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Preventable Cardiovascular Disease Events Among the U.S. Population According to 2017 ACC/AHA High Blood Pressure Guideline

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Epidemiology

by

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DEDICATION

To

my mom

for your endless love and care

and your confidence on my enlightened future.

To

all my friends

for your support and creation of our precious memories.

“What-E'er Thou Art, Act Well Thy Part.”

William Shakespeare

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ABSTRACT OF THE THESIS

Preventable Cardiovascular Disease Events Among the U.S. Population According to 2017 ACC/AHA High Blood Pressure Guideline

By

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Master of Science in Epidemiology

University of California, Irvine, 2019

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Hypertension is a risk factor for cardiovascular diseases including myocardial infarction, stroke, heart failure, angina, and coronary heart disease. It is estimated that over one third of the world population is experiencing hypertension, however, only half of the hypertensive population had blood pressure under control. In 2017, ACC/AHA published an updated high blood pressure guideline and redefine people who had their systolic blood pressure between 130-140 mmHg or diastolic blood pressure between 80-90 mmHg as having hypertension. The recommended treatment target became 130/80 mmHg instead of 140/90 mmHg. The aim of the study is to predict and compare the number of preventable CVD events if blood pressure can be successfully lowered to 140/90 mmHg and 130/80 mmHg, respectively, in an ideal scenario, using 2013-2016 National Health and Nutrition Survey (NHANES). Around 385,000 CVD events could be potentially prevented in 10 years if blood pressures were controlled under 130/80 mmHg. Around 208,000 CVD events could be potentially prevented in 10 years the target was 140/90 mmHg. Middle-aged subgroups (50-69 years old), whites, Framingham high-risk subgroup (FRS > 20%), and

comorbidity high-risk subgroup tended to have the highest increase in the number of preventable CVD events. Based on PAR, older persons, people who had FRS > 20%, and people who were in the comorbidity low-risk subgroup tended to benefit more than their respective comparison groups. This estimation provided us a with better understanding of the implications of the 2017 ACC/AHA guideline and the importance of controlling blood pressure to the new target.

CHAPTER 1

INTRODUCTION

Hypertension is a dangerous condition where pressure of the blood in the blood vessels is higher than it should be. It is estimated that over one-third (75 million people) of the world population is experiencing hypertension, and only about half of the hypertensive population has high blood pressure under control.[1,2] People with hypertension bear an elevated risk of developing cardiovascular diseases (CVD) such as myocardial infarction, stroke, angina, etc.[3-5]

The Systolic Blood Pressure Intervention Trial (SPRINT) randomly assigned participants who aged ≥ 50 years old with systolic blood pressure (SBP) ≥ 130 mmHg to either intensive SBP treatment goal (target of ≤ 120 mmHg) or standard SBP treatment goal (target of ≤ 140 mmHg). The trial reported a significant decrease in risk of experiencing CVD events (HR = 0.75, 95% CI 0.64-0.89) and a significant lower all-cause mortality (HR = 0.73, 95% CI, 0.60-0.90) in the intensive treatment group compared to those of the standard treatment group.[6] After publication of these findings, in November 2017, American College of Cardiology (ACC) and American Heart Association (AHA) published an updated guideline for hypertension, in regards to its prevention, detection, evaluation and management. The new guideline established new blood pressure categories (normal: systolic blood pressure (SBP) <120 mmHg and diastolic blood pressure (DBP) <80 mmHg; elevated: SBP 120-129 mmHg and DBP <80 mmHg; stage 1 hypertension: SBP 130-139 mmHg or DBP 80-89 mmHg; stage 2 hypertension: SBP ≥140 mmHg or DBP ≥ 90 mmHg). The most noticeable difference from previous guideline in 2003, the *Seventh*

Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7), is that the 2017 ACC/AHA guideline moved the "SBP 130-139 mmHg/ DBP 80-90 mmHg" group from prehypertension to stage 1 hypertension, thus lowering the treatment goal to <130/80 mmHg from the previously 140/90 mmHg.[7]

Muntner et al. have examined the prevalence of hypertension among U.S adults aged ≥ 20 years old based on the updated guideline. Around 14% of the population was recategorized as having hypertension.[8] Muntner et al.'s paper brought about discussions on benefits and harms of introducing new hypertension definition to the clinics. Some study groups raised the issue of "gray zone" patients (patients who have SBP between 130 and 140 mmHg and DBP between 80 and 90 mmHg) as they will be redefined as having hypertension but will not be advised to be treated antihypertensive medications.[9] However, Bell et al. commented in their review article that even though the "gray zone" patients are not the major beneficiaries, patients who have high CVD risk (those who have baseline 10-year CVD risk > 20%, or those who have a history of CVD) will benefit most by controlling blood pressure to a lower target.[10] Thus, it is necessary to estimate and quantify the benefit of the new guideline for high CVD risk population.

CHAPTER 2

OBJECTIVES

The purpose of the study is to predict and compare the number of preventable CVD events if blood pressure can be successfully lowered to 140/90 mmHg and 130/80 mmHg, respectively, in an ideal scenario, using 2013-2016 National Health and Nutrition Survey (NHANES). We also assessed the 10-year CVD risk score using D'Agostino Framingham Heart Study risk prediction algorithms for total CVD and calculated the number of predicted CVD events in 10 years. And we further stratified our estimates by age groups, gender, ethnicity, Framingham risk groups, and comorbidity risk groups.

CHAPTER 3

METHODS

3.1 Sample Description

National Health and Nutrition Examination Survey (NHANES) is designed to evaluate the health and nutritional status of civilian noninstitutionalized U.S. population. The survey uses a complex, multistage probability sampling design to select representatives. In consideration of oversampling of certain subgroups and non-responses, a sampling weight is assigned to each participant. NHANES data are publicly released in 2-year cycles since 1999.[11]

For current analysis, we merged 4 years of NHANES data from 2013 to 2016, which include 8380 participants aged 30-74 years old. After excluding participants who had any of the following conditions: 1) had previous CVD events including coronary heart disease, heart attack, angina, stroke, and heart failure (n=850), which is defined as participants who answered "yes" to the question "Have you ever told had congestive heart failure/coronary heart disease/angina/heart attack/stroke?", or 2) had missing data in total cholesterol level and high-density lipoprotein (HDL) cholesterol level (n=592), smoking status (n=5), antihypertensive medication record (n=6), blood pressure measurements (n=214), the remaining sample size was 6713 participants in our analysis. Among these 6713 participants, 1206 participants (18.0% of the initial sample population) had stage 2 hypertension. We looked at stage 2 hypertension population because they are considered having high CVD risk, and it is straightforward to compare the difference between predicted preventable CVD events after lowering the blood pressure to 140/90 mmHg and

to 130/80 mmHg; while for stage 1 hypertension population, no direct comparison can be made to show the benefits of controlling blood pressure to a lower target. Of these 1206 participants, we finalized our study population to 527 participants (6.2% of the initial sample population) with untreated stage 2 hypertension to predict the number of CVD events in 10 years, as well as the number of preventable CVD events after lowering blood pressure to certain targets. Treated stage 2 hypertension patients are not included in the study because we are interested in the benefit of initiating antihypertensive medication. Ethics Review Board has approved NHANES protocols, and signed informed consents were obtained from all participants. (A flowchart was presented in Appendix A.)

3.2 Blood Pressure Measurement

Blood pressure measurements were carried out by trained physicians using calibrated mercury true gravity wall model sphygmomanometer and appropriate calibrated V-Lok cuffs under standard physician protocol.[12] Participants were asked to sit in chair in position and rest for 5 minutes. After that up to three blood pressure readings were obtained. The average of up to three blood pressure readings was used to define SBP and DBP. If only one reading was obtained, that reading was used as the average. According to 2017 ACC/AHA Guideline[7], stage 2 hypertension is defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg.

3.3 Other Risk Factor Measurement or Definition

a. Cholesterol

Blood samples were drawn from participants at the Mobile Examination Centers (MEC) and were processed and aliquoted into vials for storage. Lipid levels were measured from serum by NHANES Diabetes Laboratory. Total cholesterol was measured using enzymatic reactions, and HDL cholesterol was measured by the direct immunoassay method.[13-15]

b. Diabetes

A participant is defined as having diabetes if he/she had any of the following conditions: 1) had fasting glucose ≥ 126mg/dL, or 2) had non-fasting glucose ≥ 200mg/dL, or 3) had HbA1c ≥ 6.5%, or 4) reported current use of diabetic medication or insulin, or 5) answered "yes" to the question "Have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?".

c. Chronic Kidney Disease

Serum creatinine level of each participant was measured from blood sample drawn at MEC. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation: $eGFR = 141*\min(\text{serum creatinine}/k,1)^{A} *\max(\text{serum creatinine}/k,1)^{-1.209} *0.993^{age} *1.018$ (if female), where A = -0.411 for men and -0.329 for women, k = 0.9 for men and 0.7 for women, min = minimum of serum creatinine/k or 1, max = maximum of serum creatinine/k or 1.[16] A person is defined as having serious chronic kidney disease if his/her eGFR is less than 60 ml/min/1.73m^2.

d. Others

Age is categorized into five subgroups: 30-39 years, 40-49 years, 50-59 years, 60-69 years, ≥ 70 years. Current smoker is defined as participants who answered "yes" to the question "Have you smoked at least 100 cigarettes in your entire life?" and who answered "yes" to the question "Do you now smoke cigarettes?". Obesity is defined as body mass index ≥ 30 kg/m^2. A person is defined to have family history of myocardial infarction (fatal or non-fatal) if he/she answered "yes" to the question "Including living and deceased, were any of your close biological that is, blood relatives including father, mother, sisters or brothers, ever told by a health professional that they had a heart attack or angina before the age of 50?".

3.4 Risk Group Definition

We used D'Agostino Framingham Heart Study risk prediction algorithms for total CVD[17] to estimate the 10-year CVD risk in the sample and weighed the risk to the U.S population. We chose this algorithm because it is the only known algorithm that estimates all CVD endpoints for the U.S population. The equation for men is: Framingham Risk Score (FRS) = 100*(1-0.88936^A), where A = exp((3.06117*log(age) + 1.1237*log(total cholesterol level) - 0.93263*log (HDL cholesterol level) + 1.93303*log(SBP if untreated with antihypertensive medication) + 1.99881*log(SBP if treated with antihypertensive medication, in our case would be 0) + 0.65451*(if current smoker) + 0.57367*(if having diabetes) - 23.9802). The equation for women is: Framingham Risk Score (FRS) = 100*(1-0.95012^A), where A = exp((2.32888*log(age) + 1.20904*log(total cholesterol level) - 0.70833*log (HDL cholesterol level) + 2.76157*log(SBP if untreated with antihypertensive

medication) + 2.82263*log(SBP if treated with antihypertensive medication, in our case would be 0) + 0.52873*(if current smoker) + 0.69154*(if having diabetes) – 26.1931). Three Framingham risk subgroups were created based on the score: low risk (FRS < 10%), intermediate risk (FRS ~ 10-20%), high risk (FRS > 20%).

To further evaluate the impact of a lower blood pressure target on population with certain CVD comorbidities or risk factors, we introduced another risk stratifying method. Referring to 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease[18], a comorbidity high-risk group among untreated stage 2 hypertension population is defined as individuals who had either 1) diabetes, or 2) chronic kidney disease (stage 3 or above), or 3) two or more risk factors including current smoking, obesity, family history of CVD, elevated total cholesterol level (≥ 200 mg/dL), and decreased HDL cholesterol level (< 40 mg/dL for men, < 50 mg/dL for women). A comorbidity low-risk group would be individuals without diabetes or chronic kidney disease and had less than two risk factors mentioned above.

3.5 10-Year CVD Events and Preventable CVD Events Prediction

Our first step was to calculate the number of predicted CVD events by multiplying the average 10-year CVD risk of the untreated stage 2 hypertension population with the NHANES population size, stratifying by age subgroup, ethnicity, Framingham risk subgroup, and CVD comorbidity subgroup. Next, we recalculated a new 10-year CVD risk by setting SBPs of our study samples to 140 mmHg. The new 10-year CVD risk was multiplied by each subgroup's population size to yield the predicted number of CVD events if controlling SBP under 140 mmHg. Difference between the two predicted number of events

would be the number of events that could be prevented by controlling SBP under 140 mmHg. Population attributable risk (PAR) is defined as the number of preventable CVD events divided by the number of initially calculated predicted CVD events. Same procedure was followed when calculating preventable CVD events by controlling SBP under 130 mmHg. Differences in cardiovascular risk factor characteristics in subgroups were assessed using independent t-test and chi-square test. The trends of continuous variables within subgroups were assessed using ANOVA. All statistical analysis was carried out using SAS 9.3 software (SAS Institute Inc, Cary, NC) and Stata (Stata, version 12.0; StataCorp).

CHAPTER 4

RESULTS

4.1 Study Population

Descriptive statistics on cardiovascular risk factors of untreated stage 2 hypertension population from 2013-2016 NHANES were summarized in Table 1. The mean age was 52.1 for males (63.3%) and 55.5 for females (36.7%). Over 60% of the population was whites and around 12% was blacks. Compared to men, women had significantly lower DBP (81.4 mmHg vs. 84.5 mmHg, $p = 0.0012$) and higher HDL cholesterol level (59.4 mg/dL vs. 48.5 mg/dL, $p < 0.001$).

After stratifying by gender and age group, ANOVA test showed a positive association between SBP and age in both men and women, while a negative association was found between DBP and age in women. For cholesterol, the oldest female group (≥ 70 years old) had, on average, the highest total cholesterol level, and the youngest male group (30-39 years old) had, on average, the lowest HDL cholesterol level. A higher diabetes prevalence was reported in 60-69 age group than in other age groups among men. It was noted that the obesity prevalence was highest in the youngest age group both in men and in women. After stratifying by ethnicity, no significant difference in risk factors between ethnic groups was observed except that Mexican American had the highest prevalence of diabetes in men.

When looking at Framingham risk subgroups, subjects in a higher Framingham risk subgroup tended to have higher SBP. Among women, as FRS increased, total cholesterol level increased and HDL cholesterol level decreased. In both men and women, prevalence of diabetes was much higher in the Framingham high-risk group compared to the

intermediate and low risk groups. Almost half of the women in the Framingham high-risk subgroup were current smokers, and nearly a quarter of the women in this subgroup had chronic kidney disease. As we moved on to the analysis of CVD comorbidity risk subgroups, we found that HDL cholesterol levels were significantly lower in comorbidity high-risk groups than the low-risk groups in both men and women. Total cholesterol level was significantly higher in high-risk group than in low-risk group in men. Around two thirds of the population in high-risk group were obese (62.5% in men, 68.7% in women), and nearly 20% had a family history of cardiovascular events (17.6% in men, 17.8% in women). 27.2% of the male participants in high-risk group reported current smoking.

4.2 The Number of Predicted CVD Events and Predicted Preventable CVD Events

The number of preventable CVD events after controlling blood pressure to lower targets, as well as the corresponding population attributable risks (PARs), stratified by gender and age group, were illustrated in Table 2. Among all age groups, even though the oldest persons (≥ 70 years old) had, on average, the highest 10-year CVD risk score, people at age 60-69 years old had the highest number of predicted CVD events due to larger population size. The youngest age group (30-39 years old) had the fewest predicted events. After controlling blood pressure to 140/90 mmHg, the 60-69 age group was predicted to have the greatest number of preventable events. However, PAR had shown that the oldest age group would benefit more compared to other age groups. Women tended to benefit more than men, and this difference was specifically significant in older persons (≥60 years old). After lowering blood pressure to the new target 130/80 mmHg, again, there were more predicted preventable events in the 60-69 age group, but the oldest age group would

benefit most. Women would significantly benefit more than men. When comparing the number of preventable events after lowering blood pressure to 140/90 mmHg and 130/80 mmHg, controlling blood pressure to a lower target would approximately double the number of preventable CVD events in each age group (Appendix B). PAR increased by a range of 9.22%-10.03% in men and a range of 12.90%-15.26% in women (Appendix C).

Table 4.1. Means/ Prevalence of Cardiovascular Risk Factors among Stage 2 Hypertension Population without Antihypertensive Treatment Based on 2013-2016 NHANES, by Gender, Age Group, Ethnicity, and Risk Groups [a]

	Unweighted Number of Sample Size	Weighted Number of Sample Size (1000s)	Proportion (%) [b]	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Total Cholesterol (mg/dL)	HDL Cholesterol (mg/dL)	Current Smoker (%)	Diabetes (%)	Chronic Kidney Disease (%)	Obesity (%)	Family History of CVD Events (%)
Total												
Men	321	6769	63.3	146.5±0.8	84.5±0.8[d]	209.1±2.6	48.5±1.3[d]	18.5	13.0	3.0	42.0	12.0
Women	206	3927	36.7	150.3±1.1	81.4±1.2[d]	212.1±4.6	59.4±2.5[d]	16.2	12.3	5.4	45.6	11.0
Age Category												
Men												
30-39 y	61	1372	20.3	142.0±1.2[e]	86.6±1.0[e]	218.3±4.1	43.9±3.0[e]	25.3	8.4[e]	0	68.2[e]	22.7
40-49 y	76	1719	25.4	142.8±1.5[e]	87.1±1.0[e]	216.1±4.3	47.3±1.6[e]	25.3	9.6[e]	0	44.1[e]	13.4
50-59 y	77	1881	27.8	148.8±1.3[e]	86.4±1.3[e]	204.8±4.0	47.2±2.5[e]	12.3	10.4[e]	2.6	35.1[e]	8.2
60-69 y	87	1466	21.7	150.5±1.2[e]	80.2±2.1[e]	200.5±4.6	56.1±1.8[e]	9.8	26.7[e]	8.0	26.8[e]	7.5
≥70 y	20	331	4.9	153.1±4.2[e]	70.7±2.4[e]	197.0±6.9	47.7±3.1[e]	27.9	3.7[e]	10.8	28.8[e]	1.4
Women												
30-39 y	22	378	9.6	145.4±1.9[e]	92.7±0.2[e]	187.5±8.9[e]	47.5±2.8	22.6	14.1	0	74.8[e]	25.5
40-49 y	37	788	20.1	147.4±1.6[e]	88.1±1.5[e]	212.1±5.3[e]	53.7±1.6	14.6	9.0	0	48.5[e]	7.9
50-59 y	64	1264	32.2	148.9±1.4[e]	79.5±1.4[e]	218.7±9.8[e]	64.1±4.2	14.1	12.3	5.9	51.5[e]	4.7
60-69 y	63	1156	29.4	153.6±2.9[e]	77.2±2.3[e]	207.7±5.9[e]	58.1±4.1	21.8	16.6	6.9	38.0[e]	14.2
≥70 y	20	341	8.7	156.9±0.8[e]	75.2±5.0[e]	229.4±7.7[e]	73.2±1.3	1.4	3.7	17.1	9.9[e]	14.5
Ethnicity												
Men												
Mexican American	50	578	8.5	144.7±1.4	84.0±1.6	222.3±5.4[f]	42.6±1.1	22.9	25.2[f]	0	48.2	13.5
Other Hispanic	34	338	5.0	149.3±1.8	83.8±2.5	206.5±4.1[f]	46.2±2.1	17.3	15.0[f]	0	42.9	11.2
White	101	4332	64.0	145.6±0.8	84.8±1.1	210.4±3.2[f]	49.1±1.9	14.8	11.3[f]	3.7	42.0	13.9
Black	79	807	11.9	149.1±1.5	83.9±1.5	197.7±5.1[f]	51.9±1.6	31.6	11.7[f]	0.9	49.5	10.4
Asian	46	442	6.5	145.8±2.1	87.3±1.1	208.6±6.3[f]	47.0±0.9	21.2	19.8[f]	7.9	21.4	2.1
Other Races	11	271	4.0	153.2	78.8	197.9[f]	46.7	26.1	4.2[f]	0	39.1	0

Women											
Mexican American	40	354	9.0	150.1±1.0	77.6±1.6[f]	208.2±4.4	59.4±0.7	11.5	13.3	5.8	48.6	10.0
Other Hispanic	38	312	8.0	152.3±1.0	79.3±1.6[f]	199.0±4.8	50.8±2.5	16.4	12.6	0	54.4	9.0
White	59	2365	60.2	150.8±1.4	81.8±1.6[f]	213.0±4.6	62.0±3.4	15.4	10.6	6.9	39.2	11.0
Black	41	491	12.5	148.0±1.8	81.4±0.7[f]	200.9±4.9	57.0±1.1	36.8	24.1	3.2	66.7	13.8
Asian	24	236	6.0	147.2±0.8	86.0±2.5[f]	202.5±7.2	62.7±1.5	0	11.5	5.3	10.9	5.1
Other Races	4	167	4.3	151.7	82.5[f]	278.1	41.3	0	0	0	100	17.2
Framingham Risk Score Group												
Men												
FRS<10%	94	2212	32.7	141.0±0.9[g]	85.7±1.2[g]	205.5±3.7	49.5±2.9	13.3	1.5[g]	0	51.5	16.4
10%≤FRS≤20%	110	2516	37.2	145.2±1.0[g]	85.3±1.5[g]	212.2±4.6	50.5±1.9	14.6	7.7[g]	0	42.9	8.8
FRS>20%	117	2041	30.2	154.0±1.2[g]	82.4±1.4[g]	209.0±3.4	45.1±1.5	28.9	31.9[g]	9.8	30.5	11.1
Women												
FRS<10%	100	2024	51.6	145.6±0.8[g]	85.3±1.0[g]	203.6±5.1[g]	62.3±2.9[g]	8.2[g]	4.2[g]	0.8[g]	48.1	9.6
10%≤FRS≤20%	76	1358	34.6	153.0±1.1[g]	76.8±1.8[g]	218.4±8.9[g]	59.6±4.0[g]	17.9[g]	12.1[g]	4.6[g]	39.1	14.0
FRS>20%	30	545	13.9	161.2±1.3[g]	78.6±2.5[g]	227.8±8.3[g]	48.3±2.5[g]	41.7[g]	42.9[g]	24.6[g]	52.2	8.8
Comorbidity Risk Group [c]												
Men												
Low Risk	138	2804	41.4	147.6±1.7	84.2±1.2	198.7±4.7[h]	56.6±2.0[h]	6.1[h]	0	0	12.9[h]	4.0[h]
High Risk	183	3965	58.6	145.7±1.0	84.7±0.9	216.5±3.0[h]	42.8±1.5[h]	27.2[h]	22.2	5.1	62.5[h]	17.6[h]
Women												
Low Risk	78	1619	41.2	152.4±0.8	84.7±1.3	210.3±6.4	72.9±4.3[h]	8.9	0	0	12.5[h]	1.3[h]
High Risk	128	2308	58.8	148.8±1.0	79.2±1.3	213.3±5.8	50.0±1.9[h]	21.3	21.0	9.2	68.7[h]	17.8[h]

[a] Analyses are based on relatively small numbers. The results are imprecise and should be interpreted with caution.

[b] Proportions don't add up to 100% due to rounding errors.

[c] A high risk group within the studied population is defined as having either 1) diabetes or 2) chronic kidney disease (Stage 3 or above) or 3) two or more risk factors including current smoking, obesity, family history of CVD, elevated total cholesterol (≥200 mg/dL), and decreased HDL cholesterol (<40 mg/dL for men, <50 mg/dL for women).

[d] Difference between men and women are statistically significant.

[e] Difference between age subgroups are statistically significant.

[f] Difference between ethnic subgroups are statistically significant.

[g] Difference between Framingham risk subgroups are statistically significant.

[h] Difference between comorbidity risk subgroups are statistically significant.

Table 2. Cardiovascular Events Prevented by Controlling Blood Pressure to 140/90 mmHg versus to 130/80 mmHg among Untreated Stage 2 Hypertension Population Based on 2013-2016 NHANES, by Gender and Age Group [a]

			Uncontrolled		Controlled to 140/90 mmHg		Controlled to 130/80 mmHg	
	Unweighted Number of People with Stage 2 Hypertension	Weighted Number of People with Stage 2 Hypertension (1000s)	10-year CVD Risk (%)	Predicted Events (1000s)	Preventable Events (1000s)	PAR (%) [b]	Preventable Events (1000s)	PAR (%) [b]
Men								
30-39 y	61	1372	5.35	73	4	5.48	11	15.07
40-49 y	76	1719	11.99	206	15	7.28	34	16.50
50-59 y	77	1881	18.55	349	41	11.75	76	21.78
60-69 y	87	1466	27.16	398	41	10.30	80	20.10
≥70 y	20	331	38.22	127	17	13.39	29	22.83
Total	321	6769	17.04	1153	118	10.23	230	19.95
Women								
30-39 y	22	378	3.82	14	1	7.14	3	21.43
40-49 y	37	788	7.55	59	9	15.25	18	30.51[c]
50-59 y	64	1264	10.67	135	21	15.56	41	30.37[c]
60-69 y	63	1156	17.62	204	42	20.59[c]	69	33.82[c]
≥70 y	20	341	18.05	62	16	25.81[c]	24	38.71[c]
Total	206	3927	12.07	474	89	18.78[c]	155	32.70[c]

[a] Analyses are based on relatively small numbers. The results are imprecise and should be interpreted with caution.

[b] PAR=population attributable risk=preventable events/predicted events.

[c] Difference between men and women are statistically significant.

Table 3 presents the number of predicted CVD events, the number of preventable CVD events after controlling blood pressure to lower targets and corresponding PARs, stratified by gender and ethnicity. Other Hispanics had, on average, higher 10-year CVD risk score compared to other ethnic groups. In the male population, Asians had a similar 10-year CVD risk score as other Hispanics. More CVD events were predicted in whites due to a larger proportion of sample. After controlling blood pressure to 140/90 mmHg, whites had the highest number of predicted preventable CVD events. For men, other Hispanics would benefit the most, followed by blacks and Mexican American. For women, PARs were similar in Mexican American, other Hispanics, and whites. After lowering blood pressure to 130/80 mmHg, similar patterns were observed in distribution of preventable events and PAR. Whites had about 136,000 predicted preventable CVD events in men and about 100,000 in women. For men, PAR was greatest in other Hispanics, followed by blacks and Mexican American. White women would significantly benefit more than white men under both situations. The number of preventable events nearly doubled when changing the control target from 140/90 mmHg to 130/80 mmHg (Appendix D), and PAR increased by a range of 8.53%-10.10% in men and a range of 12.20%-15.79% in women (Appendix E).

Table 3. Cardiovascular Events Prevented by Controlling Blood Pressure to 140/90 mmHg versus to 130/80 mmHg among Untreated Stage 2 Hypertension Population Based on 2013-2016 NHANES, by Gender and Ethnicity [a]

			Uncontrolled		Controlled to 140/90 mmHg		Controlled to 130/80 mmHg	
	Unweighted Number of People with Stage 2 Hypertension	Weighted Number of People with Stage 2 Hypertension (1000s)	10-year CVD Risk (%)	Predicted Events (1000s)	Preventable Events (1000s)	PAR (%) [b]	Preventable Events (1000s)	PAR (%) [b]
Men								
Mexican American	50	578	17.13	99	10	10.10	20	20.20
Other Hispanic	34	338	18.88	64	10	15.63	16	25.00
White	101	4332	16.49	714	65	9.10	136	19.05
Black	79	807	16.00	129	17	13.18	30	23.26
Asian	46	442	18.57	82	9	10.98	16	19.51
Other Races	11	271	23.77	64	7	10.94	13	20.31
Total	321	6769	17.04	1152	118	10.24	231	20.05
Women								
Mexican American	40	354	10.66	38	7	18.42	13	34.21
Other Hispanic	38	312	13.22	41	8	19.51	13	31.71
White	59	2365	12.55	297	59	19.87[c]	100	33.67[c]
Black	41	491	11.14	55	9	16.36	16	29.09
Asian	24	236	8.54	20	2	10.00	5	25.00
Other Races	4	167	13.90	23	5	21.74	8	34.78
Total	206	3927	12.07	474	90	18.99[c]	155	32.70[c]

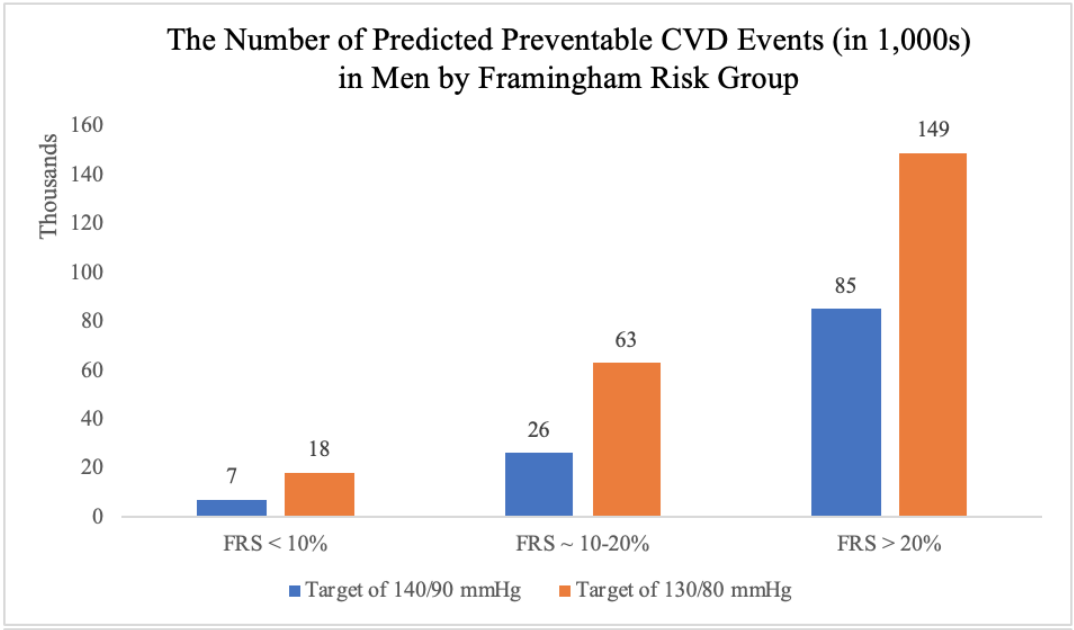
[a] Analyses are based on relatively small numbers. The results are imprecise and should be interpreted with caution.

[b] PAR=population attributable risk=preventable events/predicted events.

[c] Difference between men and women are statistically significant.

Table 4 reports the number of predicted CVD events, preventable CVD events after controlling blood pressure to lower targets and corresponding PARs stratified by Framingham risk group and comorbidity risk group. When stratified by Framingham risk group, there were more males in the Framingham high-risk group but more females in the low-risk group. In men, the higher the score, the more CVD events predicted. In women, the intermediate risk group had the most CVD events predicted. After controlling blood pressure to 140/90 mmHg, more preventable CVD events were predicted in the Framingham higher risk group, which was also true when controlling blood pressure to 130/80 mmHg (Figure 1). For both situations, PAR increased as FRS increased. Women would benefit more than men. PAR increased by a range of 8.73%-10.22% in men and a range of 12.33%-14.96% in women when blood pressure was controlled to 130/80 mmHg compared to 140/90 mmHg. (Figure 2)

Figure 1. The number of predicted preventable CVD events when controlling blood pressure under 140/90 mmHg vs. under 130/80 mmHg stratified by Framingham Risk Score subgroup and gender. Upper graph shows the number of predicted preventable CVD events for men. Lower graph shows the number of predicted preventable CVD events for women. The blue bar represents blood pressure control target of 140/90 mmHg. The orange bar represents blood pressure control target of 130/80 mmHg.



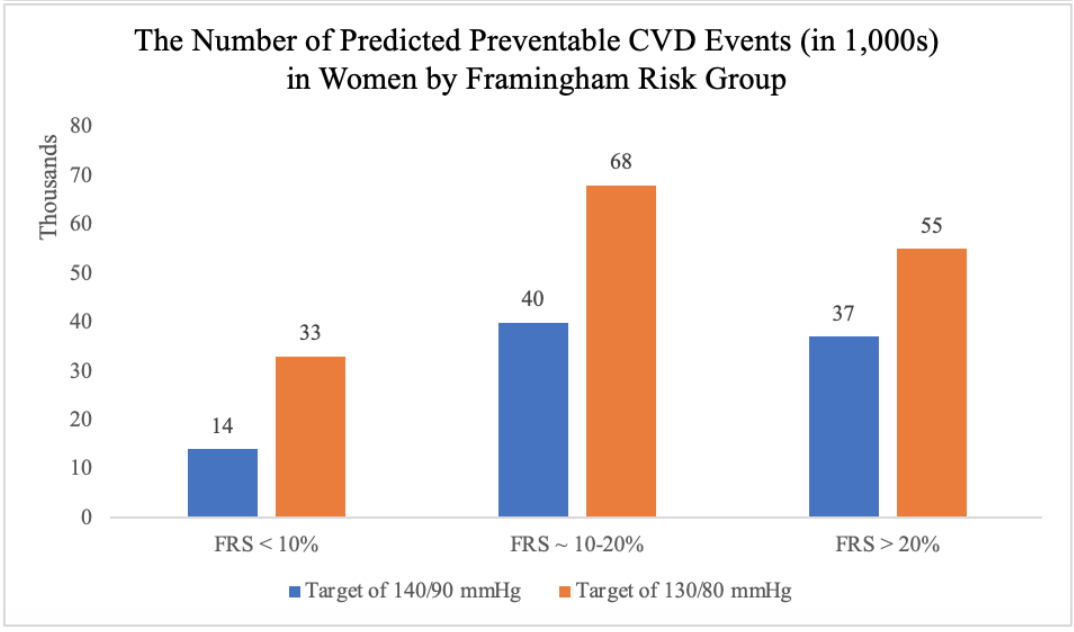
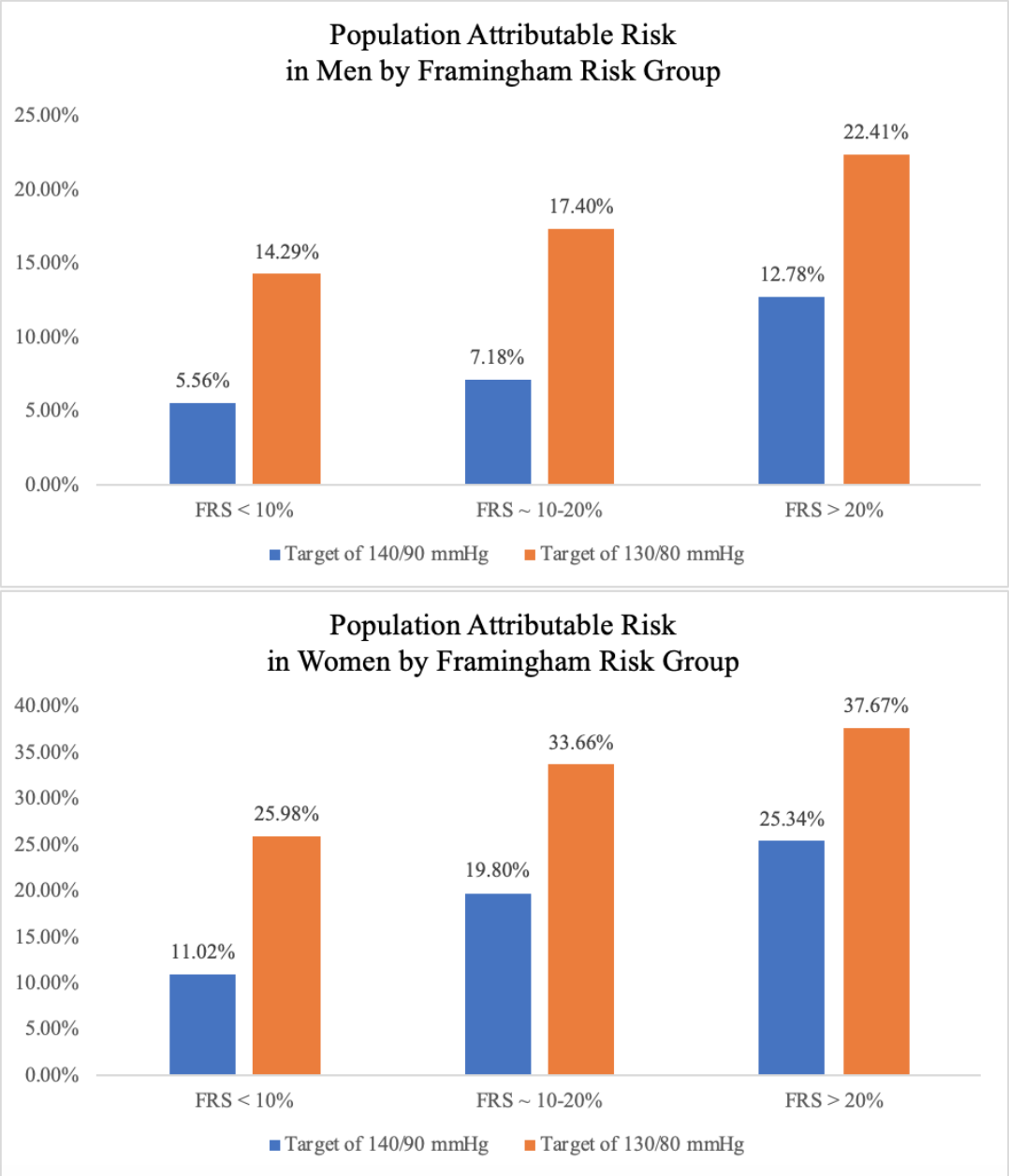


Figure 2. Population attributable risk when controlling blood pressure under 140/90 mmHg vs. under 130/80 mmHg stratified by Framingham Risk Score subgroup and gender. Upper graph shows PAR of men. Lower graph shows PAR of women. The blue bar represents blood pressure control target of 140/90 mmHg. The orange bar represents blood pressure control target of 130/80 mmHg.



When stratified by CVD comorbidity risk subgroup, nearly 60% (183 men and 128 women) of the participants were in the high-risk group. The average FRSs in comorbidity high-risk groups were 5.8% and 3.5% higher than those in low-risk groups, in men and in women, respectively. As a result, the predicted CVD events doubled in high-risk group (1083,000 in total) compared to low-risk group (544,000 in total). There were also more preventable events in high-risk group (134,000 in total) than in low-risk group (84,000 in total) after controlling blood pressure to 140/90 mmHg (Figure 3). However, when comparing PAR between comorbidity high versus low risk groups, the low-risk group actually would benefit more than the high-risk group. By further controlling blood pressure to 130/80 mmHg, again, more preventable CVD events were predicted in high-risk group (244,000 in total) than in low-risk group (144,000 in total) (Figure 3), and low-risk group would benefit more than high-risk group. PAR increased by nearly 10% in men and 15% in women when changing the control target from 140/90 mmHg to 130/80 mmHg (Figure 4).

Figure 3. The number of predicted preventable CVD events when controlling blood pressure under 140/90 mmHg vs. under 130/80 mmHg stratified by comorbidity subgroup and gender. Upper graph shows the number of predicted preventable CVD events for men. Lower graph shows the number of predicted preventable CVD events for women. The blue bar represents blood pressure control target of 140/90 mmHg. The orange bar represents blood pressure control target of 130/80 mmHg.

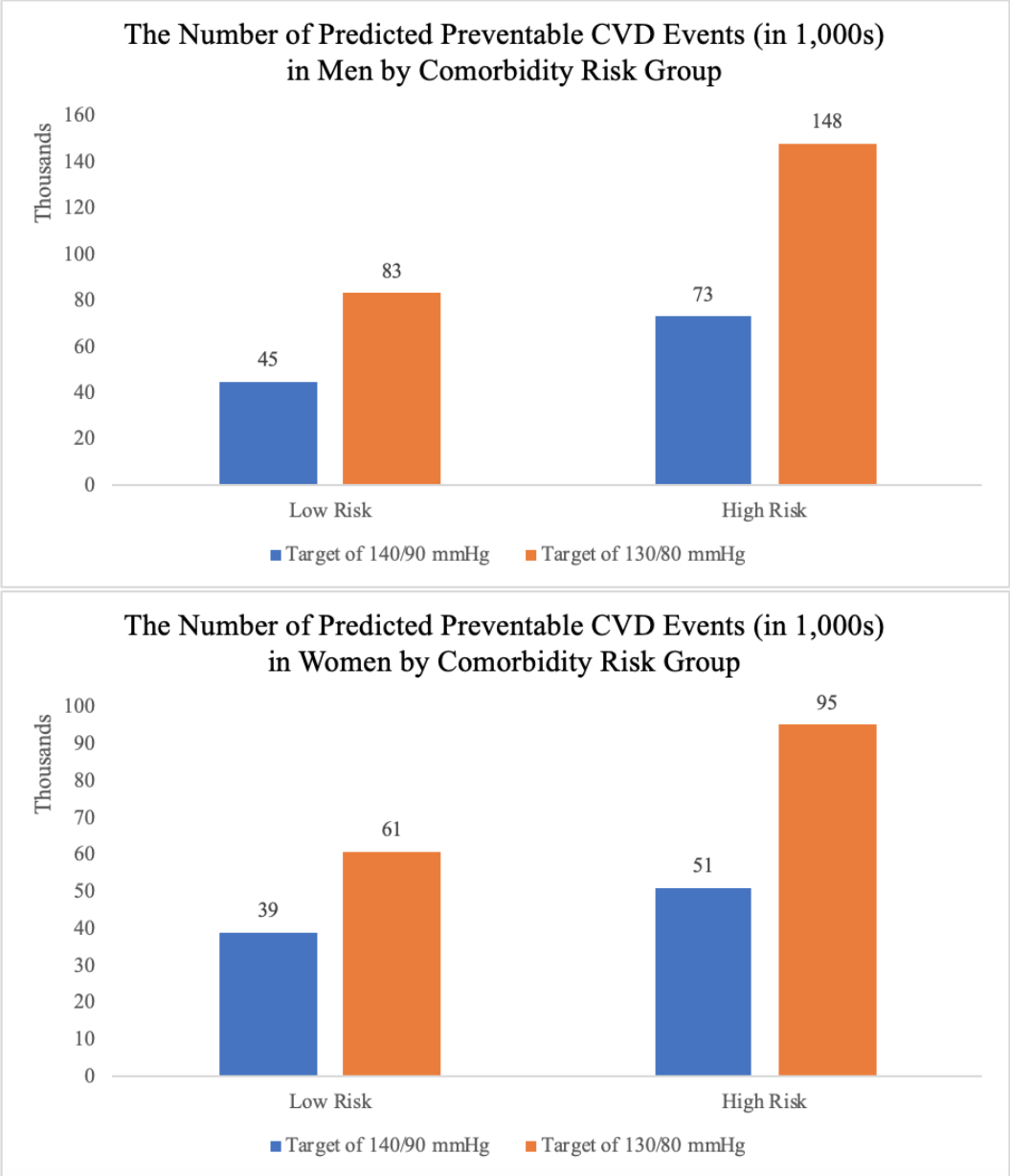
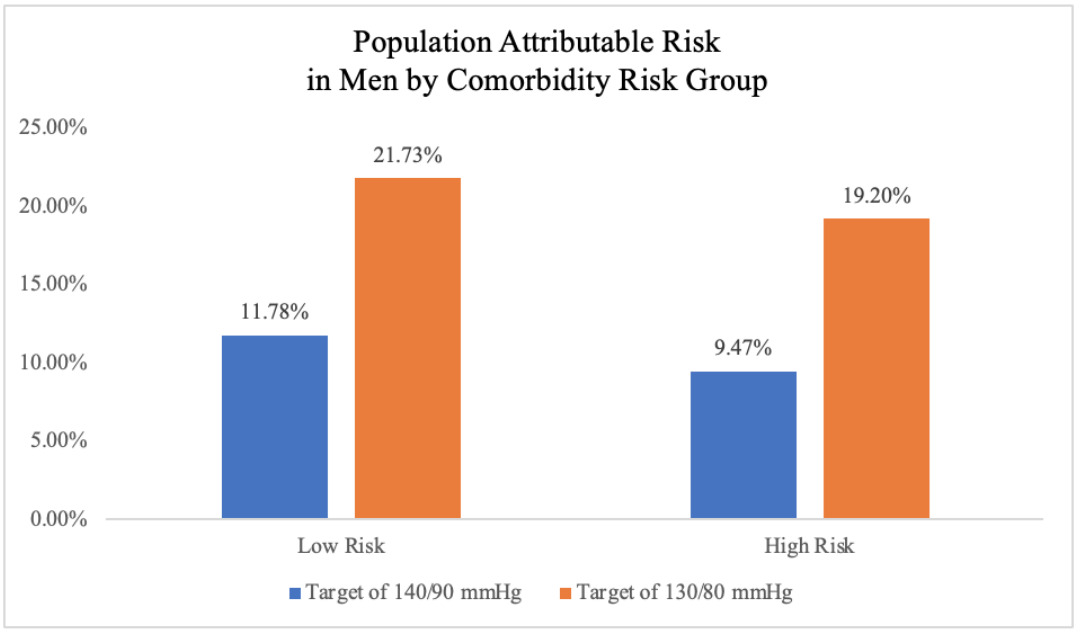


Figure 4. Population attributable risk when controlling blood pressure under 140/90 mmHg vs. under 130/80 mmHg stratified by comorbidity subgroup and gender. Upper graph shows PAR of men. Lower graph shows PAR of women. The blue bar represents blood pressure control target of 140/90 mmHg. The orange bar represents blood pressure control target of 130/80 mmHg.



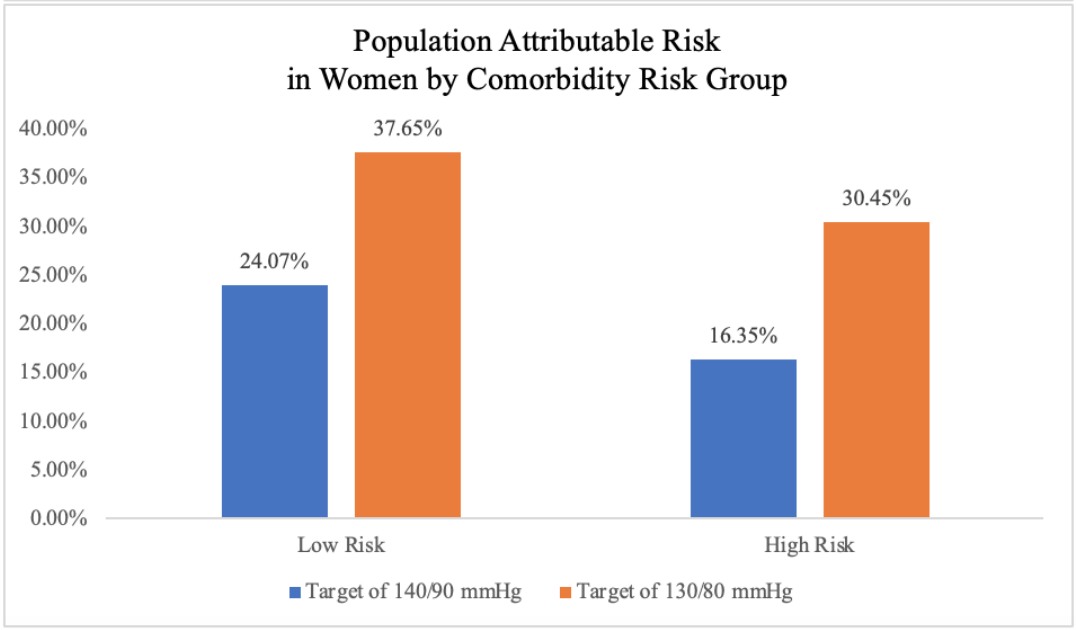


Table 4. Cardiovascular Events Prevented by Controlling Blood Pressure to 140/90 mmHg versus to 130/80 mmHg among Untreated Stage 2 Hypertension Population Based on 2013-2016 NHANES, by Gender, Framingham Risk Group, and Comorbidity Risk Group [a]

			Uncontrolled	Controlled to 140/90 mmHg		Controlled to 130/80 mmHg	
	Unweighted Number of People with Stage 2 Hypertension	Weighted Number of People with Stage 2 Hypertension (1000s)	10-year CVD Risk (%)	Predicted Events (1000s)	Preventable Events (1000s)	PAR (%) [b]	Preventable Events (1000s)	PAR (%) [b]
Framingham Risk Score Group								
Men								
FRS<10%	94	2212	5.69	126	7	5.56	18	14.29
10≤FRS≤20%	110	2516	14.39	362	26	7.18	63	17.40
FRS>20%	117	2041	32.59	665	85	12.78	149	22.41
Total	321	6769	17.04	1153	118	10.23	230	19.95
Women								
FRS<10%	100	2024	6.25	127	14	11.02	33	25.98[d]
10≤FRS≤20%	76	1358	14.86	202	40	19.80[d]	68	33.66[d]
FRS>20%	30	545	26.75	146	37	25.34[d]	55	37.67[d]
Total	206	3927	12.07	475	91	19.16[d]	156	32.84[d]
Comorbidity Risk Group [c]								
Men								
Low Risk	138	2804	13.62	382	45	11.78	83	21.73
High Risk	183	3965	19.45	771	73	9.47	148	19.20
Total	321	6769	17.04	1153	118	10.23	231	20.03
Women								
Low Risk	78	1619	10.00	162	39	24.07[d]	61	37.65[d]
High Risk	128	2308	13.52	312	51	16.35[d]	95	30.45[d]
Total	206	3927	12.07	474	90	18.99[d]	156	32.91[d]

[a] Analyses are based on relatively small numbers. The results are imprecise and should be interpreted with caution.

[b] PAR=population attributable risk=preventable events/predicted events.

[c] A high risk group within the studied population is defined as having either 1) diabetes or 2) chronic kidney disease (Stage 3 or above) or 3) two or more risk factors including current smoking, obesity, family history of CVD, elevated total cholesterol (≥200 mg/dL), and decreased HDL cholesterol (<40 mg/dL for men, <50 mg/dL for women).

[d] Difference between men and women are statistically significant.

CHAPTER 5

DISCUSSION

Our study predicted, on average, 85% more preventable CVD events if blood pressures are assumed to be successfully lowered to 130/80 mmHg instead of 140/90 mmHg in all subgroups of untreated stage II hypertension patients. Middle-aged subgroups (50-69 years old), whites, Framingham high-risk subgroup (FRS > 20%), and comorbidity high-risk subgroup tended to have the highest increase in the number of preventable CVD events. Based on PAR, older persons, people who had FRS > 20%, and people who were in the comorbidity low-risk subgroup tended to benefit more than their respective comparison groups.

5.1 The Number of People in Framingham Risk Subgroups

In our study, a gender difference in distribution of the number of people in Framingham risk subgroups was observed. Past studies using previous NHANES dataset (1999-2002, 2003-2006) or other national health survey dataset have also predicted a similar difference in FRS strata distribution between men and women. In men, more people were in high Framingham risk group than in low Framingham risk group, while in women, the distribution was the opposite.[19-21] Such distribution could be explained by the gender difference in cholesterol regulatory pathways. In women, estrogen-mediated effects can result in an increase in HDL cholesterol and decrease in LDL cholesterol, which proves to be protective against CVD.[22] This biological mechanism is supported by our study results that the HDL cholesterol level in our female study population was significantly higher than

that in male study population. Another possible explanation for the distribution is that FRS algorithm tends to underestimate the number of women at high Framingham risk group because additional risk factors for women, such as hemoglobin A1c, apolipoproteins A-I and B-100, high-sensitivity C-reactive protein, soluble intercellular adhesion molecule 1, are not included in the algorithm. This might potentially misclassify high-risk women into the low-risk subgroup.[23]

5.2 The Number of Predicted Preventable Events through Intensive Blood Pressure Control

In all subgroups, after lowering blood pressure from 140/90 mmHg to 130/80 mmHg, the number of predicted preventable CVD events nearly doubled. This prediction was consistent with the SPRINT study result, that participants who took intensive blood pressure treatment for 3 years had a significantly lower rate (hazard ratio, 0.75) of developing CVD events (including myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes) relative to standard blood pressure treatment.[6] Later studies have also shown a stronger protective association between intensive blood pressure lowering and development of CVD events when comparing with standard blood pressure lowering.[24-26] In a meta-analysis investigating intensive blood pressure lowering benefits by antihypertensive medication in older hypertensive patients (≥ 65 years), overall, there were 29% reduction in major adverse cardiovascular events (RR: 0.71; 95% CI: 0.60 to 0.84), 33% reduction in cardiovascular mortality (RR: 0.67; 95% CI: 0.45 to 0.98), 37% reduction in heart failure (RR: 0.63; 95% CI: 0.43 to 0.99) among patients who received intensive blood pressure lowering treatment compared to those who received standard

blood pressure lowering treatment.[26] Our result further quantified the predicted benefit of intensive blood pressure control among stage 2 hypertension patients.

5.3 Benefit Comparison among Subgroups

Past study has evaluated the relationship between aging and hypertension related CVD. It shows a significant increase in absolute risk with advancing age.[27] Our analysis results are consistent with their findings in that older people had higher PAR and tended to benefit more through blood pressure control than younger people. A potential reason for this observation is that the average SBP for older people was significantly higher than that for younger people. Therefore, when controlling blood pressure to lower targets (140/90 mmHg or 130/80 mmHg), blood pressure of the older population decreased more than that of the younger population, which would result in more reduction in FRS and predicted preventable events.

As for risk categories, like the results presented by Muntner et al., our analysis indicates the highest PAR appears in FRS > 20% subgroup, which means that people in the Framingham high-risk group would benefit more than those in the Framingham low-risk group. However, when we categorized the study population into two risk categories (high-risk versus low-risk) based on comorbidities and risk factors, it was the comorbidity low-risk subgroup, in which people had less than two cardiovascular risk factors and no CVD comorbidities, that would benefit more by achieving a lower blood pressure target. As people in the high-risk subgroup had more comorbidities than the low-risk subgroup, lowering blood pressure alone in the high-risk subgroup might not reduce CVD risk as effectively as in the low-risk subgroup. This is consistent with previous studies which

focused on effects of lowering blood pressure in population with cardiovascular comorbidities.[28-30] Two meta-analyses have found limited evidence of reduction difference in the number of CVD events under blood pressure control in individuals with versus without cardiovascular comorbidities including diabetes and chronic kidney disease. In order to effectively reduce CVD risk, it is necessary to initiate combination therapy in population with CVD comorbidities.[31] For example, in serious CKD patients, medication of ACE inhibitors or ARBs are recommended; in diabetes patients, all first-line classes of antihypertensive medication are effective, and ACE inhibitors or ARBs are recommended in the presence of albuminuria.[7]

5.4 Risk Score Algorithm

Our study used D'Agostino 2008 Framingham Risk Score as the major algorithm for prediction. This sex-specific multivariable risk factor algorithm estimates the 10-year risk CVD events including coronary heart disease, cerebrovascular events, peripheral artery disease, and heart failure.[17] There are also other algorithms predicting heart disease endpoints. For example, 1998 Framingham Risk Score predicts coronary heart disease risk in 10 years.[34] Systematic Coronary Risk Evaluation (SCORE), which is based on European Society of Cardiology, predicts 10-year risk for fatal atherosclerotic cardiovascular diseases (ASCVD).[35] The ASCVD Pooled Cohort Risk Equations predict 10-year ASCVD events including fatal and non-fatal myocardial infarction and stroke, but they apply to a narrower age range compared to Framingham algorithm.[36] QRISK, another CVD risk score similar to Framingham Risk Score with prediction for all CVD endpoints, was developed to evaluate CVD risk only for United Kingdom population.[37] Atherosclerosis Risk in Communities

(ARIC) Study developed equations to predict different CVD endpoints separately. The endpoints include stroke, heart failure, coronary heart diseases. Similar to Pooled Cohort Risk Equations, ARIC equations apply to a narrower age range compared to Framingham algorithm.[38] WHO/ISH Risk Prediction Chart predicts 10-year risk of a fatal or nonfatal major cardiovascular event, such as stroke and myocardial infarction. The charts can be used in countries of the specific WHO epidemiological sub-regions, but lack precision compared to Framingham algorithm.[39] After comparison, D'Agostino 2008 Framingham Risk Score is the most comprehensive algorithm to estimate risk of all CVD endpoints for the U.S population.

5.5 Limitations

There are several important limitations to be considered in this study. First, our study result can only be generalized to the untreated stage 2 hypertension population who aged 30-74 years old with no prior CVD events, which is only a small proportion of the U.S population. Separate analyses are needed in order to understand the same issues among "gray zone" patients and treated stage 2 hypertensive patients. Also, the study did not predict recurrent CVD events because D'Agostino Framingham Heart Study risk prediction algorithm is not applicable to people with previous CVD events.[17] To our knowledge, there are so far no algorithms to predict future CVD events in the population with previous CVD events, even though we are aware that the risk of recurrent CVD event is high, especially among people with comorbidities.[32,33] Second, the study result has relatively inadequate precision. Due to the exclusion criteria, our final unweighted sample size was around 500, which potentially decreases precision of the parameter estimates. Diabetes and obesity

prevalence in our study population, especially in the younger and older age subgroups, are not consistent with the general population, indicating the possibility of having a highly selective sample in this study. Conclusions made from this study should be interpreted with caution. Third, because blood pressures in NHANES were measured at MEC in a medical setting, we are not able to eliminate the white coat effect and not able to diagnose white coat hypertension and masked hypertension. Neither can we capture daily activity effect and monitor nighttime blood pressure. Estimation based on NHANES data is an oversimplification on the hypertension condition among our study sample. Fourth, clinical tests of CVD risk factors were based on one-time measurement. It is possible to introduce random errors into analysis. However, such errors won't significantly attenuate our study results. Fifth, BP recording was not taken by the SPRINT technique. It was hard to directly compare our study results to SPRINT results. Lastly, our study was based on prediction model. All predicted numbers assumed that everyone's blood pressure could be successfully controlled to the targets in ideal scenario. In reality, this is hard to achieve.

CHAPTER 6

CONCLUSION

Among untreated stage 2 hypertensive population, in an ideal scenario, if their blood pressure could be controlled under 130/80 mmHg, around 385,000 CVD events could be potentially prevented in 10 years, while controlling blood pressure under 140/90 mmHg can potentially prevent around 208,000 CVD events in 10 years. Based on Framingham CVD risk prediction algorithm, it is predicted that controlling blood pressure to a lower target nearly doubled the number of predicted preventable CVD events. This estimation provided us a with better understanding of the implications of the 2017 ACC/AHA guideline and the importance of controlling blood pressure to the new target. Older population, people with FRS > 20%, and people without CVD comorbidities or less than two CVD risk factors would be the major beneficiaries of achieving a lower blood pressure target.

REFERENCES

1. Thomas Beaney, et al. May Measurement Month 2017: an analysis of blood pressure screening results worldwide, The Lancet Global Health, Volume 6, Issue 7, 2018, Pages e736-e743, ISSN 2214-109X, https://doi.org/10.1016/S2214-109X(18)30259-6.
2. Merai R, Siegel C, Rakotz M, Basch P, Wright J, Wong B; DHSc., Thorpe P. CDC Grand Rounds: A Public Health Approach to Detect and Control Hypertension. MMWR Morb Mortal Wkly Rep. 2016 Nov 18;65(45):1261-1264.
3. Yoon SS, Fryar CD, Carroll MD. Hypertension Prevalence and Control Among Adults: United States, 2011-2014. NCHS data brief, no 220. Hyattsville, MD: National Center for Health Statistics; 2015.
4. Alma J. Adler, Dorairaj Prabhakaran, Pascal Bovet, Dhruv S. Kazi, Giuseppe Mancia, Vash Mungal-Singh, Neil Poulter, Reducing Cardiovascular Mortality Through Prevention and Management of Raised Blood Pressure: A World Heart Federation Roadmap, Global Heart, Volume 10, Issue 2, 2015, Pages 111-122, ISSN 2211-8160, https://doi.org/10.1016/j.gheart.2015.04.006.
5. Forouzanfar MH, Liu P, Roth GA, et al. Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg, 1990-2015. JAMA. 2017;317(2):165–182. doi:10.1001/jama.2016.19043
6. Wright JT Jr, Williamson JD, Whelton PK, et al; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103-2116.

7. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/ NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. A report of the American College of Cardiology/ American Heart Association Task Force on clinical practice guide- lines. Am Coll Cardiol. 2017;71; e116-e135.
8. Muntner P, Carey RM, Gidding S, et al. Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. Circulation 2018; 137:109–18.
9. Tadic, Marijana, and Cesare Cuspidi. "Does the change of hypertension guidelines actually affect our reality?." Annals of translational medicine vol. 6,18 (2018): 373. doi:10.21037/atm.2018.07.29
10. Bell KJL, Doust J, Glasziou P. Incremental Benefits and Harms of the 2017 American College of Cardiology/American Heart Association High Blood Pressure Guideline. JAMA Intern Med. 2018;178(6):755–757. doi:10.1001/jamainternmed.2018.0310
11. Zipf G, Chiappa M, Porter KS, Ostchega Y, Lewis BG, Dostal J. National health and nutrition examination survey: plan and operations, 1999–2010. National Center for Health Statistics. Vital Health Statistics 2013; 1–37.
12. National Center for Health Statistics, Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES) Physician Examination Procedures Manual. < https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/manuals/Phys_Exam_Manual_2013.pdf>
13. National Center for Health Statistics, Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES) MEC Laboratory

Procedures Manual. < https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/manuals/2013_MEC_Laboratory_Procedures_Manual.pdf>

14. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem. 1974;20(4):470-4754818200
15. Sugiuchi H, Uji Y, Okabe H, et al. Direct measurement of high-density lipoprotein cholesterol in serum with polyethylene glycol-modified enzymes and sulfated alpha-cyclodextrin. Clin Chem. 1995;41(5):717-7237729051
16. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. JAMA. 2015;313(8):837–46.
17. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008 Feb 12;117(6):743-53. doi: 10.1161/CIRCULATIONAHA.107.699579. Epub 2008 Jan 22. PubMed PMID: 18212285.
18. Arnett et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. Journal of the American College of Cardiology Mar 2019, 26029; DOI: 10.1016/j.jacc.2019.03.010
19. Tattersall MC, Gangnon RE, Karmali KN, Keevil JG (2012) Women Up, Men Down: The Clinical Impact of Replacing the Framingham Risk Score with the Reynolds Risk Score in the United States Population. PLOS ONE 7(9): e44347. https://doi.org/10.1371/journal.pone.0044347

20. Amanda K. Marma, MD , Jarett D. Berry, MD, MS , Hongyan Ning, MD, MS , Stephen D. Persell, MD, MPH , and Donald M. Lloyd-Jones, MD, ScM. Distribution of 10-Year and Lifetime Predicted Risks for Cardiovascular Disease in US Adults. Circulation: Cardiovascular Quality and Outcomes. 2010;3:8–14. https://doi.org/10.1161/CIRCOUTCOMES.109.869727
21. Selvarajah, Sharmini et al. Comparison of the Framingham Risk Score, SCORE and WHO/ISH cardiovascular risk prediction models in an Asian population. International Journal of Cardiology, Volume 176, Issue 1, 211-218
22. Sallam T, Watson KE. Predictors of cardiovascular risk in women. Womens Health (Lond). 2013;9(5):491–498. doi:10.2217/whe.13.44
23. Ridker PM, Buring JE, Rifai N, Cook NR. Development and Validation of Improved Algorithms for the Assessment of Global Cardiovascular Risk in Women: The Reynolds Risk Score. JAMA. 2007;297(6):611–619. doi:10.1001/jama.297.6.611
24. Beddhu S, Rocco MV, Toto R, Craven TE, Greene T, Bhatt U, et al. Effects of Intensive Systolic Blood Pressure Control on Kidney and Cardiovascular Outcomes in Persons Without Kidney Disease: A Secondary Analysis of a Randomized Trial. Ann Intern Med. 2017;167:375–383. doi: 10.7326/M16-2966.
25. Leo F. Buckley, Dave L. Dixon, George F. Wohlford, Dayanjan S. Wijesinghe, William L. Baker, Benjamin W. Van Tassell. Intensive Versus Standard Blood Pressure Control in SPRINT-Eligible Participants of ACCORD-BP. Diabetes Care Dec 2017, 40 (12) 1733-1738; DOI: 10.2337/dc17-1366.

26. Chirag Bavishi, Sripal Bangalore, Franz H. Messerli. Outcomes of Intensive Blood Pressure Lowering in Older Hypertensive Patients. Journal of the American College of Cardiology Feb 2017, 69 (5) 486-493; DOI: 10.1016/j.jacc.2016.10.077.
27. Lloyd-Jones DM, Evans JC, Levy D. Hypertension in Adults Across the Age Spectrum: Current Outcomes and Control in the Community. JAMA. 2005;294(4):466–472. doi:10.1001/jama.294.4.466
28. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials BMJ 2013; 347 :f5680.
29. Blood Pressure Lowering Treatment Trialists Collaboration. Effects of Different Blood Pressure–Lowering Regimens on Major Cardiovascular Events in Individuals With and Without Diabetes Mellitus: Results of Prospectively Designed Overviews of Randomized Trials. Arch Intern Med. 2005;165(12):1410–1419. doi:10.1001/archinte.165.12.1410
30. Catherine Williamson, Panniyammakal Jeemon, Claire E. Hastie, Linsay McCallum, Scott Muir, Jesse Dawson, Matthew Walters, William Sloan, David Morrison, Anna F. Dominiczak, Jill Pell, Sandosh Padmanabhan, Family history of premature cardiovascular disease: blood pressure control and long-term mortality outcomes in hypertensive patients, European Heart Journal, Volume 35, Issue 9, 1 March 2014, Pages 563–570, https://doi.org/10.1093/eurheartj/eht539
31. Schmieder, R. E. and Ruilope, L. M. (2008), Blood Pressure Control in Patients With Comorbidities. The Journal of Clinical Hypertension, 10: 624-631. doi:10.1111/j.1751-7176.2008.08172.x

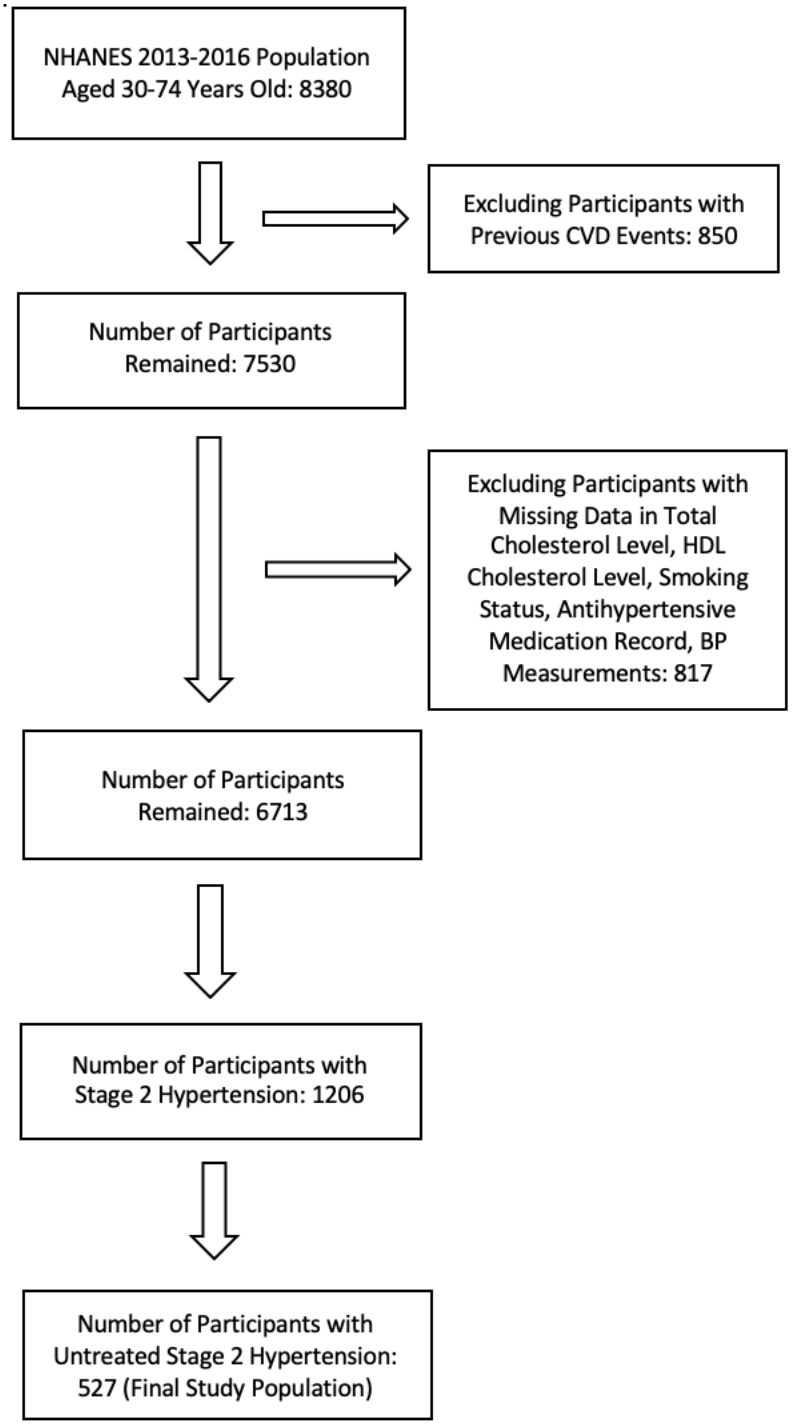
32. Amber A.W.A. van der Heijden, Esther van't Riet, Sandra D.M. Bot, Suzanne C. Cannegieter, Coen D.A. Stehouwer, Caroline A. Baan, Jacqueline M. Dekker, Giel Nijpels. Risk of a Recurrent Cardiovascular Event in Individuals With Type 2 Diabetes or Intermediate Hyperglycemia. Diabetes Care Nov 2013, 36 (11) 3498-3502; DOI: 10.2337/dc12-2691.
33. Baber U, Gutierrez OM, Levitan EB, et al. Risk for recurrent coronary heart disease and all-cause mortality among individuals with chronic kidney disease compared with diabetes mellitus, metabolic syndrome, and cigarette smokers. Am Heart J. 2013;166(2):373–380.e2. doi:10.1016/j.ahj.2013.05.008
34. Peter W. F. Wilson , MD , Ralph B. D'Agostino , PhD , Daniel Levy , MD , Albert M. Belanger , BS , Halit Silbershatz , PhD , and William B. Kannel , MD. Prediction of Coronary Heart Disease Using Risk Factor Categories. Circulation. Vol 97, Issue 18, Pages 1837-1847, 1998, doi:10.1161/01.CIR.97.18.1837
35. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Manger Cats V, Orth-Gomér K, Perk J, Pyörälä K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D, Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 2003 Sep; 24(17):1601-10.
36. David C. Goff, Jr, MD, PhD, FACP, FAHA, Co-Chair, Donald M. Lloyd-Jones, MD, ScM, FACC, FAHA, Co-Chair, Glen Bennett, MPH, Sean Coady, MS, Ralph B. D'Agostino, Sr,

PhD, FAHA, Raymond Gibbons, MD, FACC, FAHA, Philip Greenland, MD, FACC, FAHA, Daniel T. Lackland, DrPH, FAHA, Daniel Levy, MD, Christopher J. O'Donnell, MD, MPH, Jennifer G. Robinson, MD, MPH, FAHA, J. Sanford Schwartz, MD, Susan T. Shero, MS, RN, Sidney C. Smith, Jr, MD, FACC, FAHA, Paul Sorlie, PhD, Neil J. Stone, MD, FACC, FAHA, and Peter W. F. Wilson, MD, FAHA. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. Circulation. Vol 129, 25_suppl_2, Pages S49-S73, doi: 10.1161/01.cir.0000437741.48606.98.

37. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. BMJ2007;335:136.
38. The ARIC Investigators. The atherosclerosis risk in communities (aric) study: Design and objectives. The aric investigators. American journal of epidemiology. 1989;129:687–702.
39. "WHO/ISH Cardiovascular Risk Prediction Charts." World Health Organization, World Health Organization, 29 Sept. 2011, www.who.int/cardiovascular_diseases/guidelines/Chart_predictions/en/.

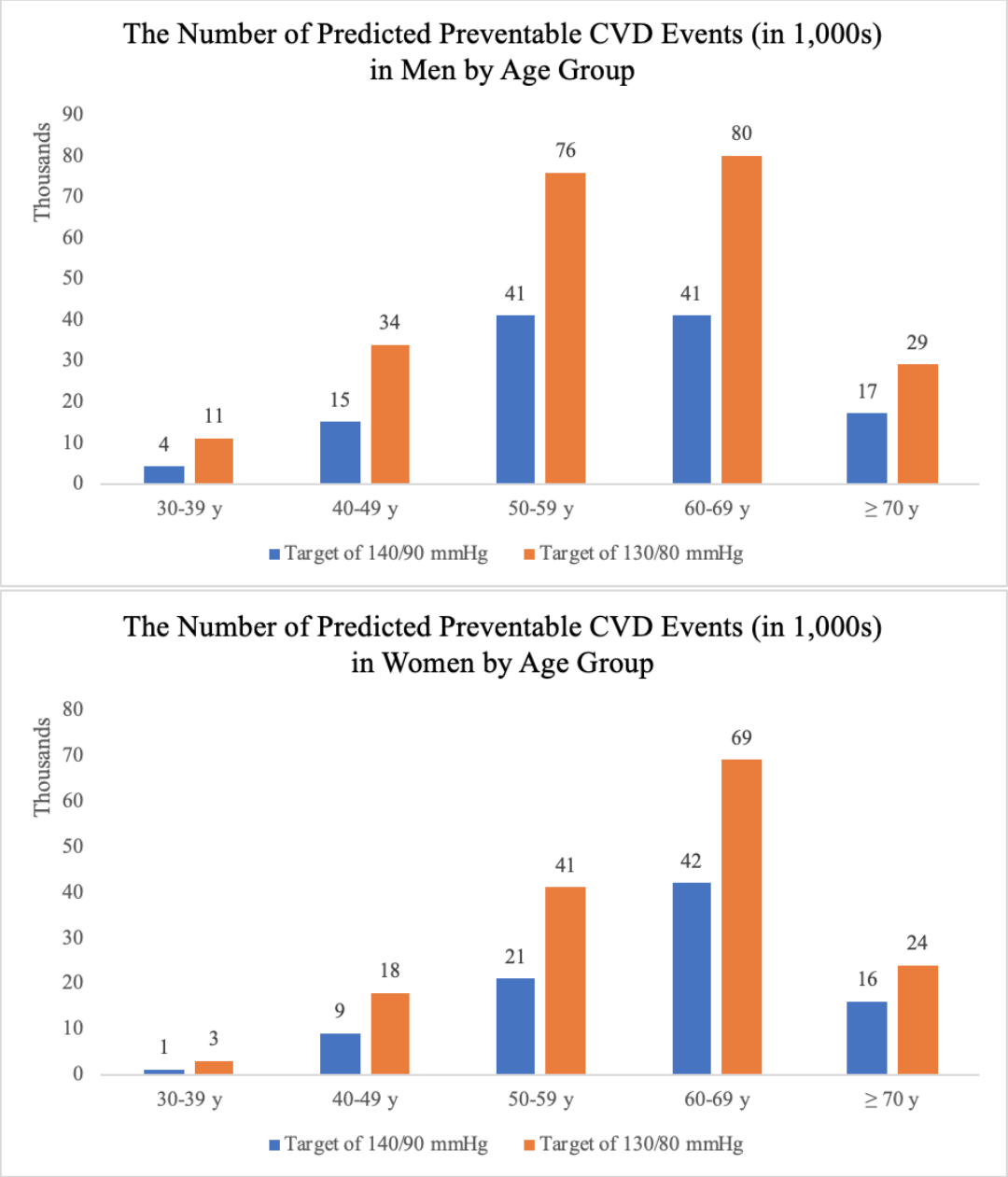
APPENDIX A

Flowchart of population inclusion and exclusion criteria



APPENDIX B

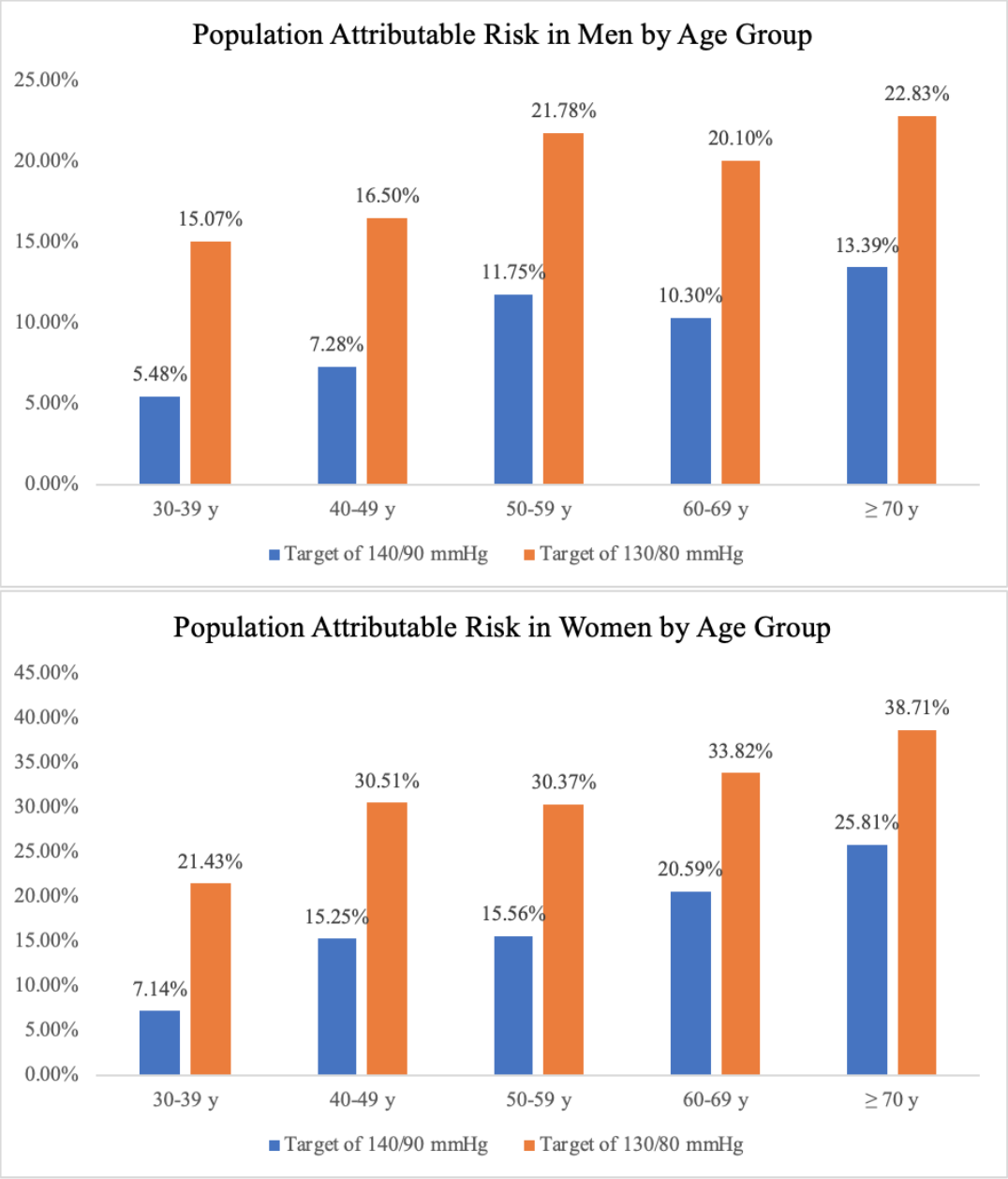
The number of predicted preventable CVD events when controlling blood pressure under 140/90 mmHg vs. under 130/80 mmHg stratified by age subgroup and gender



Upper graph shows the number of predicted preventable CVD events for men. Lower graph shows the number of predicted preventable CVD events for women. The blue bar represents blood pressure control target of 140/90 mmHg. The orange bar represents blood pressure control target of 130/80 mmHg.

APPENDIX C

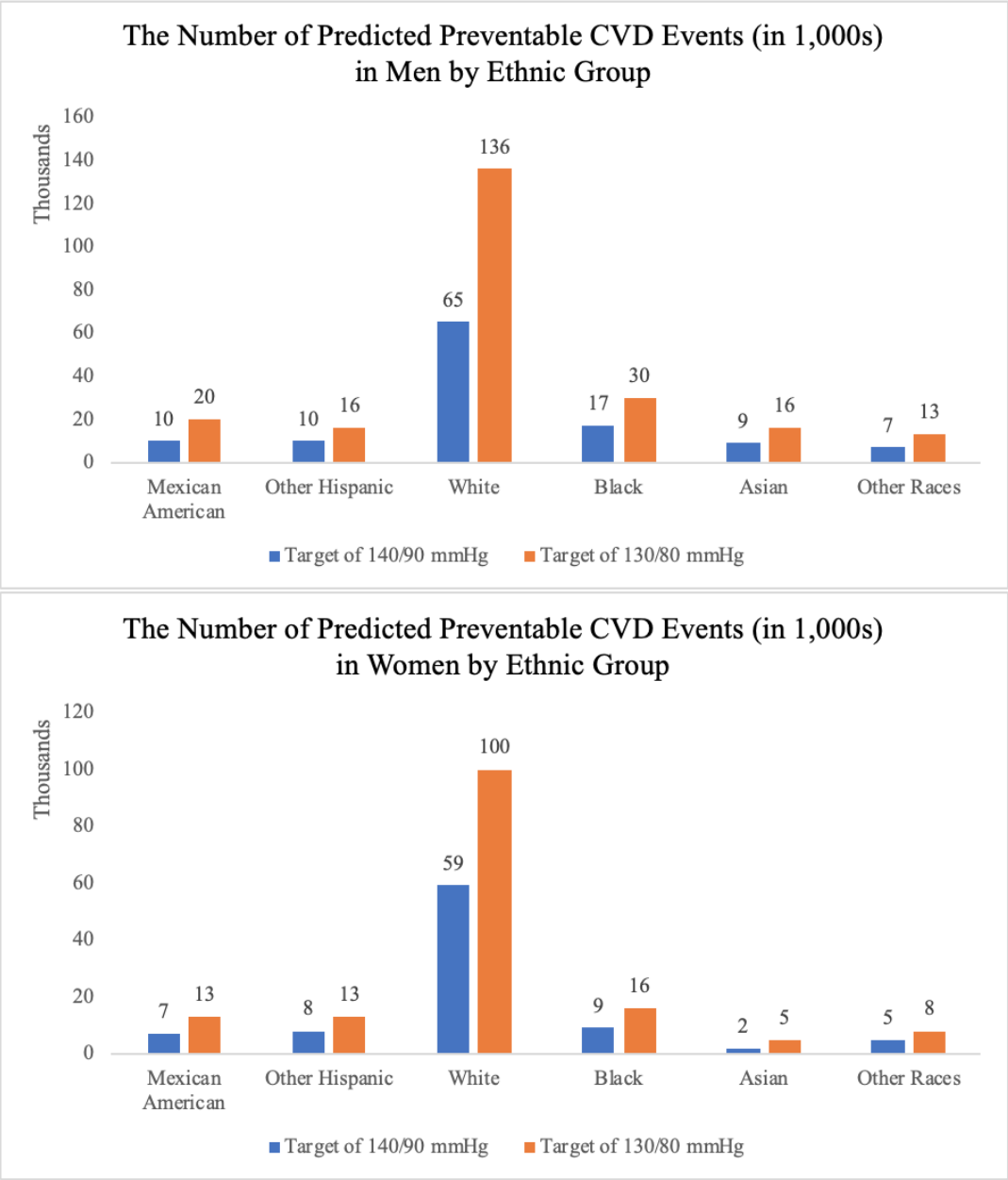
Population attributable risk when controlling blood pressure under 140/90 mmHg vs. under 130/80 mmHg stratified by age subgroup and gender



Upper graph shows PAR of men. Lower graph shows PAR of women. The blue bar represents blood pressure control target of 140/90 mmHg. The orange bar represents blood pressure control target of 130/80 mmHg.

APPENDIX D

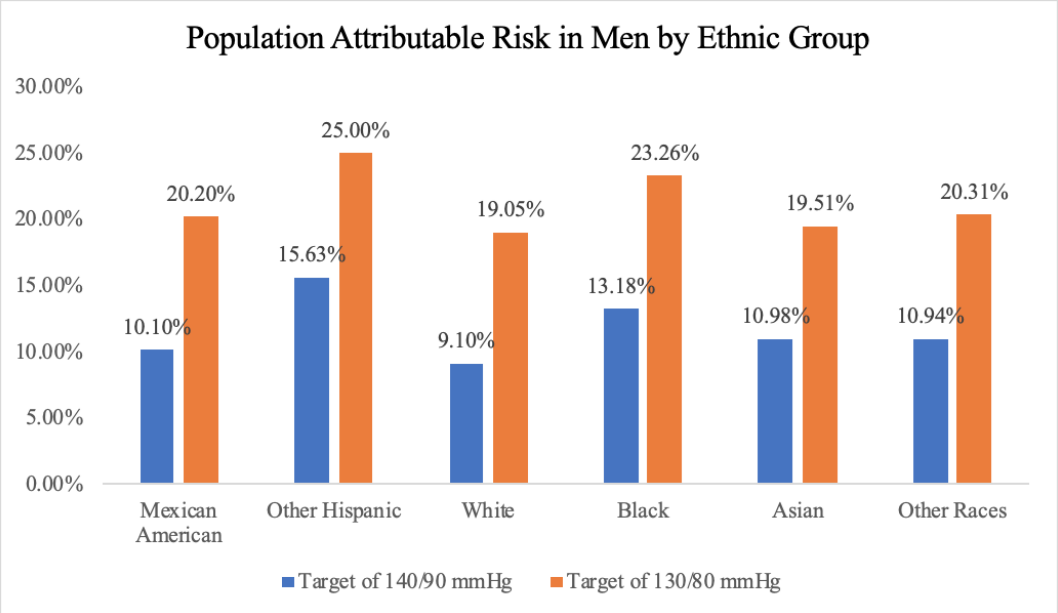
The number of predicted preventable CVD events when controlling blood pressure under 140/90 mmHg vs. under 130/80 mmHg stratified by ethnic subgroup and gender

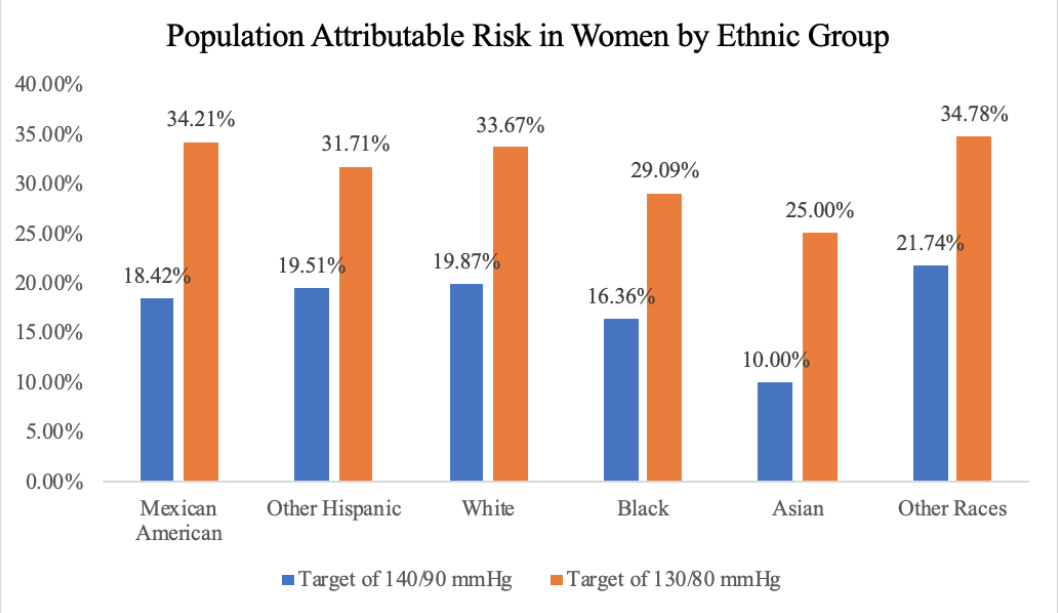


Upper graph shows the number of predicted preventable CVD events for men. Lower graph shows the number of predicted preventable CVD events for women. The blue bar represents blood pressure control target of 140/90 mmHg. The orange bar represents blood pressure control target of 130/80 mmHg.

APPENDIX E

Population attributable risk when controlling blood pressure under 140/90 mmHg vs. under 130/80 mmHg stratified by ethnic subgroup and gender





Upper graph shows PAR of men. Lower graph shows PAR of women. The blue bar represents blood pressure control target of 140/90 mmHg. The orange bar represents blood pressure control target of 130/80 mmHg.