Prioritizing Primary Prevention Strategies For Cardiovascular Disease At The Clinic Population Level

Giulio Cesare Rottaro Castejon

Yale University

Follow this and additional works at: https://elischolar.library.yale.edu/ymtdl

Part of the Medicine and Health Sciences Commons

Recommended Citation

This Open Access Thesis is brought to you for free and open access by the School of Medicine at EliScholar – A Digital Platform for Scholarly Publishing at Yale. It has been accepted for inclusion in Yale Medicine Thesis Digital Library by an authorized administrator of EliScholar – A Digital Platform for Scholarly Publishing at Yale. For more information, please contact elischolar@yale.edu.
Prioritizing Primary Prevention Strategies for Cardiovascular Disease at the Clinic Population Level

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

By

Giulio C. Rottaro Castejon

2017
Abstract

Prioritizing Primary Prevention Strategies for Cardiovascular Disease at the Clinic Population Level

Giulio C. Rottaro Castejon, Bradley Richards, and Brita Roy. Section of General Internal Medicine, Department of Medicine, Yale University School of Medicine, New Haven, CT

Cardiovascular Disease remains the number one cause of mortality in the United States with atherosclerotic cardiovascular disease (ASCVD) being a major component. Lifestyle interventions remain the first line treatment for the prevention of ASCVD, and clinic-based interventions effectively improve rates of healthy lifestyle choices. However, these programs require additional resources and there is currently no guidance for clinic directors to understand what lifestyle intervention(s) have the highest value for their unique population. We propose a novel application of the 10-year ASCVD risk calculator to a clinic patient cohort, thereby acting as a tool for providers and administrators to develop lifestyle intervention programs that will have the greatest risk reduction for their clinic population.

We first defined the ASCVD 10-year risk for patient cohorts from four different primary care clinics in New Haven, CT by normalizing and aggregating individual patient 10-year ASCVD risk scores. We then calculated changes to this normalized aggregate risk by modeling the effects of evidence-based interventions found in Cochrane Reviews of different efficacy to each of four modifiable risk factors used in the 10-year ASCVD risk calculator. The four different modifiable risk factors include systolic blood pressure, total cholesterol, HDL cholesterol and smoking status. A resulting change in each cohort's normalized aggregate risk was calculated.

The clinic cohorts had different levels of modeled risk reduction from the same interventions. The magnitude of reduction was dependent on baseline normalized aggregate risk and prevalence of risk factor(s) targeted in the interventions. The three clinics where the baseline normalized aggregate risk was above 100 events per 1,000 patients had a greater risk reduction from an organizational intervention aimed at improving the quality of treatment for hypertensive patients compared to all other evidence-based interventions found in Cochrane Reviews. In the clinic that had a lower baseline normalized aggregate risk, the highest yield intervention was dietary advice by providers. Our data demonstrate that the highest yield lifestyle intervention for any clinic may vary depending on the makeup of the populations and its risk factors.

The tool created in this study can be used by clinic providers and administrators to estimate the effects of various interventions on the ASCVD risk of their clinic cohort. The models generated by this tool can be used to guide strategy and prioritize clinic resources based on the extrapolated effects of evidence based interventions to specific clinic populations. Furthermore, it may also guide interventions planned to address needs identified by community health assessments. Because the tool predicts outcomes for specific patient populations it has the potential to foster the application of evidence-based practices to population health management.
Acknowledgements

I would first like to thank the many people involved in this project, who made it all possible. Most importantly Dr. Brita Roy and Dr. Bradley Richards for their excellent advice and guidance as well as Dr. Michael Robert O’Brien and Jinyi Zhu for all of their work on the initial development of this tool.

I would also like to thank my friends and family for providing me with unfailing support and continuous encouragement throughout the five years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them.

Thank you.

Sincerely,

Giulio C. Rottaro Castejon
# Table of Contents

Abstract ................................................................................................................................. 2

Acknowledgements ................................................................................................................ 3

Table of Contents .................................................................................................................. 4

Introduction .......................................................................................................................... 6

Statement of Purpose .......................................................................................................... 8

Methods ............................................................................................................................... 8

  Model: Baseline 10-Year ASCVD Risk and Risk Change Equations ......................... 9

  Simulation: Randomly Generated Patient Cohorts for Proof of Concept .............. 13

  Simulation: Variance in Baseline Risk of Randomly Generated Cohorts .............. 15

  Simulation: Variance in Sensitivity to Interventions of Randomly Generated Cohorts .. 15

  Application: Selection of Local Clinic Cohorts ...................................................... 16

  Application: Independent Variables from Clinic Cohorts .................................... 18

  Application: Analysis of Clinic Cohorts ................................................................. 19

  Application: Effect of Quality Improvement Interventions .................................... 20

Statement of Contributions ................................................................................................. 21

Results ................................................................................................................................. 21

  Simulation: Variance in Baseline Risk of Randomly Generated Cohorts .............. 21

  Simulation: Variance in Sensitivity to Interventions of Randomly Generated Cohorts .. 23

  Application: Comparison of Demographic Data for Clinic Cohorts .................... 27

  Application: Modeled Risk Reduction among Actual Clinic Cohorts .................... 29
Introduction

The 2013 American College of Cardiology and American Heart Association (ACC/AHA) Guideline on Lifestyle Management to Reduce Cardiovascular Risk emphasized lifestyle interventions as a crucial component of cardiovascular disease prevention.¹ These guidelines recommend that providers target poor dietary habits, and physical inactivity given both their prevalence on the general population and their indirect, yet significant, effect on cardiovascular disease risk.¹ Interventions mentioned in this report include advice to engage in physical activity two to three times per week, advice to decrease daily sodium intake, advice to follow specific diet plans available to the public, etc. The effect of such lifestyle interventions varies by patient, and the intervention with this highest cardiovascular risk reduction is determined by a patient’s risk factors.² These interventions are variable in resource requirements for implementation, but the most effective ones generally require more resources. As such, it is cost-prohibitive for clinics to make all evidence-based lifestyle interventions available to their patients.³

Given the high prevalence of modifiable behaviors contributing to cardiovascular disease risk and the cost of lifestyle interventions there is both a clinical and financial argument to approach primary cardiovascular disease prevention at the population level.⁴ In a 2011 article by Dr. Thomas A. Pearson, he described the need for both a clinical and population approach to the primary prevention of cardiovascular disease.⁴ He went on to say that much of the decline in cardiovascular mortality over the 20th century was from lifestyle changes in the American population. Clinics should focus primary prevention efforts on the lifestyle
interventions with the greatest potential risk reduction. However, the evidence available on lifestyle interventions is generalized and may not be applicable across all clinic populations. For example, smoking cessation programs have been reported to be the most cost-effective intervention for cardiovascular disease prevention. But, in a population with a low prevalence of smoking, these interventions will be less effective in reducing total risk of cardiovascular disease. There currently is no method for clinics to quantitatively estimate the expected effects of published interventions on their population's cardiovascular risk and compare interventions against each other.

The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults included a robust risk calculation model to inform individual level medical decision-making to reduce the risk of events from atherosclerotic disease. This model includes modifiable risk factors such as lipids levels, blood pressure, and smoking status. In this study, we explored the use of the ACC/AHA 10-year atherosclerotic cardiovascular disease (ASCVD) risk calculator as a predictive model to aid in primary disease prevention strategies at the clinic level. We hypothesized that this model could be modified to calculate the risk of ASCVD for an entire clinic cohort using data from electronic health records (EHR). Furthermore, we hypothesized that the effects of lifestyle interventions on modifiable risk factors can be incorporated in the predictive model to quantitatively estimate their effect on cohort-wide ASCVD prevention. The tool is meant to empower individual clinics to estimate the effectiveness of different evidence-based interventions in the primary prevention of ASCVD.
Statement of Purpose

The main goal of this study was to create a novel tool that applies the 10-year ASCVD Risk Calculator to a clinic population to guide primary preventative strategies for clinic-based patient cohorts. The tool calculated baseline ASCVD risk for each cohort and estimated the number of prevented ASCVD events for different interventions. We hypothesized that each cohort would respond differently to the same interventions, and thus the highest value intervention for a given cohort would vary depending on the demographics and the rates and distribution of clinical risk factors. In this study, we first applied the tool to randomly generated cohorts developing a simulation model as a proof of concept that the magnitude of cardiovascular event reduction in response to a given lifestyle modification strategy varies depending on the baseline risk of the population. Then we applied the tool to four real-world clinic cohorts and extrapolated the effects of several interventions. Ultimately, this tool may allow primary care clinics to implement the highest yield intervention for primary ASCVD prevention. This study focused mostly on the theory and development of such a guidance tool but did not proceed to implementation.

Methods

To study the differential effects of lifestyle modifications on diverse patient cohorts, we used a three-step analytic approach. First we developed a series of mathematical models to create a tool to test hypothetical treatment effects using the 10-year ASCVD risk calculator. We then applied the tool to randomly generated cohorts as a simulation to demonstrate the concept. These randomly generated
cohorts were designed to appear statistically indistinguishable but to have different baseline ASCVD risks, thereby being less likely to respond differently to intervention. Lastly we applied the tool to four real-world clinic cohorts. In this last application we also extrapolated the effects of non-pharmacologic interventions to determine which intervention is the best for any given cohort.

**Model: Baseline 10-Year ASCVD Risk and Risk Change Equations**

We created an algorithm that uses data that can be extracted from EHR systems to calculate a baseline 10-year ASCVD risk for each patient using the statistical model from the 2013 ACC/AHA guidelines. For an individual, \( i \), the 10-year ASCVD risk is represented by \( r_i \) which is a function of age, gender, race, total cholesterol (\( TC \)), HDL cholesterol (\( HDL \)), systolic blood pressure (\( SBP \)), diagnosis of diabetes mellitus (\( DM \)), whether or not they are receiving hypertension treatment (\( HTN \)), and whether or not they smoke (\( S \)).

\[
r_i = f_{ASCVD}(\text{age}_i, \text{gender}_i, \text{race}_i, \text{TC}_i, \text{HDL}_i, \text{SBP}_i, \text{DM}_i, \text{HTN}_i, S_i)
\]

Given the limitations of this model the individual risk scores are bounded between 1% and 30%. We add the calculated individual risk scores for a cohort (\( C \)) to get the expected number of ASCVD events in 10 years (\( R_C \)), also referred to as the aggregate risk.

\[
R_C = \sum_{i=1}^{N_C} r_i
\]

This value can be normalized to get the number of predicted ASCVD events in the next ten years per 1,000 patients, or normalized aggregate risk.
**Equation 1. Normalized aggregate risk given in number of expected ASCVD events per 1000 patients in the next 10 years.**

\[
\overline{R_c} = \frac{10^3}{N_c} \times R_c
\]

Using this method to obtain the normalized aggregate risk, we can directly calculate how changes in the modifiable risk factors will affect the number of expected ASCVD events in the next 10 years. In other words, we can directly calculate the number of prevented ASCVD events from an intervention on a clinic population. Conversely, we can quantify the required changes to a modifiable risk factor in order to achieve a specific level of reduction in the number of expected ASCVD events.

Changes in **total cholesterol** are represented by the average decrease in total cholesterol (\(\Delta TC\)) applied to all individuals with a 10-year ASCVD risk of 7.5\% or higher per ACC/AHA guidelines. Using these principles, the tool can calculate the changes to individual risk scores.

\[
\Delta r_i = 0, \text{ if } r_i < 0.075
\]

\[
\Delta r_i = f_{ASCVD}(age_i, gender_i, race_i, Max(TC_i - \Delta TC, 100), HDL_i, SBP_i, DM_i, HTN_i, S_i) - r_i,
\]

\[
\text{if } r_i \geq 0.075
\]

Note that the final total cholesterol (\(TC_i - \Delta TC\)) is bounded from below by 100 mg/dL to simulate the real-life limitations of cholesterol lowering therapies. Using these changes to individual risk scores the tool can then set up an equation for change in normalized aggregate risk, \(\Delta \overline{R_c}\).
Equation 2. General equation for change in normalized aggregate risk of ASCVD.

$$\Delta R_c = \frac{10^3}{N_c} \sum_{i=1}^{N_c} \Delta r_i$$

These sets of equations provide a direct relationship between changes to the total cholesterol and the normalized aggregate risk scores. The equations can be used to directly calculate the number of prevented ASCVD events per 1,000 patients for the expected population level change in cholesterol from a given intervention aiming to reduce total cholesterol. For any given cohort $\Delta R_c$ was calculated for a range of $\Delta TC$ values from 0 mg/dL to 150 mg/dL by increments of 1 mg/dL.

Changes in **HDL Cholesterol** are represented by the average increase in HDL Cholesterol ($\Delta HDL$) to all individuals. In this case the change in individual risk score is given by this equation:

$$\Delta r_i = f_{ASCVD}(age_i, gender_i, race_i, TC_i, HDL_i + \Delta HDL, SBP_i, DM_i, HTN_i, S_i) - r_i$$

Similar to total cholesterol, these equations can be used to directly calculate the number of prevented ASCVD events per 1,000 patients for a given intervention on HDL cholesterol. For any given cohort $\Delta R_c$ was calculated for a range of $\Delta HDL$ values from 0 mg/dL to 100 mg/dL by increments of 1 mg/dL.

Changes in **systolic blood pressure** are represented by the decrease in systolic blood pressure for all individuals under 60 years of age with a systolic blood pressure above 140 mmHg and all individuals over 60 years of age with a systolic blood pressure above 150 mmHg. These rules were adapted from the Eighth Joint National Committee guidelines. Like the total cholesterol model, we have limited the
final systolic blood pressure \((SBP_i - \Delta SBP)\) to a lower bound of 110 mmHg for treated individuals. The individual changes in risk scores are given by:

\[
\Delta r_i = f_{ASCVD}(age_i, gender_i, race_i, TC_i, HDL_i, Max(SBP_i - \Delta SBP, 110), DM_i, TRUE, S_i) - r_i,
\]
if \(SBP_i > 140\) and \(age_i < 60\), or \(SBP_i > 150\) and \(age_i \geq 60\)

\[
\Delta r_i = 0, \text{ otherwise.}
\]

As done previously, these equations can be used to directly calculate the number of prevented ASCVD events per 1,000 patients for a given intervention on systolic blood pressure. For any given cohort \(\Delta R_C\) was calculated for range of \(\Delta SBP\) values from 0 mmHg to 80 mmHg by increments of 1 mmHg.

**Smoking status** is a Boolean variable, so interventions are modeled by a probability of smoking cessation. Using a probability of smoking cessation, we model the risk score using conditional probability.

We define \(r_{i,SC}\) as the risk for patient \(i\) without smoking but leave all other risk factors unchanged. It is given by:

\[
r_{i,SC} = f_{ASCVD}(age_i, gender_i, race_i, TC_i, HDL_i, Max(SBP_i - \Delta SBP, 120), DM_i, HTN_i, FALSE)
\]

Using conditional probability, we can calculate a new risk score \((r_{i,W})\) given a probability \(p_{SC}\) that any given patient will quit.

\[
r_{i,W} = r_{i,SC} \times p_{SC} + r_i \times (1 - p_{SC})
\]

Which implies:

\[
\Delta r_i = r_{i,SC} \times p_{SC} - r_i \times p_{SC} = p_{SC}(r_{i,SC} - r_i)
\]
Note that if the patient is not a smoker, \( r_{l,sc} \) is equal to \( r_l \) and therefore \( \Delta r_l \) becomes zero. Furthermore, we can use this same principle with the whole cohort and get the following equation.

\[
\Delta R_c = p_{sc}(R_{c,sc} - R_c)
\]

\[
\Delta \overline{R}_c = \frac{10^3}{N_c} p_{sc}(R_{c,sc} - R_c)
\]

Note that the last equation reveals a direct linear relationship between \( \Delta \overline{R}_c \) and the probability and smoking cessation, \( p_{sc} \), making this calculation remarkably simpler than all others. For any given cohort \( \Delta \overline{R}_c \) was calculated for range of \( p_{sc} \) values from 0.00 to 1.00 by increments of 0.01.

All the different numerical methods discussed were used to calculate changes to \( \Delta \overline{R}_c \) based on changes to a single variable. However, they can also be combined to calculate \( \Delta \overline{R}_c \) for any multifactorial intervention such as lifestyle interventions that may have effects on all modifiable risk factors.

**Simulation: Randomly Generated Patient Cohorts for Proof of Concept**

For development and proof of concept we first aimed to show how populations with the same demographics and similar risk factors can have drastically different baseline aggregate ASCVD risk and sub-sequentially drastically different responses to risk factor modifications. Therefore, randomly generated patient cohorts were created using the same probability distribution for all variables across all patients and cohorts. The randomly generated cohorts were 300 patients in size. This sample size was chosen because it is large enough to apply the law of large numbers, yet small enough to still show variability from population to population.
Furthermore, a patient panel size of 300 patients is within the normal limits for a single primary care provider. The distribution of the variables is shown in Table 1.

Table 1. Distribution of variables for randomly generated patient cohorts.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Uniform distribution from 40 to 80</td>
</tr>
<tr>
<td>Gender</td>
<td>43% probability of Male, 57% probability of Female</td>
</tr>
<tr>
<td>Race</td>
<td>63% probability of White/Other, 37% probability of Black</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>Normal distribution ($\mu = 182, \sigma = 44$) with a lower boundary of 58</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL)</td>
<td>Normal distribution ($\mu = 55, \sigma = 19$) with a lower boundary of 6</td>
</tr>
<tr>
<td>Diabetes Mellitus Diagnosis</td>
<td>38% probability of diabetes diagnosis</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>Normal distribution ($\mu = 130, \sigma = 14$) with a lower boundary of 61</td>
</tr>
<tr>
<td>Treatment for hypertension</td>
<td>59% probability of hypertension treatment</td>
</tr>
<tr>
<td>Smoking Status</td>
<td>18% probability of smoking</td>
</tr>
</tbody>
</table>

The numbers used to set the mean and standard deviation for total cholesterol, HDL cholesterol, and systolic blood pressure were based on baseline numbers from all patients included in analyses of local clinic cohorts described in a later section (Application: Selection of Local Clinic Cohorts). The percentages of gender, race, diabetes incidence, smoking incidence and hypertension treatment incidence were based on the same clinic populations. Given that the 10-Year ASCVD Risk Calculator can only use two sets of coefficients for race, white/other and black, no other races were included in the randomly generated patient populations. The cohorts were randomly generated and therefore may be statistically different from each other if the means or percentages were compared. To create cohorts that are statistically indistinguishable, all cohorts with a statistically significant difference in mean age, total cholesterol, HDL cholesterol or systolic
blood pressure or a statistically significant difference in percentage of males, black patients, diabetes incidence, smoking incidence or hypertension treatment incidence (using a two-tailed z-test with a p-value of 5%) were discarded and replaced with new randomly generated cohorts.

Simulation: Variance in Baseline Risk of Randomly Generated Cohorts

We randomly generated ten thousand cohorts that were statistically indistinguishable from each other. Using Equation 1, the normalized aggregate risk was calculated for each of these cohorts. The results were displayed in a histogram (Figure 1) to show the variation in normalized aggregate risk for statistically indistinguishable populations.

Simulation: Variance in Sensitivity to Interventions of Randomly Generated Cohorts

We created another 10 randomly generated cohorts using the same methodology. Once again, these cohorts were statistically indistinguishable based on two-tailed Z-test with a p-value of 5%. We subjected these ten clinic cohorts to a range of changes to the modifiable risk factors and the resulting change in normalized aggregate risk was calculated. The methods by which we calculated the change in normalized aggregate risk was described in a previous section (To study the differential effects of lifestyle modifications on diverse patient cohorts, we used a three-step analytic approach. First we developed a series of mathematical models to create a tool to test hypothetical treatment effects using the 10-year ASCVD risk calculator. We then applied the tool to randomly generated cohorts as a simulation
to demonstrate the concept. These randomly generated cohorts were designed to appear statistically indistinguishable but to have different baseline ASCVD risks, thereby being less likely to respond differently to intervention. Lastly we applied the tool to four real-world clinic cohorts. In this last application we also extrapolated the effects of non-pharmacologic interventions to determine which intervention is the best for any given cohort.

Model: Baseline 10-Year ASCVD Risk and Risk Change Equations). The modifiable risk factors we tested were total cholesterol, HDL cholesterol, systolic blood pressure and smoking status.

Application: Selection of Local Clinic Cohorts

We intentionally selected four adult primary care clinics in the greater New Haven, CT area that each serve a unique population with a different demographic makeup. The first clinic we selected was the primary care internal medicine residency clinic (SRC), which has a high percentage of Medicaid and African American patients. The second clinic we selected was the categorical internal medicine residency program clinic (PCC) which is similar in demographic distribution to the SRC but larger in size. The third clinic we selected was the student-run HAVEN Free Clinic (HAVEN), which serves mostly uninsured, undocumented immigrants from Latin America. The fourth clinic we selected was Yale Internal Medicine Associates (YIMA), a general internal medicine clinic that serves a larger percentage of white patients and a lower percentage of Medicaid and uninsured patients compared to the other clinics selected. All the participating clinics shared
the same hospital-wide electronic health record (EHR) system (EPIC ™) from which patient demographic and clinical data was pulled.

For each clinic, patients younger than 40 years of age or older than or equal to 80 years of age were excluded. Patients who had been reported as deceased on the EHR were also excluded. Patients who had not visited the clinic to which they were assigned between January 1st, 2014 and January 1st, 2016 were also excluded to limit the clinic populations to the patients who are most likely to identify a physician in that clinic as their primary care provider. Patients with a prior ASCVD event based on International Classification of Diseases (ICD) 9 and 10 codes were also excluded from analysis as the ASCVD risk calculator is not designed to predict their risk. Patients without a systolic blood pressure, total cholesterol, HDL cholesterol were considered to have incomplete data and excluded from analysis.

Table 2. Description of patient selection process by clinic cohort.

<table>
<thead>
<tr>
<th></th>
<th>PCC</th>
<th>SRC</th>
<th>HAVEN</th>
<th>YIMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Count</td>
<td>9164</td>
<td>4401</td>
<td>506</td>
<td>5859</td>
</tr>
<tr>
<td>Removed for:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out of age range</td>
<td>3619</td>
<td>1261</td>
<td>292</td>
<td>1671</td>
</tr>
<tr>
<td>Deceased</td>
<td>173</td>
<td>86</td>
<td>0</td>
<td>124</td>
</tr>
<tr>
<td>Not recently seen</td>
<td>908</td>
<td>365</td>
<td>83</td>
<td>642</td>
</tr>
<tr>
<td>Previous ASCVD</td>
<td>680</td>
<td>494</td>
<td>2</td>
<td>451</td>
</tr>
<tr>
<td>Incomplete Data</td>
<td>2653</td>
<td>734</td>
<td>88</td>
<td>1046</td>
</tr>
<tr>
<td>Final Patient Count</td>
<td>1131</td>
<td>1461</td>
<td>41</td>
<td>1925</td>
</tr>
</tbody>
</table>

Data on 19,930 patients from the four different clinic sites were extracted from the shared electronic health record. Of these patients 10,851 had to be removed for meeting study criteria such as being under the age of 40, over the age of 80,
deceased, or having a prior history of ASCVD. Of the remaining patients, 4,521 had missing data such as a valid systolic blood pressure, total cholesterol or HDL cholesterol. A clinic by clinic breakdown can be found on Table 2.

**Application: Independent Variables from Clinic Cohorts**

For all patients, the most recent total cholesterol and HDL cholesterol on record were used for risk calculations. For each patient included, the systolic blood pressure used in the risk calculation was an average of all systolic blood pressures found in the EHR for the 2015 calendar year. Blood pressure data collected from an emergency department were excluded from the analysis, however data from non-primary care ambulatory visits (e.g., cardiology clinic) or inpatient hospitalizations were included. A secondary analysis was performed using only the latest recorded systolic blood pressure.

Treatment for hypertension was based on the list of active outpatient medications for any given patient. If a patient had at least one antihypertensive agent in their medication list, they were considered to be receiving hypertension treatment. The list of medications considered to be antihypertensive agents was based on the drug classes listed in Table 3.

**Table 3. Drug classes considered treatment for hypertension.**

<table>
<thead>
<tr>
<th>ACE Inhibitor</th>
<th>Alpha-1-Antagonist</th>
<th>Alpha-2-Agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin 2 Receptor Blocker</td>
<td>Beta Blocker</td>
<td>Calcium Channel Blocker</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Potassium Sparing Diuretic</td>
<td>Loop Diuretic</td>
</tr>
<tr>
<td>Renin Inhibitor</td>
<td>Thiazide Diuretic</td>
<td>Thiazide-like Diuretic</td>
</tr>
<tr>
<td>Vasodilator</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diabetes diagnosis was based on a patient’s diagnosis list, problem list, or Hemoglobin A1c. Any patient with an ICD 9 or ICD 10 code associated with diabetes
Diabetes mellitus type 1 or type 2 diagnosis was considered to have diabetes mellitus for their risk calculation. Any patient who ever had a hemoglobin A1c greater than 6.5% was also considered to have diabetes mellitus for risk calculation.

The EHR has a variable for smoking status associated with every patient encounter. For the purpose of risk calculation, the smoking status was taken from a patient’s last encounter. Any patient who identified as a smoker regardless of quantity or method was labeled as a smoker. For patients who were former smokers the amount of time since they last smoked was not taken into consideration.

Within all cohorts, there were patients with incomplete information, such as a lack of blood pressures in the past year or a lack of cholesterol lab data. For these patients, it was not possible to calculate a baseline 10-year ASCVD risk or to estimate the effect of any interventions, therefore they were excluded from the final analysis. The demographic data of patients with missing data was compared against the data of patient that were included in the final analysis for each individual cohort using a student’s T-test or a Chi Square Test of Independence with Yate’s Correction to calculate p-values.

**Application: Analysis of Clinic Cohorts**

We calculated the baseline normalized aggregate risk for the four clinic cohorts with Equation 1 using the data from patients who met inclusion criteria and had complete information. These four clinic cohorts were then subjected to a range of changes to the four modifiable risk factors. The ranges used and the calculation of the change in normalized aggregate risk were described in a previous section. (To study the differential effects of lifestyle modifications on diverse patient cohorts, we
used a three-step analytic approach. First we developed a series of mathematical models to create a tool to test hypothetical treatment effects using the 10-year ASCVD risk calculator. We then applied the tool to randomly generated cohorts as a simulation to demonstrate the concept. These randomly generated cohorts were designed to appear statistically indistinguishable but to have different baseline ASCVD risks, thereby being less likely to respond differently to intervention. Lastly we applied the tool to four real-world clinic cohorts. In this last application we also extrapolated the effects of non-pharmacologic interventions to determine which intervention is the best for any given cohort.

Model: Baseline 10-Year ASCVD Risk and Risk Change Equations) The modifiable risk factors tested were total cholesterol, HDL cholesterol, systolic blood pressure and smoking status.

Application: Effect of Quality Improvement Interventions

We conducted a literature search of Cochrane Review Articles for non-pharmacologic interventions that affected any of the four modifiable risk factors in the 10-year ASCVD risk calculator, systolic blood pressure, total cholesterol, HDL cholesterol and smoking status. From these reviews, we extracted the effect size on the modifiable risk factor if it was shown to be statistically significant. For each intervention, we then applied the effect onto each patient who would have met the inclusion criteria for the intervention and calculated a new normalized aggregate risk score.
Statement of Contributions

The original concept for the development of this tool was theorized by Dr. Michael Robert O’Brien during his first year as a Robert Wood Johnson Clinical Scholar. Early prototypes of the tool to calculate baseline 10-year ASCVD risk were developed by Giulio C. Rottaro and Jinyi Zhu. The literature search, proposal, development, and data analysis were conducted by Giulio C. Rottaro under the guidance of Dr. Bradley Richards and Dr. Brita Roy. Raw data was collected directly from the electronic health records system by the Yale Joint Data Analytics Team. The protocol was reviewed and approved by the Yale University Human Investigation Committee (Protocol number 1601017016).

Results

Simulation: Variance in Baseline Risk of Randomly Generated Cohorts

The average normalized aggregate risk for these cohorts was 124.7 events per 1,000 patients in 10 years. The standard deviation was 4.8 events per 1,000 patients in 10 years. Of the 10,000 cohorts, 464 had a normalized aggregate risk score that was outside of a 95% confidence interval set by the previously mentioned mean and standard deviation. The distribution of all 10,000 normalized aggregate risk scores is displayed on the histogram shown in

Figure 1.
Figure 1. Histogram of normalized aggregate risk for 10,000 randomly generated patient cohorts with statistically indistinguishable demographics and risk factors.
Simulation: Variance in Sensitivity to Interventions of Randomly Generated Cohorts

Figure 2. Variances in sensitivity to total cholesterol decreases for randomly generated cohorts. Each color represents a different randomly generated cohort. Decreases in normalized aggregate risk of ASCVD events are displayed in expected ASCVD events per 1,000 patients in the next 10 years.

The mean normalized aggregate risk score for ten randomly generated cohorts was 123 events per 1,000 patients in 10 years (range: 116-132). Figure 2 shows the decrease in normalized aggregate risk for all ten cohorts resulting from total cholesterol decreases from 0 to 150 mg/dL applied to patients with a baseline risk above 7.5%. At 150 mg/dL, the mean decrease in normalized aggregate risk was 20.5 ASCVD events per 1,000 patients with a standard deviation of 1.7 events.
Figure 3 shows the decrease in normalized aggregate risk for all ten cohorts resulting from HDL cholesterol increases from 0 to 100 mg/dL applied to all patients. At 100 mg/dL, the mean decrease in normalized aggregate risk was 31.4 ASCVD events per 1,000 patients with a standard deviation of 2.5 events.

Figure 3. Variances in sensitivity to HDL cholesterol increases for randomly generated cohorts. Each color represents a different randomly generated cohort. Decreases in normalized aggregate risk of ASCVD events are displayed in expected ASCVD events per 1,000 patients in the next 10 years.

Figure 4 shows the decrease in normalized aggregate risk for all ten cohorts resulting from systolic blood pressure decreases from 0 to 80 mmHg applied to patients who qualified for intervention. The intervention was only applied to patients who met criteria as described in a previous section. (To study the differential effects
of lifestyle modifications on diverse patient cohorts, we used a three-step analytic approach. First we developed a series of mathematical models to create a tool to test hypothetical treatment effects using the 10-year ASCVD risk calculator. We then applied the tool to randomly generated cohorts as a simulation to demonstrate the concept. These randomly generated cohorts were designed to appear statistically indistinguishable but to have different baseline ASCVD risks, thereby being less likely to respond differently to intervention. Lastly we applied the tool to four real-world clinic cohorts. In this last application we also extrapolated the effects of non-pharmacologic interventions to determine which intervention is the best for any given cohort.

Model: Baseline 10-Year ASCVD Risk and Risk Change Equations) At a decrease of 80 mmHg the average decrease in normalized aggregate risk was 7.2 ASCVD events per 1,000 patients with a standard deviation of 1.1 events.
Figure 4. Variances in sensitivity to systolic blood pressure decreases for randomly generated cohorts. Each color represents a different randomly generated cohort. Decreases in normalized aggregate risk of ASCVD events are displayed in expected ASCVD events per 1,000 patients in the next 10 years.

Figure 5 shows the decrease in normalized aggregate risk for all ten cohorts resulting from smoking cessation interventions. The smoking cessation interventions ranged in probability of cessation from 0.01 to 1.00. With a probability of 1.00 the average decrease in normalized aggregate risk was 8.7 ASCVD events per 1,000 patients with a standard deviation of 1.4 events.
Figure 5. Variances in sensitivity to smoking cessation interventions for randomly generated cohorts. Each color represents a different randomly generated cohort. Decreases in normalized aggregate risk of ASCVD events are displayed in expected ASCVD events per 1,000 patients in the next 10 years.

Application: Comparison of Demographic Data for Clinic Cohorts

Across all four clinic cohorts, patients with missing data were on average younger by about two years (Table 4a and 4b). For three of the clinics cohorts there were statistically significant differences in race distributions with a higher percentage of black patients among those included compared to those excluded for missing data. In three clinic cohorts, the average systolic blood pressure was higher among those included compared to those excluded for missing data. Across all cohorts
there was higher prevalence of diabetes mellitus among patients included in the study compared to those with missing data.

Table 4a and 4b. Table comparing the demographic information for patients included in the final study versus patients with missing data who were excluded from the study. Race and ethnicity categories are set by the options available in the EHR. P-values for continuous variables obtained via student’s T-test. P-values for categorical variables obtained using Chi Square Test of Independence. P-values lesser than 0.05 are bolded.

<table>
<thead>
<tr>
<th>PCC</th>
<th>Included</th>
<th>Missing Data</th>
<th>p-value</th>
<th>SRC</th>
<th>Included</th>
<th>Missing Data</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>1131</td>
<td>2653</td>
<td>&lt;0.001</td>
<td>1461</td>
<td>734</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Average Age (years)</td>
<td>55.7</td>
<td>53.0</td>
<td>&lt;0.001</td>
<td>56.1</td>
<td>53.9</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.277</td>
<td></td>
<td></td>
<td>0.541</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>41.1%</td>
<td>39.2%</td>
<td>38.5%</td>
<td>39.9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>58.9%</td>
<td>60.8%</td>
<td>61.5%</td>
<td>60.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian (%)</td>
<td>1.1%</td>
<td>1.5%</td>
<td>0.5%</td>
<td>1.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black (%)</td>
<td>41.8%</td>
<td>36.0%</td>
<td>52.1%</td>
<td>45.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>1.1%</td>
<td>0.2%</td>
<td>0.6%</td>
<td>0.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (%)</td>
<td>0.1%</td>
<td>25.3%</td>
<td>20.9%</td>
<td>28.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>27.0%</td>
<td>36.1%</td>
<td>25.8%</td>
<td>24.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>0.001</td>
<td></td>
<td>0.090</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>25.1%</td>
<td>30.5%</td>
<td>23.8%</td>
<td>20.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>74.9%</td>
<td>69.5%</td>
<td>76.2%</td>
<td>79.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Smokers (%)</td>
<td></td>
<td></td>
<td>0.143</td>
<td></td>
<td></td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Diabetes Prevalence (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td>42.5%</td>
<td>21.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average Systolic Blood Pressure (mmHg)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td>131.8</td>
<td>130.6</td>
<td>0.102</td>
</tr>
<tr>
<td>Average Total Cholesterol (mg/dL)</td>
<td></td>
<td></td>
<td>0.783</td>
<td></td>
<td>184.2</td>
<td>195.4</td>
<td>0.007</td>
</tr>
<tr>
<td>Average HDL Cholesterol (mg/dL)</td>
<td></td>
<td></td>
<td>0.883</td>
<td></td>
<td>55.9</td>
<td>56.7</td>
<td>0.662</td>
</tr>
<tr>
<td></td>
<td>HAVEN Included</td>
<td>HAVEN Missing Data</td>
<td>P-Value</td>
<td>YIMA Included</td>
<td>YIMA Missing Data</td>
<td>P-Value</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------</td>
<td>--------------------</td>
<td>---------</td>
<td>---------------</td>
<td>--------------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Number of Patients</td>
<td>41</td>
<td>88</td>
<td></td>
<td>1925</td>
<td>1046</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average Age (years)</td>
<td>51.5</td>
<td>50.3</td>
<td>0.458</td>
<td>59.0</td>
<td>57.6</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.513</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>48.8%</td>
<td>55.7%</td>
<td></td>
<td>41.6%</td>
<td>42.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>51.2%</td>
<td>44.3%</td>
<td></td>
<td>58.4%</td>
<td>57.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0.128</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Asian (%)</td>
<td>0.0%</td>
<td>0.0%</td>
<td></td>
<td>3.7%</td>
<td>4.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black (%)</td>
<td>2.4%</td>
<td>3.4%</td>
<td></td>
<td>18.8%</td>
<td>10.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>19.5%</td>
<td>4.5%</td>
<td></td>
<td>0.7%</td>
<td>0.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (%)</td>
<td>2.4%</td>
<td>5.7%</td>
<td></td>
<td>66.8%</td>
<td>76.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other/Unknown (%)</td>
<td>75.6%</td>
<td>86.4%</td>
<td></td>
<td>9.8%</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>0.957</td>
<td></td>
<td></td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>87.8%</td>
<td>86.4%</td>
<td></td>
<td>10.1%</td>
<td>7.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic (%)</td>
<td>12.2%</td>
<td>13.6%</td>
<td></td>
<td>89.9%</td>
<td>92.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Smokers (%)</td>
<td>7.3%</td>
<td>15.9%</td>
<td>0.287</td>
<td>9.1%</td>
<td>8.7%</td>
<td>0.772</td>
<td></td>
</tr>
<tr>
<td>Diabetes Prevalence (%)</td>
<td>17.1%</td>
<td>12.5%</td>
<td>0.671</td>
<td>22.6%</td>
<td>12.0%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Average Systolic Blood Pressure (mmHg)</td>
<td>125.9</td>
<td>119.4</td>
<td><strong>0.012</strong></td>
<td>128.0</td>
<td>126.8</td>
<td><strong>0.016</strong></td>
<td></td>
</tr>
<tr>
<td>Average Total Cholesterol (mg/dL)</td>
<td>193.7</td>
<td>195.0</td>
<td>0.904</td>
<td>190.3</td>
<td>189.5</td>
<td>0.579</td>
<td></td>
</tr>
<tr>
<td>Average HDL Cholesterol (mg/dL)</td>
<td>52.0</td>
<td>57.6</td>
<td>0.225</td>
<td>60.2</td>
<td>55.9</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Application: Modeled Risk Reduction among Actual Clinic Cohorts**

The baseline normalized aggregate risk of the SRC cohort was 117.3 ASCVD events per 1,000 patients in the next 10 years. For the HAVEN cohort it was 55.2 and for the PCC and YIMA cohorts it was 104.6 and 100.8 respectively. For an intervention targeting reduction of systolic blood pressure, 158 patients from PCC, 251 from SRC, 4 from HAVEN and 183 from YIMA met criteria for hypertension treatment based on age and systolic blood pressure. The effects of interventions
targets ranging from a decrease of 0 mmHg to 80 mmHg for each cohort is shown in Figure 6.

![Variances in Sensitivity to SBP Decreases for Different Clinic Cohorts](image)

**Figure 6.** Variances in sensitivity to systolic blood pressure decreases for the four clinic cohorts. The clinic cohorts shown are PCC (Blue), SRC (Green), HAVEN (Brown), and YIMA (Black). Decreases in normalized aggregate risk of ASCVD events are displayed in expected ASCVD events per 1,000 patients in the next 10 years.

For an intervention on total cholesterol, 557 patients from PCC, 822 from SRC, 9 from HAVEN and 901 from YIMA meet criteria for treatment based on a baseline ASCVD risk score greater than 7.5%. The effects of interventions targets ranging from a decrease of 0 mg/dL to 150 mg/dL for each cohort is shown in Figure 7.
Figure 7. Variances in sensitivity to total cholesterol decreases for the four clinic cohorts. The clinic cohorts shown are PCC (Blue), SRC (Green), HAVEN (Brown), and YIMA (Black). Decreases in normalized aggregate risk of ASCVD events are displayed in expected ASCVD events per 1,000 patients in the next 10 years.

An increase in HDL cholesterol was applied broadly to all patients in all clinic cohorts. The effects of intervention targets ranging from an increase of 0 mg/dL to 100 mg/dL in HDL cholesterol for each cohort is shown in Figure 8.
Figure 8. Variances in sensitivity to HDL cholesterol increases for the four clinic cohorts. The clinic cohorts shown are PCC (Blue), SRC(Green), HAVEN (Brown), and YIMA (Black). Decreases in normalized aggregate risk of ASCVD events are displayed in expected ASCVD events per 1,000 patients in the next 10 years.

Among the four cohorts the smoking prevalence was 14.1%, 30.9%, 7.3%, and 9.1% for the PCC, SRC, HAVEN and YIMA clinic cohorts respectively. The effects of smoking cessation interventions with probabilities ranging from 0 to 1.0 for each cohort is shown in Figure 9.
Figure 9. Variances in sensitivity to smoking cessation interventions for the four clinic cohorts. The clinic cohorts shown are PCC (Blue), SRC(Green), HAVEN (Brown), and YIMA (Black). Decreases in normalized aggregate risk of ASCVD events are displayed in expected ASCVD events per 1,000 patients in the next 10 years.

Application: Secondary Analysis of Clinic Cohorts

A secondary analysis of the clinic cohorts was performed to determine if using the last known blood pressure instead of the one-year average significantly changed any of the results. The baseline normalized aggregate risk for all clinic cohorts were within 1 ASCVD event of the previously calculated baseline using the average systolic blood pressure. The rest of the analysis remained mostly unchanged except
for a slightly different sensitivity curve to systolic blood pressure interventions, shown in Figure 10.

**Figure 10.** Variances in sensitivity to systolic blood pressure decreases for the four clinic cohorts using the last known systolic blood pressure instead of the average. The clinic cohorts shown are PCC (Blue), SRC (Green), HAVEN (Brown), and YIMA (Black). Decreases in normalized aggregate risk of ASCVD events are displayed in expected ASCVD events per 1,000 patients in the next 10 years.

**Application: Effect of Quality Improvement Interventions on the Clinic Cohorts**

A total of 38 different Cochrane Review articles describing lifestyle interventions for direct or indirect ASCVD prevention were found. Twelve described diet and exercise interventions, eight described interventions on blood pressure
alone, fourteen described different methods of smoking cessation, and one described effects of statin therapy.

Of the twelve diet and exercise interventions, seven had statistically significant effects on at least one of the modifiable risk factors. These seven interventions are described below.

- **Usinger et al.** (2012) described the use of fermented milk to lower systolic blood pressure on a general population by 2.45 mmHg. This effect was applied to all patients in all clinic cohorts who had a baseline systolic blood pressure above 110 mmHg.⁸

- **Rees et al.** (2013) described the use of general dietary advice given by providers. As compared to no advice, this intervention was found to have statistically significant effects on total cholesterol and systolic blood pressure on a general population. For male patients, total cholesterol decreased by 9.2 mg/dL, but no significant effect was found for women. For patients with a high risk of cardiovascular disease, the decrease in systolic blood pressure was 2.95 mmHg, but there was no statistically significant effect for the general population. High risk was not well defined in Rees et al. and therefore a cutoff of 7.5% per individual patient was used for the purpose of our analysis. A lower bound of 80 mg/dL for total cholesterol and 110 mmHg was used for systolic blood pressure interventions.⁹

- **Hartley et al.** (2013) reviewed the effects of interventions to increase fruit and vegetable consumption. Although studies which provided
fruits and vegetables were included in the review, they were found to have no benefit across all variables compared to interventions which focused on advice only. Among a general population, advice to increase fruit and vegetable consumption was found to have a 3.0 mmHg decrease in systolic blood pressure. We used the lower bound of 110 mmHg for this intervention.¹⁰

- **Rees et al.** (2013) reviewed the effects of a Mediterranean diet on many risk factors. It was found that among a general population adhering to a Mediterranean diet, total cholesterol was decreased by 6.2 mg/dL. A lower bound of 80 mg/dL was utilized when applying this intervention to the clinic cohorts.¹¹

- **Ebrahim et al.** (2011) compiled the results of multifactorial interventions for the primary prevention of ASCVD. These interventions consisted of counseling and education. They found that these interventions had no benefit for a general population but had significant beneficial effects for patients with hypertension or diabetes mellitus. Therefore, this intervention was only applied to those patients with either hypertension or diabetes within our clinic cohorts. Total cholesterol was reduced by 2.7 mg/dL, while systolic blood pressure was decreased by 2.74 mmHg for those not on antihypertensive drugs while it was decreased by 3.89 mmHg for patients on antihypertensive drugs. Smoking cessation counseling and education resulted in a 15% reduction in smoking prevalence.¹²
• **Adler et al.** (2013) studied the effects of a reduced salt diet on the general population. The advice to decrease dietary salt had a 4.14 mmHg decrease in systolic blood pressure among patients with hypertension but no effect on normotensive patients.\(^\text{13}\)

• **Siebenhofer et al.** (2011) covered the effects of dietary interventions aimed at weight reduction on ASCVD prevention. The only significant effect was on systolic blood pressure with an average decrease of 4.49 mmHg among hypertensive patients. A lower bound of 110 mmHg was again used on the intervention.\(^\text{14}\)

Of the eight Cochrane Reviews found to target hypertension as a primary prevention strategy for ASCVD, only three were included in this study. Reasons for exclusion were that they were either based on pharmacotherapies, which is out of the scope of this study, or did not include outcomes on systolic blood pressure. Since these interventions were focused on hypertension, the effects were applied only to patients who had a systolic blood pressure above 140 mmHg if they were under 60 years of age or 150 mmHg for 60 or more years of age, or patients who were already in treatment for hypertension. These interventions are described below.

• **Glynn et al.** (2010) reviewed the effects of multiple types of interventions including self-monitoring, health professional led care, organizational interventions, and appointment reminders, respectively. Organizational interventions were further described as interventions that aimed to improve the delivery of care. One example includes the
Hypertension Detection and Follow-Up Program from 1979. These interventions reduced systolic blood pressure by 2.53 mmHg, 2.52 mmHg, 6.00 mmHg and 4.56 mmHg, respectively. Patient and physician education were also studied independently but neither was found to have a significant effect on systolic blood pressure.

- **Dickinson et al.** (2006) described the use of calcium supplements for the treatment of hypertension. For hypertensive patients with a baseline systolic blood pressure above 145 mmHg, calcium supplements were shown to decrease systolic blood pressure by 2.49 mmHg.

- **Dickinson et al.** (2008) compiled the effects of relaxation techniques on hypertensive patients. These techniques were found to have a 5.5 mmHg decrease in systolic blood pressure.

The fourteen Cochrane Reviews found describing smoking cessation interventions all reported the odds ratio as its final outcome. The odds ratio was not possible to use in this model as we would need to know the smoking cessation rate without an intervention. Therefore, smoking cessation interventions were omitted from this part of the study. Similarly, the one intervention found specifically for lowering of total cholesterol was pharmacologic in nature and out of the scope of this study. The overall results for each of the interventions described above are shown in Table 6.
**Table 5.** Summary of interventions chosen for application from Cochrane reviews. Some of the interventions described have different effects on different populations.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Target patient population</th>
<th>Changes to Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total Cholesterol (mg/dL)</td>
</tr>
<tr>
<td>Diet Advice from Rees et al., 2013 (Chol and BP)</td>
<td>Male patients / Patients with an ASCVD risk &gt; 7.5%</td>
<td>-9.2 / 0</td>
</tr>
<tr>
<td>Fermented Milk from Usinger et al., 2012 (BP)</td>
<td>All patients</td>
<td>-2.45</td>
</tr>
<tr>
<td>Advice to eat F&amp;V from Hartley et al., 2013 (BP)</td>
<td>All patients</td>
<td>-3.00</td>
</tr>
<tr>
<td>Mediterranean Diet from Rees et al., 2013 (Chol)</td>
<td>All patients</td>
<td>-6.20</td>
</tr>
<tr>
<td>Multifactor Intervention from Ebrahim et al., 2011 (Chol, BP, Smoke)</td>
<td>Hypertension or diabetes mellitus diagnosis (Antihypertensives / No treatment)</td>
<td>-2.7/-2.7</td>
</tr>
<tr>
<td>Low Salt Diet from Adler et al., 2013 (BP)</td>
<td>Patients with hypertension</td>
<td>-4.14</td>
</tr>
<tr>
<td>Weight Reduction Diet from Siebenhofer et al., 2011 (BP)</td>
<td>Patients with hypertension</td>
<td>-4.49</td>
</tr>
<tr>
<td>Self Monitoring of HTN from Glynn et al., 2010 (BP)</td>
<td>Patients with hypertension</td>
<td>-2.53</td>
</tr>
<tr>
<td>Health Professional Led Care of HTN from Glynn et al., 2010 (BP)</td>
<td>Patients with hypertension</td>
<td>-2.52</td>
</tr>
<tr>
<td>Organizational Interventions on HTN from Glynn et al., 2010 (BP)</td>
<td>Patients with hypertension</td>
<td>-6.00</td>
</tr>
<tr>
<td>Appointment Reminders on HTN from Glynn et al., 2010 (BP)</td>
<td>Patients with hypertension</td>
<td>-4.56</td>
</tr>
<tr>
<td>Calcium Supplements for HTN from Dickinson et al., 2009 (BP)</td>
<td>Patients with hypertension</td>
<td>-2.49</td>
</tr>
<tr>
<td>Relaxations for HTN from Dickinson et al., 2009 (BP)</td>
<td>Patients with hypertension</td>
<td>-5.50</td>
</tr>
</tbody>
</table>
Table 6. Estimated changes in normalized aggregate risk of various interventions. Each of the interventions listed has an effect on systolic blood pressure, total cholesterol, HDL cholesterol or smoking status. Data on the effect size was pulled from Cochrane Reviews. The baseline risk and the changes are shown in expected ASCVD events per 1,000 patients in the next 10 years. Dark green shading indicates the interventions with the greatest positive outcome for each clinic cohort. The HAVEN clinic with its lower baseline risk appears to respond more efficiently to interventions aimed at the general population compared to the other three clinics.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Change in Normalized Aggregate Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCC</td>
</tr>
<tr>
<td>Baseline risk (events per 1,000 patients)</td>
<td>104.60</td>
</tr>
<tr>
<td>Diet Advice from Rees et al., 2013 (Chol and BP)</td>
<td>-4.71</td>
</tr>
<tr>
<td>Fermented Milk from Usinger et al., 2012 (BP)</td>
<td>-3.25</td>
</tr>
<tr>
<td>Advice to eat F&amp;V from Hartley et al., 2013 (BP)</td>
<td>-3.97</td>
</tr>
<tr>
<td>Mediterranean Diet from Rees et al., 2013 (Chol)</td>
<td>-2.30</td>
</tr>
<tr>
<td>Multifactor Intervention from Ebrahim et al., 2011 (Chol, BP, Smoke)</td>
<td>-4.63</td>
</tr>
<tr>
<td>Low Salt Diet from Adler et al., 2013 (BP)</td>
<td>-2.20</td>
</tr>
<tr>
<td>Weight Reduction Diet from Siebenhofer et al., 2011 (BP)</td>
<td>-4.53</td>
</tr>
<tr>
<td>Self-Monitoring of HTN from Glynn et al., 2010 (BP)</td>
<td>-2.57</td>
</tr>
<tr>
<td>Health Professional Led Care of HTN from Glynn et al., 2010 (BP)</td>
<td>-2.56</td>
</tr>
<tr>
<td>Organizational Interventions on HTN from Glynn et al., 2010 (BP)</td>
<td>-6.00</td>
</tr>
<tr>
<td>Appointment Reminders on HTN from Glynn et al., 2010 (BP)</td>
<td>-4.60</td>
</tr>
<tr>
<td>Calcium Supplements for HTN from Dickinson et al., 2009 (BP)</td>
<td>-0.99</td>
</tr>
<tr>
<td>Relaxations for HTN from Dickinson et al., 2008 (BP)</td>
<td>-5.52</td>
</tr>
</tbody>
</table>
Discussion

The results from our simulations with randomly generated cohorts with indistinguishable demographics demonstrated that there is a large amount of potential variance in baseline normalized aggregate risk of ASCVD and response to interventions. As a proof of concept these results support the utility of the tool we have created to analyze clinic populations. These results were replicable when applied to four real clinic cohorts. The ASCVD risk reduction from a given intervention was dependent on baseline normalized aggregate risk and average value of the modified risk factor. Furthermore, the effects of lifestyle interventions on ASCVD risk could be modeled through their effects on the modifiable risk factors by our tool. The intervention with the highest ASCVD risk reduction was not the same across all cohorts.

The 10,000 randomly generated cohorts with the same demographic characteristics had significantly different baseline normalized aggregate risk. Importantly, this demonstrates that population averages should not be used in the 10-year ASCVD risk calculator to estimate the risk of a population. Doing so would result in inaccurate prediction of normalized aggregate risk. Further, when we tested the response of these randomly generated cohorts to single variable interventions, the response curves indicated that there is decreasing marginal risk reduction to interventions aiming to reduce total cholesterol, HDL cholesterol, and systolic blood pressure. These patterns were also observed on the four real clinic populations with the addition of the fact that response to the same interventions differed by baseline risk. In the case of total cholesterol and systolic blood pressure, we observed that
cohorts responded differently to interventions on the same risk factor but that these relationships may change depending on the effect size of said intervention. In other words, the effect of interventions on systolic blood pressure will not always be better for cohort A compared to cohort B but that this relationship depends on the amount of change in systolic blood pressure.

Chu et al. (2016) demonstrated that the use of simulation with the 10-year ASCVD risk calculator has a role in choosing high-yield primary prevention interventions.\(^2\) They created hypothetical patients of different characteristics and estimated the effect of different interventions on each of these patients. That study created a chart that would allow a provider to prioritize an intervention for any given patient based on the expected ASCVD risk decrease. However, their models are limited to individual patients and not whole populations. Our results suggest that similar methods are applicable to whole populations. Franco et al. (2007) used similar statistical techniques to our model using the Framingham Risk Score.\(^3\) They concluded that smoking-cessation was the most cost-effective intervention for the primary prevention of ASCVD within the Framingham cohorts. With our tool, we aimed to combine the principles of these two papers to guide clinics in choosing the best primary prevention intervention(s) for their specific patient population.

The effect of thirteen different non-pharmacologic evidence-based interventions on systolic blood pressure, total cholesterol, HDL cholesterol and/or smoking prevalence had different effects on ASCVD risk across four clinic cohorts. According to our model, the highest yield intervention for the HAVEN clinic was to implement a diet advice program as described in Rees at al., while all the other
clinics would benefit most from an organizational quality improvement project to address hypertension as described in Glynn et al.\textsuperscript{9,16} However, the organizational interventions described in Glynn et al. varied in type and effect size making the effects less reproducible. The only shared commonality is that they “aimed to improve the delivery of care.” Another high yield intervention among three of the cohorts was a weight reducing diet as described by Siebenhofer et al. (2011)\textsuperscript{14} It is worth noting that this intervention was not limited to advice only and may require a great amount of resources to fully implement. Therefore, any clinic using the tool to choose an intervention could face a choice between these two difficult to implement options. However, they approach this decision with more knowledge of the expected outcomes. Alternatively, other interventions could be relatively easy to implement and have a great impact, such as diet advice as described by Rees et al.\textsuperscript{9}

The HAVEN clinic had the most significantly different population among the four clinics. The patients were younger, there were far more patients who identified as Hispanic and the baseline normalized aggregate ASCVD risk was significantly lower. As such it was not surprising that its responses to the many non-pharmacologic interventions were also different from the other three clinics. At the HAVEN clinic, interventions that target the general population were much more successful than interventions that target high risk populations (i.e. patients with hypertension). This is in contrast to the three other clinics where the opposite was true.

Another factor clinics may consider is the number of patients involved in each intervention. The fruits and vegetable dietary interventions were applied to entire
clinic cohorts whereas the hypertension interventions described by Glynn et al. were only applied to hypertensive patients. So providers will have a tradeoff between high yield interventions on a few high risk patients or more broad interventions with similar results on the overall ASCVD risk.

The tool we have created allows the ACC/AHA 10-year ASCVD risk calculator to be used as a metric to monitor and reduce ASCVD risk in a clinic cohort. Clinic providers and/or administrators will be able to use the tool to allocate their limited resources to the ASCVD prevention strategy with the highest predicted impact based on quantitative predictions. Ultimately we envision such a tool being used by clinics to select and monitor primary prevention strategies for ASCVD, similarly to how a physician already uses the tool to guide prevention strategies at the individual patient level. For example, a clinic hires a new health educator and they are faced with choosing a new project for this employee: smoking cessation, or hypertensive management education. While it would be simple choice if everyone in the clinic cohort is a smoker but there are no patients with hypertension (or vice versa), the choice becomes more complicated if that is not the case. The current literature does not offer a threshold prevalence above which a smoking cessation intervention becomes more efficient at reducing ASCVD risk than hypertension education; we discovered that the change in risk varies significantly by cohort. The tool we have created would be able to tell the health educator which of these interventions would have the greatest impact on the population of this clinic. After initiation of the intervention, the tool can also be used to continuously monitor the ASCVD risk in the community for continuing quality improvement cycles.
At a larger scale, hospitals are now mandated to conduct community health assessments and identify areas of need. By incorporating data from the EHR and community health assessments, the tool we created can model the effects of interventions on whole communities. This data can be utilized by hospitals or public health departments to supplement community needs assessments and guide policy/programs. Community leaders would, for example, be able to prioritize their resources to an exercise campaign or a farmers’ market, depending on the effect sizes estimated by our tool. The reports generated by our tool may even be used as supporting evidence in grant application or project proposals. The 2003 AHA Guide for Improving Cardiovascular Health at the Community Level suggests that community based interventions be chosen based solely on the identification of high risk groups and/or the feasibility of said interventions (i.e. the prevalence of smoking, and the feasibility of an ad campaign). In this guideline, efficacy of interventions at the community level is not accounted for, however our tool can supplement this decision-making process by providing quantitative efficacy predictions.

**Limitations of This Study**

This study has important limitations. Our study relies on assumptions made for our statistical prediction method. The first assumption is that all factors except the one being modified remain unchanged during the interventions. For example, we assume that while patients participate in an intervention on blood pressure that their age, smoking status, diabetes diagnosis and cholesterol levels remain unchanged.

Another assumption in our study is that effects described in Cochrane reviews will be the same among the patient populations in our study. There are likely factors
beyond our model that will affect the results and therefore the observed ASCVD risk reduction observed will also differ.

Another set of assumptions are the lower boundaries of 110 mmHg and 80 mg/dL used for systolic blood pressure and total cholesterol, respectively. Here we assumed that patients who started above these lower boundaries would not be able to go below it. This was meant to simulate the way real patients may respond to interventions and the natural limits of any intervention. Though the boundaries were chosen based on clinical experience, the real response by patients may vary.

Our included sample may have been biased. The patients with missing data across all clinics had at least one statistically significant difference in their demographics, suggesting systematic differences between these populations. For example, patients with missing data tended to be younger in all clinics, likely because they did not receive cholesterol screening or did not return to clinic. Among three of the four clinics, patients with missing data were less likely to have a diagnosis of diabetes mellitus. This likely reflects either not enough follow up to establish the diagnosis or a closer follow up of patients who do have the diagnosis. These differences indicate that patients excluded from analyses may have different baseline risk and therefore may respond differently to the interventions. This also brings up the fact that patient cohorts are not static and that new patients will join the panel while other patients leave. These factors are not accounted for in our estimates.

Lastly, we do not account for any of the other positive or negative effects of any intervention outside of the ASCVD risk factors or on overall ASCVD risk. In the
case of total cholesterol reduction for example, it has been shown that using statin therapy has an effect on ASCVD risk beyond what is accounted for by total cholesterol reduction.\textsuperscript{21}

**Next Steps**

Ultimately, we aim to provide clinicians with the tools necessary to choose the most efficient ASCVD prevention strategy. Though this application is currently only able to identify the goals of therapy and expected impact of evidence-based interventions, in the future it can be adapted to make recommendations using cost efficiency data and/or cost estimates from the literature. For example, Pandya et al. (2015) built a model that estimated cost-effectiveness for different statin therapy thresholds using known data on their efficiency, their cost and the ASCVD 10-year risk calculator.\textsuperscript{5} We envision statistical models similar to those used in Pandya et al. 2015 except applied at the clinic population level, using real-time data and across all modifiable risk factors.\textsuperscript{5}

Furthermore, the feasibility and adoption of such a tool remains to be elucidated. We plan to perform a qualitative study to assess primary care clinic directors’ ease of use, interpretation and applicability of the application. We then aim to conduct a controlled trial involving several clinics randomized to use the tool or to use usual quality improvement strategies to decrease ASCVD events. The objective of such a trial would be to determine if the strategies and goals suggested by the tool can outperform standard practices.
References


15. Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure, including mild


