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USING LONGITUDINAL HEALTH RECORDS TO SIMULATE THE IMPACT OF NATIONAL TREATMENT GUIDELINES FOR CARDIOVASCULAR DISEASE

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ABSTRACT

Continuous tracking of patient's health data through electronic health records (EHRs) has created an opportunity to predict healthcare policies' long-term impacts. Despite the advances in EHRs, data may be missing or sparsely collected. In this article, we use EHR data to develop a simulation model to test multiple treatment guidelines for cardiovascular disease (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. Our methodology consists of using the EM algorithm to fit sparse health data and a discrete-time Monte-Carlo simulation model to test guidelines for different patient demographics. Our results suggest that, among published guidelines, those that focus on reducing CVD risk are able to reduce treatment without increasing the risk of severe health outcomes.

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 amassing large amounts of longitudinal data that can be used to create a deeper understanding of how patients' health conditions change over time. This resource creates opportunities for health systems to extend beyond just the patients' current health status to predict long-term impact of healthcare policies over a patient's lifetime. This is particularly relevant for chronic diseases and other permanent conditions that patients may live with for many years. Nevertheless, many important questions must be answered when converting raw longitudinal data to build well-validated simulation models. In particular, a modeling framework is needed in the context of missing or sparsely populated data (which naturally occurs due to variation in patients' interaction with health systems).

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" (La Rochelle and Amling 2010). 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 (Habbema et al. 2014).

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We focus on cardiovascular disease (CVD) prevention in this article as an important example of how longitudinal EHR data can improve care. We chose CVD prevention because it is a common condition, requiring treatment decisions over time. Moreover, it is one of the leading causes of death worldwide (Virani et al. 2020). In this context, physicians treat patients based on recommended guidelines which are created based on clinical trials and clinical judgment (Grundy et al. 2018; Whelton et al. 2017). Most clinical trials have a short duration, and patients enrolled in trials could differ from the population of patients seen in any one 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 article is twofold. First, we provide a case study of the development of a simulation model from longitudinal EHR data in the context of CVD prevention. Second, 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 medication 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 article is organized as follows: In Section 2, we provide background on CVD and a brief review of some of the most related prior studies. In Section 3 we describe our model inputs and assumptions. In Section 4 we describe our simulation model. In Section 5, we apply our model to a longitudinal database of the Veteran Affairs department and present the results. Finally, in Section 6 we discuss the results and propose the next steps.

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 (Pool et al. 2018). 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) (Grundy et al. 2018; Whelton et al. 2017) and the Joint National Committee (JNC) (James et al. 2014). These guidelines prescribe treatment decisions that depend on health risk factors, which affect the relative benefits of treatment for patients (Karmali and Lloyd-Jones 2017; Marrero et al. 2021). 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) (Goff et al. 2014). 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 Sussman et al. (2017) recalibrated the ACC calculator using the observation data in the Veterans' Affairs system, which provides more accurate estimates of risk for the population considered in this paper. Risk factors such as blood pressure and cholesterol for CVDs 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 of new products. The two most common approaches for

dealing with missing data in this context are imputation and maximum likelihood methods. In particular, stochastic regression imputation and estimating standard errors are helpful when dealing with continuous data (Enders 2010). EM algorithms are well suited to dealing with discrete or categorical data to estimate discrete time Markov chains, which we estimate in this article. EM algorithms have been applied in many healthcare settings, for example mental health (Yeh et al. 2010), patient flow in a hospital (Ranjan et al. 2017), prostate cancer active surveillance (Li et al. 2020), and emergency medical services (Knight and Harper 2012), among other applications. We apply these algorithms to our data for what is, to the best of our knowledge, the first application CVD prevention.

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, Garber et al. (1994) estimated a time series model to predict high-risk cholesterol levels. Hollander et al. (2003) estimated the incidence, survival, and lifetime risk of stroke in a Rotterdam population. Pandya et al. (2013) and Pandya et al. (2015) 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 behavior through their lifetime.

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.

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 (Sussman et al. 2017) 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, and it has 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 also 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 who had 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 who had 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 were remaining.

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 1 (Grundy et al. 2018; Benjamin et al. 2019).

Table 1: Risk factors levels: The discrete sets of published clinically relevant cholesterol ranges used to define cholesterol states (Grundy et al. 2018) and systolic blood pressure ranges used to define blood pressure states (Benjamin et al. 2019).

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): ≥ 70 and < 100	Borderline High (B): ≥ 200 and < 240	Elevated (E): ≥ 120 and < 130
Acceptable (A): ≥ 100 and < 130	High (H): ≥ 240	Hypertension I (H1): ≥ 130 and < 140
Borderline High (B): ≥ 130 and < 160		Hypertension II (H2): ≥ 140 and < 180
High (H): ≥ 160 and < 190		Hypertensive Crisis (HC): ≥ 180
Severe (S): ≥ 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 1. Prior studies have proposal risk thresholds ranging from 5% to 7.5% (Nayor and Vasan 2016). A lower threshold means that patients will begin treatment sooner, while a higher threshold will defer treatment.

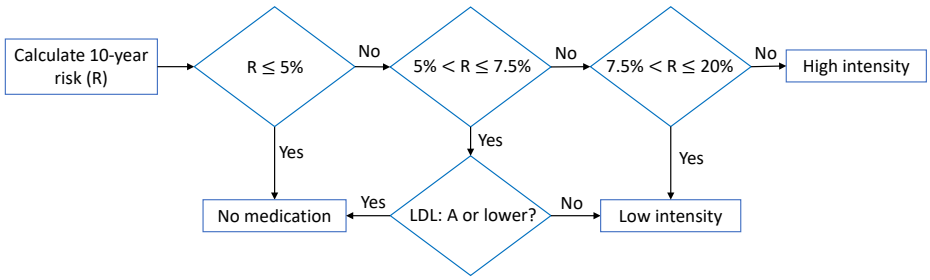


Figure 1: The ACC guideline for cholesterol treatment.

For blood pressure medications, we focus on the JNC8 guideline (James et al. 2014) (which we refer to as simply the JNC guideline) and the ACC guideline (Grundy et al. 2018). 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 we present both guidelines.

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 (Mason et al. 2014). We validate this assumption in Section 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.

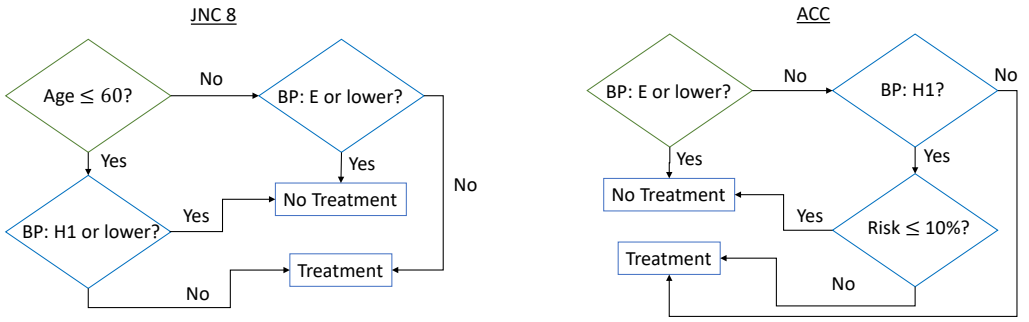


Figure 2: Blood pressure treatment guidelines: Both guidelines suggest that a blood pressure of Hypertension 1 (H1) should be the first threshold to assess if the patient needs medication. JNC increases the threshold for older patients since blood pressure tends to increase naturally with age. On the 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.

3.3 Estimation of Markov Chain Parameters for Blood Pressure and Cholesterol

The time between data collection for patients' appointments may vary due to different factors, such as health status, demographics, and whether they are undergoing any treatment. Different authors have worked on the problem of how to estimate transition probabilities based on missing data. We based our study on the work of Yeh et al. (2010), which improves upon the EM algorithm presented by Sherlaw-johnson et al. (1995) to estimate the transition probabilities. The EM algorithm we employed uses observational data to estimate a Markov chain. The algorithm is divided into the imputation step (E-step) and the optimization step (M-step).

The E-step begins by using the observational data where we define O_{uvw} as the number of observed transitions from state u to state v in w quarters of a year. During the E-step, the algorithm converts the data to an quarterly Markov chain by iteratively imputing the missing data to "complete" the data set. We accomplish this by first defining $P^{(k)}$ as the matrix in the $k-th$ iteration of the algorithm. We also define $\mathbb{P}_{ijl,uvw}$ as the probability that a transition between state i and j occurs in l quarters, where the patient was observed to be in state u at quarter $w-l$ and then observed in state v at quarter w and can be estimated as follows:

$$\mathbb{P}_{ijl,uvw} = \frac{P^{l} P_{ij} P_{jv}^{w-l-1}}{P_{uv}^{w}} \tag{1}$$

The E-step result is matrix $S_{ij}^{(k)}$, defined as the expected number of transitions from state i to state j occurring if there is complete data in the $k-th$ iteration. We estimate this matrix as follows:

$$S_{ij}^{(k)} = \sum_{u}\sum_{v}\sum_{w} O_{uvw} \sum_{l=0}^{w-1} \mathbb{P}_{ijl,uvw} \tag{2}$$

Then, the M-step uses the "complete" data to estimate the Markov chain. We estimate the k-th Markov chain $P^{(k+1)}$, as follows:

$$P_{ij}^{(k+1)} = \frac{S_{ij}^{(k)}}{\sum_{w} S_{iw}^{(k)}} \tag{3}$$

This equation represents the ratio of expected transitions from state i to j over the expected number of transitions from state i. With the new estimated Markov chain, the algorithm goes back to the E-step to reconstruct the data again. These two steps are done until the error is minimized. We apply the EM-algorithm

for LDL, SBP, and Total Cholesterol, and when the patient is on treatment or not. Additionally, the risk factors vary depending on the patient's age. Therefore, we divide the data by age ranges of 5 years, from 40 to 80 years old, and run the algorithm for each age range.

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 Sherlaw-johnson et al. (1995) 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.

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 (Sussman et al. 2017). 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 et al. (2021) presents risk reduction factors depending on the statin intensity when controlling cholesterol. Also, Karmali and Lloyd-Jones (2017) presents risk reduction factors depending on blood pressure medication and the 10-year CVD risk. Finally, we estimate the dying probability for other causes with the *CDC* tables of life years (Arias and Xu 2019).

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.

4.1 Modelling Patient Flow

The guidelines suggest surveilling patients over 40 years old, prone to increase the chance of cardiovascular disease. Figure 3 presents the simulation flow for each patient, divided into two main time frames: events during an appointment with the physician and events between appointments.

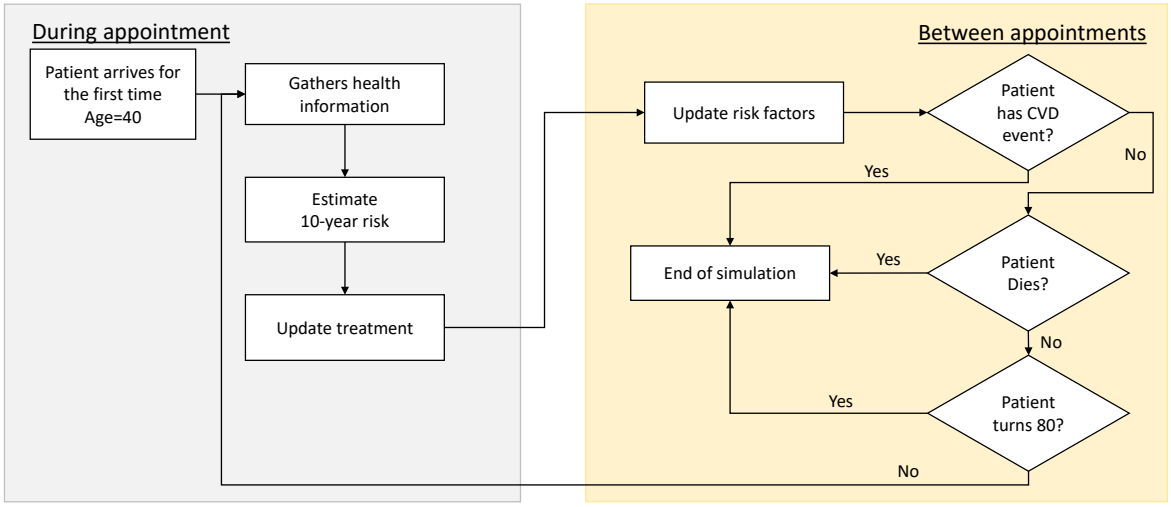


Figure 3: Simulation flow: The simulation model focuses on preventing CVD events. We simulated the health factors during and between appointments, assuming that on every epoch the patient has a probability of having a cardiovascular event.

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.

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.

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).

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.

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.

In our data, 69.1% of the patients were White male, 20.4% of them were African-American male, 6.7% as White female, and 3.8% of them were African-American female. Due to an insufficient number of samples for female patients, we are unable to 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. We divided male patients into two different groups, African-American Male and White Male because race is an important factor for 10-year risk prediction (Sussman et al. 2017). We validate the cholesterol and blood pressure stochastic behaviors, for each group, by dividing the available patient group data into training and test data sets. For this purpose, we randomly split each group data into a two-thirds training dataset and a one-third testing set. Finally, using the test set, we run a likelihood ratio test to validate the Markov chains (Besag and Mondal 2013). In Table 2 we present the p-value for each test, where the null hypothesis represents that the Markov chain fits the observational data's behavior.

Table 2: Markov chain validation: For each patient group we compared the observations with the estimated Markov chain and estimate the p-value of the likelihood ratio test. The null hypothesis states that at a smaller ratio, the Markov Chain fits better the data.

Patient Group (% of Total)	**Age Range**	**P-Value**		
		No Medication	**Low intensity Statins**	**High intensity Statins**
African-american Male (20.4%)	40	0.241	0.847	0.080
	45	0.890	0.997	**0.019**
	50	1.000	0.830	**0.000**
	55	0.980	1.000	**0.031**
	60	0.355	0.744	0.158
	65	0.989	0.982	**0.001**
White Male (69.1%)	40	1.000	1.000	0.997
	45	1.000	1.000	0.183
	50	0.999	0.998	0.703
	55	0.747	0.871	0.601
	60	0.228	0.188	0.969
	65	0.491	0.128	0.145

For the patient groups with the most samples, such as White Male, the likelihood ratio test does not reject the null hypothesis. In some cases, when the sample size is small, such as young people on high-intensity statins, the null hypothesis is rejected; however, it is worth noting that a small portion of patients will initiate high-intensity statins. Because the number of blood pressure samples per patient is higher than cholesterol samples (due to the simplicity of collecting BP data over lab tests for cholesterol), the test did not reject any BP cases.

To validate the number of deaths by natural causes, we compared our results with the CDC tables (Arias and Xu 2019). Moreover, to validate the number of CVD events, we compared our results with the 2020 American Heart Association report (Virani et al. 2020). 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 3. We got consistent results when validating for the other age ranges.

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 cardiovascular 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.

Table 3: Simulation validation: Simulation results versus the CDC life tables (Arias and Xu 2019) and the American Heart Association report (Virani et al. 2020).

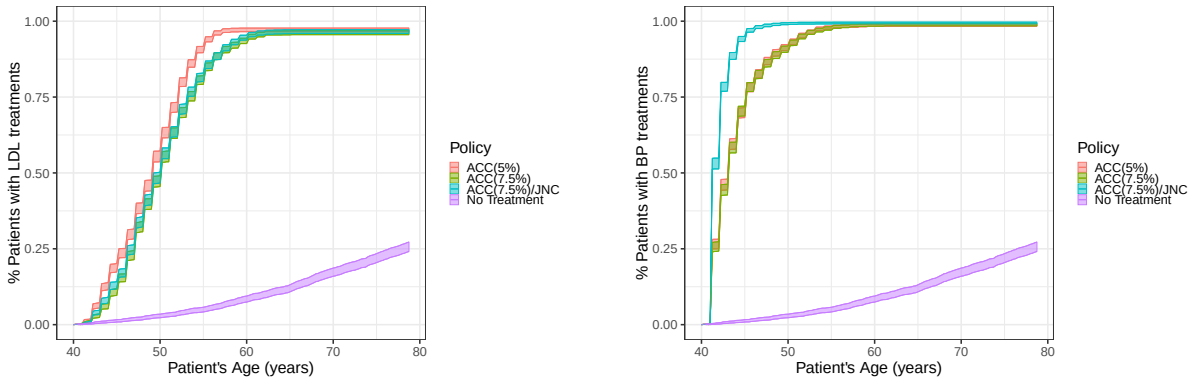
Measurement-patient group	Simulation (Mean value $\pm$ SD)	American population data
Death rate		
White Male	48.7% $\pm$ 1.7%	48.92%
African American Male	60.5 % $\pm$ 1.5 %	60.28%
Cardiovascular Events		
White Male	22.4% $\pm$ 1.49%	25.1%
African American Male	22.4% $\pm$ 1.5%	25.1%

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 African-American 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 4a 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 between 40 and 50 by 2.5 % on average. This may 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 4b, 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 5 there is no statistical difference in 10-year risk among the three scenarios.



(a) LDL Treatment

(b) BP Treatment

Figure 4: Percentage of patients on treatment: Recall that patients start treatment when they have a cardiovascular event, for this reason, there can be patients with treatment in the No-Treatment Scenario.

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

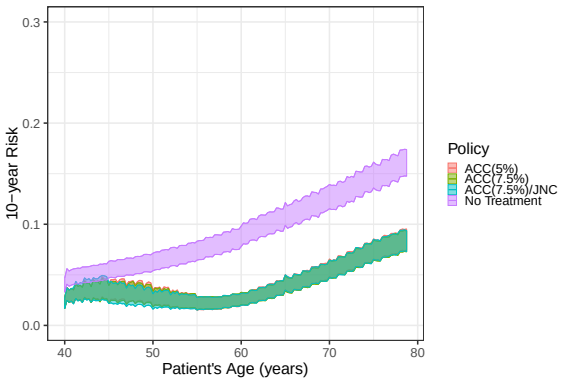


Figure 5: 10-year risk: As patients begin treatment, the scenarios with treatment begin to differ with the no treatment scenario. Where at the age of 50, the risk is reduce by 3% on average and after the by the age of 80, the risk is reduced by 9% on average.

missing or sparsely populated, which raises questions on how to build validated simulation models. These simulation models can be excellent resources for physicians and policymakers 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: African-American males and white males. 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 where 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 assumed independence between cholesterol and blood pressure and estimated individual Markov chains for each of them. While this is unlikely to be true in reality, it looks like a reasonable estimation of the real case in light of our validation study results. Also, 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, as White Female and African-American Female.

Despite the limitations, we believe our study demonstrates a productive use of longitudinal EHR data that most health systems have collected. We were able to show that using EM-algorithms is a suitable approach to deal with sparse data in EHRs when building simulation models based on non-stationary Markov chains. Our work focuses on cardiovascular disease, 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.

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