3.3: 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

Characteristic	Mean ( $\pm$ SD) or No.(%)		P
	Patients without CVD Events	Patients with CVD events	
n	9675	325	
Gender			
male	8751 (90.4)	318(97.8)	<0.001
Female	924 ( 9.6)	7 ( 2.2)	<0.001
Race			
White	7254 (75.0)	266 (81.8)	0.006
Black	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
Months between visits	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
Months between visits	10.46 (6.52)	9.66 (5.81)	0.032

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.



As exclusion criteria, we do not consider patients with a prior CVD event or diabetes because our model focuses on prevention. Since diabetes is a major risk factor for CVD, patients in this group typically follow 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 mainly consists of the adult age group.

### 3.4.1.1 Model Parameters

We gathered some of the model parameters for the reward function of our MDP from the literature. We divide these parameters into two groups: costs and benefits and disutilities. We show their values and sources in Table 3.4.

Table 3.4: Reward function parameters and sources used in the model. All the values shown in this table are adjusted for inflation to 2020 USD [5]

Parameter Type	Parameter	Value	Source
<b>Costs and Benefits</b>			
	Going to an appointment ( $c_{APP}$ )	\$142	[47]
	A month of Low intensity statin ( $c_L$ )	\$8	[71]
	A month of High intensity statin ( $c_H$ )	\$16	[72]
	First year CHD event ( $c_{CHD_1}$ )	\$68,677	[73]
	Subsequent years after CHD event ( $c_{CHD_2}$ )	\$4,588	[73]
	First year stroke event ( $c_{ST_1}$ )	\$22,645	[73]
	Subsequent years after stroke event ( $c_{ST_2}$ )	\$7,240	[73]
	Benefit of being healthy per year (WTP)	\$100,000	[74]
	Expected remaining Life years ( $LY(\text{age})$ )	CDC LY tables	[3]
	Discount factor	0.97	[47]
<b>Disutilities</b>			
	CHD event QALY decrement per year ( $\delta_{CHD}$ )	0.07	[42]
	Stroke event QALY decrement per year ( $\delta_{ST}$ )	0.21	[42]
	Statins decrement ( $\delta_\tau$ )	0.003	[42]
	Life years decrement due to CHD ( $\eta_{CHD}$ )	0.625	[47]
	Life years decrement due to stroke ( $\eta_{ST}$ )	0.435	[47]

The cost of going to an appointment ( $c_{APP}$ ) 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 [47]. 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 [75]. As the physician orders a cholesterol test on each appointment, we add \$35 for this test [47]. Finally, we set \$75 as the visit cost with a general practitioner [47].

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 ( $c_L$ ), and we use the Statin Rosuvastatin 20mg for the cost of the High-intensity statin ( $c_H$ ). 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. We consider the costs of two CVD events, CHD and strokes, for our analysis. 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 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 our baseline, as is common in literature [74]. We also vary this to investigate the sensitivity of our results to WTP. We consider the CDC life year tables for the expected life years given that the patient is healthy [3]. 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 [76]. Finally, we estimate the probability of having a CHD event ( $d_{\text{CHD}}(\text{age})$ ) and the probability of having a stroke ( $d_{\text{ST}}(\text{age})$ ) using the American Heart Association CHD statistics and the American Heart Association stroke statistics [77].

### **3.4.2 Model validation**

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. With respect to the validation of the transition probability matrices, we follow the same process as shown in Section 2.5.

#### **3.4.2.1 Transition probability matrices**

Compared to Chapter 2, for this model, we include the white women population. In Table 3.5, we present the EM algorithm validation for the new patient group.

#### **3.4.2.2 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 patient groups mentioned in the last section, using a sample of 1/3 of the VA population in each group. We have as a null hypothesis that the model’s life-years are equal to the American population. Table 3.6 presents the model results compared to the CDC life tables.

Table 3.5: EM algorithm validation for white female patients. For white female patients, 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

Patient Group (% of Total)	Age Range	P-Value		
		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	<b>0.000</b>

Table 3.6: Simulation validation. The validation shows that our model increases the average life years for black males and is not statistically different for the other two groups.

Patient Group	Model's Avg life years	CDC life years	p-value
White male	77.3 ± 0.71	76.4	0.205
Black male	74.5 ± 0.72	71.9	≤ 0.05
White female	80.9 ± 0.61	81.2	0.623

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 [78]. It is worth noting that the highest difference between our model and the CDC life tables is for black 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 due 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 is estimated that 13.3 % of non-veterans do not have access to healthcare [78]. A second possible reason is that our model does not attempt to directly consider racial disparities that cause lower life expectancy for black males compared to white males in the CDC life tables.

We estimate the optimal policy for three demographic groups: white male, black 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 3.2 we present the optimal policy by age range, treatment, and 10-year risk for the white male group. We divided the 10-year risk into low, borderline, intermediate, and high.

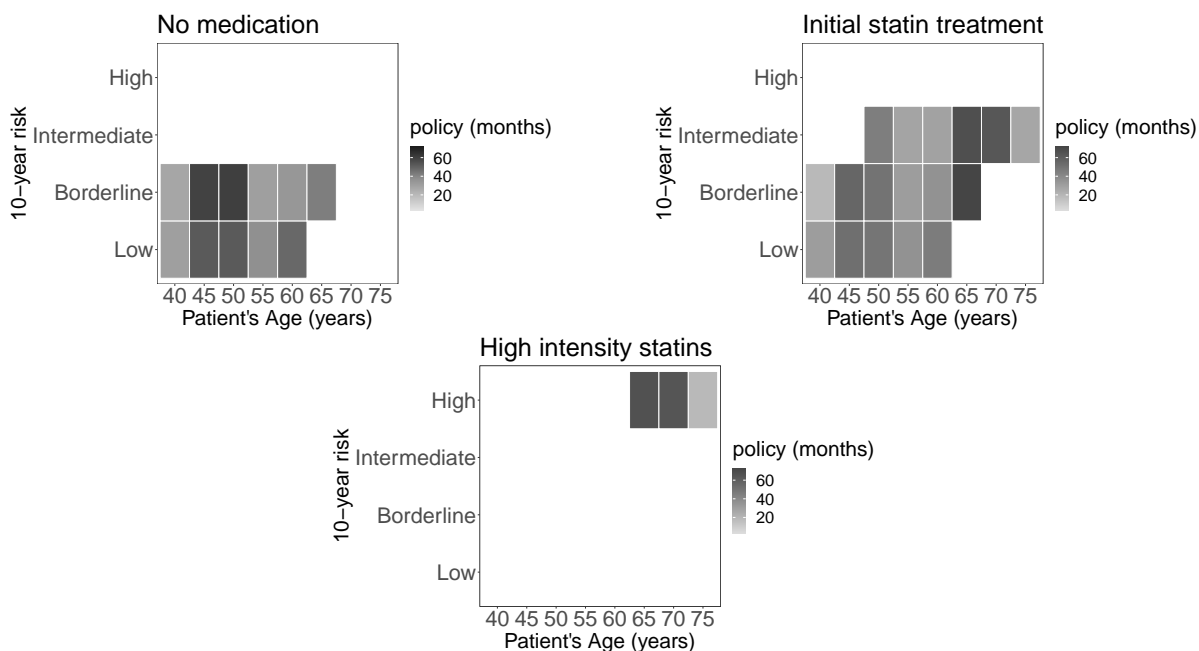
For younger white male patients who are not on preventive treatment, age 45 to 55, the MDP policy falls into the range of the current ACC guidelines. It differs for white male patients between 40 and 45, where the policy recommends that cholesterol tests be taken on average every 30 months, lower than what the ACC guidelines recommend. The model recommends more time between appointments for a white male patient on treatment between 40 to 55 than ACC guidelines (3 to 12 months).

The patient's age dramatically affects the MDP policy due to the natural risk associated with age. 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 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, the model suggests a higher time between appointments for white male patients on statins between 60 to 70 years old than the current ACC guidelines. This behavior is explained by the natural risk increase when the patients get older. Nonetheless, at age 75, the time between appointments decreases, similar to the current ACC guidelines. Finally, the policy recommends 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. As the patient gets older, the 10-year risk tends to increase. Nonetheless, the policy must account for the benefits of having additional appointments and treatment. Additionally, when the patient ages, the percentage of strokes increases compared to CHD events. On average, strokes have a lower average cost than

CHD. Therefore, as the model maximizes the overall societal rewards, the resulting policy is not monotone as the patient ages.

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 the Appendix in Figure A.1.

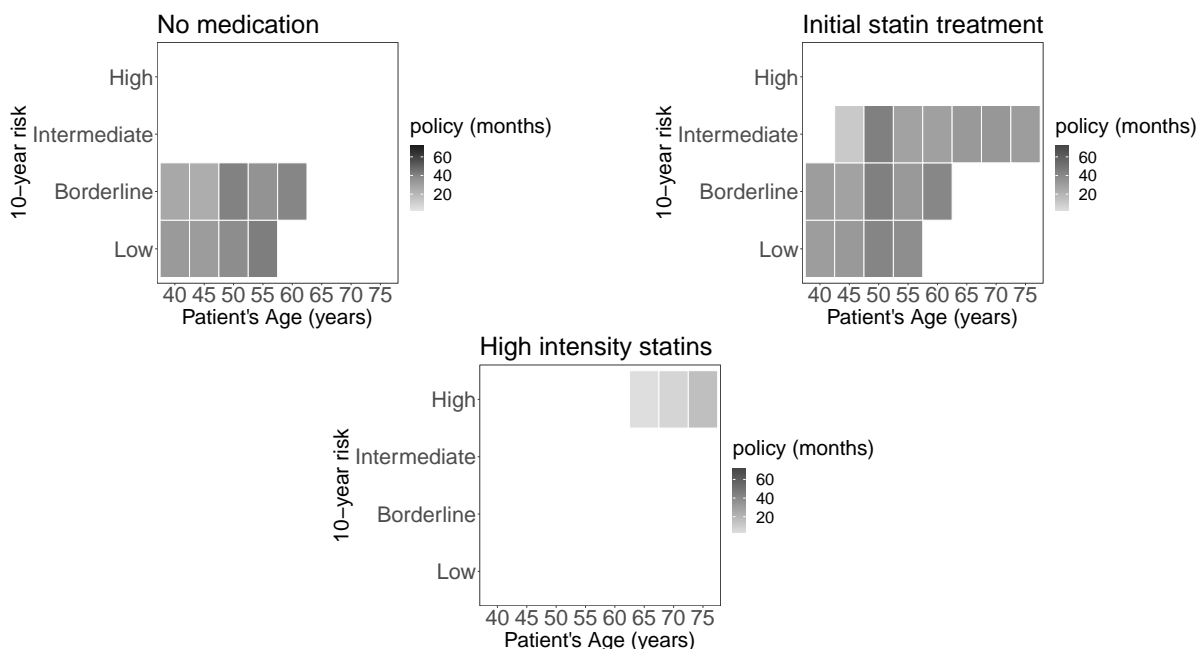
Figure 3.2: White male optimal policy by 10-year risk. The optimal policy varies depending on the patient’s age, treatment, and 10-year risk. The color represents the time between appointments, where lighter is less time between appointments and darker is more time between appointments. The optimal policy 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 black males is affected by the patient’s age, the 10-year risk, and the treatment. In Figure 3.3, we present the optimal policy. This policy suggests that black male patients should have a shorter time between cholesterol tests than white male patients, where none of the cases exceed 40 months between visits. Similarly, the recommended time between visits decreases for black male patients 55 years old and older.

Finally, the policy for white female patients suggests having more time between cholesterol tests for patients who have not started preventive treatment than for white male patients, as shown in Figure 3.4. For those patients on treatment, the MDP policy recommends less time between ap-

Figure 3.3: Black 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

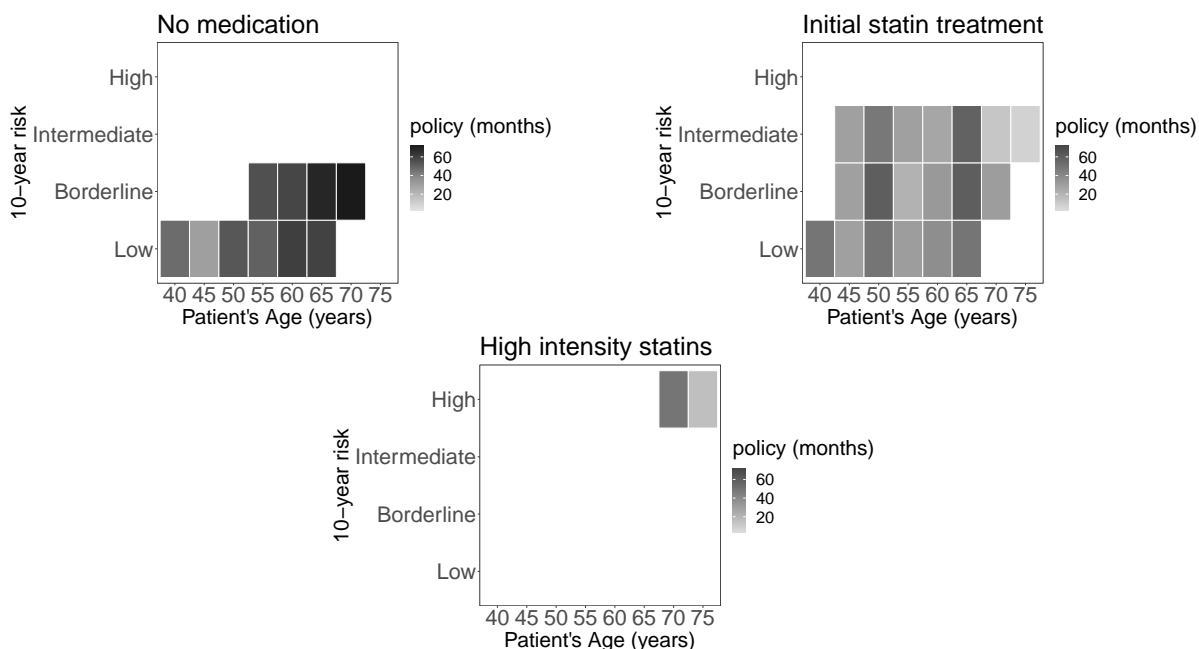


pointments for this demographic group than for white males but more time between appointments than for black males. These results are consistent with the lower 10-year risk that women have according to the VA risk models [19]. Nonetheless, this policy also shows that gender is essential for cholesterol testing policies.

### 3.4.3 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. (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 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

Figure 3.4: 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



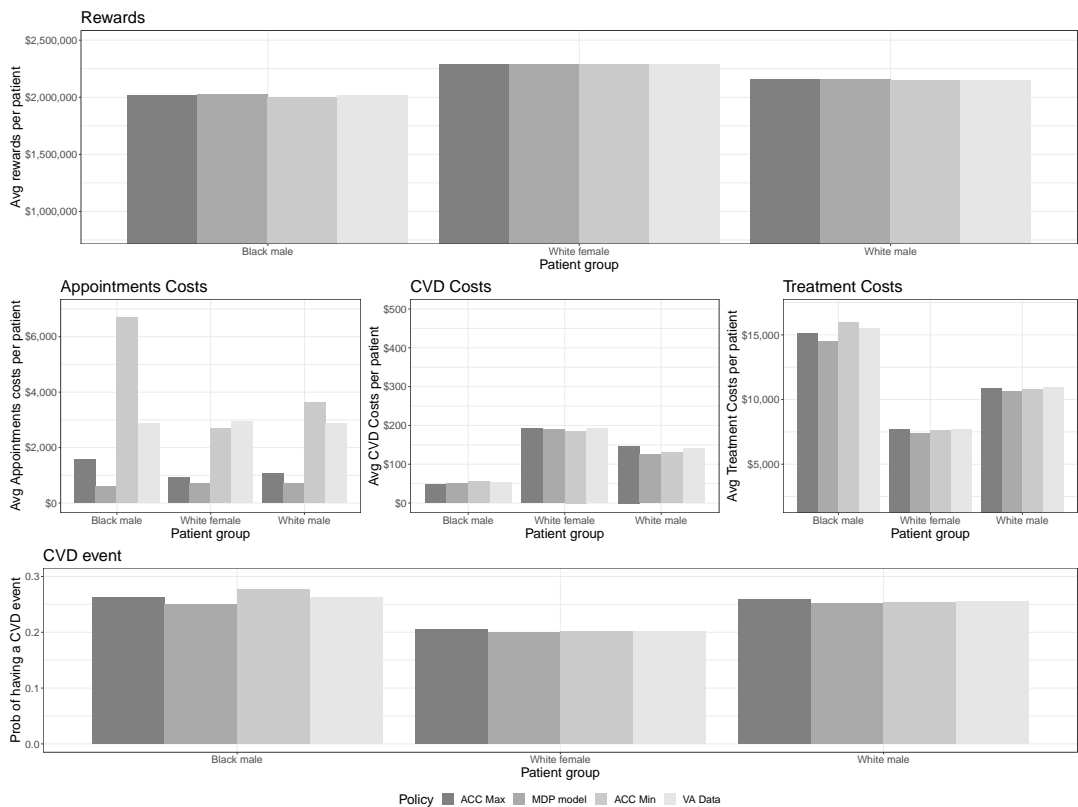
level, blood pressure level, and treatment.

We compare the policies by evaluating them using the MDP model and compare the patients’ total expected discounted rewards, total expected 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.

Figure 3.5 shows 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. For each group, the percentage of CVD events is lower than 30%. Our model shows improvements, as for the American population, the percentage of death caused by CVD events is 33%. Besides the benefits of the MDP policy, we are feeding our model with VA data, which, as mentioned before, are more likely to have access to healthcare [78].

As shown before, our policy monitors untreated patients more frequently than ACC Min and

Figure 3.5: Policies evaluation. We present the rewards, appointment costs, CVD costs, and treatment costs, 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





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, 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 \$2,514 (0.12%) 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 \$609.14 (5.05%). These discounted rewards and costs are measured, on average, over 37 years. We observed similar results for the other patient groups, where we compared the results versus the following best policy, ACC Max. For black men, the MDP policy increases the total discounted rewards on average \$5,822 (0.29%) and decreases the total discounted costs by \$1,600 (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 black male patients over the age of 40, and 0.6 million white female patients over the age of 40 [78]. The estimated changes due to the MDP policy suggest the potential for increasing the VA population’s societal rewards by approximately \$28.5 billion. Furthermore, the societal costs will decrease by around \$7.1 billion.

Other countries suggest a once-a-year cholesterol testing policy if the patient is healthy [67]. We analyzed this policy for healthy patients and used a three-month testing policy when patients are on treatment. In Table 3.7, we show the results for white male patients and add the standard deviation for each metric. The one-year policy has fewer rewards as the appointment costs increase. Nonetheless, this policy has a smaller probability of having a CVD event. Additionally, the standard deviation for each of these measurements is small compared to the mean.

Table 3.7: Policies costs and rewards comparison part 1. We compare the results for white male patients using each of the policies. Additionally, we add the one-year policy that other countries suggest. Part 1

Measurement	Measurement value - Mean ( $\pm$ SD)			
	MDP	ACC Min	ACC Max	VA Data
<b>Rewards (\$ in K)</b>	2159.1 (0.408)	2151.1 (0.404)	2156.6 (0.405)	2152.5 (0.403)
<b>Appointments costs</b>	713.9 (0.32)	3625.4 (1.92)	1074.7 (0.52)	2881.2 (75.9)
<b>Treatment costs</b>	10606 (60.8)	10820 (60.8)	10860 (60.5)	10931 (60.2)
<b>CVD costs</b>	125.84 (0.07)	129.59 (0.07)	146.98 (0.08)	140.60 (0.08)
<b>CVD event</b>	0.252 (0.00)	0.254 (0.00)	0.259 (0.00)	0.256 (0.00)

Table 3.8: Policies costs and rewards comparison part 2. We compare the results for white male patients using each of the policies. Additionally, we add the one-year policy that other countries suggest. Part 2

<b>Measurement</b>	<b>Measurement value - Mean (<math>\pm</math> SD)</b>	
	<b>MDP</b>	<b>One year</b>
<b>Rewards (\$ in K)</b>	2159.1 (0.408)	2146.3 (0.398)
<b>Appointments costs</b>	713.9 (0.32)	5878.1 (2.93)
<b>Treatment costs</b>	10606 (60.8)	10812 (60.28)
<b>CVD costs</b>	125.84 (0.07)	130.09 (0.07)
<b>CVD event</b>	0.252 (0.00)	0.251 (0.00)

### 3.4.4 Sensitivity analysis

In practice, the healthcare providers, physicians, and patients may evaluate each cost and the WTP differently. For this reason, we tested how the costs and WTP affect the policy of the white male population by varying each of them and the other ones held constant. For the costs, we analyzed how the total expected discounted rewards, the average number of appointments, and the probability of a CVD event behave in extreme values. Additionally, we analyzed how different WTP values affect the monitoring policy.

We analyzed the effects of the costs of appointments, CVD events, and treatments between 0 (lower bound) and 10 (upper bound) times the initial case study value. We present the results in Table 3.9. In general, decreasing either of the costs increases the total expected discounted rewards, and increasing the costs decrease the total expected discounted rewards. Nonetheless, there are additional charges in the policy when these costs change. When the cost of an appointment decreases, the policy suggests more appointments throughout the patient's lifetime. Increasing the appointment cost decreases the number of appointments, increasing the probability of having a CVD event. This change decreases the rewards by approximately \$6,000 compared to the case study.

When the cost of a CVD event decreases, it does not affect the number of appointments. On the other hand, when this cost increases, the number of appointments increases, decreasing the probability of having a CVD event. Increasing this cost decreases the total expected discounted rewards by \$16,500.

Finally, decreasing the treatment cost increases the number of appointments compared to the case study. Likewise, increasing the cost also increases the number of appointments. This behavior suggests that increasing the number of appointments helps prevent the patient from starting high-intensity statins.

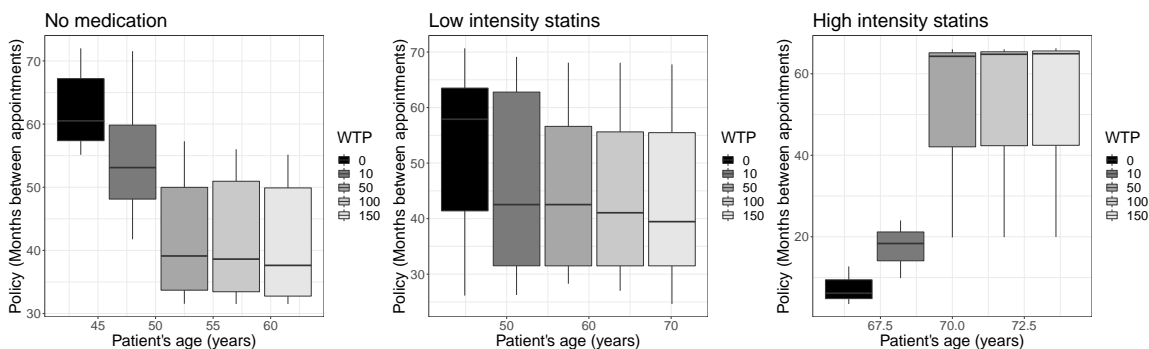
For the WTP, our policy is robust with changes of WTP unless a value of \$10,000 or less is

Table 3.9: Cost sensitivity analysis. For each cost we evaluate the total expected discounted rewards, the expected number of appointments, and the probability of having a CVD event. We show the results for a lower bound of a cost of 0 and an upper bound of a cost of 10 times the initial case study value.

Cost	Measurement	Measurement value - Mean ( $\pm$ SD)		
		Lower bound	Case study	Upper bound
<b>Appointment</b>	Rewards (\$ in K)	2169.3 (0.35)	2168.6 (0.36)	2162.7 (0.35)
	Appointments	11.8 (0.01)	7.2 (0.003)	7.1 (0.003)
	CVD probability	0.250 (0.00)	0.254 (0.00)	0.254 (0.00)
<b>CVD event</b>	Rewards (\$ in K)	2170.4 (0.34)	2168.6 (0.36)	2152.1 (0.48)
	Appointments	7.2 (0.003)	7.2 (0.003)	8.8 (0.004)
	CVD probability	0.254 (0.00)	0.254 (0.00)	0.252 (0.00)
<b>Treatment</b>	Rewards (\$ in K)	2169.3 (0.36)	2168.6 (0.35)	2163.0 (0.35)
	Appointments	8.1 (0.004)	7.2 (0.003)	7.5 (0.004)
	CVD probability	0.253 (0.00)	0.254 (0.00)	0.255 (0.00)

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 3.6.

Figure 3.6: Sensitivity analysis of the policy by varying the WTP value per year. We present in the boxplots the median and each of the quartiles

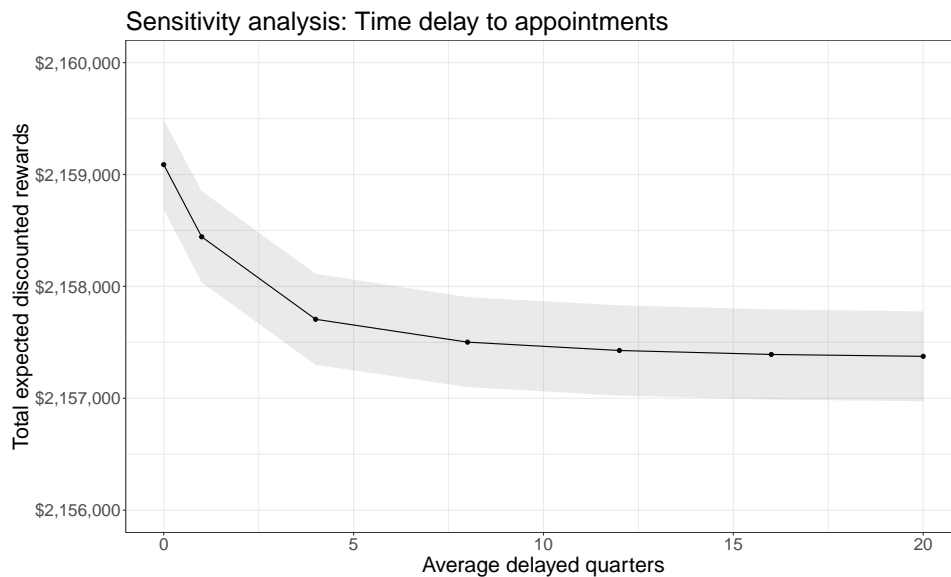


Also, patients may not comply with the physician's recommendation on when the next cholesterol test should occur. There are multiple reasons why this behavior happens, such as access to healthcare, misconceptions over their health, and additional costs [79]. Access to healthcare and additional costs limit the patient's mobility to appointments, delaying their next visit. Also, due to misconceptions about their health, patients overestimate their conditions and may decide to

postpone the appointment. Nonetheless, it is possible to estimate the delay if we have access to this data and the physician’s actual recommendation. Therefore, we need to incorporate this new stochastic behavior to Equations 3.1 to 3.4.

We analyzed our policy’s robustness when adding a stochastic delay to the patient’s arrival for the next cholesterol test. We estimate the expected discounted rewards for different delay rates. We simulated exponential distributions with different rates for the time delay while using the MDP resulting policy. Each exponential distribution tested had an average number of delayed quarters, ranging from 0 (100% compliance) to 20 quarters. We first tested the scenarios where all patients followed the same distribution, which we present in Figure 3.7. Also, we tested scenarios where the patients had different distributions. We assume that patients with treatment have a shorter delay than patients without treatment, as these patients are monitored more frequently. In the Appendix, we present the additional scenarios where patients with treatment have a shorter average delay than those without treatment. We present these results in Figure A.2.

Figure 3.7: Sensitivity analysis of the rewards when adding a time delay to the patient’s arrival at the next appointment. We present on the x-axis the average number of delayed quarters, where 0 represents 100% compliance from the patient. We show the rewards and the confidence interval.



As expected, increasing the average time delay decreases the total expected rewards. Notice that the rewards are not statistically different after 5 quarters of a year. Moreover, compared to a scenario without delay, the total expected discounted rewards only decrease on average by \$1, 500. This result shows that the model’s policy is robust to changes in patient compliance with physician recommendations. Additionally, we saw similar results when testing different average delays depending on whether the patient is on treatment.

## 3.5 Discussion

Our framework proposed and validated multiple statistical models that learn from EHRs. First, we used an EM algorithm to fit the cholesterol and blood pressure behaviors. We believe these algorithms will help estimate patients' risk factors for other healthcare applications, as healthcare data are 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 decreasing 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 black males benefit from more frequent surveillance than white males. On the other hand, for white females, the MDP model recommended less frequent monitoring, compared to white males, 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 black male patients. When the model recommends less frequent surveillance, the patient's health is not negatively affected. For these particular cases, the model decreases appointment 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 black patients have over white patients. Studies suggest that differences in risk among patients are associated with access to healthcare and racial inequalities [64]. Unfortunately, the difficulty in measuring the patients' risk factors may delay treatment to the patients, hence increasing their CVD risk [80]. 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 black 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 [1] and one-year monitoring policies applied in other countries [67], our model suggests that considering patients' demographics could increase the societal rewards by approximately \$28.5 billion for the VA health system.

This increase was associated with an MDP policy that decreased unnecessary appointments and set 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. Furthermore, our policy varies depending on the patient’s age, sex, and race, which the current guidelines do not consider. Our policy reduces the probability of having a CVD event, resulting in a reduction of approximately \$7.1 billion 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. Other healthcare systems may have a diverse population and different dataset attributes, such as length of follow-up, risk factors history, and when to prescribe medications [81, 82, 83]. These differences need a thorough analysis of whether the proposed methods to estimate transition probabilities are sufficient. Additionally, we recognize that underlying causes affect each demographic group’s risk of CVD. Unfortunately, we did not have access to this data, which was not feasible to gather. Nevertheless, our results suggest that patients’ demographics and other social variables may be key risk factors for healthcare, helping motivate the importance of thoroughly collecting such data in the future. One-size-fits-all policies may be associated with higher costs and lower quality-adjusted lifespan. Additionally, the MDP model structure serves as a prototype to help physicians and public health experts improve cholesterol control. Applying the model to other races and including ethnicity will help physicians understand the strategies needed to prevent CVD events. 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).

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

Future work might consider adding the probability distributions of how the patient responds to

recommendations. Patients do not always follow physicians' recommendations, so 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 return to an appointment as the physician recommends. Therefore the time between appointments could also be considered stochastic. Our research provides a starting point to investigate some of these questions further. For our case study, we validate that the stochastic behaviors follow the Markov assumption and are independent between them. However, we acknowledge that this may not be true for other healthcare applications. Therefore, we recommend studying other fitting approaches that better align with the available data. Also, we follow the treatment guidelines suggested by the American College of Cardiology to treat high cholesterol and high blood pressure. In practice, the physician has the final say in applying these guidelines according to the patient's health history. Therefore, in future work, we will consider the impact of relaxing the assumption toward using different treatment guidelines. Finally, our approach to building a model for CVD using longitudinal EHR data and other data sources could find application in other diseases that involve periodic monitoring of risk factors.

## CHAPTER 4

# Prediction of Long-Term Medication Adherence and Its Potential Benefits for Intervention

### 4.1 Introduction

Correct long-term use of medications is one of the primary methods to prevent chronic diseases effectively [11]. In Chapters 2 and 3, we focus on policies to prevent cardiovascular diseases (CVD) within the population, assuming that patients comply with physicians' recommendations. However, studies have shown that many patients will eventually stop taking medications at the end of the first year of prescription, increasing the risk of developing diseases or experiencing adverse outcomes [11]. The lack of medication adherence has been attributed to several factors, including patients' misconceptions over their health, the cost of medication, and the complexity of treatment when multiple medications are involved [79]. Healthcare providers use interventions to mitigate decays in adherence, where clinical trials have tested these interventions in various settings by varying cost, patient involvement, and healthcare provider involvement [12]. These interventions are divided into different categories: patient education, medication management, clinical pharmacist education, cognitive behavioral training, reminders, and financial incentives [84], [85].

Interventions within the categories of patient education, clinical pharmacist education, and cognitive behavioral training show the best results, where the percentage of patients that adhere increases to almost 90% [12]. Nonetheless, these interventions require significant time from the healthcare providers, including training. Moreover, they also need time commitments from patients. Therefore, not all patients have the opportunity to participate. On the other hand, interventions, such as reminders via text messages, phone calls, and brochures, are less expensive, and most patients are included. Unfortunately, the success of these interventions is low [12] unless they are applied alongside patient education and follow-up to identify and address barriers [86]. Nevertheless, reminders via electronic pill counts are successful, where the percentage of patients adhering



increases to almost 90%. Similar to previous interventions, these tend to be costly, as these methods use electronic pill bottles that track when patients are opening the boxes, taking medication, refilling, and giving alerts when missing doses. Additionally, to increase effectiveness, electronic pill count methods need additional support from clinicians [12].

In general, effective interventions have a limited capacity. A limited budget restricts health-care providers regarding how many patients they can recommend for interventions to offset non-adhering behavior [12]. Additionally, these interventions are most effective from a population perspective if they can be allocated to patients at the greatest risk of non-adherence [87], [88]. A variety of factors could potentially help predict future adherence, such as demographic information, clinical information, and prior adherence [89]. However, it is unclear how to predict long-term adherence and how to update predictions as new information about the patients is obtained over time. Moreover, patient adherence varies over time and dynamically changes depending on the patient's health behavior [90]. Therefore, the primary goals of this chapter are as follows:

1. Propose and validate dynamic prediction models that use claims data to identify when patients will stop adhering to medications.
2. Understand how the dynamic prediction improves the selection of patients that should be included in adherence-improving interventions subject to budget constraints.

To accomplish these goals, we present a forecasting model using *dynamic logistic regression* (DLR) to predict whether patients will experience persistent periods of non-adherence to help providers decide which patients in their panel should be recommended for adherence-improving interventions. We apply DLR in the context of primary prevention of CVD and compare the performance to previously proposed methods. We use CVD as an example because it is one of the leading causes of death in the United States [6], however, our approach can be easily extended to other contexts. We focus on patients' adherence to statins given their widespread use and because past studies have shown that half of the population who start statins will stop adhering by the end of the first year of prescription, and only 35% of the patients will adhere by the end of the second year [11]. Additionally, we develop a *binary integer programming* (BIP) model that uses adherence predictions to select which patients should be assigned to an intervention subject to a budget constraint at each epoch. We apply our model to longitudinal data for a large cohort of patients seen in the national Veterans Affairs health system who initiate statin treatment for primary prevention of CVD [91]. We evaluate a prediction horizon of 1 to 5 years because we focus on long-term adherence, and statins are effective if they are regularly taken for an extended period [92]. Additionally, we create a simulation model to test recommendations from the DLR to optimize the selection of patients for interventions subject to a budget constraint. We validate the simulation

model by comparing the number of CVD events without adherence-improving interventions versus the current number of CVD events in the studied population. This framework has the objective of helping providers decide which patients to recommend for adherence-improving interventions, acknowledging their budget constraints.

The rest of the chapter is organized as follows. In Section 4.2, we present the literature review related to adherence forecasting and patient selection models under limited resources and highlight the differences between our approach and the ones presented in the literature. In Section 4.3, we present our modeling framework consisting of the DLR model, the BIP model, and the simulation environment where we test our approach. In Section 4.4, similar to previous chapters, we apply this framework to a case study based on patients seen in the national Veterans Affairs health system. We compare our model versus current selection rules for adherence interventions. Finally, we discuss our results and summarize our main conclusions.

## 4.2 Literature Review

The most relevant research related to our work falls into the following fields: (1) adherence prediction models; (2) DLR models for healthcare; and (3) optimization models for resource allocation. This section highlights papers related to our work and briefly describes how our proposed methodology differs.

Prior literature proposes classifying patients' adherence based on pharmacy claims data using the initial fill and subsequent refill dates together with the pill count to estimate the percentage days covered (PDC). Two approaches that use PDC are commonly applied: *binary classification* or classification based on the *adherence trajectory*. Binary classification assigns the patient to be adherent or not adherent using multivariate logistic regression [93] or logistic regression with lag [94] to predict if the patient's adherence will drop below a predefined threshold. The trajectory method classifies the patient according to predefined trajectories based on how quickly the patient goes below a predefined adherence threshold using group-based trajectory models [90] or logistic group-based trajectory models [95]. Unfortunately, these papers classify patients in predefined trajectories, which may exclude patients with different adherence behaviors. We propose to apply a DLR model, which can construct an individual adherence trajectory for each patient that learns from past medical records and sequentially updates predictions over time as new information is obtained.

In healthcare, DLR has been used to forecast high blood pressure in children [96], surgical errors [97], and blood pressure in adults [98]. For trajectory methods, the literature suggests that adherence follows an autocorrelation pattern [90]. Therefore, DLR is a great candidate as this model constructs the trajectory by dynamically estimating adherence using previous estimations

and including the autocorrelation effect. The literature also uses different machine learning approaches to model adherence for multiple periods, such as temporal deep learning for five years into the future [99] and random forests for the next two weeks [100]. Similarly, our model can predict how patient adherence will evolve, giving healthcare providers additional information beyond a classification method. Furthermore, our DLR model’s dynamic nature can fit each patient’s initial adherence trajectory and improves prediction accuracy when new information is available. Finally, the DLR model can also estimate the relationship between key factors and adherence behavior, which black box models struggle with and is needed to understand why patients stop adhering [101].

To develop these models, we use key factors comprising demographics, historical clinical information, and historical adherence information. For predicting adherence to statins, most of the prior literature considers covariates such as demographic characteristics, medical risk factors, and health provider-related factors [102], [103]. We included the adherence history as a covariate, improving upon previous studies that suggest including only the last measurement of adherence [104]. Also, DLR models usually forecast short-term risk, i.e., days [105], [106]. For example, a recent study forecasts blood pressure on the time scale of days [98] for CVD. In contrast, we forecast adherence to statins five years into the future because cholesterol tends to follow closely within 1 to 6 years for patients with an increased likelihood of having a CVD event [1]. We also include random effects in our model to acknowledge different adherence patterns among patient groups.

Regarding resource allocation, the literature focuses on two types of problems: immediate scheduling of patients, for example, ICUs and surgery [107] [108] [109] [110] [111], and resource allocation for long-term scheduling, such as screenings, follow-ups, and transplants [57] [112] [113]. Depending on the application, the literature presents different methods to solve this problem, such as linear programming models [114], dynamic programming [115] [116], and simulation [117]. Regarding long-term resource allocation for multiple patients and resource constraints, multiple models used dynamic approaches such as reinforcement learning [118], multi-armed bandits [21], restless multi-armed bandits [119]. Most of these models allocate resources for one patient per epoch, differing from our problem, where the physician allocates resources for multiple patients during the same year. Other papers, which allocate resources for multiple patients, assumed a homogeneous population [52], [120]. Regarding allocating resources for multiple patients in a heterogeneous population, studies have assumed perfect compliance to physician recommendations [121] [122] [123] [124]. In our approach, we consider resource allocation for multiple patients in a heterogeneous population with limited resources and imperfect compliance. We model compliance as adherence to medication and the success of interventions, as adherence-improving interventions are not perfect; for some patients, these interventions may not work [101]. Therefore, we consider the probability of the intervention not working as part of the decision.

Finally, studies that define resource allocation models have focused on different aspects of adherence-improving interventions. Studies have assumed cost-effectiveness approaches to define when a patient should be selected for intervention [125]. Other approaches defined the optimal coinsurance rates that maximize the population’s welfare and select patients that should receive better reductions [28]. Studies have also focused on defining the optimal incentive rate for financial incentive interventions [126] [127]. Related to intervention capacity, studies estimated the minimum capacity needed to satisfy the required adherence level in the population [128] and developed techniques for patient care within the pharmacy to serve the maximum amount of patients[129]. Our work focuses on fixed-capacity interventions such as patient education, clinical pharmacist education, and reminders. Therefore, we assume that the intervention capacity and the intervention effect on the patient are known. We propose a binary integer programming (BIP) model in which we select multiple patients in a heterogeneous population per epoch. Given the dynamic aspect of our problem, we propose an adaptive heuristic that combines the BIP and DLR models and updates the selection policy in each epoch depending on the patients’ health behavior.

In summary, our work differs from previous studies in three main ways. First, we propose a DLR model to predict the patient’s adherence trajectory to identify when they stop adhering, thus avoiding the need to assign patients to predefined trajectories. Second, our DLR model is updated every time new information is gathered from the patient. Third, we propose an adaptive heuristic to select patients for adherence-improving interventions that combine the BIP model with the DLR model. This heuristic selects multiple patients in a heterogeneous population and updates itself when new information is collected. We show that this adaptive heuristic reduces the number of CVD events in a population by helping identify which patients benefit the most from the interventions.

### **4.3 Methods**

This section describes our implementation of the DLR method for predicting patients’ adherence and the BIP model for assigning patients to intervention. We present definitions and assumptions, describe the dynamic forecasting model with random effects, and present alternative patient selection rules for adherence-improving interventions. Further, we present a simulation model to test the forecast results. Table 4.1 presents the notation used throughout this chapter, where vectors are highlighted in bold.

Table 4.1: List of notation for the forecasting model.

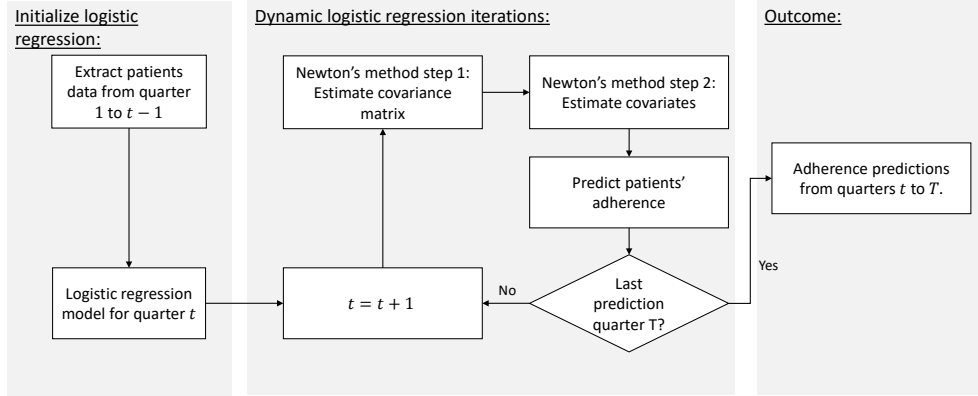
Notation	Description
$\mathbb{I}$	Set of patients indexed by $i$ where $\mathbb{I} \equiv \{1, \dots, n\}$ .
$\mathbb{E}$	Set of epochs indexed by $t$ where $\mathbb{E} \equiv \{1, \dots, T\}$ .
$w_{it}$	Binary response variable that represents if patient $i$ adheres or not at quarter $t$ .
$x_{ikt}$	Covariate $k$ , for patient $i$ in quarter $t$ .
$u_i$	Random effect associated with patient $i$ .
$y_{it}$	Probability that $w_{it}$ is equal to 1 given the covariates.
$\hat{y}_{it}$	Estimation of $y_{it}$ .
$\beta_t$	Vector of coefficients at time $t$ associated to variables.
$\hat{\beta}_t$	Estimation of $\beta_t$ .
$\Sigma_{\beta t}$	Correlation matrix at quarter $t$ for the coefficients $\beta_t$ .
$q$	Probability of success of an intervention.
$r$	Adherence effect on risk reduction.
$P_{it\tau}$	Probability that patient $i$ does not adhere for $\tau$ epochs until the end of the planning horizon if intervened in epoch $t$ .
$c$	The number of available interventions at each epoch.
$S_{it}$	Binary variable where if $S_{it} = 1$ then patient $i$ is selected for intervention in epoch $t$ .

### 4.3.1 Dynamic logistic regression

Let  $\mathbb{I}$  be the set of patients indexed by  $i$  where  $\mathbb{I} \equiv \{1, \dots, n\}$  and  $n$  is the total number of patients. Also, let  $\mathbb{E}$  be the set of epochs to forecast indexed by  $t$  where  $\mathbb{E} \equiv \{1, \dots, T\}$  and  $T$  is the total number of epochs. We define our epochs in quarters of the year, as the American College of Cardiology suggests that patients on statins take cholesterol tests every 3 to 12 months [1]. Additionally, statin medication is usually prescribed for 90 days at a time. We aim to predict whether patient  $i$  adheres at quarter  $t$ ; therefore, we let  $w_{it}$  denote the binary response variable that represents if patient  $i$  adheres or not at quarter  $t$ . We also define  $x_{ikt}$  as the value of covariate  $k$  for patient  $i$  at quarter  $t$ . Finally, we assume we have prior data from the date of the first refill, denoted as quarter 1, until quarter  $t - 1$ . We use this data to predict adherence for quarter  $t$  onward. We begin by predicting adherence for quarter  $t$  using a logistic regression model and then use this result as an input for the DLR model to forecast quarters  $t + 1$  onward. Then this process continues recursively until the final quarter  $T$  as shown in Figure 4.1. More data becomes available when patients return to an appointment or refill medication. Therefore, for a quarter  $t + \tau$ , if more data is available, we rerun the DLR model using data from quarters 1 to  $t + \tau$  and predict for quarters  $t + \tau + 1$  to  $T$ .

As our goal is to estimate the probability that  $w_{it} = 1$ , we define  $y_{it}$  as the probability that  $w_{it}$  is equal to 1 given the covariates. Let us define  $\mathbf{x}_{i..}$  as the vector containing the covariates history associated with patient  $i$ . Then, we estimate the probability  $w_{it}$  is equal to 1 as  $y_{it} = P(w_{it} =$

Figure 4.1: DLR flowchart. The DLR model initializes by using a logistic regression model to predict the patient adherence for quarter  $t$ . Then, the DLR model employs a recursive process using Newton's method to estimate the covariance matrix and the covariates for quarters  $t + 1$  to  $T$ . With the resulting covariance matrices and covariates, we predict the patient's adherence behavior from quarters  $t$  to  $T$ .



$1|\mathbf{x}_{i..}, \boldsymbol{\beta}_t)$ , which is estimated by a logistic regression model, where  $w_{it} = 1$  represents that the patient does not adhere and  $w_{it} = 0$  otherwise. Notice that, for quarter  $t$ ,  $\mathbf{x}_{i..}$  contains data from the first quarter to quarter  $t - 1$ . As each patient may behave differently, we define  $u_i$  as the random effect associated with patient  $i$ . Therefore we estimate  $\hat{y}_{it}$  as:

$$\hat{y}_{it} = P(w_{it} = 1|\mathbf{x}_{i..}, \boldsymbol{\beta}_t) = \frac{\exp(u_i + \boldsymbol{\beta}_t \mathbf{x}_{i..})}{1 + \exp(u_i + \boldsymbol{\beta}_t \mathbf{x}_{i..})}. \quad (4.1)$$

We use the data until quarter  $t - 1$  to forecast the adherence in  $t$  by estimating the coefficients  $\boldsymbol{\beta}_t$ . The logistic regression model only predicts one quarter at a time. Therefore, we use the DLR model that starts from the standard logistic regression to iteratively generate predictions of the remainder of the time horizon  $T$ .

Using the estimates of the coefficients  $\hat{\boldsymbol{\beta}}_t$ , we can forecast adherence for time  $t + 1$  by estimating  $\boldsymbol{\beta}_{t+1}$ . In the literature, there are several proposed approaches to estimate  $\hat{\boldsymbol{\beta}}_{t+1}$  [106]. In our case, we update the coefficients dynamically by defining the posterior distribution of  $\boldsymbol{\beta}_t$ , after observing the probability of non-adherence for each patient in quarter  $t$  (defined as vector  $\mathbf{y}_t$ ) as follows:

$$p(\boldsymbol{\beta}_t|\mathbf{y}_t) = p(\mathbf{y}_t|\boldsymbol{\beta}_t)p(\boldsymbol{\beta}_t|\mathbf{y}_{t-1}). \quad (4.2)$$

Given the amount of data for each patient, we assume that the right-hand side of the equation is approximated by a normal distribution [105], where  $\beta_{t+1}|\mathbf{y}_{..t} \sim N(\hat{\beta}_t, \hat{\Sigma}_{\beta_t})$ . The vector  $\hat{\beta}_t$  is the estimation of the coefficients at the end of period  $t$ , and  $\hat{\Sigma}_{\beta_t}$  is the estimation of the associated covariance matrix. The exact estimation of these values is difficult, but using Newton's method, we can approximate  $\hat{\beta}_{t+1}$  [105]:

$$\hat{\beta}_{t+1} = \hat{\beta}_t - \hat{\Sigma}_{\beta_{t+1}}^{-1}(\mathbf{w}_{..t} - \hat{\mathbf{y}}_{..t})\mathbf{x}_{..t}, \quad (4.3)$$

where the covariance matrices are updated as follows:

$$\hat{\Sigma}_{t+1} = \hat{\Sigma}_t^{-1} + \hat{\mathbf{y}}_{..t}(1 - \hat{\mathbf{y}}_{..t})\mathbf{x}_{..t}\mathbf{x}_{..t}^T. \quad (4.4)$$

Having estimated  $\hat{\beta}_{t+1}$ , then we can estimate  $\hat{y}_{it+1}$  using the updated logistic regression model. This process continues recursively until the last prediction quarter  $T$  as shown in Figure 4.1.

### 4.3.2 Patient selection model

We formulate a BIP model to select patients for adherence-improving interventions. The model's objective is to maximize the total CVD risk reduced in the population. Given a limited intervention capacity per epoch, the objective is achieved by deciding which patients to intervene in each epoch. Therefore, in this model, we assume that: (1) the patient receives intervention at most once over the planning horizon; if the intervention does not work, the patient is not selected again for an intervention, (2) the CVD risk is reduced if the patient is selected for intervention and the intervention works, and (3) the probability that the intervention works ( $q$ ) and the adherence effect on relative risk reduction ( $r$ ) are the same for all patients, where  $r \in [0, 1]$ .

The risk reduction per patient is estimated in terms of the initial 10-year risk for a CVD event ( $CVD_i$ ). If a patient adheres, the new 10-year CVD risk will be  $CVD_i \times (1 - r)$  by the end of 1 epoch into the intervention. The DLR model outputs the probability  $\hat{y}_{it}$ , that patient  $i$  does not adhere in epoch  $t$ . As there is a natural risk reduction for patients that adhere, assigning patients to interventions, who would otherwise have adhered, does not provide any additional reduction in risk. To estimate how much the CVD risk is reduced for multiple periods due to the intervention, we define  $a_{it}$  as the total risk reduction throughout the planning horizon for patient  $i$  if selected for intervention in epoch  $t$ . For example, if patient  $i$  does not adhere, we let  $q = 1$ . If that patient is selected to receive an intervention at epoch  $t$ , the risk after the intervention is  $(1 - r)^{T-t+1}CVD_i$  and  $a_{it} = CVD_i - (1 - r)^{T-t+1}CVD_i$ . Nonetheless, as there is a probability that the patient adheres in any epoch  $\tau \geq t$ , estimated as  $(1 - \hat{y}_{i\tau})$ , we incorporate this probability into estimating  $a_{it}$ . For example, let  $t = T - 2$  and  $q = 1$ , then  $a_{iT-1} = CVD_i - (1 - \hat{y}_{iT-1})(1 - \hat{y}_{iT})CVD_i -$

$\hat{y}_{iT-1}(1 - \hat{y}_{iT})(1 - r)CVD_i - (1 - \hat{y}_{iT-1})\hat{y}_{iT}(1 - r)CVD_i - \hat{y}_{iT-1}\hat{y}_{iT}(1 - r)^2CVD_i$ . We define  $P_{it\tau}$  as the probability that patient  $i$  does not adhere for  $\tau$  epochs until the end of the planning horizon if intervened in epoch  $t$ . The total expected risk reduced for patient  $i$  is estimated as:

$$a_{it} = CVD_i - q \sum_{\tau=0}^{T-t+1} P_{it\tau}(1 - r)^\tau CVD_i. \quad (4.5)$$

Finally, we define  $S_{it}$  as a binary variable where  $S_{it} = 1$ , if patient  $i$  is selected for intervention in epoch  $t$  and  $S_{it} = 0$  otherwise. Because the patient is only selected once for an intervention, we need to add the constraint  $\sum_{t \in \mathbb{E}} S_{it} \leq 1$ . Given this constraint, the expected risk reduction for patient  $i$  will be  $\sum_{t \in \mathbb{E}} a_{it}S_{it}$ . As  $a_{it}$  represents the expected CVD risk reduced, it provides an estimate of the reduction of the probability of having a CVD event in the next ten years. Therefore,  $\sum_{t \in \mathbb{E}} a_{it}S_{it}$  also represents the decreased number of expected CVD events for patient  $i$  over the planning horizon  $T$ . We can now formulate the problem as a BIP model to maximize the expected total reduction of CVD events in the population, as follows:

$$\text{maximize } \sum_{t \in \mathbb{E}} \sum_{i \in \mathbb{I}} a_{it}S_{it} \quad (4.6)$$

subject to

$$\sum_{i \in \mathbb{I}} S_{it} \leq c \quad \forall t \in \mathbb{E}, \quad (4.7)$$

$$\sum_{t \in \mathbb{E}} S_{it} \leq 1 \quad \forall i \in \mathbb{I}, \quad (4.8)$$

$$S_{it} \in \{0, 1\} \quad \forall i \in \mathbb{I}, \quad \forall t \in \mathbb{E}. \quad (4.9)$$

The constraint in Equation 4.7 is associated with the intervention capacity per epoch, and Equation 4.8 enforces that patients are selected once. Recall that  $a_{it}$  is estimated using the intervention and non-adherence probability. This BIP is a special case of the multiple knapsack problem, where finding the optimal solution is, in general, NP-hard [130]. However, we show the instances we are concerned with are easy to solve,

We want to understand the additional reduction of CVD events when selecting a patient in epoch  $t$  versus waiting. Having estimated this difference, we want to define a policy that selects patients based on marginal risk reduction between epochs. Therefore, in Proposition 4.3.1, we show that  $a_{it}$  decreases in time and how to estimate  $a_{it}$  and  $a_{it-1}$ .

**Proposition 4.3.1.** *For patient  $i$ ,  $a_{i1} \geq a_{i2} \geq \dots \geq a_{iT}$ . Furthermore,  $a_{it-1} - a_{it} = r\hat{y}_{i(t-1)}(CVD_i - a_{it})$ .*



*Proof.* : We prove this proposition by estimating the difference between  $a_{it-1}$  and  $a_{it}$ . Then we show that  $a_{it-1} - a_{it} \geq 0$  for all  $t \leq T$ . For the complete proof, refer to Appendix A.2.  $\square$

We use Proposition 4.3.1 to prove Theorem 4.3.1, which shows that the optimal policy from the BIP model is obtained by ranking patients in each epoch  $t$  by  $a_{it} - a_{it+1}$ . This result means that patients with the highest marginal risk reduction of CVD events between epoch  $t$  and  $t + 1$  should be prioritized first.

**Theorem 4.3.1.** *Let  $z$  be the optimal value of the BIP presented in Equations 6 to 9. If  $cT < n$ , then,*

$$z = \sum_{i=1}^c a_{i1} + \sum_{i=c+1}^{2c} a_{i2} + \cdots + \sum_{i=(T-1)c+1}^{Tc} a_{iT}.$$

*If  $n \leq cT$ , then let  $\gamma$  be a positive integer such that  $(\gamma - 1)c \leq n \leq \gamma c$ . Then,*

$$z = \sum_{i=1}^c a_{i1} + \sum_{i=c+1}^{2c} a_{i2} + \cdots + \sum_{i=(\gamma-1)c+1}^n ca_{i\gamma}.$$

*Where patients are sorted as follows: For any particular epoch  $t < T$ , patient  $i$  is prioritized over patient  $j$  if  $a_{it} - a_{it+1} \geq a_{jt} - a_{jt+1}$ . For epoch  $t = T$ , patient  $i$  is prioritized over patient  $j$  if  $a_{iT} \geq a_{jT}$ .*

*Proof.* : We prove the theorem by induction. We define a Markov decision process (MDP) model that represents the BIP formulation. For each epoch  $t$ , we use the MDP model to prove that the optimal value is reached when the patients are sorted by  $a_{it} - a_{it+1}$  for all epochs  $t$  to  $T - 1$ . For epoch  $T$ , the patients are sorted by  $a_{iT}$ . For the complete proof, refer to Appendix A.3.  $\square$

The result of Theorem 4.3.1 yields an easy-to-apply policy based on ranking and selecting the patients from highest to lowest total CVD event reduction at each epoch. We will refer to this solution as the *BIP policy*. It is important to note that this policy implies the decision-maker makes decisions at epoch 1, assuming no changes in the relative ordering of patients at each future epoch. This may or may not be true depending on observations over the course of the time horizon. In the next section, we propose an adaptive heuristic motivated by the BIP policy that uses the DLR model of Section 4.3.1. Additionally, we introduce alternative patient-intervention assignment decision rules with which we will compare our adaptive heuristic.

### 4.3.3 Patient-intervention decision rules

In this section, we propose two rules motivated by the BIP policy and the DLR model and compare their results versus a standard rule used in practice. (1) The *standard rule* represents a plausible

approach used by healthcare providers in which they prioritize patients with higher risk first. (2) The first rule that we propose is to prioritize patients using the BIP policy without DLR (*BIP Rule*), as discussed in the previous section. (3) The second rule we propose is prioritizing using the BIP policy and updating the adherence probabilities using the DLR model (*BIP-DLR rule*). For each of these rules, we assume that in each epoch, we have access to  $CVD_{it}$ , define as the CVD risk for patient  $i$  in epoch  $t$  as seen in the data.

We first start describing how the standard rule operates. From the pool of patients, we only consider patients for selection if their PDC is lower than 80% at a given epoch and they are not on intervention. Because there is a finite capacity for the intervention, we sort patients by CVD risk. After each intervention, we update each patient’s adherence depending on: (1) if the patient was intervened or not, (2) the intervention worked, and (3) the pharmacy claims data between epochs. We present the rule in Algorithm 1.

---

**Algorithm 1** Standard Rule

---

```

1: procedure ASSIGNMENT
2:   Patients  $\leftarrow$  Patients information: adherence and CVD risk
3:   for  $t=1$  to  $T$  do
4:     Patients =  $Sort(Patients)$   $\leftarrow$  Sort non-adherent patients by CVD risk (decreasing)
5:      $int = 0$ 
6:     for  $i=1$  to  $P$  do
7:       if  $int < c$  then
8:          $S_{it} = 1$ 
9:          $int = int + 1$ 
10:      else
11:         $S_{it} = 0$ 
12:      end if
13:    end for
14:    Patients =  $Update(Patients, t, S_{..})$   $\leftarrow$  Update patients adherence and risk
15:  end for
16: end procedure

```

---

For the first proposed rule, the BIP rule, we run the logistic regression once to estimate the adherence for future epochs 1 to  $T$  without applying the updating of the DLR model. This regression, without the updating, outputs the probabilities that will be used in the BIP formulation. Therefore we choose the patients with the highest  $a_{it} - a_{it+1}$  for each epoch  $t$ , estimated as  $r\hat{y}_{i(t-1)}(CVD_i - a_{it})$ , as shown in Proposition 1. Notice that we use  $CVD_{i1}$ , as we only have access to the current CVD risk when we run the BIP model. Also,  $\hat{y}_{it}$  represents the output probabilities from the standard regression model based on historical data. We present this rule in Algorithm 2.

Finally, the BIP-DLR rule consists of an adaptive heuristic that runs the DLR model to update adherence probabilities at each epoch and then applies the policy obtained from Theorem 1. In

---

**Algorithm 2** BIP Rule

---

```
1: procedure ASSIGNMENT
2:   Patients  $\leftarrow$  Patients information: adherence and CVD risk
3:   Prediction =  $LR(\text{Patients}, t)$   $\leftarrow$  Logistic regression model output using historical data
4:    $A = \{a_{it}\}$   $\leftarrow$  Estimate  $a_{it}$  for all patients and for all  $1 \leq t \leq T$ 
5:   Patients =  $Update(\text{Patients}, A)$   $\leftarrow$  Update the patients information with A
6:   for t=1 to T do
7:     Patients =  $Sort(\text{Patients})$   $\leftarrow$  Sort patients by  $a_{it} - a_{it+1}$ (decreasing)
8:      $int = 0$ 
9:     for i=1 to P do
10:      if  $int < c$  then
11:         $S_{it} = 1$ 
12:         $int = int + 1$ 
13:      else
14:         $S_{it} = 0$ 
15:      end if
16:    end for
17:    Patients =  $Update(\text{Patients}, t, S_{..})$   $\leftarrow$  Update patients adherence and risk
18:  end for
19: end procedure
```

---

this algorithm, we re-estimate  $a_{it}$  after updating the adherence probabilities with the DLR model at each epoch. Notice that at each step  $t$  we only need to update the coefficients from epoch  $t$  to  $T$ . We present the rule in Algorithm 3.

We next introduce the simulation model used to test the three intervention rules.

---

**Algorithm 3** BIP-DLR Rule

---

```
1: procedure ASSIGNMENT
2:   Patients  $\leftarrow$  Patients information: adherence and CVD risk
3:   for t=1 to T do
4:     Prediction =  $DLR(\text{Patients}, t) \leftarrow$  DLR output using data until t-1
5:      $A_t = \{a_{it}\} \leftarrow$  Estimate  $a_{it}$  for all patients and for all  $t \leq \tau \leq T$ 
6:     Patients =  $Update(\text{Patients}, A_t) \leftarrow$  Update the patients information with  $A_t$ 
7:     Patients =  $Sort(\text{Patients}) \leftarrow$  Sort patients by  $a_{it} - a_{it+1}$  (decreasing)
8:      $int = 0$ 
9:     for i=1 to P do
10:      if  $int < c$  then
11:         $S_{it} = 1$ 
12:         $int = int + 1$ 
13:      else
14:         $S_{it} = 0$ 
15:      end if
16:    end for
17:    Patients =  $Update(\text{Patients}, t, S_{..}) \leftarrow$  Update patients adherence and risk
18:  end for
19: end procedure
```

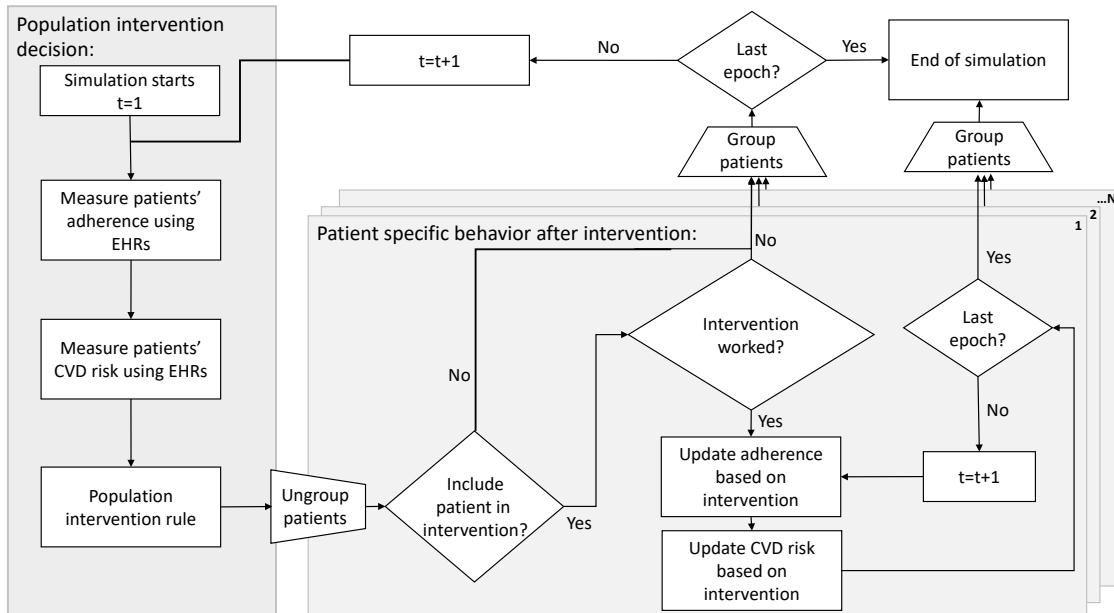
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#### 4.3.4 Simulation model

We developed a simulation model to assess the potential benefits of using the BIP-DLR rule to assign a limited number of patients to an adherence-improving intervention based on a hypothetical budget constraint. To initialize the simulation, we define year  $t$  as a clinical decision maker's decision point. We divided the data into two sets, before  $t$  (the past) and  $t$  onward (the future). The data set before year  $t$  is used to initialize a logistic regression model. We update the DLR model to predict future adherence at each future time period. We compare alternative resource allocation algorithms (described in the previous section) to assign limited interventions to patients using factors that include future predicted adherence. We continue with the assumptions presented regarding how the intervention works for this model. Nevertheless, we relax the assumption that the patient is only selected once for the intervention. For the simulation model, we assume that patients not selected for intervention or if previous interventions did not work will be available to be selected again for future periods with the same success probability  $q$ . This relaxation is given such that patients have future opportunities to be included in an intervention again. On the other hand, patients with a successful intervention will not be selected again, as they are assumed to adhere to medications. We continue this iterative process until the last simulated epoch  $T$ . This relaxation is included within the three rules presented in the previous section, where the pool of patients to select from includes patients that have not been selected for intervention or whose

previous interventions did not work. We present the simulation flowchart in Figure 4.2.

Figure 4.2: Simulation flow. The model simulates how the patient’s adherence and CVD risk behave depending on whether or not the patient is assigned to an intervention.



After selecting patients for intervention and updating the adherence if the intervention is successful, the epoch is updated to  $t + 1$ . We divide the EHR and claims data up to  $t + 1$  and after  $t + 1$ , with the difference that we do not include patients that had a successful intervention. We simulate a 5-year time horizon, where each year is considered an epoch. At each iteration, time advances by one year, where we update the patients’ risk using the EHR data if the patient is not on an intervention or update the risk using the risk reduction parameter if the patient is on an intervention and the intervention worked. To test the effectiveness of the intervention rules, we estimate the reduction in the number of CVD events after the simulated intervention horizon. To estimate the number of events, we calculate the absolute 10-year CVD risk for each patient after the simulation and the number of CVD events after ten years. We compare the model’s results versus when no adherence-improving intervention exists.

## 4.4 Results

This section presents the case study, the results of the DLR model, the patient-intervention decision rules, and the simulation model. We initialize the DLR model by estimating a standard logistic regression model on a training set to calibrate our model, then estimate the prediction for the studied time horizon, and finally simulate the patients' CVD risk with and without the prediction.

### 4.4.1 Case study

We used a longitudinal data set of randomly selected patients seen in the national Veterans Affairs (VA) health system between 2003 and 2018. The data set was based on a cohort of 10,000 patients sampled from the national VA population. We included patients with at least one year on statins, without diabetes, and without any previously diagnosed heart disease or related conditions. Using these selection criteria yielded 3753 patients with data between 2003 to 2018, between the ages of 40 to 80 years old.

Covariates included demographics, medical health factors, blood pressure and cholesterol levels, and observation dates. Within demographics, we consider sex, race, smoking habits, and age. The smoking status was assumed to be constant throughout the study, as we only had access to the patient's smoking status at the beginning of the study. We considered low-density lipoprotein cholesterol (LDL), total cholesterol, and systolic blood pressure (SBP) as medical health factors. We considered the number and dates of cholesterol tests and blood pressure tests. Finally, we used pharmacy claims data (start date, pill quantity, and refill dates) to compute the PDC, estimated as the percentage of the number of days with medication over the total number of days between refills quarterly [11]. We estimated the PDC quarterly as the American College of Cardiology suggests that patients on treatment be seen at least every three months[1]. Using a common assumption in the literature, we defined a patient as adherent in a given quarter if their PDC was greater than or equal to 80%; otherwise, they were considered non-adherent [11].

We present an overview of the study population in Table 4.2. Most of the population is comprised of white male patients (70% of the population), followed by black men (20%), then white women (6.5%), and finally, black women (2%). Within the data, other races represent less than 1% of the data points and are not differentiated. For this reason, we focused on the four patient groups mentioned before. The sex, race, and smoking habits data represent the number of patients with each characteristic. For age, PDC over the time horizon, blood pressure, and cholesterol, we estimated the mean and standard deviation of the population for adherent and non-adherent patients. Finally, the number of cholesterol and blood pressure tests represents the average per patient of the number of tests they take throughout the study period of 5 years. In summary, Table 4.2 shows that non-adherent patients tend to be younger, have fewer cholesterol and blood pressure tests, and

Table 4.2: Baseline characteristics of the population. We divide the patients based on their lifetime adherence behavior.

Characteristic	Mean ( $\pm$ SD) or No.(%)		P
	Non-adherent patients	Adherent patients	
n	1569	2095	
Sex			0.001
Male	1430 (91.1%)	1973(94.2%)	
Female	139 (8.9%)	122 (5.8%)	
Race			<0.001
White	1196 (76.2%)	1842 (87.9%)	
Black	373 (23.8%)	253 (12.1%)	
Smoking Habits			0.026
Smoker	372 (23.7%)	431 (20.6%)	
Non-smoker	1197 (76.3%)	1664 (79.4%)	
Age	59.22 (11.76)	63.84 (11.05)	<0.001
Percentage Days Cover	63% (15%)	90% (5%)	0.79
Blood Pressure			
SBP	129.90 (9.71)	128.99 (8.72)	0.003
Number of tests	34.03 (33.54)	42.40 (47.16)	<0.001
Cholesterol			
LDL	123.06 (28.76)	103.54 (23.60)	<0.001
Total Cholesterol	199.09 (33.13)	177.08 (29.92)	<0.001
Number of tests	10.99 (7.11)	14.22 (7.25)	<0.001

have higher LDL and total cholesterol.

#### 4.4.2 Logistic regression initialization and covariates

The initial logistic regression at the start of the time horizon comprises three types of covariates: random effects, categorical covariates, and numerical covariates. The random effects are represented within the intercept term, which is significant regarding the probability that a patient does not adhere to medication. This denoted intrinsic behaviors regarding each patient, which are not evaluated by any other variables. Regarding past adherence, the study includes patients with at least one year on medication. Therefore, there is always enough history to predict future adherence.

Table 4.3: Coefficients for the logistic regression for historical data. We also present the variance inflation factors (VIF) to test for multicollinearity.

Covariate	Estimate	Std. Error	P-value	VIF
Intercept	3.449	0.545	<0.001*	
Sex	-0.285	0.195	0.144	1.04
Race	-0.324	0.121	0.013*	1.03
Smoking habits	0.062	0.100	0.541	1.06
Age	$4.22 \times 10^{-3}$	$3.91 \times 10^{-3}$	0.280	1.24
Blood Pressure				
SBP	$7.69 \times 10^{-5}$	$2.77 \times 10^{-3}$	0.978	1.03
Number of tests	0.105	0.033	0.001*	1.06
Cholesterol				
LDL	$5.55 \times 10^{-3}$	$2.42 \times 10^{-3}$	0.022*	4.22
Total Cholesterol	$1.37 \times 10^{-3}$	$2.05 \times 10^{-3}$	0.51	4.29
Number of tests	-0.093	0.071	0.191	1.14
Percentage days cover				
1st Quarter	-0.755	0.136	<0.001*	2.71
2nd Quarter	-0.707	0.149	<0.001*	3.06
3rd Quarter	-0.190	0.149	0.204	3.11
4th Quarter	-0.420	0.152	0.006*	3.09
5th Quarter	-0.296	0.151	0.049*	3.02
6th Quarter	-0.091	0.148	0.541	2.94
7th Quarter	-0.221	0.146	0.130	2.78
8th Quarter	-0.033	0.133	0.807	2.30

Table 4.3 presents the coefficients of the logistic regression model. Additionally, we calculated the variance inflation factors (VIF) to test for multicollinearity. We noticed that cholesterol LDL and total cholesterol have a VIF greater than 4, and the PDC also has larger VIF values, between 2.3 and 3.1. We further estimated the correlation between the coefficients (see Figure A.3 in Appendix A.4). The high VIF values for LDL and total cholesterol are due to the high correlation (0.87)



between these covariates. This correlation is explained as the total cholesterol is estimated from LDL via Friedewald's equation [131]. On the other hand, the high correlation between the different quarters of PDC shows an autocorrelation behavior for adherence, between 0.57 and 0.74. Notably, the correlation decreases with respect to time between PDC estimates, indicating that the value of PDC history decreases over time. We can look at these results by studying which covariates are significant to forecasting future adherence.

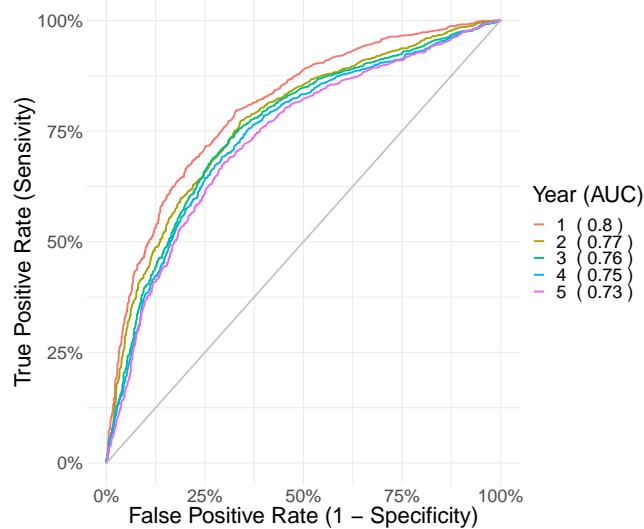
Regarding the categorical variables, Table 4.3 shows race is the only variable that affects the probability of not adhering. From our analysis, we note that black patients are associated with lower adherence to statins which has been observed in other studies as well [78] [68] [69].

Other statistically significant numerical covariates (based on a p-value threshold of 0.05) are the number of blood pressure tests from the beginning of the study until the current refill date, the LDL, and past percentage days covered (PDC) were significant variables related to not adhering to medication. There is a positive correlation between a higher LDL with non-adhering behavior. On the other hand, when patients take more blood pressure tests, they are more likely to stop adhering. Previous studies suggest this may be related to patients taking less medication when their test results show that their health has improved [11]. Finally, we noticed that the patient's PDC behavior from the last year and a half dramatically affects the probability of not adhering, whereas, at a high previous PDC, the probability of not adhering to medication decreases. It is worth noting that prior PDC behavior from more than a year and a half affects less the current adherence. This result suggests that a moving time window with a year and a half of prior history is sufficient to predict the likelihood that a patient will stop adhering.

### **4.4.3 Dynamic logistic regression**

After estimating the initial logistic regression covariates, we run the DLR model to forecast the probability that patients do not adhere over the next five years. We needed sufficient data to include the patients' random effects in the model. From the data set, which comprises data between 2003 to 2018, we assigned observational data from 2009 and before to be the training set. Therefore, the testing set consisted of data from 2010 onwards, so we have sufficient data for the 5-year rolling time horizon. We define a patient as not adhering if, at least for two quarters within a particular year, the patient does not adhere. Additionally, we test the DLR model using different values for the adherence threshold. We test the model using the base case threshold of 80% for adherence and estimate the AUC, as shown in Figure 4.3. We perform sensitivity analysis with respect to this base case, as shown in Appendix A.4 Figure A.4. We performed a 3-fold cross-validation to validate the results, dividing the patients into three groups and estimating the average AUC. We present these results as the healthcare provider may use a different threshold based on the evaluated panel [11].

Figure 4.3: ROC and AUC curves. We present the ROC and AUC for each of the five forecasting years for an adherence threshold of 0.8



For the first year, the average AUC ranges from 79% to 84%, depending on the threshold chosen. The AUC decreases when forecasting for more years into the future, whereas, for the fifth year, the AUC ranges from 71% to 74%.

We also measured how many patients the model forecasts correctly. We assume the decision-maker desires the logistic regression threshold that maximizes the model’s accuracy. Therefore, we estimated the percentage of true positives, true negatives, false positives, and false negatives for the population, as shown in Figure 4.4.

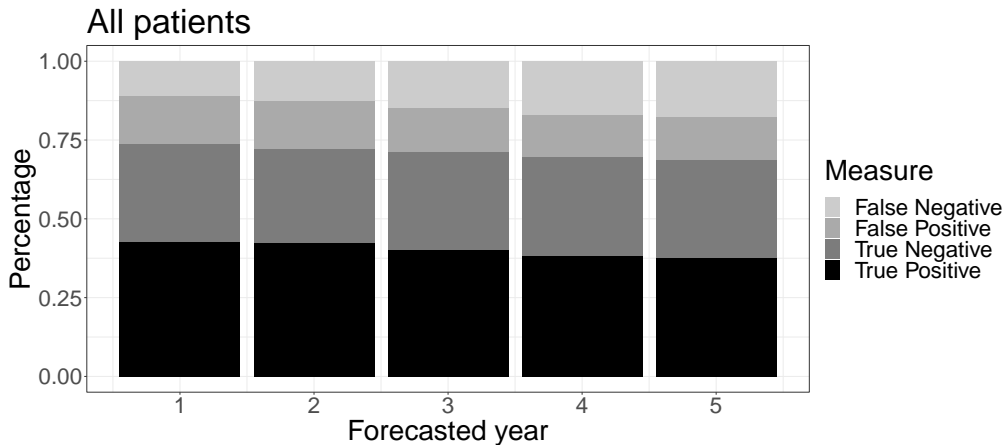
The model correctly forecasts 75% of the patients for the first year and decreases to 70% for the fifth year. This result shows that the model accuracy decreases when forecasting more years into the future.

As the forecast model is intended to help healthcare providers decide which patients to include in an intervention, we focus on the percentage of false negatives. False negatives represent the portion of patients who stop adhering but for whom the model forecasts that they will adhere. Therefore, these are patients not considered for intervention. The percentage of false negatives ranges between 11% for one year to 17% for five years.

#### 4.4.4 Simulation results

We simulated the panel of patients consisting of 3753 patients from the VA population present in the case study. We apply each patient-intervention decision rule, assuming published estimates for adherence-improving interventions as shown in Table 4.4. As the available capacity may change

Figure 4.4: Forecast performance measurements by forecast year. For each forecast year, we present the false negative, false positive, true negative, and true positive percentages. In summary, the accuracy decreases when forecasting a later year.



depending on the intervention, we analyze how our model performs depending on different values.

Table 4.4: Parameters estimates for the simulation model. The success of an intervention depends on the type of intervention provided to the patients. We present the range of each parameter when using the most common interventions.

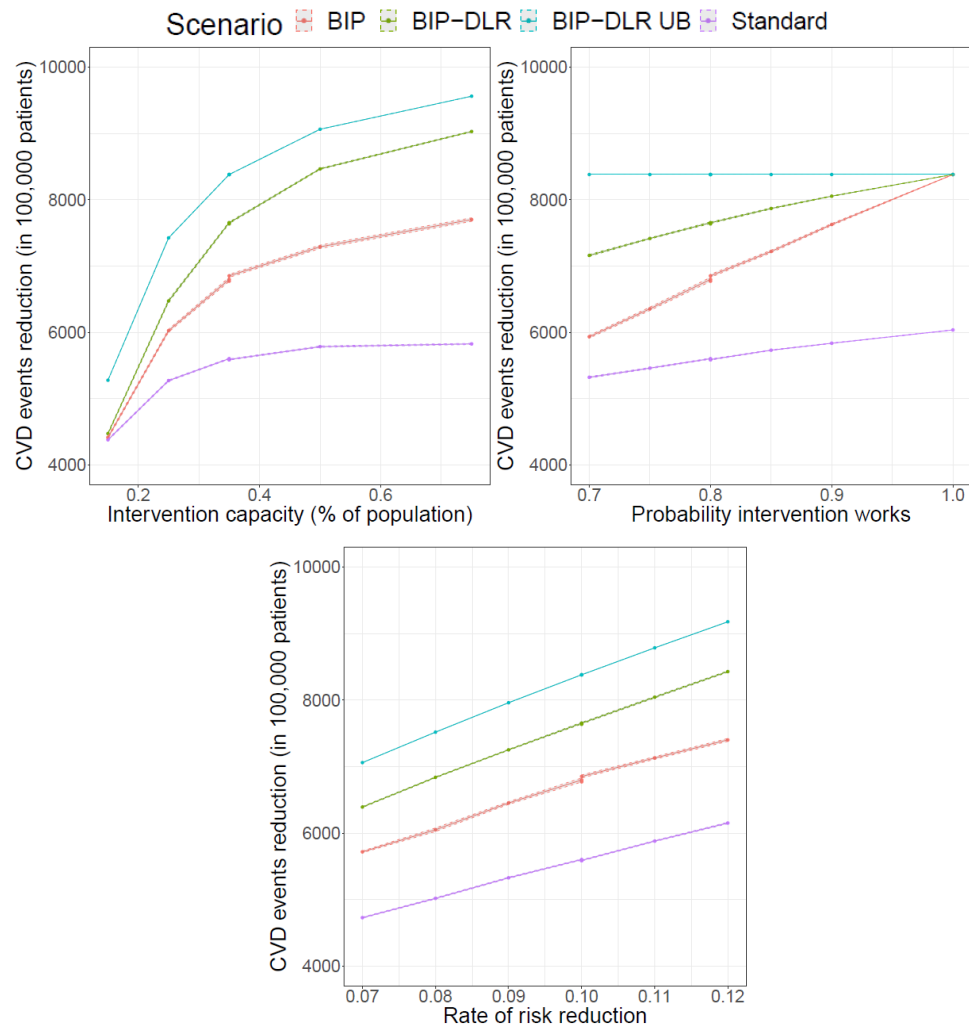
Notation	Description	Value	Reference
$q$	Probability of success of the intervention	70% to 90%	[12]
$r$	Adherence effect on risk reduction	7% to 12%	[19]

Additionally, we analyze the scenarios where the intervention capacity is between 15% to 75% of the population per year. We assume that the average capacity of 35% of the population can be allocated and a probability of 80% that the intervention works. We validate the model by comparing the simulation output risk without intervention, i.e., when the capacity of the intervention is 0. As there is no intervention, we update the patients based on available data. Therefore, the confidence intervals are 0, as no stochastic behavior is added to the model. The VA population average risk is 17%, while the simulation output is  $17.5\% \pm 0\%$ , hence validating the model. This represents that 17,500 patients, in a population of 100,000, will have a CVD event in the next ten years if there is no adherence-improving intervention.

We simulate the three patient-intervention decision rules, standard rule, BIP rule, and BIP-DLR rule. Additionally, we add an upper bound to the BIP-DLR rule (BIP-DLR-UB), in which we assume the probability that the intervention works is 1. This scenario represents the best-case scenario so that we can analyze the effectiveness of the BIP-DLR algorithm. Additionally,

we performed a sensitivity analysis, changing the capacity of the intervention, the probability of success, and the risk reduction. We present the sensitivity analysis in Figure 4.5.

Figure 4.5: Sensitivity analysis. We studied how the intervention capacity, the probability that intervention works, and CVD risk reduction for patients in intervention affect each of the selection rules. We estimate the number of CVD events reduction in a population of 100,000 patients.



When using the base case parameters, we see that the standard rule reduces the number of CVD events by  $5610 \pm 8.2$  in a population of 100,000 patients compared to not having adherence-improving interventions. Applying the BIP rule further reduces the number of CVD events by  $1190 \pm 28.86$  compared to the standard rule. Finally, when adding the DLR model, the BIP-DLR rule further reduces the number of CVD events by approximately 700 more, for a total of  $1890 \pm 12.63$  CVD events compared to the standard rule. This result shows that the BIP-DLR rule

can reduce the number of CVD events by 36.5% compared to the standard rule.

Analyzing how the intervention capacity affects the rules, we notice that when it increases, the difference increase furthermore between the three rules. This result shows that selecting patients by the marginal difference in risk has better performance than selecting by the patient’s current CVD risk. Additionally, updating the adherence probabilities with the DLR model improves the results furthermore. With respect to the probability that the intervention succeeds, we notice that when it is closer to 1, there is no difference between using or not using the DLR model. This result is explained given that when the probability increases, the need to look into further periods in the future diminishes and it is only necessary to look into the marginal difference in risk between the current and next epoch. Finally, we see that the rate of risk reduction does not affect the difference between the rules.

As mentioned in Section 4.3, Theorem 4.3.1 proposes an algorithm for estimating the BIP optimal solution. Nevertheless, as shown in Figure 4.5, the difference between the BIP-DLR rule and the upper bound is less than the reduction that the rule already offers. This result acknowledges that using the BIP and DLR models together offers excellent results.

## 4.5 Discussion

We developed a DLR model that forecasts adherence for multiple years into the future. Our model determined the probability that the patient would stop adhering. Compared to the prior literature discussed in Section 4.2, our approach further relaxed the assumption that adherence follows a specific behavior from a pool of defined trajectories. We incorporated random effects into our model, including patients’ healthcare background, lifestyle, and access to healthcare, which is novel in the adherence forecasting literature. We also included the adherence history as a covariate, improving from previous studies that suggest including only the last measurement of adherence [104]. We found that including a year and a half of past adherence behavior, between 4 to 6 measurements, has a low prediction error, and including more history does not significantly improve the accuracy. Therefore, healthcare systems only need to store a year and a half of data to use this forecasting approach, reducing the computing time and data requirements.

We tested the DLR model with longitudinal data for cholesterol and blood pressure of a cohort of 10,000 randomly selected patients seen in the Veteran Affairs health system. The AUC ranged from 79% to 84% for the first year, depending on the PDC threshold chosen. Then, the AUC range decreased year by year until getting from 71% to 74% for the fifth year, depending on the PDC threshold chosen. Our model false positive measure tends to remain constant when predicting different years into the future. Therefore, the error of choosing patients for intervention when they do not need it is always relatively low, increasing the chances that patients that benefit the most

from the interventions are chosen first.

We developed a BIP model that selects patients from a heterogeneous population for interventions. Additionally, we estimated the marginal risk reduced when selecting a patient for intervention versus waiting for the next intervention cycle. We proved that the BIP optimal policy is equivalent to sorting patients by the marginal risk reduced and selecting patients from highest to lowest until the intervention capacity is depleted. Thus, the BIP has a simple polynomial time solution for this special case of the multiple knapsack problem.

We simulated the application of DLR within the BIP when deciding which patients to include in an increase-adherence intervention. Applying the adaptive heuristic that includes the BIP and DLR models reduces the number of CVD events by 36.5% compared to a base case rule of sorting patients by their current risk. This result shows that adaptive approaches successfully capture adherence dynamics that fluctuate over time.

We understand that our model has some limitations, mainly on the population we are using. The VA data set corresponds to patients with better access to healthcare, tend to have more frequent follow-ups, and have higher adherence to medication [78]. Additionally, the VA population primarily corresponds to white and black male patients; unfortunately, we cannot access information about other races or ethnicities. Nevertheless, our model shows that the forecast has similar outcomes to other demographic groups. Therefore, a population with less access to healthcare will benefit from a more significant risk reduction, as the intervention will improve health benefits. Additionally, we understand that using PDC to estimate adherence implies the assumption that patients take all the refilled medication. We also assume adherence patterns are similar for the various types of statins. Most authors agree that questionnaires, constant surveillance, and electronic pill counts are the most effective to measure adherence [132] [133]. However, gathering information for these methods is costly [134], and usually, healthcare providers have access to medication refill dates. Finally, we apply a BIP model that estimates the expected risk reduced, which may hide the variability behind the adherence behavior and the intervention success. Nonetheless, dynamically updating the BIP helps capture this variability and gives healthcare providers a starting point to improve the selection of patients for adherence-improving interventions.

## 4.6 Conclusions

After the first year on medication, only 50% of the patients will adhere, increasing the risk of cardiovascular diseases. This adherence behavior changes over time, and healthcare providers must identify when patients will stop adhering to prevent further complications. Different adherence-improving interventions exist, where the most efficient ones have a limited capacity. Therefore, healthcare providers need to choose patients for intervention to mitigate future low adherence. Our

study shows that using DLR models with random effects can potentially alert healthcare providers to which patients will stop adhering. Additionally, the forecast supports decisions associated with which patients should be included in increase-adherence interventions. We propose an adaptive heuristic that combines a BIP model with the DLR model to select patients. We prove that to minimize the number of CVD events in the population, healthcare providers need to select patients with the highest marginal risk reduced. Thanks to our adaptive heuristic, physicians' time and intervention-associated resources are better utilized relative to the patients' future adherence behaviors. Therefore, patients will receive timely support, increasing medication effectiveness and improving overall health.

Future work might consider improving the patient selection model by defining a dynamic stochastic model that includes the DLR prediction and the patients' health stochastic behavior. Our adaptive heuristic provides a starting point to investigate some of these approaches and further decrease the number of CVD events in the population. Additionally, we understand that our studied population has certain characteristics that differ from the general population. We propose to analyze the model's accuracy with a different population mix as a natural next step. Finally, our model assumes that the probability of the intervention working and the adherence effect on risk reduction is the same for all patients. The surveyed studies on adherence interventions analyze the overall effects of successful interventions on patients. Therefore, we recommend updating the patient selection model with studies that analyze the differences between patients regarding intervention success. Testing the model with data that has constant adherence follow-up or electronic pill count may increase the forecast accuracy. Finally, our approach could find applications in multiple diseases that rely on adherence to medication for long periods.

## CHAPTER 5

### Conclusion and Future Work

Access to electronic health records has created opportunities to understand how patients' health conditions change over time by analyzing the disease progression and developing strategies to prevent them. This research created operations research methods to (1) monitor and identify patients at high risk of suffering cardiovascular disease (CVD) events and (2) prevent adverse events by prioritizing patients for adherence-improving interventions. The research in this dissertation establishes the analytical and theoretical foundation for building stochastic models that help understand disease progression and prevent cardiovascular diseases.

In Chapter 2, we developed an EM algorithm that is able to use sparse longitudinal data and correctly fit cholesterol and blood pressure behaviors into Markov chains. Additionally, we developed a discrete-time Monte-Carlo simulation framework used to test policies throughout our research. We tested the simulation framework by comparing multiple treatment guidelines for cholesterol and blood pressure-lowering medications. We concluded that guidelines focusing on reducing CVD risk could also reduce treatment overuse without increasing the potential risk of having a disease.

In Chapter 3, we presented a finite-time and finite-state MDP model to recommend to patients when to take their next cholesterol test. This model's objective is to maximize the societal rewards, which include the costs of appointments, costs of treatment, cost of cardiovascular events, and the patient's willingness-to-pay to be healthy. The resulting MDP-based policies suggest that including the patient's age, sex, and race improves the societal rewards by \$28.5 billion for the VA system compared to existing one-size-fits-all policies.

Finally, In Chapter 4, we developed a dynamic logistic regression model which estimates the probability that a patient will stop adhering in multiple periods. We proposed a binary integer programming (BIP) that selects patients for intervention with the purpose of maximizing the total reduction of the number of CVD events. Given that solving the BIP model to optimality is NP-hard, we provided an algorithm that uses the dynamic logistic regression (DLR) probabilities to reduce the CVD events. Our approach results in approximately 1,900 fewer heart attacks and strokes, in



a population of 100,000 patients seen in the Veteran Affairs health system, compared to current prioritization rules.

In the following sections, we discuss how future work can extend our analysis and modeling frameworks.

## 5.1 Achieving health equity

The Center for Medicare and Medicaid Services in the U.S. estimates that healthcare spending represents 18.3% of the GDP and will continue to be the same until 2030 [135]. Health equity has yet to be achieved as access to healthcare in the U.S. differs vastly across groups. Since healthcare spending cannot be further increased, new ways must be considered to increase equity. We proceed to describe two potential research directions: 1) data-driven models to understand patient compliance for underrepresented populations and 2) equitable models for distributing limited resources.

According to the CDC, health equity is reached when “every person has the opportunity to attain their full health potential, and no one is disadvantaged from achieving this potential because of social position or other socially determined circumstances” [136]. Therefore, increasing health equity means better health outcomes from equitable access to prevention, treatment, and interventions.

When building mathematical frameworks to improve patient outcomes, health equity requires precise model performance, fair resource allocation, and aiming toward better health outcomes throughout patients’ lifetimes [12]. Precise model performance is obtained when models correctly fit the patients’ health behavior, even for underrepresented subgroups within the population. Fair resource allocation represents that resources are distributed based on patients’ needs. Aiming toward better outcomes means that all patients achieve their health potential while accounting for socially and demographic diverse patient populations. Increasing equity and reducing disparities is more challenging when you must account for resource allocation over time and under conditions of uncertainty, which is typical for chronic diseases.

Medical decision-making models need to pay more attention to the importance of equity and diversity in measuring success and intervening to improve patient outcomes. In Chapters 2 and 4, we focused on improving the models’ performance by analyzing how to fit the patient’s disease progression. Additionally, in Chapters 3 and 4, we started looking into resource allocation with our patient selection model for adherence-improving interventions. We consider these contributions as foundations to work towards health equity in this field.

### 5.1.1 Data-driven models for patient compliance

High-risk patients do not comply with physicians' recommendations for different reasons, such as misconceptions about their health, access to healthcare, and side effects. Besides treatment adherence, patients might not comply with other physicians' recommendations, which directly affects the gathering of health data, such as appointment dates, laboratory tests, and screenings. These patients assume they are healthy, mistrust their physicians, or it is enough for them not to spend additional resources such as time, money, and inconvenience. These socioeconomic variables, among others, are unmeasurable or unavailable due to patients' privacy. Unfortunately, having these patients means fewer data, increasing the prediction complexity and affecting underrepresented populations even more. In Chapter 2, we introduced the EM algorithm that can handle non-autocorrelated data. Nonetheless, when data has a time series behavior, we need new data-augmentation techniques and forecasting models [29].

There has been increased research on techniques to estimate future trajectories for time series with sparse data. For a short prediction horizon, ARIMA with Kalman smoothing models has high accuracy [137]. Nonetheless, when the prediction horizon increases, the accuracies decrease rapidly. For healthcare applications, it is uncommon to report and handle missing data in practice. Nonetheless, methods such as ARIMA, mixed effects, and generalized linear models have been used to forecast future health behavior from sparse data [138]. Due to their low accuracy, other methods, such as probabilistic principal components analysis, show excellent results when dealing with data missing at random [139]. Still, the accuracy decreases when the missing data happens for continuous multiple periods, which is common when patients stop adhering to physicians' recommendations. Therefore, there is a need to develop time series forecasting techniques that have high accuracy for long time horizons and feed from sparse data with continuous data missing. Finally, when new data is gathered, models can learn to dynamically increase the accuracy of the prediction to guide decision-making, as shown in Chapter 4. Nevertheless, dynamic logistic relations accuracy decreases when the historical data is insufficient. Deep learning techniques show excellent results when applied to blood glucose. Unfortunately, their accuracy decreases when exogenous and endogenous variables, such as socioeconomic factors, are included [140].

Future research may focus on unsupervised and supervised machine learning models, which can handle the discussed complexities. In particular, hierarchical models may offer the opportunity to complete information on underrepresented groups by estimating a joint probability distribution that captures the overall behavior of the population [141]. For healthcare, researchers use hierarchical models to understand diseases by classifying patients based on conditions, estimating the probability of future disease severity, and estimating the disease progression [142]. These models have been used for cardiovascular diseases to predict hypertension for different patient groups divided by sex and age [143]. Additionally, a time-varying approach has been used to understand how each

CVD event increases the death probability [144]. Therefore, future work could explore how these models could be used for subgroup analysis when there is limited data for some subgroups.

### 5.1.2 Sequential equity decisions under limited resources

Different equity objectives may counteract each other. Focusing on improving the overall patients' health may result in assigning more resources to younger and healthier patients to prevent chronic disease. As a result, this may draw resources away from older patients at risk of serious adverse outcomes of chronic diseases. This example is one of many that illustrates the difficulty of achieving health equity and the complex tradeoffs that must be considered. Therefore, it is necessary to correctly define equity metrics and analyze their effects on the population. After defining these metrics, the challenge is to decide when to assign resources to each patient, acknowledging that the models must represent time-varying systems (disease progression and resource availability) under uncertainty. Additionally, it is important to include how patients respond to recommendations, as mentioned before, considered strategic decision-makers aiming toward their benefits. Future research may focus on the definition of equity metrics to represent different stakeholder needs and expectations with consideration of underserved and at-risk populations. Equity metrics tend to be non-linear, as they change depending on the patient background, the interactions within the population, and other reasons. These components add complexity to optimization models, which may be handled by developing sequential decision-making models with multiple criteria. These models will contribute by expanding the literature on multi-objective, multi-agent, and equitable sequential decision-making under limited resources. The outcomes of these models will assist healthcare providers in making equitable decisions that will benefit all subgroups within the population.

## 5.2 Prioritization models under uncertainty and with limited resources

In addition to addressing health equity, another key extension to the work presented in this dissertation is to add the patient's health behavior to the allocation models. This may be done by developing a finite-state and finite-time Markov decision process (MDP) model to include two new components: (1) the stochastic behaviors that are associated with the patients' disease progression and (2) the stochastic behaviors associated to the patients' compliance to physicians recommendations (i.e. adherence to medication), as follows:

**Epochs:** Let  $E := \{1, \dots, T\}$  be the set of epochs such that  $t \in E$  represents the instant in time when patients are selected for interventions.

**States:** Define  $s_{it}$  such that if  $s_{it} = 1$  then patient  $i$  was selected for intervention before  $t$ , and 0 otherwise. Define  $S_t$  as the vector that contains this information. Define  $R_{it}$  as the CVD risk of patient  $i$  at the start of epoch  $t$  and  $\mathbf{R}_t$  as the vector containing these CVD risks. Finally, define  $A_{it}$  such that if  $A_{it} = 1$ , then patient  $i$  adheres to medication at the start of epoch  $t$ , and 0 otherwise. Then  $\mathbf{A}_t$  is the vector that contains the patients' adherence information.

**Decisions:** Define  $\mathcal{D}_t$  as the set of feasible decisions to make in epoch  $t$ . If  $\mathbf{d}_t \in \mathcal{D}_t$ , then  $\mathbf{d}_t$  is a vector of size  $n$  where  $d_{it} = 1$  if patient  $i$  is selected for intervention in epoch  $t$  and 0 otherwise. Additionally, if  $s_{it} = 1$ , then  $d_{it} = 0$  such that  $\sum_i d_{it} \leq c \forall i, t$ .

**Transition Probabilities:** We define  $p_{R_i}(r_i|R_{it}, A_{it}, s_{it}, d_{it})$  as the probability that in epoch  $t + 1$  patient  $i$  has risk  $r_i$  given that in epoch  $t$ , the patient had risk  $R_{it}$ , they adhere or not to medications, was selected or not for intervention before epoch  $t$ , and the decision  $d_{it}$ . We also define  $p_{A_i}(a_i|A_{it}, s_{it}, d_{it})$ , where if  $a_i = 1$ , as the probability that in epoch  $t + 1$  patient  $i$  adheres to medication given the current adherence behavior if the patient was selected or not for intervention before starting epoch  $t$ , and the decision  $d_{it}$ , and  $a_i = 0$  otherwise. Notice that if  $s_{it} = 1$  then  $p_{A_i}(1|A_{it}, s_{it}, d_{it}) = 1$ . Finally, we define  $p_{I_i}(s_i|s_{it}, d_{it})$ , where if  $s_i = 1$ , as the probability that the intervention works for patient  $i$  if the patient was selected or not for intervention before starting epoch  $t$ , and the decision  $d_{it}$ , and  $s_i = 0$  otherwise. Notice that if  $s_{it} = 1$ , then  $p_{I_i}(1|s_{it}, d_{it}) = 1$ .

As every single patient evolves independently, we can assume that the stochastic behaviors are independent of each other. We define  $p_t(\mathbf{S}_{t+1}, \mathbf{R}_{t+1}, \mathbf{A}_{t+1}|\mathbf{S}_t, \mathbf{R}_t, \mathbf{A}_t, \mathbf{d}_t)$  as the transition probabilities given by the patients selected for intervention, and estimated this value as follows:

$$p_t(\mathbf{S}_{t+1}, \mathbf{R}_{t+1}, \mathbf{A}_{t+1}|\mathbf{S}_t, \mathbf{R}_t, \mathbf{A}_t, \mathbf{d}_t) = \prod_i \left( p_{R_i}(r_i|R_{it}, a_i, s_i, d_{it}) p_{A_i}(a_i|A_{it}, s_i, d_{it}) p_{I_i}(s_i|s_{it}, d_{it}) \right). \quad (5.1)$$

**Immediate rewards:** The model objective is to minimize the number of CVD events by the end of the planning horizon. Therefore we assume that for all epochs  $t < T$ , the immediate rewards will be 0 and for  $\sum_i R_{iT}$  for epoch  $T$ .

Given the components of the MDP, define  $V_t(\mathbf{S}_t, \mathbf{R}_t, \mathbf{A}_t)$  as the total expected CVD events at the end of the planning horizon depending on the selection rule from  $t$  to  $T$ , where the Bellman's equations are as follows:

$$V_t(\mathbf{S}_t, \mathbf{R}_t, \mathbf{A}_t) = \min_{\mathbf{d}_t \in \mathcal{D}_t} \left\{ \sum_{A \in \mathbf{S}_{t+1}} \sum_{R \in \mathbf{R}_{t+1}} \sum_{A \in \mathbf{A}_t} p_t(S, R, A|\mathbf{S}_t, \mathbf{R}_t, \mathbf{A}_t, \mathbf{d}_t) V_{t+1}(S, R, A) \right\} \quad \forall t \in \mathbb{E} - \{T\}, \quad (5.2)$$

where the boundary conditions are  $V_T(\mathbf{S}_T, \mathbf{R}_T, \mathbf{A}_T) = \sum_i R_{iT}$ .

This MDP model suffers the curse of dimensionality, as when the number of patients increases, the number of feasible states and decisions also increases exponentially. However, one may study this problem as a restless multi-armed bandit model that considers resource restriction. Given that physicians may prioritize multiple patients in each period, one may focus on a particular bandit model called combinatorial multi-armed bandit (CMAB), where the literature has studied different algorithms to reach a nearly optimal result [145] [146] [147]. Most of these algorithms suggest ranking methods [148] [122]. Nevertheless, these algorithms assume that pulled arms (patient prioritized) always show results (Interventions always work), and not pulled arms will not change between epochs (non-restless bandits). Therefore there are opportunities to develop algorithms that include the patient’s adherence to recommendations. Future research may also focus on understanding how heuristics perform for different patient groups within the population in terms of health equity. Also, depending on the definition of equity, develop heuristics that builds towards improving equity between each patient group.

### 5.3 Concluding remarks

This dissertation applies operations research methods and develops policies to answer the following key challenges:

1. Understanding how the patient demographics influence the disease progression.
2. Developing sequential decision-making models under uncertainty that pursue the best health outcomes for individual patients.
3. Developing sequential decision-making models with limited resources to prevent chronic diseases for a population.

Our findings highlight important insights into identifying high-risk patients and preventing CVD. This research contributes to the operations research body of knowledge by developing forecasting models using sparse longitudinal data and proposing new approaches to model stochastic healthcare systems to improve medical treatment decisions and the allocation of adherence-improving interventions. While much work remains to be done, we hope this dissertation establishes the analytical and theoretical foundation for building stochastic models that assist in addressing future healthcare challenges.

# **APPENDIX A**

## **Appendix**

# A.1 Chapter 3: Additional graphs

Figure A.1: 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

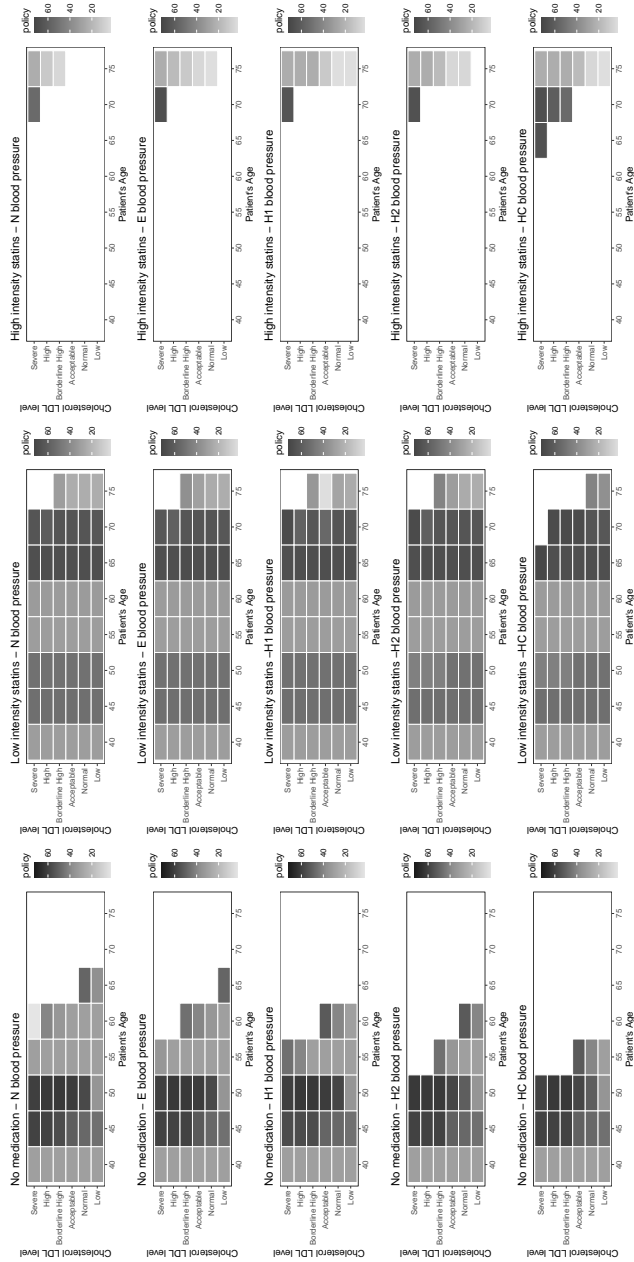
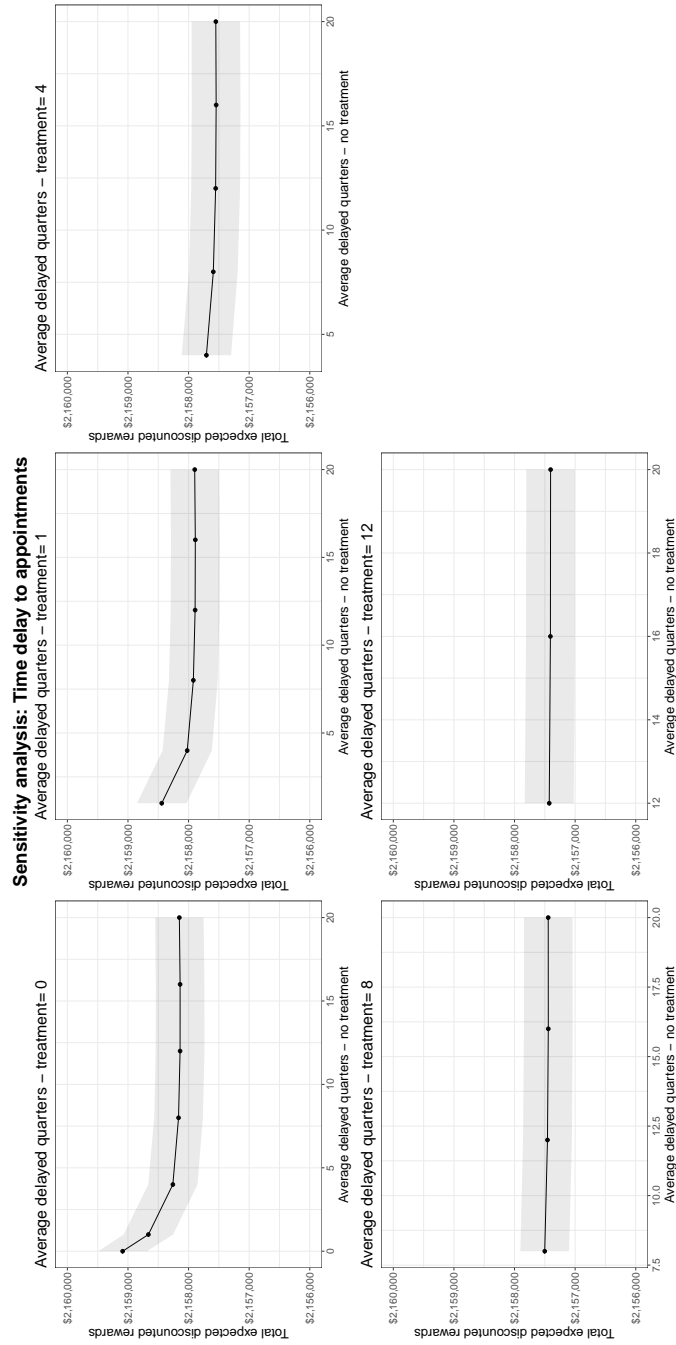


Figure A.2: Sensitivity analysis of the rewards when adding a time delay to the patient’s arrival at the next appointment. We present on the x-axis the average number of delayed quarters, where 0 represents 100% compliance from the patient. We show the rewards and the confidence interval. We present the scenarios where patients with treatments have a shorter delay than those with treatment.





## A.2 Chapter 4: Proof for Proposition 1

For any epoch  $t$ ,  $P_{it0} = (1 - \hat{y}_{it})(1 - \hat{y}_{it+1}) \cdots (1 - \hat{y}_{iT})$  and  $P_{i(t-1)0} = (1 - \hat{y}_{it-1})(1 - \hat{y}_{it}) \cdots (1 - \hat{y}_{iT})$ . Then,  $P_{i(t-1)0} = (1 - \hat{y}_{it-1})P_{it0}$ . For any  $\tau > 0$  and  $\tau < T - t + 2$ ,  $P_{i(t-1)\tau} = P_{it\tau}(1 - \hat{y}_{it-1}) + \hat{y}_{it-1}P_{it(\tau-1)}$ , as  $P_{it\tau}(1 - \hat{y}_{it-1})$  represents the probability that in  $\tau$  epochs the patient is non-adherent between  $t$  and  $T - t + 2$  and is adherent en  $t - 1$ , and  $\hat{y}_{it-1}P_{it(\tau-1)}$  represents the patient is non-adherent in  $\tau - 1$  epochs between  $t$  and  $T - t + 2$  and is non-adherent en  $t - 1$ . Finally,  $P_{i(t-1)(T-t+2)} = \hat{y}_{it-1}P_{it(T-t+1)}$ . Then the difference between  $a_{it-1}$  and  $a_{it}$  is estimated as:

$$\begin{aligned}
a_{it-1} - a_{it} &= CVD_i - q \sum_{\tau=0}^{T-t+2} P_{it-1\tau}(1-r)^\tau CVD_i - CVD_i + q \sum_{\tau=0}^{T-t+1} P_{it\tau}(1-r)^\tau CVD_i \\
&= q \sum_{\tau=0}^{T-t+1} P_{it\tau}(1-r)^\tau CVD_i - q \sum_{\tau=0}^{T-t+2} P_{it-1\tau}(1-r)^\tau CVD_i \\
&= qCVD_i \left( \sum_{\tau=0}^{T-t+1} P_{it\tau}(1-r)^\tau - \sum_{\tau=0}^{T-t+2} P_{it-1\tau}(1-r)^\tau \right) \\
&= qCVD_i \left( P_{it0} - (1 - \hat{y}_{it-1})P_{it0} - \hat{y}_{it-1}P_{it(T-t+1)}(1-r)^{T-t+2} \right. \\
&\quad \left. + \sum_{\tau=1}^{T-t+1} P_{it\tau}(1-r)^\tau - (P_{it\tau}(1 - \hat{y}_{it-1}) + \hat{y}_{it-1}P_{it(\tau-1)})(1-r)^\tau \right) \\
&= qCVD_i \left( \hat{y}_{it-1}P_{it0} - \hat{y}_{it-1}P_{it(T-t+1)}(1-r)^{T-t+2} \right. \\
&\quad \left. + \sum_{\tau=1}^{T-t+1} P_{it\tau}\hat{y}_{it-1}(1-r)^\tau - \hat{y}_{it-1}P_{it(\tau-1)}(1-r)^\tau \right).
\end{aligned}$$

By reorganizing the terms, the difference is estimated as:

$$\begin{aligned}
a_{it-1} - a_{it} &= qCVD_i \left( \hat{y}_{it-1} P_{it0} - \hat{y}_{it-1} P_{it0} (1-r) + \hat{y}_{it-1} P_{it1} (1-r) - \hat{y}_{it-1} P_{it1} (1-r)^2 \right. \\
&\quad \left. + \cdots + \hat{y}_{it-1} P_{it(T-t+1)} (1-r)^{T-t+1} - \hat{y}_{it-1} P_{it(T-t+1)} (1-r)^{T-t+2} \right) \\
&= qCVD_i \left( \hat{y}_{it-1} P_{it0} (1 - (1-r)) + \hat{y}_{it-1} P_{it1} (1-r) (1 - (1-r)) \right. \\
&\quad \left. + \cdots + \hat{y}_{it-1} P_{it(T-t+1)} (1-r)^{T-t+1} (1 - (1-r)) \right) \\
&= qCVD_i \sum_{\tau=0}^{T-t+1} r \hat{y}_{it-1} P_{it\tau} (1-r)^\tau \\
&= r \hat{y}_{it-1} q \sum_{\tau=0}^{T-t+1} P_{it\tau} (1-r)^\tau CVD_i \\
&= r \hat{y}_{it-1} (CVD_i - a_{it}).
\end{aligned}$$

Therefore, since  $r \hat{y}_{it-1} (CVD_i - a_{it}) \geq 0$ , it follows that  $a_{i1} \geq a_{i2} \geq \cdots \geq a_{iT}$ .  $\square$

### A.3 Chapter 4: Proof for Theorem 1

Define a Markov decision process (MDP) model with the following components:

- Epochs: Instant in time when patients are selected for interventions.
- States: Define  $s_{it}$  such that if  $s_{it} = 1$  then patient  $i$  was selected for intervention before  $t$ , and 0 otherwise. Define  $X_t^0$  as the set of patients who are available for interventions in epoch  $t$ , then if  $s_{it} = 0$ , then  $i \in X_t^0$ . Define  $X_t^1$  as the set of patients who are not available for interventions at the start of epoch  $t$ , then if  $s_{it} = 1$ , then  $i \in X_t^1$ .
- Decisions: Define  $D_t$  as the set of feasible decisions to make in epoch  $t$ . If  $\mathbf{d}_t \in D_t$ , then  $\mathbf{d}_t$  is a vector of size  $n$  where  $d_{it} = 1$  if patient  $i$  is selected for intervention in epoch  $t$  and 0 otherwise. Additionally, if  $i \in X_t^1$ , then  $d_{it} = 0$  such that  $\sum_i d_{it} \leq c \forall i, t$ .
- Transitions: If in  $t$ ,  $i \in X_t^0$  and  $d_{it} = 1$ , then  $i \in X_{t+1}^1$  and  $i \notin X_{t+1}^0$ . Otherwise, patient  $i$  will remain in  $X_t^0$  until the next epoch. Then we define  $\bar{w}^0$  and  $\bar{w}^1$  as the functions that represents the sets in  $t+1$ , such that  $X_{t+1}^0 = \bar{w}^0(X_t^0, \mathbf{d}_t)$  and  $X_{t+1}^1 = \bar{w}^1(X_t^1, \mathbf{d}_t)$ .
- Immediate rewards: The immediate rewards of taking decision  $\mathbf{d}_t$  in epoch  $t$  are estimated as  $\sum_{i \in X_t^0} a_{it} d_{it}$ .

Given the components of the MDP, define  $V_t(x_t^0, x_t^1)$  as the total maximal risk reduction from epoch  $t$  to epoch  $T$ , where the Bellman's equations are as follows:

$$V_t(x_t^0, x_t^1) = \max_{\mathbf{d}_t \in D_t} \left\{ \sum_{i \in X_t^0} a_{it} d_{it} + V_{t+1}(W^0(x_t^0, \mathbf{d}_t), W^1(x_t^1, \mathbf{d}_t)) \right\} \quad \forall (x_t^0, x_t^1), \forall t \in E - \{T\},$$

where the boundary conditions are  $V_T(x_T^0, x_T^1) = \max_{\mathbf{d}_T \in D_T} \left\{ \sum_{i \in X_T^0} a_{iT} d_{iT} \right\}$  for all  $(x_T^0, x_T^1)$ . This MDP is equivalent to the BIP in Equations 4.6 to 4.9, where the constraints are represented in the decision set. Therefore, the MDP's optimal value and policy are the same optimal value and solution of the BIP model.

Now we prove the theorem by induction. For epoch  $T$ , without loss of generality, the patients in  $X_T^0$  can be organized such that for all  $i$  and  $j$  where  $i \leq j$  we have that  $a_{iT} \geq a_{jT}$ . Then, the policy that maximizes the rewards is to choose the first  $c$  patients that belong to  $X_T^0$ , i.e., the first  $c$  patients with the highest values of  $a_{iT}$ .

For  $t = T - 1$ , define  $d_T^*$  as the optimal policy for epoch  $T$  and  $d_{T-1}^*$  as the optimal policy for epoch  $T - 1$ . Given the construction of  $D_T$  and  $D_{T-1}$  we know that if  $d_{iT-1}^* = 1$  then  $d_{iT}^* = 0$  and if  $d_{iT}^* = 1$  then  $d_{iT-1}^* = 0$ . Let  $n_{0T-1} = |X_{T-1}^0|$ , then, without loss of generality, assume that patients 1 to  $n_{0T-1}$  belong to  $X_{T-1}^0$  and patients  $n_{0T-1} + 1$  to  $n$  belong to  $X_{T-1}^1$  and are organized such that if  $i, j \in X_{T-1}^0$  and  $i < j$ , then  $\hat{y}_{it}(CVD_i - a_{iT}) \geq \hat{y}_{jt}(CVD_j - a_{jT})$ .

Let  $\mathbf{d}'_{T-1}$  be such that  $d'_{1T-1} = d'_{2T-1} = \dots = d'_{cT-1} = 1$  and  $d'_{(c+1)T-1} = \dots = d'_{nT-1} = 0$ . Also, let  $V'_{T-1}(x_{T-1}^0, x_{T-1}^1)$  be the expected maximum total risk reduced from epoch  $T - 1$  when taking decision  $\mathbf{d}'_{T-1}$ , then:

$$V'_{T-1}(x_{T-1}^0, x_{T-1}^1) = \sum_{i=1}^c a_{iT-1} + V_T(W^0(x_{T-1}^0, \mathbf{d}'_{T-1}), W^1(x_{T-1}^1, \mathbf{d}'_{T-1})).$$

Let  $\mathbf{d}''_{T-1}$  be such that for a particular  $j \leq c$ ,  $d''_{jT-1} = 0$ ,  $d''_{(c+1)T-1} = 1$ , and for all  $i \neq j, c + 1$ ,  $d''_{iT-1} = d'_{iT-1}$ . Also, let  $V''_{T-1}(x_{T-1}^0, x_{T-1}^1)$  be the expected maximum total risk reduced from epoch  $T - 1$  when taking decision  $\mathbf{d}''_{T-1}$ , then:

$$V''_{T-1}(x_{T-1}^0, x_{T-1}^1) = \sum_{i=1}^{j-1} a_{iT-1} + \sum_{i=j+1}^{c+1} a_{iT-1} + V_T(W^0(x_{T-1}^0, \mathbf{d}''_{T-1}), W^1(x_{T-1}^1, \mathbf{d}''_{T-1})).$$

Let  $\delta = V'_{T-1}(x_{T-1}^0, x_{T-1}^1) - V''_{T-1}(x_{T-1}^0, x_{T-1}^1)$ , then:

$$\begin{aligned}
\delta &= V'_{T-1}(X_{T-1}^0, X_{T-1}^1) - V''_{T-1}(X_{T-1}^0, X_{T-1}^1) \\
&= a_{jT-1} - a_{c+1T-1} + V_T(W^0(X_{T-1}^0, \mathbf{d}'_{T-1}), W^1(X_T^1, \mathbf{d}'_{T-1})) - V_T(W^0(X_{T-1}^0, \mathbf{d}''_{T-1}), W^1(X_T^1, \mathbf{d}''_{T-1})) \\
&= a_{jT-1} - a_{c+1T-1} + \sum_{i=c+1}^{2c} a_{iT} - a_{jT} - \sum_{i=c+2}^{2c} a_{iT} \\
&= a_{jT-1} - a_{c+1T-1} + a_{c+1T} - a_{jT}.
\end{aligned}$$

Using Proposition 4.3.1, given that for all  $i$ ,  $a_{iT-1} - a_{iT} = \hat{y}_{it}(CVD_i - a_{iT})$ , then  $\delta = \hat{y}_{jt}(CVD_j - a_{jT}) - \hat{y}_{c+1t}(CVD_{c+1} - a_{c+1T})$ . The patients were sorted such that if  $j < c + 1$ , then  $\delta \geq 0$  and  $V'_{T-1}(X_{T-1}^0, X_{T-1}^1) \geq V''_{T-1}(X_{T-1}^0, X_{T-1}^1)$ . Therefore  $d'_{T-1}$  is the policy that maximizes the total risk reduced from  $T - 1$  to  $T$ . Repeating the steps for  $t = 1$  to  $T - 2$ , we have that:

$$V_1(X_1^0) = \sum_{i=1}^c a_{i1} + \sum_{i=c+1}^{2c} a_{i2} + \cdots + \sum_{i=(T-1)c+1}^{Tc} a_{iT}.$$

If  $n \leq cT$  then define  $\gamma$  where  $(\gamma - 1)c \leq n \leq \gamma c$ . Then,

$$V_1(X_1^0) = \sum_{i=1}^c a_{i1} + \sum_{i=c+1}^{2c} a_{i2} + \cdots + \sum_{i=(\gamma-1)c+1}^n ca_{i\gamma}. \quad \square$$

## A.4 Chapter4: Additional graphs

Figure A.3: Correlation matrix for the logistic regression. We present the correlation between each of the variables used for the DLR model.

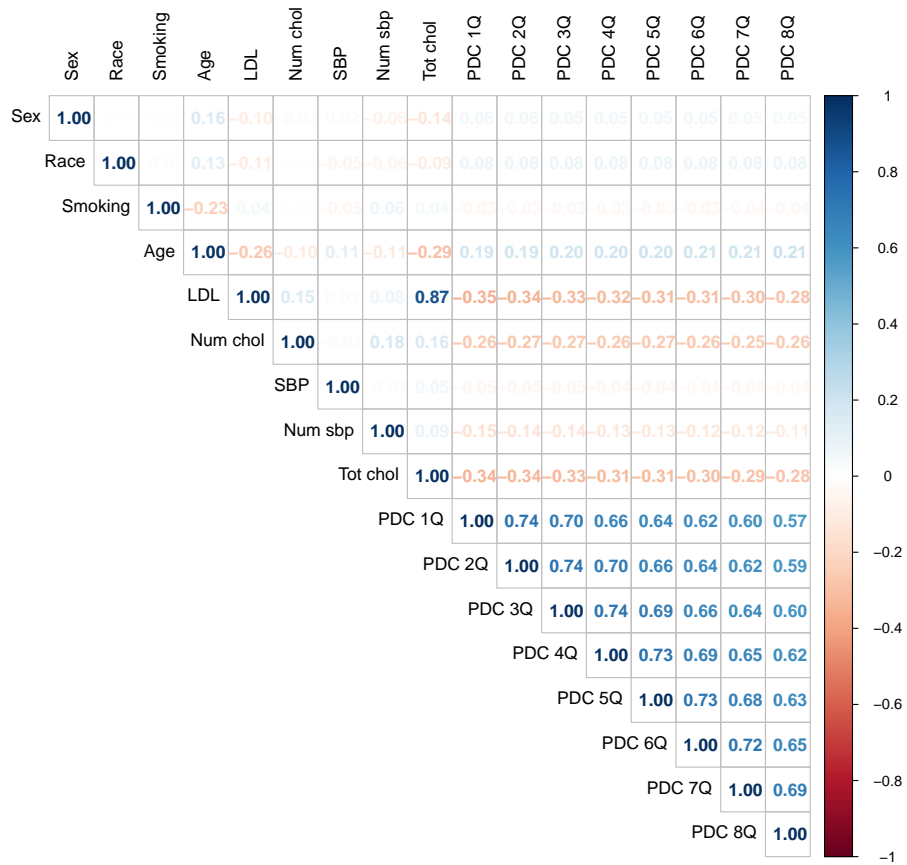
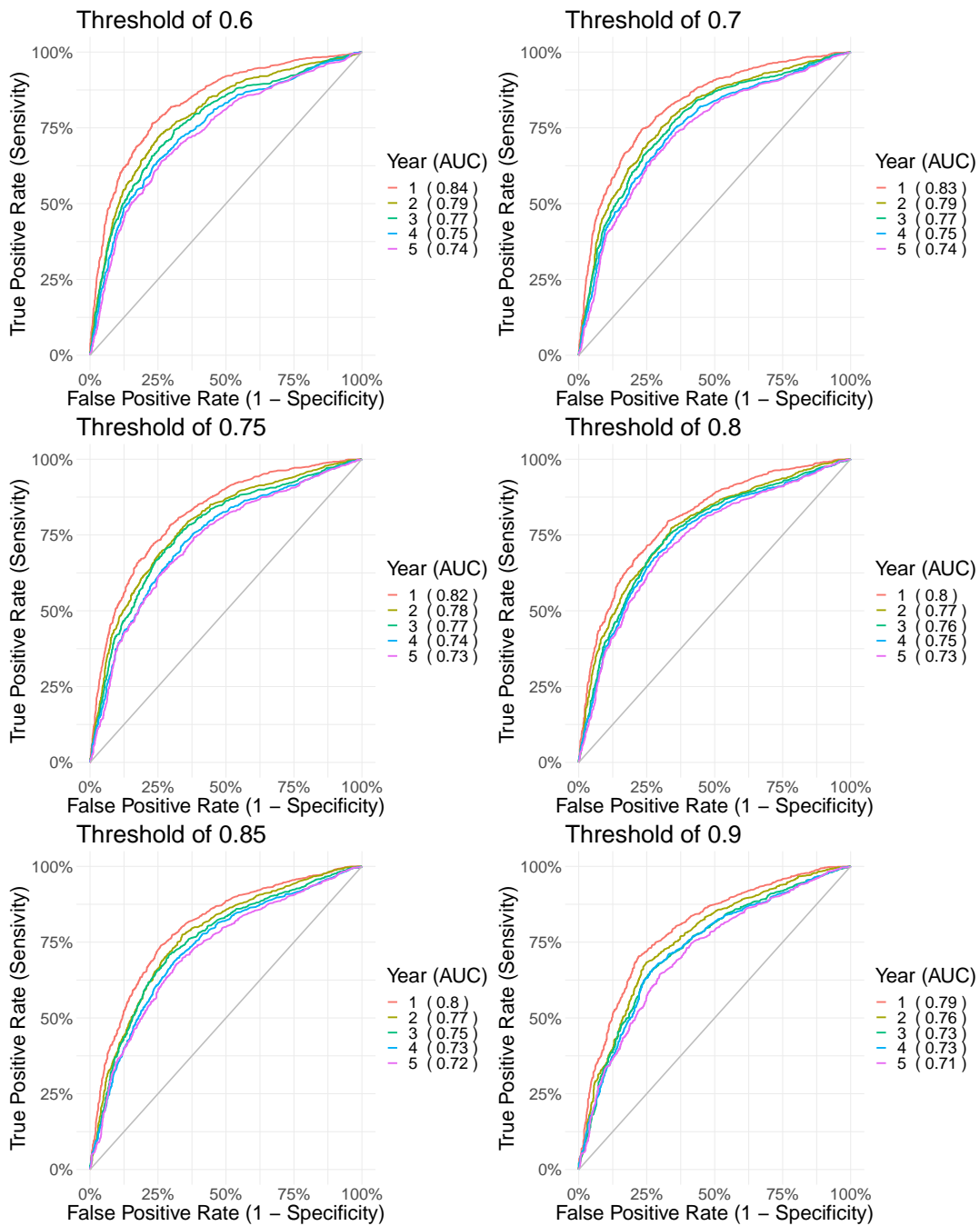


Figure A.4: ROC and AUC curves. ROC and AUC for each of the 5 forecasting years for adherence thresholds of 0.6 to 0.9.



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