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Cardiovascular Disease Risk Scores and Novel Risk Factors in Relation to Race and Gender

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Cardiovascular Disease Risk Scores and Novel Risk Factors in Relation to Race and Gender

by

Johanna Wilson

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Nursing Department of Nursing College of Nursing University of South Florida

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Keywords: Cardiovascular Risk, Cardiovascular Risk Score, Novel Cardiovascular Risk Factor

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DEDICATION

This dissertation is dedicated to my children Trevor and Lorelei. This dissertation is also dedicated to the women and men with multiple sclerosis and mental illness. Especially for my brother Mark, because I know that had life been fair he would have pursued his doctorate.
ACKNOWLEDGMENTS

To Dr. Kevin Kip, thank you for your support and encouragement over the years. Your kindness and guidance as a mentor will stay with me always. To Dr. Cecile Lengacher, thank you for your continuous support, warmth, and guidance throughout the years. I am thankful to my other committee members Dr. Ponrathi Athilingam and Dr. Yangxin Huang for their insights and recommendations related to this dissertation work. To Dr. Jason Beckstead, thank you for teaching me statistics and for your support.

To my husband Chris, who is my rock and my best friend, I thank you for loving me and supporting me. To my mother I thank you for your being there when I needed you most. I would like to thank my friends and family for their support and encouragement. It is the love that you gave me that makes my success meaningful.
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<td>ACC</td>
<td>American College of Cardiology</td>
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<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<tr>
<td>ATP</td>
<td>Adult Treatment Panel</td>
</tr>
<tr>
<td>ARIC</td>
<td>Atherosclerosis Risk Communities Study</td>
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<tr>
<td>ASCVD</td>
<td>Atherosclerotic Cardiovascular Disease</td>
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<tr>
<td>BP</td>
<td>Blood Pressure</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary Artery Bypass Graft</td>
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<tr>
<td>CAC</td>
<td>Coronary Artery Calcium</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary Heart Disease</td>
</tr>
<tr>
<td>CIMT</td>
<td>Carotid Intima Media Thickness</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes Miletus</td>
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<tr>
<td>FRS</td>
<td>Framingham Risk Score</td>
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<tr>
<td>HDL</td>
<td>High-Density Lipoprotein Cholesterol</td>
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<tr>
<td>HTN</td>
<td>Hypertension</td>
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<tr>
<td>Hs-Crp</td>
<td>C reactive protein</td>
</tr>
<tr>
<td>LDL</td>
<td>Lipid-density lipoprotein</td>
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<tr>
<td>MetS</td>
<td>The Metabolic Syndrome</td>
</tr>
<tr>
<td>MESA</td>
<td>Multi-Ethnic Study of Atherosclerosis</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
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<tr>
<td>NCEP</td>
<td>National Cholesterol Education Program</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutritional Examination Survey</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<td>PAT</td>
<td>Pulse amplitude tonometry</td>
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<tr>
<td>RRS</td>
<td>Reynolds Risk Score</td>
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<td>TC</td>
<td>Total Cholesterol</td>
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<td>VV</td>
<td>Vasa Vasorum</td>
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ABSTRACT

The use of cardiovascular risk scores remains the foundation for risk stratification to guide clinical management. Clinicians have access to several cardiovascular risk scores in practice settings. While having several risk scores with different risk factors may provide more information, it does not imply accuracy of the cardiovascular risk score used to calculate individual patient cardiovascular risk. The objective of this study was to compare the Framingham Risk score, Reynolds Risk scores, and the Pooled Cohort Risk Equation (3 commonly used equations) scores with respect to ability to predict cardiovascular events in a diverse ethnic population. Additionally, the potential predictive utility of three novel risk factors (carotid intima media thickness, peripheral arterial tonometry and vasa vasorum) was examined in relation to ability to improve 10-year cardiovascular risk prediction.

A secondary analysis of the longitudinal prospective study cohort known as Heart Strategies Concentrating On Risk Evaluation (Heart SCORE) was conducted. The cardiovascular risk scores of study participants who did and did not experience a cardiovascular event composite index consisting of myocardial infarction, death, stroke, acute ischemic stroke, or revascularization were assessed using methods of calibration and discrimination overall and by race and gender. When examining performance of the 3 risk scores, the overall 10-year absolute predicted cardiovascular risk varied substantially (e.g. approximately 2-fold) and this wide variation in predicted 10-year cardiovascular risk was present across race and gender. Nonetheless, despite the wide variation in estimates of absolute risk, the 3 cardiovascular risk score equations were strongly associated with future cardiovascular risk overall and by race and
gender. There was some indication that the Reynolds risk score was the most accurate measure of future cardiovascular risk. The 3 novel risk factors examined did not significantly improve 10-year cardiovascular risk prediction above and beyond the standard demographic and clinical variables used in these well-known equations.
CHAPTER 1: INTRODUCTION

Background

Cardiovascular Disease

The overall rate of death attributable to cardiovascular disease was 222.9 people per 100,000 Americans in 2013 (Mozaffarian et al., 2015). Coronary heart disease causes 1 of every 7 deaths in the United States (Mozaffarian et al., 2015). By 2030, cardiovascular disease (CVD) will account for 32.5% of all deaths; with coronary heart disease estimated to be the primary cause of death in 14.9% of males and 13.1% in females (Gaziano & Gaziano, 2012). Governance and policy documents recommend the use of multivariate risk assessment scores to identify high-risk individuals, as well as to identify novel risk factors for coronary heart disease and cardiovascular disease (Brindle, Beswick, Fahey, & Ebrahim, 2006; Siontis, et al., 2012, Goff et al., 2013; Mozaffarian et al., 2015).

Heart disease terminology includes coronary heart disease (CHD), coronary artery disease (CAD), cardiovascular disease (CVD), and most recently, atherosclerotic cardiovascular disease (ASCVD). Coronary heart disease (CHD), also referred to as coronary artery disease (CAD), is the narrowing of the small blood vessels that supply blood and oxygen to the heart (United States National Library of Medicine, 2016). Cardiovascular disease (CVD) encompasses a group of major disorders of the heart and the arterial circulation supplying the heart, brain and peripheral tissues. Cardiovascular disease includes all diseases of the circulatory system, coronary heart disease, cerebrovascular disease, hypertension, peripheral arterial disease,
rheumatic heart disease, congenital disease, heart failure, deep vein thrombosis and pulmonary embolism (Go et al., 2014; Goff et al., 2013). Atherosclerotic cardiovascular disease (ASCVD) includes coronary heart disease (CHD), stroke, and peripheral arterial disease, all of presumed atherosclerotic origin (Stone et al., 2014). Atherosclerotic cardiovascular disease (ASCVD), coronary heart disease (CHD), and cardiovascular disease (CVD) are not interchangeable terms.

The Framingham Heart Study risk scores and the Reynolds Risk Scores for men and women are established multivariate risk assessment scores designed to predict the absolute risk (as a percentage) for coronary heart disease or cardiovascular disease events over a specified period of time (usually 10 years). In the 2013, the American College of Cardiology/American Heart Association guidelines recommended a new multivariate risk assessment score called the Pooled Cohort Equations Risk Score (Goff et al., 2013). The terminology used in the development of cardiac risk assessment scores is purposeful and distinct from one another. The Pooled Cohort Equations Risk Score assesses the risk of experiencing an initial atherosclerotic cardiovascular disease (ASCVD) event (opposed to coronary heart disease or cardiovascular disease event). Coronary death, nonfatal myocardial infarction or CHD death, fatal or nonfatal stroke are considered an ASCVD event (Goff et al., 2013). Of note, all of these well-established risk scores use many of the same variables, such as age and blood pressure, yet with different weighting criteria.

In 1948, little was known about cardiovascular heart disease, which was the leading cause of death in the United States (Framingham Heart Study, 2016). The Framingham Heart Study began under the direction of the United States National Health Institute to identify common risk factors or characteristics contributing to heart disease. The cardiovascular risk factors identified from the previous fifty years of this research are classified as non-modifiable or
modifiable risk factors. Non-modifiable risk factors include age, gender, family history, and having had a previous heart attack. Modifiable risk factors are hypertension (HTN), hyperlipidemia, diabetes mellitus (DM), and smoking (Framingham Heart Study, 2016). Currently, as a society, we have failed to modify largely preventable (modifiable) risk factors and the crisis of cardiovascular risk and disease prevalence exists due to deficient management of modifiable risk factors (Wachira & Stys, 2013).

**Racial disparities in cardiovascular risk.** The increase in burden of cardiovascular disease risk factors and the deficient management of cardiovascular risk factors in minorities is well established (Go et al, 2014; Mozaffarian et al., 2015). In the previous fifty years of cardiovascular research, minorities have been poorly represented within the study populations (Goff et al, 2013). To address this known disparity, the American College of Cardiology/American Heart Association 2013 guidelines emphasize the need for cardiovascular disease risk assessment and intervention research to include minorities in their study populations to address and alleviate their undeserved cardiovascular risk burden. According to 2012 estimates from the National Health Interview Survey, 6.3% of blacks, 5.4% of Hispanics or Latinos, and 21.0% of Asians have coronary heart disease. Among American Indians or Alaska Natives, 8.2% have heart disease (Mozaffarian et al., 2015). Non-Hispanic black males and females have the highest overall death rate attributed to cardiovascular disease compared to non-Hispanic white males and females, as well as Hispanic males and females (Mozaffarian et al., 2015). Blacks in the United States endure the highest prevalence (44%) of high blood pressure in the world (Go et al, 2014). The prevalence and treatment of high blood pressure in minorities continues to challenge the health care community. Blacks develop high blood pressure earlier in life and have 1.5 times greater death rate of death attributable to heart disease than do whites.
While there have been great strides to increase awareness of high blood pressure among blacks, the odds of controlling blood pressure among blacks is 27% lower than it is in whites, and blood pressure of Mexican American males and females are the least controlled of all subgroups (Go et al., 2014). Blacks, Mexican Americans, and Hispanics/Latinos also bear a disproportional burden of the cardiovascular disease risk factor of diabetes mellitus in the United States (Go et al., 2014). Diabetes diagnosed by a physician in adults is more prevalent in black men (13.5) and Mexican American men (11.4) compared to white men. There is also an increased prevalence of diabetes in black females and Mexican American females compared to white women (Go et al., 2014).

**Cardiovascular Risk Scores**

Physicians use the cardiovascular risk factors (non-modifiable and modifiable) to identify patients who will benefit from primary prevention therapies, and most importantly, to deliver preventative care for asymptomatic individuals and for those identified as at risk for cardiovascular disease (Anderson et al., 2013; Brindle, Beswick, Fahey, & Ebrahim, 2006; Siontis et al., 2012). With the use of these scores, an individual’s cardiovascular risk factors are entered into a multivariate equation, which quantifies their estimated risk for both fatal and non-fatal cardiac events. When referring to cardiovascular risk, the term “risk” can mean the cause or probability of an unwanted event (e.g. myocardial infarction), or the expected value of the probability of an unwanted event multiplied by a measure of event severity, (e.g. the probability of myocardial infarction and the associated probability of death) (Payne, 2012).

Generally, an individuals’ cardiovascular risk is considered over a fixed, finite period of time, most commonly over 10 years (Payne, 2012). A 20% probability of risk for developing cardiovascular disease over a finite period of time is considered high risk, intermediate risk is 10-
20%, and low risk is considered less than 10% risk (Kones, 2011). These risk categories are not derived empirically, nonetheless, are accepted and widely utilized throughout the medical community. The utility for calculating cardiovascular risk from various multivariate equations, such as the Framingham Risk Score, is to identify high-risk patients and provide information for clinical decision-making (Barroso et al., 2010).

**Framingham risk score.** The Framingham Risk Scores were created as part of the Framingham Heart Study, and they are among the most thoroughly validated and widely used predictive scores in the medical literature (Tzoulaki, Liberopoulous, & Ioannidis, 2009). The Framingham risk score(s) were developed during the peak incidence of cardiovascular disease in the United States (Mendes, 2010; Payne, 2012), with the intention of prospective risk assessment for coronary heart disease (CHD) in both men and women without overt CHD (Tzoulaki, et al., 2009). Initially, the Framingham Heart Study developed a multivariate equation to predict individual risk of developing of coronary heart disease (CHD) in both men and women without overt CHD (Wilson, Casetelli, & Kannel, 1987). A modified version of this multivariate equation is used to predict the 10-year risk for coronary heart disease using the known constituent risk factors (age, blood pressure, total cholesterol or low density lipoprotein (LDL) level, high density lipoprotein (HDL) level, smoking status, and the presence of diabetes mellitus) (D’Agostino et al., 2001). These risk factors (modifiable and non-modifiable) are used in the multivariate equation to derive Framingham Risk, and are also referred to as traditional risk factors. As the research focus evolved from prediction of coronary heart disease risk to prediction of cardiovascular disease risk, D’Agostino et al. (2008) published a 10-year Framingham Risk Score (FRS) for cardiovascular disease assessment. However, a well-known limitation of the Framingham Risk Scores is that primarily male white cohorts were used to develop and assess the performance of the Framingham models. The extent to which the
scores would generally to future risk of women and other races and ethnicities was not initially considered.

**Reynolds risk score.** As described above, a significant potential limitation of the development and validation of model performance of the Framingham Risk Scores for coronary heart disease and cardiovascular disease is the use of primarily male white cohorts. To address this gender disparity in cardiovascular risk assessment, Ridker, Buring, Rifal, and Cook (2007) developed a cardiovascular risk score specifically for women called the Reynolds Risk Score. The Reynolds Risk Score is a multivariate equation that includes the same cardiovascular risk factors used in the Framingham Risk Score, but importantly, includes a family history of cardiovascular disease, which is not used in the calculation of the Framingham Risk Score. The inclusion of lifestyle factors, and family history of cardiovascular disease as well as markers of preclinical disease (high sensitivity C-reactive protein) is recommended to guide clinical decisions regarding preventative therapy in women (Mosca, Barrett-Connor, & Wenger, 2011).

**Pooled cohort risk equations.** In 2008, the National Heart, Lung, and Blood Institute (NHLBI) in a collaboration with the American College of Cardiology (ACC) and American Heart Association (AHA) sought to develop updated clinical practice guidelines to assess cardiovascular risk, reduction of risk through lifestyle modification, management of cholesterol, as well as overweight/obesity management by 2014 (Stone et al., 2014). Work groups appointed by the National Heart Lung and Blood Institute updated guidelines on blood cholesterol, blood pressure and overweight/obesity. Expert panels were tasked with providing current evidence based foundation for treating cholesterol, as well as primary and secondary prevention of Atherosclerotic Cardiovascular Disease (ASCVD) in men and women. Expert panels reviewed data from randomized control trials, systematic reviews, and meta-analyses on treating blood
cholesterol, blood pressure, obesity, and ASCVD. Their findings were conveyed in The 2013 American College of Cardiology/ American Heart Association/ The Obesity Society/ Guidelines for the Management of Overweight and Obesity in Adults (Jensen et al., 2014), and The 2013 American College of Cardiology/ American Heart Association Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (Stone et al., 2014).

The Work Group was tasked with charging the separate expert panels to update guidelines on cholesterol, blood pressure, and overweight/obesity with the optimal clinical cardiac risk assessment model (Goff et al., 2013). A review of risk assessment methodology for cardiovascular risk scores was conducted for the purpose of recommending a clinical risk assessment for clinical practice to the work groups. The Work Group found that existing risk score research used non-representative populations or data with limited ethnic diversity, narrowly defined endpoints, endpoints influenced by provider preferences (e.g. revascularization), and endpoints with poor reliability (e.g. angina and heart failure) (Goff et al., 2013). Furthermore, the Framingham Risk Score recommended by previous guidelines, was not based on contemporary data, and was dominated by a white population with limited coverage of other ethnic groups, and had an insufficient focus on ischemic stroke (Preis & Kristensen, 2015).

Therefore, using a current United States population, the Work Group developed a cardiovascular risk assessment equation called the Pooled Cohort Risk Score Equation. The Pooled Cohort Risk Equation is the clinical risk assessment score recommended in the 2013ACC/AHA Guidelines on the Assessment of Cardiovascular Risk (Goff et al., 2013). These current guidelines specify the current cardiovascular research aims of investigating the use of traditional and non-traditional (novel) cardiovascular risk factors in risk assessment research.
with the inclusion of minorities in study populations to address the known racial disparities (Goff et al., 2013).

**Novel Cardiovascular Risk Factors**

Extensive epidemiological, pathological, and basic science data indicate that the development of atherosclerosis, the precursor of atherosclerotic cardiovascular disease (ASCVD), occurs over decades and is related to long-term and cumulative exposure to causal, modifiable risk factors (Goff et al., 2013). The American College of Cardiology (ACC) and American Heart Association (AHA) advocate for the inclusion of non-traditional (novel) risk factors to assess cardiovascular risk assessment. Novel risk/non-traditional risk factors were included in the rigorous review of clinical research by the expert panels charged with updating the ACC/AHA Guidelines. The Work Group assessments of the novel risk factors of family history of premature cardiovascular disease, high sensitivity C-reactive protein, coronary artery calcium (CAC), and arterial brachial index (ABI) indicate promise for clinical utility among the novel risk markers, based on limited data (Goff et al., 2013). The improvement of existing cardiovascular risk factors as well as the innovation of improving cardiovascular risk estimation is reliant on the search for new cardiovascular risk factors beyond the traditional four major risk factors of hypertension, hypercholesterolemia, diabetes mellitus an smoking (Goff et al.,). This pursuit is apparent by the inclusion of the non-traditional/novel risk factors of inflammatory marker high sensitivity C-reactive protein by Ridker et al., (2007), subclinical atherosclerosis measures of coronary artery calcium (CAC) scores by Lakoski et al., (2007), genetic risk scoring by Morrison et al, (2007) in cardiovascular risk scores and cardiac risk research. Whereas there are many novel risk factors that could be examined, three potentially promising novel risk factors are described below and form the basis for some of the analyses conducted in this research.
**Carotid intima media thickness.** The innermost layer of the arterial wall is the intima and consists of a single layer of endothelial cells coming into direct contact with blood. The media layer is mainly smooth muscle and provides the majority of thickness of the arterial wall. The adventitia is the outer most layer and is composed of primarily collagen (Naik, Gamad, & Bansod, 2013). Atherosclerosis is responsible for the thickening of the arterial wall. The intima media thickness is a validated measure to evaluate atherosclerosis presence in the arterial wall, particularly in carotid artery. The increase of intima media thickness threatens a brain infarction or cardiac attack (Naik et al., 2013).

Using high-resolution ultrasound imaging, the assessment of carotid intima media thickness is a validated assessment tool for the detection of atherosclerosis (Nair, Malik, & Khatter, 2012; Naik, et al., 2013). Importantly, carotid intima media thickness (CIMT) correlates with traditional risk factors and coronary atherosclerosis severity (Nair et al., 2012). Carotid intima media thickness was used as an endpoint in the Multi-Ethnic Study of Atherosclerosis (MESA) (Folsom et al., 2008), the Atherosclerosis Risk Communities Study (Chambless et al., 1997; Chambless, et al., 2000), and Framingham Offspring Study (Polak et al., 2011) as a marker of atherosclerosis. Importantly, findings indicated an association of carotid intima media thickness with coronary heart disease and stroke making carotid intima media thickness a potentially useful independent predictor of cardiovascular disease.

**Pulse amplitude tonometry.** It is suggested that dysfunction of the endothelial layer of blood vessels is participatory in the pathogenesis of atherosclerosis (Briasoulis et al., 2012). Loss of utility from endothelial dysfunction plays a role in anti-atherogenic effects and all stages of atherosclerosis including plaque formation rupture. There are data showing that the endothelial dysfunction in coronary arteries is analogous to endothelial dysfunction in vascular peripheral
arteries (Briasoulis et al., 2012). Initial diagnostic tests to measure endothelial function were invasive and timely. Pulse amplitude tonometry (PAT) is a non-invasive diagnostic test of endothelial function by measuring pulse amplitude with a fingertip plethysmography to sense the changes in blood volume of a digit with each arterial pulsation (Briasoulis et al.). The inclusion of PAT in multivariate risk assessments offers potential promise in understanding the role endothelial dysfunction in cardiovascular risk assessment.

**Vasa vasorum.** Endothelial dysfunction is the first step in the development of atherosclerosis (Mortiz et al., 2012). In the walls of larger arteries, progressive inflammatory disease results in atherosclerosis lesions. The role of the vasa vasorum (in the adventitia of large arteries) is a central tenant of atherosclerosis development (Mortiz et al., 2012). The vasa vasorum (VV), or ‘the vessels of the vessels’, deliver nutrients and oxygen to arterial walls and removes waste produced by cells in the wall or introduced by diffusional transport through the endothelium of the artery (Ritman & Lerman, 2007). In the presence of disease, thickening of the intima wall inhibits oxygen diffusion (Moreno, Purushothaman, Sirol, Levy, & Fuster, 2006), and causes media thinning and necrosis (Baikoussis et al., 2011).

The neovascularization (formation of vasa vasorum ‘vessels of the vessels’) seems to be closely associated with carotid plaque progression and lesion vulnerability. Atherosclerotic plaque rupture is the critical, final event leading to unstable angina and myocardial infarction (Baikoussis et al., 2011). Research has shown an association between the increase of vessel-wall (vasa vasorum) as well as plaque micro vessels and ruptured atherosclerotic plaques (Baikoussis et al., 2011). Thus, there is reason to pursue the detection of the presence of vasa vasorum in the vascular wall and in the atherosclerotic lesions in early atherosclerosis (Mortiz et al., 2012).
**Statement of the Problem**

Death attributable to cardiovascular disease remains the number one killer of men and women in the United States (Mozaffarian et al., 2015). The burden of disease is high (Go et al., 2014) with the consequences of this preventable epidemic including individual mortality and morbidity, family suffering and staggering economic costs (Gaziano & Gaziano, 2012). The head to head comparisons of emerging cardiovascular risk models are important to perform so as to identify and document the improvements in cardiovascular risk prediction (Go et al., 2014; Goff et al, 2013; Siontis et al., 2012). A research study to compare the predictions of 10-year cardiovascular disease risk using the Framingham Risk Score, the Reynolds Risk Score for Women, the Reynolds Risk Score for Men, as well as the Pooled Cohort Risk Equations comparing predicted cardiovascular risk by race and gender has not been previously conducted and published. The Pooled Cohort Risk Equations application to an ethnically diverse population addresses the known research gap to assess both short and long term atherosclerotic cardiovascular disease (ASCVD) risk with outcomes in all race/ethnic groups, and across age spectrums and in women and men (Goff et al., 2013).

**Statement of the Purpose**

The purpose of this research study was to assess and compare the Framingham Risk score, Reynolds Risk score, and the Pooled Cohort Risk Equations score with respect to ability to predict cardiovascular events in a diverse ethnic population.

**Study Aims**

The specific aims of this study were:
1. Examine the overall predictive utility of the Framingham cardiovascular risk score, Reynolds Risk Score for women, Reynolds Risk Score for Men and the Pooled Cohort Risk Equations using methods of calibration and discrimination.

2. Examine the overall predictive utility by race of the Framingham cardiovascular risk score, Reynolds Risk Score for women, Reynolds Risk Score for Men and the Pooled Cohort Risk Equations using methods of calibration and discrimination.

3. Assess the predictive utility of the Framingham cardiovascular risk score, Reynolds Risk Score for women, Reynolds Risk Score for Men and the Pooled Cohort Risk Equations with the inclusion of the variables (novel risk factors) carotid intima media thickness (CIMT), pulse amplitude tonometry (PAT), and/or vasa vasorum (VV).

**Study Implications**

The results of this study may provide additional knowledge for cardiovascular disease risk assessment and management. In particular, by examining 3 different risk scores in the same study population, and with separate consideration of race and gender, finding may shed insight as to which score may be most appropriate for certain individuals. These findings can be compared with current guidelines promulgated by the American College of Cardiology/American Heart Association to estimate risk and predict cardiovascular events. Furthermore, the effects on risk prediction with the inclusion of the variables carotid intima media thickness (CIMT), pulse amplitude tonometry (PAT), and vasa vasorum (VV) will permit assessment of their predictive value and clinical utility in cardiovascular risk assessment.

**Definition of Terms**

The following terms are defined and used throughout this research.
Atherosclerotic Cardiovascular Disease - coronary heart disease (CHD), stroke, and peripheral arterial disease, all of presumed atherosclerotic origin (Stone et al., 2014).

Atherosclerotic Cardiovascular Disease Event—an initial ASCVD event of a nonfatal myocardial infarction or CHD death, fatal or nonfatal stroke, over a ten year time period among people free of ASCVD at the initiation of the time period (Goff et al., 2014).

Cardiovascular Disease—includes all diseases of the circulatory system and prevalence of cardiovascular disease includes individuals with hypertension, heart disease, stroke, peripheral artery disease, and diseases of the veins.

Coronary Heart Disease—includes acute myocardial infarction, other acute ischemic (coronary) heart disease, angina pectoris, atherosclerotic cardiovascular disease, and all other forms of chronic ischemic coronary heart disease (Go et al., 2014)

Mortality—The total number of deaths attributable to a given disease in a population during a specific interval of time, usually 1 year, reported. These data are compiled from death certificates and sent by state health agencies to the NCHS (Go et al., 2014).

Morbidity—Incidence and prevalence rates are both measures of morbidity (e.g., measures of various effects of disease on a population) (Go et al., 2014).

Myocardial Infarction—a heart attack occurs when flow of oxygen rich blood is suddenly blocked from going to a section of the heart. If blood flow is not restored quickly the section of the heart, the muscle begins to die. National Heart, Lung, and Blood Institute, 2016).

Coronary heart disease risk factors—conditions or habits that raise ones’ risk of coronary heart disease (CHD) and heart attack. These risk factors also increase the chance that existing CHD will worsen (National Heart, Lung and Blood Institute, 2011).
CHAPTER 2: LITERATURE REVIEW

Introduction

This literature review examines the established cardiovascular disease risk factors of race, age, lipids (low density lipoprotein, triglycerides, high density lipoprotein) physical inactivity, obesity, hypertension, diabetes, the metabolic syndrome, smoking, and a family history of cardiovascular disease (CVD). The novel cardiovascular risk factors C-reactive protein (hs-CRP), carotid intima media thickness (CIMT), pulse amplitude tonometry (PAT) and vasa vasorum (VV) are also reviewed. The Framingham Heart Risk Score (2008), Reynolds Risk Score for women (2007), Reynolds Risk Score for men (2008), and Pooled Cohort Risk Equations Score (2013) used to predict 10-year cardiovascular risk are reviewed. In addition, the methods of calibration and discrimination used to evaluate cardiovascular risk score models are reviewed.

A series of searches in CINAHL, Pubmed, and Ovid Medline were conducted to support the aims of this research from August 2013 until January 2016. Searches were refined for the search terms cardiovascular risk, cardiovascular risk factors, and cardiovascular risk models. The search terms of Framingham risk equation, Reynolds Risk Score, and American Heart Association guidelines were used as well. Additionally, a search was performed for each of cardiovascular risk factors used for this research.

Throughout Chapter 2, when reporting the percentage of individuals in the population with the cardiovascular risk factors of high lipids, DM, and obesity, the American Heart Association used data from the 2007-2010 National Health and Nutrition Examination Survey
[NHANES]. NHANES surveys to assess the health and nutritional status of adults and children in the United States through both participant interviews and physical examinations. The prevalence of cigarette smoking and physical inactivity data were reported using the National Health Interview Survey [NHIS].

**Cardiovascular Risk Factors**

**Race.** The racial disparity of a higher burden of cardiovascular disease risk factors in minorities is well known. Specifically, there is known racial disparity of cardiovascular risk factors of diabetes mellitus, hypertension, high triglycerides, and low high-density lipoprotein among Blacks, Mexican Americans, and Hispanic/Latinos. According to the American Heart Association, black males have the highest prevalence of cardiovascular disease followed by Whites, then Mexican American men. This prevalence pattern is also seen among Black, White, and Mexican American women (Goff et al., 2013). Interestingly there appears to be a lower prevalence of high low-density lipoprotein (LDL) and triglycerides among blacks compared to other cardiovascular disease risk factors such as physical inactivity, hypertension and diabetes mellitus. The American College of Cardiology/American Heart Association 2013 guidelines highlight the need for cardiovascular disease risk assessment and intervention research to include minorities in their study populations to address and alleviate their undeserved cardiovascular disease risk burden.

**Age.** Aging is associated with significant structural and functional changes in skeletal muscle (Garcia & Goldenthal, 2008b). After the fourth decade of life, the decline of muscle mass and muscle quality is paralleled by the decline in both muscle strength and maximal oxygen uptake (Garcia & Goldenthal, 2008a). These changes decrease total energy expenditure and physical activity that then increase the prevalence of obesity, particularly abdominal obesity.
These physiological changes contribute to the prevalence of insulin resistance, hyperlipidemia and hypertension in individuals over the age of forty. Insulin resistance increases with age independent of total adiposity changes (Garcia & Goldenthal, 2008a). Insulin resistance and obesity accelerate aging due to the oxidative stress and inflammation resulting in a shorter life span. Increased fat mass, particularly visceral adiposity, increased circulation of inflammatory proteins and the increased cellular accumulation of triglycerides that result from aging may predispose individuals to insulin resistance. However, in men and women in their eighth and ninth decades of life, triglycerides, total cholesterol, and LDL-C tend to be lower (Garcia & Goldenthal, 2008a).

Independently, cardiovascular risk is influenced by age, but is not necessarily an invariant risk factor and is highly dependent on the presence of other risk factors (Kannel & Vasan, 2009). Cumulative exposure of anthropogenic risk factors occurs with aging (National Cholesterol Education Program (NCEP) Expert Panel on Detection, 2002). Cardiovascular remodeling results from the long-term burden of cardiovascular risk factors (Kannel & Vasan, 2009). Results of the Framingham Heart Study data indicated that non-smoking 50-year olds who were not diabetic, with total cholesterol less than 180 mg/dl, and blood pressure less than 120/80 mmHg had a 5% to 8% risk of developing cardiovascular disease (Lloyd-Jones et al., 2006). Individuals of the same age with two or more risk factors had a 50% to 68% lifetime risk (Lloyd-Jones et al., 2006). Kannel and Vasan (2009) presented the notion of age itself as a risk factor as contrasted with the long term exposures to risk factors over time. However, the complexity and individuality of the aging process lend itself to variations in cardiovascular risk acquisition. Therefore, age is imperative to include in multivariate cardiovascular risk models, but is
intertwined with other cardiovascular risk factors such as triglycerides, low-density lipoprotein (LDL), and diabetes (Kannel & Vasan, 2009).

**Lipids.** Low-density cholesterol (LDL) comprises sixty to seventy percent of the total serum cholesterol and is the major anthropogenic lipoprotein (Grundy et al., 2004). Cholesterol is a fat-like substance (lipid) that travels in the blood within lipoproteins, of which contain both lipid and proteins (NCEP, 2002). The current ACC/AHA guidelines recommend untreated total cholesterol of <200mg/dL for cardiovascular health and to reduce CVD and stroke risk (Go et al., 2014). Currently, it is estimated that 31.9 million (13.8%) adults have serum cholesterol levels ≥ 240mg/dL (Go et al., 2014).

**Low density lipoprotein.** Low-density lipoprotein is the primary target of cholesterol-lowering therapy (NCEP, 2002). According to the Adult Treatment Panel III, a LDL cholesterol level of 130 to 159mg/dL is classified as borderline high, 160 to 189 mg/dL is considered high; an LDL of 190mg/dL and above is considered very high. Data from the NHANES 2007-2010 indicated adults had a mean LDL cholesterol level of 115.8mg/dL. The reported LDL levels for non-Hispanic white men (115.1 mg/dl) and women (115.7 mg/dL), non-Hispanic black men (115.9 mg/dL) and women (114.2mg/dL), and Mexican American men (119.7mg/dL) and women (115.0mg/dL) indicated less racial disparity compared to other cardiovascular disease risk factors, such as hypertension and diabetes mellitus.

**Triglycerides.** A fasting triglyceride level of 150mg/dL and above is considered high and a risk factor for cardiovascular disease and stroke (Go et al., 2014). Adult triglyceride levels according to the NHANES 2007-2010 averaged 130.3 mg/dL. Overall, men had a higher mean level of triglycerides (141.7 mg/dL) compared to women (119.1 mg/dL). Mexican American men (161.4 mg/dL) and women (134.1 mg/dl) had the highest mean triglycerides compared to
non-Hispanic white men (140.0 mg/dL), non-Hispanic white women (121.5 mg/dL) and non-Hispanic black men (111.3 mg/dL) and non-Hispanic black women (94.4 mg/dL) (Go et al., 2014).

**High density lipoprotein.** High-density lipoprotein comprises twenty to thirty percent of the total serum cholesterol (NCEP, 2002). A HDL cholesterol level of <40 mg/dL in adult males and <50 mg/dL in adult females is considered to be a risk factor for heart disease and stroke. The NHANES 2007-2010 data indicated a mean HDL level of 52.5 mg/dL as well as greater racial and gender variation in HDL levels compared to LDL levels. High density lipoprotein levels were as follows: non-Hispanic white men (46.7 mg/dl) and women (58.1 mg/dL); non-Hispanic black men (52.6 mg/dL) and women (58.7 mg/dL), and Mexican American men (45.4 mg/dL) and women (53.7 mg/dL) (Go et al., 2014). The triad of high triglycerides, high LDL-C and low high-density lipoprotein cholesterol (HDL), is strongly associated with type 2 diabetes and the metabolic syndrome (Payne, 2012.) Disappointingly, combining statins with additional medications targeting lipid abnormalities has lacked efficacy and hyperlipidemia continues to plague the at risk population (Payne, 2012).

**Lipids and aging.** In both men and women, total cholesterol increases with age and peaks in the fifth decade for men and in the sixth decade for women (Kolovou, Marvaki, & Bilianou, 2011). Both aging and menopause are posited to cause an unfavorable lipid profile that increases cardiovascular risk (Kolovou & Bilianou, 2008). Compared to premenopausal women, postmenopausal women have higher total cholesterol, low-density lipoprotein, and triglycerides and lower high-density lipoprotein. As men age, androgens negatively influence their lipid profile in conjunction with the increased accumulation of abdominal fat associated with aging. Importantly, the presence of central obesity correlates with low HDL and high triglycerides
(Kolovou et al., 2011). Kolovou et al., (2011) propose the ideal lipid profile for healthy aging that consists of a lipid panel typical of low risk for atherosclerotic disease, such as found in centenarians, as well as the protective factors of no smoking, body mass index (BMI) below 25kg/m² proper lifestyle, and a set of ‘longevity’ genes. Centenarians possess a lipid profile (high HDL, low LDL) indicative of low risk of atherosclerotic disease and research has yet to determine the role of genetic factors in these individuals that possess “familial” longevity (Kolovou, Kolovou, Vasiliadas, Wierzbicki, & Mikhilidis, 2011). Longevity is defined as survival to the age of 90 and older and has been observed to cluster within families (Murabito, Yuan, & Lunetta, 2012). Lower levels of cardiovascular risk factors in middle life or early years predict survival and health up to 85 years of age. Yet the interaction between genes, modifiable behaviors, and environmental factors on longevity is unknown (Murabito et al., 2012).

**Physical inactivity.** Physical inactivity remains a major risk factor the development of cardiovascular disease and diabetes mellitus type 2 (Anderson et al., 2013). The current ACC/AHA guidelines indicate that 150 minutes a week of moderate-intensity activity (≥75 min/week of vigorous activity) are needed to achieve cardiovascular health (Go et al., 2014). As of 2010, only 41.5% of adults met this criteria. According to 2014 National Health Interview Survey data, women were less active than men and inactivity increased with age (Mozaffarian et al., 2015). Non-Hispanic black and Hispanic adults were more likely to be inactive compared to non-Hispanic white adults (Mozaffarian et al., 2015).

Adherence to the recommended CVD risk factor guidelines has been associated with a 27% lower mortality in those individuals without chronic conditions (diabetes mellitus, cancer, myocardial infarction, angina, cardiovascular disease, stroke, or respiratory disease) and for individuals with chronic comorbidities mortality was reduced by up to 46% (Schoenborn &
Stommel, 2011). Physical activity has been reported to reduce low-density lipoprotein (LDL) and triglyceride levels, raise high-density lipoprotein (HDL) cholesterol, improve insulin sensitivity, and lower blood pressure (NCEP, 2002).

**Obesity.** Obesity is a well-known risk factor for the development of the cardiovascular disease risk factors of HTN, dyslipidemia, DM and the Metabolic Syndrome (Fox et al., 2014; Mozaffarian et al., 2015). The health risks imposed by obesity may also be mediated by hypertension, diabetes mellitus, and lipid profile imbalances (Gaizano & Gaizano, 2012; NCEP, 2002). A complete cardiovascular disease risk assessment includes measures for being overweight, obesity and for central adiposity. Central adiposity (abdominal fat) is considered to be more atherogenic compared to total body fat (Everson-Rose et al., 2009). Obesity is defined as a body mass index (BMI) of at least 30 kilograms/m².

Currently, 68% of US adults are overweight or obese and 35% of US adults (13 million individuals) are considered to be obese (Go et al., 2014). Mexican American men (36%) and women (45%) as well as non-Hispanic black men (38%) and women (54%) were more likely to be overweight or obese than non-Hispanic white men (34%) and women (33%) (Go et al., 2014). Additionally, data from the Multi-Ethnic Study of Atherosclerosis (MESA) study concluded a larger proportion of white, black and Hispanic participants were overweight (60-85%) or obese (30%-50%) compared to Chinese American participants who were overweight (33%) or obese (5%) (Burke et al., 2008). Obesity remains an epidemic that plagues the United States. While obesity is more prevalent among Mexican American and non-Hispanic black men and women, its impact on cardiovascular risk is prevalent in all races and ethnicities.

**Hypertension.** High blood pressure (hypertension) is a prevalent and most importantly is a preventable risk factor for cardiovascular disease and stroke (James et al., 2014). High blood
pressure (HTN) is defined as systolic blood pressure $\geq 140$ mm Hg, or a diastolic blood pressure $\geq 90$ mm Hg, or as taking antihypertensive medication (Go et al., 2014). High blood pressure causes extensive force of the blood against arterial walls which creates microscopic tears in the artery walls, which then results in scar tissue and accelerates the arterial wall hardening process that occurs with aging (American Heart Association, 2012). It is not surprising that seven of ten individuals who experience their first heart attack, and eight out of ten individuals who experience their first stroke, have high blood pressure (Go et al., 2014).

Hypertension (HTN) is a major independent risk factor for CHD. Regrettably, the treatment of HTN is unable to fully diminish the coronary heart disease risk it causes (Grundy et al., 2004). According to current estimates, 78 million (33%) adults in the United States who are 20 years of age or older have high blood pressure (Go et al., 2014). Hypertension is more prevalent in men 45 years and younger compared to women. However, women are about as likely as men to develop high blood pressure during their lifetimes (Go et al., 2014; Mozaffarian et al., 2015) Of those individuals with hypertension, individuals 60 years and older have the highest prevalence of HTN (66.7%) (Go et al., 2014). However, high blood pressure affects more women that are 65 years and older compared to men of the same age category (Go et al., 2014; Mosca, Barrett-Connor, & Wengeret, 2011).

The prevalence and treatment of high blood pressure in minorities continues to challenge the health care community. In the United States, hypertension is most prevalent among non-Hispanic black males (43.0%) and females (45.7%), as well as white men (33.9%) and women (31.3%)(Go et al., 2014). Mexican American men (27.8%) and women (28.9%), represent the ethnicity with the least controlled blood pressure, which in turn puts them at greater risk.
African Americans have the highest prevalence (44%) of high blood pressure in the world (Go et al., 2014; Mozaffarian et al., 2015). Blacks develop high blood pressure earlier in life and have a 1.5 times greater rate of death attributable to heart disease compared to whites (Center for Disease Control, 2014). While great strides have been made to increase awareness of high blood pressure among blacks, the odds of controlling blood pressure among blacks is 27% lower than it is in whites (Center for Disease Control, 2014). According to the National Health and Nutritional Examination Survey (NHANES) 2007-2010, the blood pressure of Mexican American males and females are the least controlled of all (Go et al. 2014).

**Diabetes.** According to the National Health and Nutritional Examination Survey (NHANES) 2007-2010 and 2012 statistics, currently 19.7 million people have physician-diagnosed Type 2 diabetes mellitus (DM) and 56.5% of adults met the criteria for type 2 diabetes mellitus (Mozaffarian et al., 2015). Of those 19.7 million, 6.8 million were not treated with glucose lowering therapy. Among the 12.9 million adults on glucose lowering therapy, 7.8 million (60.5%) did not have their hyperglycemia controlled (Go et al., 2014). Blacks, Mexican Americans, and Hispanic/Latino also bear a disproportional burden of the cardiovascular disease risk factor of Diabetes Mellitus (DM) in the United States (Go et al., 2014). The risk of being diagnosed with DM is disproportionality higher among Asian Americans (18%), Hispanic/Latino (66%) and non-Hispanic blacks (77%) as compared to whites (Mozaffarian et al., 2015).

The increased incidence of diabetes mellitus (DM) has resulted in an increase in coronary heart disease, stroke, and heart failure associated with diabetes (Go et al., 2014). Diabetics are considered at a high risk for cardiovascular disease regardless of the presence of other factors (NCEP, 2002; Payne, 2012). Additionally, diabetes is associated with at least a 60% increased prevalence of elevated low density lipoprotein, hypertension, and obesity (Go et. al., 2014).
Mortality among adults with diabetes is two to four times higher compared to non-diabetic adults. With the stakes so high for individuals with diabetes, the outlook is ominous when 8.2 million U.S. adults remain undiagnosed by a physician with diabetes and 87.3 million adults are considered pre-diabetic.

**The metabolic syndrome.** Cardiovascular risk prediction was propelled by the introduction of the Metabolic Syndrome (MetS) in the late 1990’s. A consensus within the medical community is that medical obesity, its medical complications, and the metabolic syndrome, warrant greater attention. The National Health and Nutrition Examination Survey (NHANES) III (1988-1994) affirmed that approximately 24% U.S. adults over the age of 20 had the metabolic syndrome, a clustering of at least 3 of 5 CVD risk factors (Ford et al., 2004). According to the NHANES 1999-2000 and the NHANES 2003-2006, the rates of metabolic syndrome have continued to rise from 27% to 34%. Individuals with the metabolic syndrome are twice at risk of developing cardiovascular disease in 5 to 10 years and have a five-fold increase in risk for type 2 diabetes mellitus as compared to those individuals without metabolic syndrome (Eckel, Alberti, Grundy, & Zimmet, 2010). The priority is the identification of patients with the metabolic syndrome in the clinical arena, and to promote the reduction of lifestyle risk factors (Alberti, Zimmet, & Shaw, 2006).

The term metabolic syndrome is the condition of the presence of risk factors of a metabolic origin for cardiovascular disease and diabetes (Alberti et al., 2009). However, there has been considerable disagreement in the medical community regarding the terminology and diagnostic criteria of the metabolic syndrome over the last decade. The World Health Organization (WHO) proposed a formal definition of metabolic syndrome in 1998. Insulin resistance was emphasized as the major underlying risk factor. Insulin resistance was required
for diagnosis of the metabolic syndrome. Individuals with type 2 diabetes were not excluded from the diagnosis. Diagnosis was made on the basis of several markers of insulin resistance plus two additional risk factors of either hypertension (blood pressure ≥160/90 mmHg), hyperlipidemia (triglyceride concentration ≥150 mg/dL and or high-density lipid (HDL) cholesterol <35 mg/dL in men and <39 mg/dL in women), central obesity (waist-to-hip ratio >0.90 in men or >0.85 in women and/or body mass index (BMI) >30 kg/m²), or microalbuminuria (urinary albumin excretion rate ≥20 μg/min or an albumin-to-creatinine ratio ≥20 mg/g) (Ford et al., 2004).

Definitions of metabolic syndrome put forth by the International Diabetes Federation (IDF) in 2005 and the ATP-III definitions that would follow in 2009, differed from the 1998 World Health Organization definition. Ethnic-specific criteria for waist circumference measurement to emphasize the role of insulin resistance and central adiposity in the metabolic syndrome was included in the definition of metabolic syndrome according to the International Diabetes Federation (IDF) in 2005 (Wyne, 2005).

Assessment for metabolic syndrome includes the presence of central obesity (waist circumference >94 cm for European men and >80 cm for European women, with ethnicity-specific values for other groups) plus two of the following factors are required to diagnose the metabolic syndrome: elevated triglyceride level (> 150 mg/dL or undergoing specific treatment for increased triglycerides), low HDL cholesterol (< 40 mg/dL in men and <50 mg/dL in women or undergoing specific treatment for reduced HDL cholesterol), presence of hypertension (systolic blood pressure >130 mm Hg or diastolic blood pressure > 85 mm Hg or undergoing treatment for previously diagnosed hypertension), and elevated fasting plasma glucose (> 100 mg/dL or previously diagnosed type 2 diabetes) (Grundy et al., 2004). Ethnic-specific values for
waist circumference have been established for the following groups: European, Sub-Saharan, Eastern and Middle Eastern (males: ≥ 94 cm, females: ≥ 80 cm), South Asian (based on a Chinese, Malay and Asian- Indian population: males: ≥ 90 cm, females: ≥ 80 cm), and Japanese (males: ≥ 95 cm, females: ≥ 90 cm) (Gaizano & Gaizano, 2012; Grundy et al., 2004; Wayne 2005).

In 2002, the Third Report of the National Cholesterol Education Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, published by the American College of Cardiology/American Heart Association, concluded an individual can be classified as having the metabolic syndrome if three or more of the following five criteria are met: abdominal obesity (waist circumference >102 cm in men and >88 cm in women), hypertriglyceridemia (triglyceride concentration ≥150 mg/dL), low HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women), high blood pressure (≥130/85 mg Hg), or high fasting glucose (≥100 mg/dL) (Ford et al., 2004). The International Diabetes Federation has recognized that in the United States, the Adult Treatment Panel (ATP) III values for waist circumference (males ≥ 102 cm, females ≥ 88) are likely to continue to be used for clinical purposes.

The metabolic syndrome is not an absolute risk indicator for cardiovascular disease, but rather encompasses the risk factors of a pro-inflammatory state (elevated high sensitivity C-reactive protein), and other non-metabolic factors such as physical inactivity, advanced age, sex, diet, cigarette smoking, and family history of premature coronary heart disease. These were considered risk factors but were not specified in the definition of the metabolic syndrome (Alberit et al., 2009; Grundy, et al., 2004,.). Acquired underlying risk factors of metabolic syndrome include obesity, weight gain, physical inactivity, and unhealthy diet (Carnethon et al., 2004; Eckel et al., 2010).
Smoking. The devastating effects of smoking on the body, in particular on the cardiovascular system, are well known. Smoking is regarded as the most important preventable risk factor for cardiovascular disease (Anderson et al., 2013) with cessation significantly reducing the risk of coronary heart disease and cardiovascular disease morbidity and mortality (National Cholesterol Evaluation Program, 2002; Go et al., 2014). Of the 5 million deaths caused by tobacco, approximately 1.6 million are CVD related (Gaziano & Gaziano, 2012). Worldwide, it is projected that 1.6 billion people will smoke cigarettes (Gaziano & Gaziano, 2012).

Approximately 20% of adults currently smoke with a greater prevalence in U.S men (20.5%) compared to women (15.9%)(Go et al., 2014; Mosca et al., 2011). Overall mortality among smokers in the United States is three times higher than non-smokers (Go et al., 2014). Smoking is a cardiovascular risk factor to those who do not smoke due to exposure to second hand smoke. According to the 2006 United States Surgeon General’s Report, the exposure to second hand smoke at home or at work increases the risk of developing coronary heart disease by 25% to 30% (Go et al., 2014). Regardless of the measures taken to educate and raise awareness of the morbidity and mortality associated with smoking cigarettes, it still remains a prevalent risk factor for cardiovascular disease. According to the trajectory for 2030, the burden of disease attributed to tobacco will be 10 million deaths annually (Gaizano & Gaizano, 2012).

Family history of cardiovascular disease. Family history of cardiovascular disease is a risk factor for the presence of coronary heart disease, and may be used to identify younger patients who may benefit from early intervention (Kones, 2011). Family history is considered coronary heart disease in a first-degree relative (parent, sibling, or offspring) (NCEP, 2002). Among adults in the United States 20 years and older, 12.6% reported a parent or sibling that had a myocardial infarction or angina prior to the age of 50 (Go et al., 2014). A paternal history of
premature heart attack doubles the risk of a heart attack in men and more than doubles the risk in women (Mozaffarian et al., 2015). Sibling history of cardiovascular disease increases the odds of cardiovascular disease in men and women by 45% (Mozaffarian et al., 2015).

Several cardiovascular risk models QRISK (Q Research Cardiovascular Risk Algorithm), ASSIGN (Assessing Cardiovascular Risk to Scottish Intercollegiate Guidelines Network), and the Reynolds Risk Score include a family history of cardiovascular disease as a risk factor. Genetic markers discovered thus far have not provided additional benefit to cardiovascular risk assessment beyond the incorporation of family history in multivariate risk models (Ranthe et al., 2013).

**Cardiovascular Risk Assessment**

Terminology of heart disease has evolved over the last fifty years from CHD (coronary heart disease) referring to diseases of the vessels supplying the heart, to cardiovascular disease (CVD), which encompasses diseases arterial circulation supplying the heart, brain and peripheral tissues. The more recent evolution has been to atherosclerotic cardiovascular disease (ASCVD) that entails coronary heart disease (CHD), stroke, and peripheral arterial disease, all of presumed atherosclerotic origin. Therefore, the requirements for cardiovascular risk assessment have evolved as well. The recommended risk assessment focused on estimation of ASCVD (Atherosclerotic Coronary Disease) events. ASCVD events were defined as the first occurrence of non-fatal myocardial infarction or coronary heart disease death, or non-fatal and fatal stroke.

Therefore, cardiac risk assessment has expanded beyond the traditional risk factors (e.g. hypertension, hypercholesterolemia, diabetes mellitus and smoking). Investigators included the non-traditional/novel risk factors of the high sensitivity C-reactive protein (hs-CRP) (Ridker et al., 2008), subclinical atherosclerosis measures of coronary artery calcium (CAC) scores
(Lakoski et al., 2007), and genetic risk scoring (AIRC cohort, Morrison et al., 2007) to predict cardiovascular risk. However, and perhaps to some surprise, the inclusion of novel risk factors into multivariate cardiovascular risk equation has generally failed to show even a nominal level of improvement in discrimination (C-statistic). In the Atherosclerosis Risk in Communities cohort (Folsom et al., 2006), combinations of inclusion of 19 novel risk factors increased the C-statistic by just 0.000 and 0.005, and several decreased the C-statistic slightly compared to the traditional risk factors. The inclusion of brain natriuretic peptide levels plus microalbuminuria to a traditional cardiovascular risk model increased the C-statistic from 0.76 to 0.77 (Wang et al., 2006). The inclusion of high sensitivity C-reactive protein (hs-CRP) and a family history of cardiac events to the traditional risk factors in cardiovascular multivariate risk produced a minimal change in overall model discrimination (Lloyd-Jones et al., 2004). However, the inclusion of coronary artery calcium (CAC) scores to the Framingham Risk Score increased the C-statistic more substantially from 0.02 to 0.11 (Hong et al., 2004). When evaluating the addition of novel risk factors, it is important to consider that most are correlated with traditional risk factors and the ability to change the C-statistic substantially is difficult (Lloyd-Jones, 2010).

This research study considered the novel risk factors high sensitivity C-reactive protein, carotid intima media thickness, Peripheral Arterial Tonometry, and Vasa Vasorum. These novel risk factors are reviewed below.

**High sensitivity C-reactive protein.** High Sensitivity C-reactive protein (hs-CRP) is an inflammatory biomarker primarily produced in the liver in response to the inflammatory cytokine, interleukin-6, and is synthesized in adipose tissue, by arterial smooth muscle cells, and by endothelial cells (Anderson et al., 2013). High sensitivity C-reactive protein is associated with risk for both coronary artery disease (CAD) and stroke (Anderson et al., 2013). The Women’s
Health Initiative study and the Physicians’ Health Study showed an association of hs-CRP and cardiovascular disease events that were independent of other cardiovascular risk factors (Ridker, Cushman, Stampfer, Tracy, & Hennekens, 1997; Ridker, Hennekens, Buring, & Rifai, 2000). In the Women’s Health Initiative study, healthy women belonging to the highest quartile of hs-CRP had an increased risk of cardiovascular disease events compared with those in the lowest quartile. In the Physicians’ Health Study, baseline hs-CRP concentrations were significantly higher among initially healthy men who had myocardial infarction or stroke compared to men who did not. Concentrations of hs-CRP concentrations were also associated with future risk of myocardial infarction and stroke when added to the model containing other cardiovascular risk factors. More recently, Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) (Ridker et al., 2008) demonstrated that a high sensitivity C-reactive protein level successfully identified a population with “hidden risk” for cardiovascular disease and provided evidence for the potential utility of hs-CRP as an indicator of therapy efficacy in CVD primary prevention.

According to Yousuf et al. (2013), the use of a single measurement of high sensitivity C-reactive protein (hs-CRP) for risk assessment may misclassify individuals. Sources of hs-CRP variations are body mass index, metabolic syndrome, diabetes mellitus, hypertension, oral contraceptive use, physical exercise, moderate alcohol consumption, periodontal disease, dietary patterns, environmental pollutant burden, and smoking, all of which can cause significant baseline variation. Findings from a reexamination of the National Health and Nutritional Examination Survey (NHANES) database indicated intra-individual variation among hs-CRP measurements. Among individuals, a second discordant measurement of hs-CRP reclassified 32% of the individuals previously classified as having a high hs-CRP. There was additional
empirical evidence of intra-individual variation, which resulted in overall risk reclassification in the Multi-Ethnic Study of Atherosclerosis (MESA) trial. In the MESA follow up, 54% of individuals had discordant hs-CRP levels and 69% of individuals with elevated baseline hs-CRP were reclassified into a lower cardiovascular risk category after subsequent measurements (Yousuf et al., 2013). Using a risk threshold of hs-CRP > 2mg, hs-CRP is advocated by some in the medical community. However, more than 50% of all adults and 41% of 20-year-olds in the United States have a hs-CRP levels >2 mg (deGoma et al., 2013).

Findings from the Dallas Heart Study and the Multi-Ethnic Study of Atherosclerosis (MESA) trial indicate the lack of a direct association between high sensitivity C-reactive protein and coronary atherosclerosis (Blaha et al., 2011; Gupta et al., 2012). Obesity is suggested as the biological modifier between hs-CRP and coronary atherosclerosis. DeGoma, Dunbar, Jacoby, & French (2013) reported hs-CRP was useful in the identification of patients classified as at high risk according to the Framingham Risk Score. However, its use may need to be restricted to only those patients identified as at intermediate or high risk for cardiovascular disease. However, the reclassification of intermediate-risk patients with the addition of hs-CRP to existing Framingham Risk Score variables may not meaningfully alter clinical management. Lastly, there is inconclusive evidence that reducing high sensitivity C-reactive protein hs-levels prevents coronary heart disease (deGoma et al., 2013).

**Carotid intima media thickness.** Carotid intima media thickness (CIMT) measures the thickness of the intima and media walls of the carotid arteries intima, which are the largest conduits of blood going to the brain (Go et al., 2014). Carotid intima media thickness is an earlier manifestation of atherosclerosis than coronary artery calcium, because thickening precedes the development of frank atherosclerotic plaque (Go et al., 2014). Carotid intima media
thickness is a known risk factor for cardiovascular disease and has been shown to predict the risk of stroke and coronary events (Bots, Hoes, Koudstaal, Hofman, & Grobbee, 1997; Chambless et al., 2000; Lorenz, Markus, Bots, Rosvall & Sitzer, 2007; O’Leary et al., 1999). Risk assessment among individuals at intermediate risk for cardiovascular disease is most likely to be improved by means of carotid ultrasound measurements to determine carotid intima media thickness or carotid plaque (Peters, Bakker, den Ruijter & Bots, 2012).

Men from the Kuopio Ischemic Heart Disease Risk Factor Study (Salonen & Salonen, 1991), free of vascular disease and aged 43–60 years at baseline (n=1257) were followed for 3 years. Findings indicated men with a 0.1 mm increase in thickening of the carotid artery wall were at an 11% increased risk of myocardial infarction (Salonen & Salonen, 1993). Moreover, greater progression of carotid intima media thickness (CIMT) values over a 2-year period was found in men with high low-density lipoprotein cholesterol levels (Salonen & Salonen, 1990). In the Atherosclerosis Risk in Communities (ARIC) cohort (Folsom et al., 2006), the mean CIMT measures were higher in men of all ages compared to women. However, the rate of intima media thickness progression in the common carotid artery was 0.01 mm/year for men and women.

Carotid intima media thickening (CIMT) has been associated with smoking (Raitakari et al. 2003; Howard, et al. 1994), and was significantly higher in patients with familial hypercholesterolemia (Wittekoek et al., 1999). Additionally, findings from The Insulin Resistance and Atherosclerosis study (Wagenknecht et al., 2003) indicated the CIMT of diabetic patients without known coronary artery disease was similar to the CIMT of non-diabetics with known coronary artery disease. Carotid intima media thickness progression has been found to be significantly associated with age, race, systolic blood pressure, and diabetes (Ahuja et al., 2014).
Of note, blacks have higher CIMT burden than whites (Mackinnon, Jerrard-Dunne, Porteous, & Markus, 2010; Manolio, et al., 1995).

Ahuja et al. (2014) aimed to study the racial differences in carotid intima media thickness progression over a four to six year period in 393 middle-aged men. The population-based sample consisted of whites (n=199), blacks (n=39), and Japanese Americans (n=155) aged 40-49 years who were not diabetic, hypertensive, or taking lipid-lowering medication and were free of clinical cardiovascular disease at baseline. Carotid intima media thickness progression was the highest in Japanese American compared to white and black men. Intima thickness progressed faster in blacks compared to whites (Ahuja, et al., 2014).

Despite the association with smoking and high cholesterol, the inclusion of carotid intima media thickness (CIMT) to traditional risk factors in multivariate cardiovascular risk prediction models does not appear to improve risk prediction. Data from the Carotid Atherosclerosis Progression Study (CAPS) found that when added to the Framingham Risk Score and Systematic Coronary Risk Evaluation (SCORE) models, carotid intima media thickness did not significantly improve risk prediction (Lorenz, Schaefer, Steinmetz, & Sitzer 2010). In a review by Simon Megnien and Chironi (2010), only modest improvement to risk prediction occurred with the addition of carotid intima media thickness despite its ability to independently predict coronary heart disease (Robertson, Fowkes, & Price, 2012). In a rigorous review of twelve studies by Peters, den Ruijten, Bots & Moons (2012); nine studies demonstrated an increase in discrimination (C-statistic) when CIMT was added to the traditional risk assessment. Importantly, there were various definitions for CIMT and cut-offs for intermediate cardiovascular risk used across the 12 studies reviewed.
According to the most recent American College of Cardiology/American Heart Association guidelines, carotid intima media thickness (CIMT) is not recommended for routine measurement in clinical practice for risk assessment for a first atherosclerotic cardiovascular disease event. The Peters et al (2012) findings were not supported by the meta-analysis done by Den Ruijter et al. (2012) analysis of 14 cohorts consisting of 45,828 individuals during a median follow up of 11 years (Go et al., 2014). During the follow up period 4,007 individuals experienced either an initial myocardial infarction or stroke. The Framingham Risk Score (FRS) and an extended FRS model with common CIMT measurements were used to estimate the absolute 10-year risks to develop a first-time myocardial infarction or stroke. The discrimination (C-statistic) of both models was similar C = 0.75, 95% CI [0.74 - 0.76] and 0.75, 95% CI, [0.75 - 0.76] respectively. However Den Ruijter et al. (2012) stated that the improvement in 10-year risk to predict first-time myocardial infarction or stroke was not likely to be of clinical importance.

According to Nair, Malik and Khatter (2012), in the earlier studies measuring CIMT the measurements were performed by visually detecting the leading edges of the blood intima, media, and adventitia interfaces. This is in contrast to more recent studies that use a computer based automated edge detection method. Therefore, among many of the large population based studies the reported carotid IMT measurement, they may have included plaque thickness in the derived mean (Nair et al., 2012).

The reviewed studies utilized the study outcomes for coronary heart disease events and cardiovascular disease events, and not atherosclerotic cardiovascular disease events. The American College of Cardiology and American Heart Association guidelines described incongruent findings as evidence for their current recommendation regarding not to include CIMT in risk assessment for an atherosclerotic cardiovascular event.
Peripheral arterial tonometry. The dysfunction of endothelial cells from decreased nitric oxide (NO) bioactivity is associated with vascular inflammation, vasoconstriction, and thrombosis which contributes to the development of atherogenesis which then progresses to cardiovascular disease (Hamburg & Vita, 2006; Rubenstein et al., 2010; Widlansky, Gokce, Keaney, & Vita, 2003).

Therefore, the assessment of microcirculatory vasomotor function may afford the identification of early coronary arthrosclerosis. Endothelial function in coronary arteries is closely related to the endothelial function in peripheral arteries (Briasoulis, et al., 2012). Measurement of peripheral vasodilator response using fingertip pulse amplitude tonometry (PAT) as a measure for endothelial dysfunction has been correlated with cardiovascular risk factors, coronary artery disease, cardiovascular hospitalization, cardiovascular death, death, and myocardial infarction (Patvardhan, et al., 2011; Rubenstien et al., 2010). The non-invasive digital amplitude tonometry-detected endothelial dysfunction measures correlate with the more invasive measures (coronary and brachial artery) measures of endothelial dysfunction, which are known predictors of cardiovascular disease events. (Bonetti al., 2004; Kuvin, et al., 2003; Naik, & Khatatter, 2012).

Assessment of vascular function with pulse amplitude tonometry (PAT) involves measuring pulse amplitude in the fingertip at rest and following the induction of reactive hyperemia. Hamburg et al. (2008) evaluated the vascular response in relation to baseline PAT, and expressed the hyperemic response (called the PAT ratio) as the natural logarithm of the ratio of post-inflation to baseline pulse amplitude in the hyperemic finger divided by the same ratio in the contralateral finger that served as the study control. Pulse amplitude tonometry assessment of arterial reactive hyperemia from the Framingham Third Generation Cohort participants (n =
1957) with a mean age of 40.9 years and comprised of 49% women, was associated with cardiovascular disease risk factors (Hamburg et al., 2008). The baseline pulse amplitude was higher in men than in women. However, male gender, body mass index, total and high-density cholesterol ratio, diabetes mellitus, smoking, and lipid-lowering treatment were all associated with a lower a PAT.

Mulukutla et al. (2010) evaluated whether black race is independently associated with arterial endothelial dysfunction with digital pulse amplitude response to forearm occlusion-induced hyperemia. Among the 1,377 subjects, of which 41% were black, 67% were female and had a mean age of 58.5 years enrolled in the Heart Strategies Concentrating on Risk Evaluation (Heart SCORE) study, the authors found that black race was independently associated with a lower pulse amplitude tonometry (PAT) ratio. Subjects were assigned to low, intermediate, and high Framingham risk strata. Within each Framingham risk strata, blacks consistently had significantly lower PAT ratio than whites signifying greater endothelial dysfunction in blacks (Mulukutla et al., 2010).

Pulse amplitude tonometry ratios of white and black races in the low Framingham risk strata were higher (i.e. better endothelial function) when compared with individuals in the intermediate or high-risk strata. Importantly, a lower PAT ratio in both races was associated with a higher body mass index and cholesterol/high density lipoprotein ratio. These findings were consisted with Hamburg et al. (2008), which further the postulate that race, gender, and traditional cardiovascular risk factors are associated with PAT assessment of endothelial dysfunction. Furthermore, PAT may be a useful measure of assessing overall risk for coronary artery disease and may provide additional risk stratification to supplement the traditional Framingham cardiovascular risk assessment.
Peripheral arterial tonometry (stiffness) has been shown to be an important risk factor for cardiovascular disease (Go et al., 2014). Coronary endothelial dysfunction evaluated by invasive methods to predict coronary disease events and stroke (Lerman & Zither, 2005; Schachinger, Britten & Zeiher, 2000; Suwaidi et al., 2000; Targonski et al., 2003) correlate with abnormal non-invasive peripheral arterial tonometry results. However, current guidelines do not recommend measuring peripheral arterial tonometry for cardiovascular risk in asymptomatic adults. Endothelial function assessment is currently not standardized. This lack of standardization remains a barrier to its use in risk assessment and in being recommended in the current American College of Cardiology and American Heart Association guidelines (Go et al., 2014).

**Vasa vasorum.** The inner most layer of the artery is the intima, the muscular middle layer is the media and the adventitia is the outer most layer. The vasa vasorum (VV) or ‘the vessels of the vessels’, form a network of micro vessels within the wall of the blood vessel in the adventitia and infiltrate the outer media of vessel wall (Baukousis et al., 2011). In the absence of disease, the vasa vasorum provide nutrition to the adventitia and the intima is fed oxygen by diffusion from the lumen (Moreno et al., 2006). However the thickening of the intima wall with disease progression inhibits oxygen diffusion (Moreno et al., 2006).

In the presence of hypoxia neovascularization, inflammation, and the activate angiogenic factors occur (Pelisek, 2012). In atherosclerosis, the predominant form of neovascularization is endothelial cell mediated angiogenesis (Manero et al., 2006). The resulting hyperplasia of the adventitial vasa vasorum and intraplaque neovascularization is critical to plaque development (Staib et al., 2010). Importantly, a hallmark of cardiovascular vulnerability is the neovascularization of carotid plaque (Staib et al., 2013). Pelisek et al. (2012) found
neovascularization to be closely associated with carotid plaque progression and lesion vulnerability. Cardiac events leading to plaque rupture and clinical events appear to be consistent with the plaque inflammation process (vascular leakage, inflammatory cell recruitment, and intraplaque hemorrhage) (Staib, et al., 2010, 2013).

Contrast enhanced carotid ultrasound (CEUS) allows for noninvasive visualization of vasa vasorum in the adventitial layer and of the vasa vasorum derived from intraplaque neovascularization (Staib et al., 2013). This technique uses intravenous injection of commercially available perflutren microspheres that serve as true intravascular tracers that can be imaged in the carotid artery by real-time 2D ultrasonography. The imaging correlated strongly with conventional angiography and magnetic resonance imaging studies (Staib et al. 2013). The assessment of intraplaque neovascularization using CEUS correlated with the histological examination results in animals and humans following a carotid endarterectomy (Coli et al., 2008; Hoogi et al., 2011; Moguillansky et al., 2011). Currently, CEUS is used with great success, but software to standardize intraplaque neovascularization quantitative assessments using CEUS is still needed.

Contrast enhanced carotid ultrasound (CEUS) of the carotid artery has been shown to accurately depict carotid stenosis of 70 % or more luminal narrowing and improve visualization of wall irregularities including soft plaques, plaque ulcerations, and dissections (Staib et al., 2013). Van den Oord et al. (2013) found the detection of atherosclerotic plaques using CEUS (88%) compared to standard carotid ultrasound (77%) to be significantly higher. Based on these findings, CEUS has an incremental value for the detection of subclinical atherosclerosis in the carotid arteries. Cardiovascular disease risk estimation from a carotid intima media thickness (CIMT) in combination with the presence of plaque in the carotid artery has been found to
significantly improve the prediction of cardiovascular events (Nambi et al., 2010). Vasa vasorum assessment using CEUS is both non-invasive and novel. The full capacity of vasa vasorum assessment to improve cardiovascular risk assessment is not currently known.

**Cardiovascular Risk Scores**

Cardiovascular risk scores permit the stratification of risk providing information to health professions permitting the delivery of preventative services. Likewise, cardiovascular risk estimation guides the selection of those who will receive more intensive disease preventative intervention (Lloyd-Jones, 2010). Furthermore, the National Cholesterol Education Program Adult Treatment Panel, the Seventh Joint Commission Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) and U.S Preventative Services Task Force (USPSTF), and the American Diabetes Association promote cardiovascular disease risk assessment research to aid in the prevention of morbidity and mortality. However, there is no ideal risk assessment equation or set of risk factors to identify high-risk and/or low-risk individuals (Anderson et al., 2013).

A risk score distinguishes disease burden and severity, cost benefit, and facilitates the effectiveness of disease prevention intervention (Lloyd-James, 2010). A risk score is derived from a multivariate equation (algorithm) comprised of risk factors that are used to quantify cardiac risk when preforming a risk assessment. To develop a multivariate risk equation the cardiovascular risk factors used to predict risk for the selected cardiac event over a set time period are predetermined. Likewise, the cardiac events cardiac heart disease (CHD) events, cardiovascular disease (CVD) events, or atherosclerotic cardiovascular disease (ASCVD) events are predetermined and are referred to as the risk study outcomes.
The outcomes of risk assessment models are chosen to reflect disease prevention and prevalence as well as the scientific statements and guidelines of medical research and science. The evolution of cardiovascular disease guidelines and research findings is evident in cardiovascular risk outcomes. In 1998, the Framingham Risk Score outcomes were focused on coronary heart disease and coronary artery disease (disease of arteries supplying the heart) events of angina pectoris, unstable angina, myocardial infarction (MI), and coronary heart disease (CHD) death. The inclusion of cardiovascular disease (major disorders of the heart and the arterial circulation supplying the heart, brain and peripheral tissues) focused risk prediction by using the risk study outcomes of stroke, stroke death, and cardiac failure in addition to myocardial infarction, and coronary heart disease death. The Framingham Risk Score (2008) and Reynolds Risk Score for women and men (2007, 2008) reflect the change in the state of the science in risk prediction to a focus on cardiovascular disease opposed to coronary heart and artery disease. Recently, the American College of Cardiology and American Heart Association 2013 guidelines recommended atherosclerotic cardiovascular disease (ASCVD) events to be used as the risk assessment outcomes. An ASCVD event includes nonfatal myocardial infarction or coronary heart disease, (CHD) death, or fatal or nonfatal stroke (Goff et al., 2014). Again, the Pooled Risk Cohort Equations were created to assess the risk of ASCVD events; which reflect the ongoing advancement of research in cardiovascular risk assessment. As risk factors that measure disease and risk scores were developed, a statistical method to quantify the association between risk factors and disease (represented by cardiovascular risk outcomes) was needed (Lloyd-Jones, 2010).
Cardiovascular Risk Model Evaluation

A cardiovascular disease risk model is capable of providing the risk of having the specified cardiac events based on the presence or absence of cardiovascular risk factors. The appropriate interpretation of 10-year risk of 10% is the following. Given 100 hundred similar individuals, it is expected that 10 out of 100 will experience an event in the next ten years and 90% will not. In addition to obtaining absolute risk, the utility of a cardiac risk estimation model includes the ability to discriminate future cases (presence of disease) from non-cases (absence of disease), and the model provides information for the outcome of interest (Lloyd-James, 2010). A formal statistical evaluation of model performance was needed with the epidemics of risk prevalence, cardiovascular disease development with a subsequent observation of cardiovascular events (Lloyd-Jones, 2010). Discrimination and calibration are the most widely used statistical evaluation methods for cardiovascular disease risk models.

**Discrimination.** The ability of the model to rank order individual risk is assessed using the Harrell’s C-index (C-statistic) and is the most widely reported measure of cardiovascular disease risk model discrimination. Discrimination provides assessment of whether a risk prediction model accurately rank orders individuals (e.g., are individuals with higher predicted risk more likely to have events (Muntner et al., 2014). A risk model with perfect discrimination would produce two non-overlapping sets of risk predicted probabilities, one for the probability of an event and the other for non-events.

A C-statistic indicates the probability that a randomly selected individual who develops the disease (case) will have a higher risk score compared to a randomly selected individual who did not develop a disease (non-case) (Lloyd-Jones, 2010). The C-statistic ranges from 0.5 indicating that a score applied to the risk model is no better than random chance, to a 1.0 that
indicates perfect discrimination. A C-statistic of less than 0.70 in a risk model indicates the model provides less than adequate discrimination; a C-statistic between .70 and .80 is considered acceptable. C-statistics between 0.80 to 0.90 are considered to provide excellent discrimination. The use of the C-statistic as the sole measure to assess risk model discrimination has been criticized since the rank comparison of cases and non-cases does not quantify the difference in estimated risk between selected cases and non-cases.

**Calibration.** Calibration provides an assessment of whether a risk prediction model accurately estimates the observed risk level (Muntner, et al. 2014). Calibration quantifies the closeness of the predicted probabilities of an event to the observed event rates. The most widely reported measure of model calibration for cardiovascular disease risk models is the Hosmer-Lemeshow $\chi^2$ test. In order to assess a model’s calibration, the population is divided into quartiles or related levels (e.g. quintiles, deciles) in order to visually assess the predicted risk versus the observed event rate for each quartile. A Hosmer-Lemeshow $\chi^2$ value of greater than 20 or a $p$-value of less than .05 indicates poor calibration for that cardiovascular disease risk model (Muntner et al, 2014). Importantly a risk model can have discriminatory ability with poor calibration. This would mean that the risk model was not an accurate predictor of future risk of CVD at different levels of risk.

**The Framingham Heart Score**

The Framingham Heart Study is still considered to be groundbreaking research since its inception in 1948 and continues to date with new generations of cohorts. It was a remarkable advance in the understanding of the complexities of cardiovascular disease (CVD) etiology, risk assessment, and the primary prevention of cardiovascular morbidity and mortality (Kones, 2011). The traditional risk factors identified in the Framingham Heart Study remain central to
cardiovascular risk assessment sixty years later. Since the earlier publications of the multivariate Framingham risk equations, several models have been adapted to estimate “cardiovascular age, vascular age, and cardiovascular age risk” (Anderson, Wilson, Odell, & Kannel, 1991; Anderson et al, 2013; Brittain, 1982; Kannel, McGee, & Gordon, 1976; Levy, Wilson, Anderson & Castelli, 1990; Wilson et al., 1987, 1988).

The Framingham Risk Score developed by Wilson et al. (1998) predicted the risk of the development of coronary heart disease (CHD) not cardiovascular disease (CVD). To enhance the utility of the Framingham Risk Score D’Agostino et al., 2008 developed a 10-year cardiac risk score with cardiovascular disease outcomes of myocardial infarction, coronary heart disease death, stroke, death from stroke, cardiac failure. The sample consisted of Framingham heart study participants (n =8,491) included women (n=4,522) and men (n=3,969) ages 30 through 74 all being initially free of cardiovascular disease. Participants were followed over a 12-year period for the development of coronary artery disease, stroke, peripheral artery disease (PAD), and heart failure (HF). A sex-specific general cardiovascular risk function was also generated to estimate 10-year CVD risk and the ability of the risk prediction model to discriminate individuals who experienced a CVD event from those who did not. Discrimination was evaluated using an overall C-statistic. The sex-specific cardiovascular functions performed well, the C-statistics for the risk function ranged from 0.763, 95% CI, [0.74 to 0.78] in men to 0.79, [0.77 to 0.81] in women. This highly regarded research provided a 10-year general cardiovascular risk algorithm that is well known and used throughout the world. The limitations of this research are the predominately white male sample that has been continuously used in Framingham Risk Score research. Risk factors of abdominal obesity, electrocardiogram evidence of left ventricular hypertrophy, indications of insulin resistance, triglycerides, and a strong family history of premature
cardiovascular disease are not included. However, D’Agostino et al. (2008) emphasize their importance in the assessment of cardiovascular risk. An important limitation for all risk assessment research identified by the authors is that risk scores, per se, do not translate to better patient outcomes.

**Issues with Framingham scoring.** Previous research indicates that with recalibration, the Framingham Risk scores can be tailored for use in non-Framingham populations (Marrugat et al., 2003, 2007; Taylor et al., 2008). The Framingham Risk Score has been criticized for its application to research populations with the under-representation of specific populations, a lack of ethnic diversity, and over-estimating risk (Payne, 2012). Additionally, this risk score has been criticized for under-representation of patients with diabetes and stages III and IV of kidney disease (Payne, 2012). Furthermore, the Framingham Risk Score was found to under predict risk in patients with stages III and IV of kidney disease (Chang & Kramer, 2011).

An overestimation of risk leads to overtreatment and underestimation of risk leads to under treatment (deGoma et al., 2013). The Framingham Risk Score was developed using a primarily male population, yet was subsequently deemed to be applicable to both men and women. Findings from Framingham Risk Score research indicated under prediction of women’s cardiovascular risk. According to research by Kones (2011), among women who sustained their first myocardial infarction, 95% had Framingham Risk Scores in the low risk category, with the remaining 5% in the intermediate category.

The Framingham Risk Score (FRS) preforms optimally (discrimination and calibration) in white and black populations in the United States. In Asian American, American Indian, Hispanic Americans, and Native Chinese populations, this method has only an acceptable evidence of discrimination and overestimates cardiovascular risk (D’Agostino et al., 2001; Liu et
The FRS has been found to overestimate risk by 50% in Non-White populations and therefore is less applicable in many non-western populations (Mendis, 2010). Moreover, in some European regions considered as low-risk populations, the Framingham Risk Score may overestimate risk (Kones, 2011).

**Reynolds Risk Score**

Cardiovascular disease (CVD) remains the leading cause of death among women in the United States (Go et al., 2014). The risk of acquiring cardiovascular disease increases after age 40. Women free of CVD at age 40 have a greater than 50% lifetime risk for developing CVD, while women free of CVD at age 50 continue to have a high lifetime risk of 39.2% (Roger et al., 2011). The premise that women should be treated the same as men in their prevention and interventions for cardiovascular disease was challenged during the assembly of numerous organizations in 2004 including the American Heart Association to sponsor the female specific guidelines “Evidence Based Guidelines for Cardiovascular Disease Prevention in Women” (Mosca et al., 2011b). To address the known gender disparity in cardiac risk assessment, Ridker, Buring, Rifal, and Cook (2007) developed a cardiovascular risk score specifically for women called the Reynolds Risk Score.

The Women’s Health Initiative study (Ridker et al., 2005) a nationwide cohort of U.S. women free of cardiovascular disease and cancer at study entry was initiated in September 1992, was used to develop the RRS for women. A prediction model was creating using development (n=16,400) and validation (n=8,158) cohorts of women ages 45 and older who were followed for a median a time period of 10.2 years. The cardiovascular events over the 10 years of 24,553 women ages 45 and older were used. The predicted risk model (developing Reynolds Risk
Score) was compared to the Adult Treatment Panel III risk score model and Framingham Risk Score using the events of the 24,553 women.

Discrimination was evaluated with Harrell’s C-index, and model calibration was assessed with the Hosmer-Lemeshow $\chi^2$. The RRS ($C = .80$) demonstrated superior discrimination compared to the ATP III 2001 score ($C = .78$), and the FRS ($C = .75$). Model calibration of the RRS ($\chi^2 = .62$) was also superior to the APT III ($\chi^2 < .001$) and FRS ($\chi^2 < .001$). The resulting model known as the Reynolds Risk Score includes the risk factors of age, systolic blood pressure, high-sensitivity C-reactive protein, total cholesterol, high density lipoprotein cholesterol, hemoglobin $\text{A}_{1C}$, diabetes status, smoking status and the presence of family history of premature myocardial. Variables used in the 3 risk score of interest are listed in Table 1. (Ridker et al., 2007).

**Table 1.** Risk Factors used in the Framingham Risk Score, Reynolds Risks Scores and Pooled Risk Equation Risk Scores

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</table>

*Note. FRS= Framingham Risk Score; RRS (W) = Reynolds Risk Score for Women; RRS (M) = Reynolds Risk Score for Men; Pooled= Pooled Cohort Risk Equation; TC = Total Cholesterol; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; SBP = Systolic Blood Pressure; BP Rx = Blood Pressure Prescriptions Medication; DM = Diabetes Mellitus; Hs-Crp = High Sensitivity C-reactive protein; FH = Family History.*

**Reynolds risk score for men.** Based on the superior performance of the Reynolds Risk Score (RRS) for women, Ridker, Paynter, Rifai, Gaziano, and Cook et al. (2008) aimed to use
the same risk factors to develop a risk score for men. The RRS for men was developed using participants (n=10,724) from the Physicians Health Study II (Christen, Gaziano, & Hennekens, 2000), a nationwide cohort of U.S. men 50 years and older free of cardiovascular disease, diabetes mellitus, and cancer. A total of 1,294 cardiovascular events occurred (1,072 were classified as incident coronary heart disease events of coronary revascularization or fatal or nonfatal myocardial infarction) over the median follow up period of 10.8 years.

A traditional risk model based on age, blood pressure, smoking status, total cholesterol, and high-density lipoprotein was compared to the Reynolds Risk Score model risk factors (age, blood pressure, smoking status, total cholesterol, and high-density lipoprotein cholesterol, high-sensitivity C-reactive protein and parental history of myocardial infarction before age 60). Risk prediction of the traditional model and the RRS both utilize cardiovascular disease outcomes. Additional analysis comparing the performance of the RRS form men to the ATP-III global risk assessment (which incorporates the treatment of hypertension) using coronary heart disease as the model outcome was conducted. The authors also compared the ATP-III risk model and the RRS using a subgroup of study participants not taking lipid-lowering therapy at baseline.

Discrimination was evaluated with Harrell’s C-index, and model calibration was assessed with the Hosmer-Lemeshow $\chi^2$. Calibration was computed with risk at 7 years since the majority of participants had follow up completed through this time. Findings from the primary analysis indicated the traditional risk factor model (Hosmer-Lemeshow $\chi^2 = 11.3$) and Reynolds Risk Score (RRS) for men (Hosmer-Lemeshow $\chi^2 = 12.9$) demonstrated similar levels of calibration. For both the cardiovascular disease (CVD) and coronary heart disease (CHD) endpoints, the Reynolds Risk Score had a better model fit ($p < 0.001$). The C-statistic of the traditional model for cardiovascular disease ($C = 0.69$) and coronary heart disease ($C = 0.68$) was compared to the
Reynolds Risk Score for men C-statistic for the cardiovascular disease endpoint (C = 0.70) and the coronary heart disease endpoint (C = 0.70). This comparison indicated that the Reynolds Risk Score improved discrimination. Model fit and C-statistics were superior in models that included hs-Crp and parental history of myocardial infarction from the analysis of the cohort limited to men not taking lipid-lowering therapy at baseline, and with the end point of coronary heart disease. Despite these findings, the Reynolds Risk Score for men is rarely used. The Reynolds Risk Score for women is more widely accepted and used within the medical community.

**Reynolds risk score and the Framingham risk score.** Cook et al., (2012) directly compared three (Framingham Risk Score, Reynolds Risk Score for women, and the Adult Treatment Panel III Risk Score) cardiovascular disease risk scores using a multi-ethnic case cohort sample from the Women’s Health Initiative (WHI) Study observational cohort. A sample of 1,722 women with major cardiovascular disease, as well as a random sub cohort of 1,994 women without prior cardiovascular disease, were assigned a Reynolds Risk Score, Framingham Risk Score and Adult Treatment Panel III Risk Score. To foster an ethnically diverse sample, black (n=200), Hispanic (n=53), and Asian (n=55) women and women with other/unknown ethnicity (n=55) with major cardiovascular disease were included.

The risk study outcomes used in WHI data were coronary heart disease (CHD) events, which consisted of myocardial infarction, coronary death, ischemic stroke, and cardiovascular disease death. The Adult Treatment Panel III risk score is used to predict the same CHD events. The Framingham Risk Score predicts cardiovascular disease risk (myocardial infarction, coronary death, coronary insufficiency, and angina), cerebrovascular events (including ischemic stroke, hemorrhagic stroke, and transient ischemic attack), peripheral artery disease (intermittent claudication), and heart failure. While the Reynolds Risk Score also predicts cardiovascular
disease risk, it is defined as incident myocardial infarction, ischemic stroke, coronary revascularization, and cardiovascular death. The cardiovascular events experienced by the 1,722 individuals included 752 myocardial infarctions, 754 ischemic strokes, and 216 cardiovascular disease deaths.

Instead of reporting the Hosmer-Lemeshow $\chi^2$ statistic, calibration plots were used. The study sample was divided into deciles of risk, and the predicted risk according to the Adult Treatment Panel III risk score (ATP-III) was compared with observed 10-year rates of coronary heart disease among only non-diabetics (since the ATP –III is intended for non-diabetic individuals). According to the calibration plots, the ATP-III model overestimated risk of coronary heart disease, but demonstrated better calibration of the risk of major cardiovascular disease for women. Both the ATP-III model for coronary heart disease and the Framingham Risk Score for cardiovascular disease (CVD) overestimated risk in black and white women.

Importantly, the poor calibration of the Framingham Risk Score may be due to it being developed for the broader study outcome of total cardiovascular disease, including several other conditions, namely angina, coronary insufficiency, transient ischemic attack, peripheral artery disease, and congestive heart failure (Cook et al., 2012).

The C-statistics of the Adult Treatment Panel III risk score model ($C = .75$), Reynolds Risk Score model ($C = .76$), and the Framingham Risk Score ($C = .75$) were similar. The Reynolds Risk Score demonstrated statistically significant improvement in discrimination in all women ($p = .03$) compared to the ATP-III model and the Framingham Risk Score model ($p < 0.0001$). Reynolds Risk Score discrimination was statistically significant among white ($p <0001$) and black ($p = .01$) women, as compared to Framingham Risk Score model discrimination (Cook et al., 2012).
Using the National Health and Nutritional Examination Survey (NHANES) data sets from 1999–2000 and 2001–2002, Tattersall, Ganon, Karmali, & Keevil (2012) examined the cardiovascular risk of a representative U.S. population with the Reynolds Risk Score and the Framingham Risk Score. Prior to the publication of the update lipids guidelines, Tattersall et al., (2012) examined two cardiovascular risk scores and the current lipid classification in a representative population. The study population was intended to represent 53.6 million eligible U.S. adults. In order to equate the population used to develop the Reynolds Risk Score (Ridker et al., 2007, 2008), 1440 women ages 45-79 and 1,062 men ages 50-79 free of coronary heart disease and diabetes mellitus were included in the representative population. Cardiovascular risk categories of low, moderate, moderate-high, and high-risk categories risk values were defined and were consistent with guidelines. Additionally, the number of adults with the representative population who reached their low-density lipoprotein (LDL) goal was also assessed. The LDL goals listed for each risk category were derived using the optional clinical goals of the U.S. lipid guidelines (Grundy, et al., 2004). Low risk was indicated by a cardiovascular risk score less than 6% and LDL cholesterol <160 mg/dL; moderate-risk was indicated by a risk score between 6% and 10% and LDL of <130 mg/dL; Moderate-high Risk was defined as a score between 10% and, 20% and LDL < 100 mg/dL; and finally, high risk was indicated by a score of 20% and LDL <70 mg/dL (Tattersall et al., 2012).

Findings indicated that use of the Reynolds Risk Score (RRS) assigned 13.9 % of women and 9% of men to a higher risk category, while 37.5% of men and only 2% of women were reclassified into a lower risk category. Using the RRS opposed to the Framingham Risk Score (FRS), 10.5% of men and 0.6% of women met their low-density lipoprotein goal. According to
these findings, the clinical management of 1.6 million women and 2.1 million men would change using the Reynolds Risk Score, as opposed to the Framingham Risk Score.

Tattersall et al., (2012) noted the importance of the differing risk score outcomes, such as those used for the Reynolds Risk Score and the Framingham Risk Score, for clinicians who may seek to use these models as interchangeable. Models may be reported to be superior against comparators when the examined outcome was the one that the model was developed for, but not for one, which the comparator was developed (Siontis et al., 2012). Diverse endpoints of myocardial infarction, stroke, coronary revascularization, and any cardiovascular death used for the Reynolds Risk Score, compared to Framingham Risk Score endpoints of myocardial infarction and fatal coronary heart disease, may limit comparison. It is known that differing endpoints may impact risk classification, and consequently treatment decisions. Statistical adjustments must be made to permit model comparison (Siontis et al., 2012).

Furthermore, the U.S. cohorts used to derive the Framingham Risk Score (FRS) and the Reynolds Risk Score (RRS), as well as the populations of which these risk equations have been applied, limits generalizability to other populations. Both the RRS and the FRS were developed and validated in homogenous ethnicities within the U.S. and future studies of broader populations across the U.S. that track event outcomes would allow better comparisons of the calibration, discrimination and generalizability of these risk models (Tattersall et al., 2012). The follow up period for the Women’s Health Initiative (WHI) used to develop the Reynolds Risk Score (RRS) for women was 10.2 years (Tattersall, et al., 2012). In the Physicians Health Study (PHS) II study used to develop the Reynolds Risk Score for men, the follow up period was shorter at 7.2 years. The ethnically diverse population of women used to develop the RRS for women allowed greater generalizability of results. However, the PHS II was not an ethnically
diverse population, as it was comprised of U.S. male physicians at least 50 years of age with relatively high socioeconomic status, excellent access to health care and information on preventive therapies. Adjustment of risk estimates based on ethnicity are required to account for different underlying rates of disease incidence, and prevalence of risk factors (Tattersall, et al., 2012).

The use of cardiac risk scores is limited in certain areas of the world, and finding low-cost strategies for clinicians to obtain cardiac risk scores is essential (Berger, Jordan, Lloyd-Jones, & Blumenthal, 2010). The Framingham Risk Score and both Reynolds Risk Scores contains some laboratory tests to estimate risk, and therefore, the risk of an individual cannot easily be assessed without access to a laboratory. This may limit the use of the FRS and RRS, particularly the Reynolds Risk Score requiring hs-CRP, to populations without laboratory access.

The Pooled Cohort Risk Equations

In 2008, the National Heart, Lung, and Blood Institute (NHLBI) in a collaboration with the American College of Cardiology (ACC) and American Heart Association (AHA) sought to develop updated clinical practice guidelines for assessment of cardiovascular risk, reduction of risk through lifestyle modification, management of cholesterol, as well as overweight/obesity management. One of the expert panels was tasked with providing current evidence based foundation for primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) in men and women. Recommendations were made from data reviewed from randomized control trials, systematic reviews, and meta-analysis of ASCVD literature. Specifically, one work group was tasked to provide risk assessment input to expert panels for cholesterol, blood pressure, and overweight/obesity guidelines (Goff et al, 2013). Their purpose was to recommend a cardiac risk assessment model to these work groups. A rigorous review of
risk assessment methodology for cardiovascular risk scores was conducted. Findings from existing cardiac risk scores research used non-representative or data populations, had limited ethnic diversity, narrowly defined endpoints, endpoints influenced by provider preferences (e.g. revascularization), and endpoints with poor reliability (e.g. angina and heart failure) (Goff, et al 2013).

**2013 ACC/AHA Guidelines**

The Framingham Risk Score, recommended in the previous American Heart Association guidelines, was found to be void of contemporary data, and dominated by a white population with limited coverage of other ethnic groups (Preis and Kristensen, 2015). A more limited outcome scope of coronary heart disease (CHD) and insufficient focus on ischemic stroke as a cardiac risk score outcome were additional factors in the lack of endorsement of the Framingham Risk Score to be used for cardiac risk assessment model in the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Risk Assessment Guidelines (Goff et al., 2013; Preis & Kristensen, 2015)

The Work Group developed a cardiovascular risk assessment equation called the Pooled Cohort Risk Score Equation. The 2013 ACC/AHA Risk Assessment Guidelines included the recommendations of the American Diabetes Association and the American Stroke Association on a cardiac risk assessment model focused on the predicted estimation of ASCVD (Atherosclerotic Coronary Disease) events (Goff et al., 2013). The Work Group developed the Pooled Risk Cohort Equation that provided an estimation of risk for an initial Atherosclerotic Coronary Disease event. Atherosclerotic cardiovascular disease (ASCVD) events were defined as the first occurrence of non-fatal myocardial infarction or coronary heart disease death, or non-fatal and fatal stroke. The Pooled Cohort Risk Score was the clinical cardiovascular risk
assessment score recommended in the 2013 ACC/AHA Risk Assessment Guidelines (Goff et al., 2013) and 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (Jensen et al., 2014).

**Pooled cohort risk Equation development.** The Pooled Cohort Risk Equations was developed using the prior experiences with the development of the Framingham Heart Study risk prediction equations (NCEP, 2002; Wilson et al., 1998), and the Framingham Risk Score cardiovascular disease risk prediction equation (D’Agostino, et al, 2008; Goff et al, 2013). Data was used from several large, racially and geographically diverse cohort studies, including the ARIC (Atherosclerosis Risk in Communities) study (Folsom et al, 2006), Cardiovascular Health Study (Fried, et al., 1991), and the CARDIA (Coronary Artery Risk Development in Young Adults) study (Friedman, et al., 1998). The use of pertinent data from the Framingham Original and Offspring Study cohorts (Dawber, Kannel, & Lyell, 1963; Kannel, Feinleib, McNamara, Garrison, & Castelli, 1979) was used with the goal of expanding the utility and generalizability of the Pooled Cohort Risk Equations (Goff et al., 2013). Risk factors with statistical justification for inclusion in the risk assessment equations were age, total and high-density lipoprotein cholesterol, systolic blood pressure (including treated or untreated status), diabetes, and current smoking status. In addition to the traditional risk factors, the inclusion of the novel risk factors of high-sensitivity C-reactive protein (hs-CRP), apolipoprotein B (ApoB), glomerular filtration rate (GFR), micro albuminuria, family history, cardiorespiratory fitness, ankle-brachial index (ABI), carotid intima-media thickness (CIMT), or coronary artery calcium (CAC) were evaluated. The outcome of ten-year cardiovascular risk was defined as the risk of developing a first atherosclerotic cardiovascular disease (ASCVD) event (nonfatal myocardial infarction, or
coronary heart disease (CHD) death, or fatal or nonfatal stroke) among individuals free from prior ASCVD (Goff et al., 2013).

Inclusion criteria were the following: 40 to 79 years of age, and apparently, free of history of nonfatal myocardial infarction, stroke, heart failure, percutaneous coronary intervention, coronary artery bypass surgery, or atrial fibrillation. A total of 11,240 white women (who experienced 902 events), 9,098 white men (1,259 events), 2,641 black women (290 events), and 1,647 black men (238 events) comprised the population to develop sex-and race-specific equations to predict 10-year risk for a first hard atherosclerotic cardiovascular disease (ASCVD) event (Goff et al., 2013).

The performance of the risk score in predicting atherosclerotic cardiovascular disease (ASCVD) was assessed using development cohorts (specifically, most recent examination cycles from Atherosclerosis Risk in Communities Study (ARIC) and the Framingham Heart Study for which 10 years of follow up is available) and external cohorts consisted of whites and blacks from the Multi-Ethnic Study of Atherosclerosis (MESA) and the Reasons for Geographic And Racial Differences in Stroke Study (REGARDS) (Howard, et al., 2005). However, both the MESA and REGARDS study had less than 10 years of follow up data (Goff et al, 2013). For MESA, a 6-year rate of cardiac event occurrence was used, while a 4-year rate was used for the REGARDS (Goff et al, 2013).

Sex and race specific Cox proportional hazard models including age, systolic blood pressure (treated and non-treated), total cholesterol, high-density lipoprotein, smoking status (yes or no), and diabetes (yes or no) were used to develop the Pooled Cohort Risk Equations. As seen in Table 2, the calibration of the models ranged from a low C-statistic of C= 0.71 for black men
to $C = 0.81$ for black women. Discrimination statistics ranged from a low of $\chi^2 = 4.86$ for non-Hispanic white men to $\chi^2 = 7.25$ for black women (Goff et al., 2013).

Table 2. Pooled Risk Equations Calibration and Discrimination for White and Black Men and Women from the Derivation and External Cohorts.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>C</th>
<th>$\chi^2$</th>
<th></th>
<th>n</th>
<th>C</th>
<th>$\chi^2$</th>
</tr>
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<tbody>
<tr>
<td><strong>Black females</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>Black males</strong></td>
<td></td>
<td></td>
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<td>Derivation</td>
<td>2641</td>
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<td>7.2</td>
<td>1647</td>
<td>0.71</td>
<td>6.71</td>
<td></td>
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<td>MESA</td>
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<td>0.76</td>
<td>18.51</td>
<td>799</td>
<td>0.66</td>
<td>24.40</td>
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<td>REGARDS</td>
<td>5275</td>
<td>0.70</td>
<td>48.22</td>
<td>2969</td>
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<td><strong>White females</strong></td>
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<td></td>
<td></td>
<td><strong>White males</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Derivation</td>
<td>11240</td>
<td>0.80</td>
<td>6.43</td>
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<td>0.74</td>
<td>4.86</td>
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<td>1273</td>
<td>0.71</td>
<td>14.56</td>
<td>1184</td>
<td>0.70</td>
<td>21.43</td>
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<td>REGARDS</td>
<td>6333</td>
<td>0.65</td>
<td>44.93</td>
<td>5296</td>
<td>0.59</td>
<td>66.71</td>
<td></td>
</tr>
</tbody>
</table>

Note. C-Statistic = Harrell’s C Statistic, $\chi^2 = $ Hosmer-Lemeshow Chi Square Statistic; MESA = Multi-Ethnic Study of Atherosclerosis; REGARDS = Reasons for Geographic and Racial Differences in Stroke Study.

The number of predicted cardiac events compared to the actual events was over predicted in all of the validation groups. Calibration chi-squared statistics were well above the threshold of 20 for white men and women as well as black men and women from the REGARDS population due to a low observed event rates at higher predicted risk. The 4-year prediction window for REGARDS may have been a factor in the poor validation results. The derivation cohort consistently demonstrated greater discrimination than the validation cohorts. However, there was overall lower discrimination and over prediction in the validation samples. The absence of other ethnicities and low number of blacks, particularly men, limits the applicability of the equations to other populations, in particular to lower risk populations, such as Asians or Hispanics/Latinos (Goff et al., 2013). Given the requisite for new prediction model scores needed for external validation, Muntner, et al., (2014) assessed the calibration and discrimination of the Pooled Cohort Risk Equation in a contemporary population-based cohort from the Reasons for
Geographic and Racial Differences in Stroke (REGARDS) study. Analysis on the REGARDS population (n=18,498) without atherosclerotic cardiovascular disease at baseline was conducted. Additional analysis of a sub-population (n=10,997) for which the Pooled Cohorts Risk Equations were intended to provide information for initiating statin use (participants without clinical atherosclerotic cardiovascular disease or diabetes, with low-density lipoprotein cholesterol levels between 70 and 189 mg/dL, and not taking statins) was also preformed (Muntner, 2014).

The REGARDS study conducted in January 2003 and October 2007 with follow up through December 2010 did not have active surveillance of atherosclerotic cardiovascular events (e.g., review of hospital discharges and obituaries in local newspapers) to detect atherosclerotic cardiovascular disease events not reported by participants. To address this limitation, cardiovascular disease events identified in Medicare claims data were used to supplement routine cohort follow-up. The Medicare system provides health insurance to adults ages 65 years or older, and to those with end stage renal disease or disability.

The predicted number of events consisting of nonfatal myocardial infarction, coronary heart disease (CHD) death, and nonfatal or fatal stroke) was calculated based on the mean predicted atherosclerotic cardiovascular disease incidence at 5 years. Observed and predicted atherosclerotic cardiovascular disease incidence rates at 5 years within the 4 atherosclerotic cardiovascular disease risk groups were used since the REGARDS study had not completed the 10 years of follow up. Participants were categorized according to their 10-year predicted atherosclerotic cardiovascular disease risk: less than 5%, 5% to less than 7.5%, 7.5% to less than 10%, and 10% or greater. Participants were grouped into deciles of predicted atherosclerotic cardiovascular disease risk. Calibration was determined using observed and predicted number of
events at 5 years of follow up with a Hosmer-Lemeshow $\chi^2$ statistic. C-statistics were calculated to estimate discrimination of the Pooled Cohort Risk Equations.

The predicted five-year atherosclerotic cardiovascular disease was calculated using the Pooled Cohort Risk Equations. At 5 years of follow-up, 53.6% of REGARDS participants were free of atherosclerotic cardiovascular disease events. Individual 10-year atherosclerotic cardiovascular disease risk was calculated using the Pooled Cohort Risk Equations.

**Table 3. Pooled Cohort Risk Equations Discrimination and Calibration Statistics by Gender and Race.**

<table>
<thead>
<tr>
<th></th>
<th>$N$</th>
<th>$\chi^2$</th>
<th>$p$</th>
<th>$C$</th>
</tr>
</thead>
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<td>Overall</td>
<td>18498</td>
<td>84.2</td>
<td>&lt;.001</td>
<td>.71</td>
</tr>
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<td>Men</td>
<td>62.8</td>
<td>&lt;.001</td>
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<td>.65</td>
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<td>Women</td>
<td>27.9</td>
<td>&lt;.001</td>
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<td>Black</td>
<td>41.9</td>
<td>&lt;.001</td>
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<td>.68</td>
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<td>White</td>
<td>44.1</td>
<td>&lt;.001</td>
<td></td>
<td>.72</td>
</tr>
<tr>
<td>Overall (S)</td>
<td>10997</td>
<td>19.9</td>
<td>.01</td>
<td>.72</td>
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<tr>
<td>Men</td>
<td>16.5</td>
<td>.04</td>
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<td>.66</td>
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<tr>
<td>Women</td>
<td>8.3</td>
<td>.41</td>
<td></td>
<td>.75</td>
</tr>
<tr>
<td>Black</td>
<td>11.8</td>
<td>.16</td>
<td></td>
<td>.69</td>
</tr>
<tr>
<td>White</td>
<td>14.0</td>
<td>.08</td>
<td></td>
<td>.74</td>
</tr>
<tr>
<td>Medicare</td>
<td>6121</td>
<td>11.4</td>
<td>.18</td>
<td>.65</td>
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<tr>
<td>Medicare (S)</td>
<td>3333</td>
<td>5.4</td>
<td>.71</td>
<td>.67</td>
</tr>
</tbody>
</table>

*Note. (S)= Subgroup, $\chi^2$ = Hosmer-Lemeshow Chi Square statistic, C-Statistic = Harrell’s C Statistic. p < .05 = Statistically Significant.*

In the overall cohort, there were 674 atherosclerotic cardiovascular disease events (382 coronary heart disease events and 292 strokes). Calibration for the overall population was poor (Hosmer-Lemeshow $\chi^2 = 84.2$, $p < .001$). Risk was overestimated for white and black men and women. The C-statistic for the overall population was 0.71, 95% CI [0.69-0.72] and discrimination of risk was better in women compared with men and whites compared with blacks.
Among the individuals in the subgroup (n=10,997), for whom statin treatment should be considered based on atherosclerotic cardiovascular disease risk, there were 338 atherosclerotic cardiovascular disease events (192 coronary heart disease events and 146 strokes). Calibration was better indicating greater precision in the estimation of cardiovascular disease risk (Hosmer-Lemeshow \( \chi^2 = 19.9, p = .01 \)). Furthermore, the Hosmer-Lemeshow \( \chi^2 \) indicated good calibration among women (\( \chi^2 = 8.3, p = .41 \)), blacks (\( \chi^2 = 11.8, p = .16 \)), and whites (\( \chi^2 = 14.0, p = .08 \)). The C-statistic was 0.72, 95%CI [0.70-0.75] and indicated better discrimination among women and whites compared with men and blacks.

In individuals with Medicare-linked data from the overall REGARDS population (n = 6,121), of the 457 atherosclerotic cardiovascular disease events (225 coronary heart disease events and 232 strokes), 112 of these events were identified in Medicare claims. Within the sub-population of those individuals with Medicare linked data (n=3,333), 57 included in the 234 atherosclerotic cardiovascular disease events (120 coronary heart disease events and 114 strokes,) were identified in Medicare claims. The Hosmer-Lemeshow \( \chi^2 \) indicated good calibration in the overall population of Medicare linked individuals (\( \chi^2 = 11.4, p = .18 \)) and in the subgroup Medicare linked individuals (\( \chi^2 = 5.4, p = .71 \)). For both groups of Medicare-linked individuals, a C-statistic of .67 in the overall population and a C-statistic of .65 in the sub-group indicated poor discrimination. Medicare patients are those individuals 65 years and older and/or those with end-stage renal disease or disability.

DePhilips et al. (2015) compared the calibration and discrimination of the Pooled Cohort Risk Equations endorsed by American Heart Association (AHA) and American College of Cardiology (ACC) with the Framingham Risk Score to predict coronary heart disease (FRS-CHD), as well as the Framingham Risk Score to predict cardiovascular disease (FRS-CVD), The
ATP III Risk Score (Grundy et al., 2004) and Reynolds Risk Scores were used to explore preventive therapy and perhaps identify a cause of the reported risk overestimation from the Pooled Cohort Risk Equations. The use of common preventive therapies of aspirin, lipid-lowering or antihypertensive therapies, and revascularization were investigated as the cause of overestimation of the Pooled Cohort Risk Equations.

The Multi Ethnic Study of Atherosclerosis (MESA) (2000 to 2002) cohort included a diverse sample of 53.5% women, 42% whites, 26% blacks, 20% Hispanics, and 12% Chinese (see Folsom et al., 2008). The mean age of the participants was 61.5 years old. Participants were free of clinical CVD at enrollment. Discrimination and calibration were assessed using the endpoints/events for the Pooled Cohort Risk Equation, and the respective end points for the other cardiovascular risk score. Observed events included in the assessment occurred within 10.2 years of follow-up in MESA. Additionally, 3,175 MESA participants included in the Part A hospital claims within the Centers for Medicare & Medicaid Services (CMS) billing database were reviewed in order to identify any atherosclerotic cardiovascular events not used in the MESA study. However, diabetics were excluded from analyses due to inability to calculate risk scores using the ATP III and RRS for men.

The Hosmer-Lemeshow $\chi^2$ statistic was used to assess the calibration and Harrell’s C-statistic was used to assess discrimination. The FRS-CHD, FRS-CVD, ATPIII-FRS-CHD, and the Pooled Cohort Risk Equations overestimated risk for their designated cardiovascular end points in men and women. The Reynolds Risk Scores demonstrated the least discordance in predicted and observed risk in all men and women. Overestimation was across low, intermediate and high deciles of cardiovascular risk. The authors point out that their analysis indicated that women tended to have less overestimation than men in these models. The FRS-CVD, RRS, and
Pooled Cohort Risk Equations had adequate discrimination in men and women. DeFillips et al., (2015) did not report analyses by race. The reported over prediction and discriminatory ability of risk scores is presumed to be across race and gender. Additionally, the use of common preventive therapies (aspirin, lipid-lowering or antihypertensive therapy, and revascularization) did not explain the overestimation by the Pooled Cohort Risk Equations (DeFillips et al., 2015).

The recent research conducted by DeFillips et al. in 2015, was the most similar to the present study conducted. However, this research excluded the Framingham Risk Score to predict coronary heart disease (FRS-CHD), and the ATP III (Adult Treatment Panel) risk score. Discrimination and calibration analyses differed, and analyses were conducted by race and gender. Additionally, the Heart SCORE study had more recent data that included cardiovascular events.

According to Preis & Kristensen, (2015) the strengths of the Pooled Cohort Equations included better risk prediction with the inclusion of race, especially in black individuals, and the inclusion of stroke as a cardiac endpoint. However, the important risk factors of chronic kidney disease and social deprivation were not included. Lastly, atherosclerotic cardiovascular disease (ASCVD) risk was overestimated, which might result in statin therapy being prescribed to many individuals based on joint American College of Cardiology/ American Heart Association guidance on cholesterol treatment (Preis & Kristensen, 2015).

**Other Cardiovascular Risk Scores**

The same cardiovascular risk factors used in the Framingham risk score, Reynolds Risk Score for women, Reynolds Risk Score for men, and the Pooled Cohort Risk Equations (see Table 1) are used in Europe. The PROCAM (Prospective Cardiovascular Munster Study) and British (Brindle et al., 2003) adapted the Framingham Risk equation (Anderson et al., 1991) to
assess global cardiovascular disease risk. The risk score developed in 2007 called the QRISK score (Hippisley-Cox et al., 2007) was formulated in the United Kingdom from over 1 million non-diabetic participants. The QRISK risk score developed in 2007 incorporated the Framingham risk factors, family history, and social deprivation. The risk score ASSIGN was developed using the SIGN guidelines to identify and assign patients to preventive treatment in the United Kingdom. The risk score algorithm was developed with individuals from the Scottish Heart Health Extended cohort (Woodward et al., 2007). The ASSIGN score incorporated family history and social deprivation in addition to Framingham risk factors (D’Agostino et al., 2008).

These risk scores developed in Britain and Scotland, which incorporated family history and social deprivation as risk factors, provide additional, yet minimal, accuracy in cardiovascular risk assessment when compared to the Framingham Risk Score in the British and Scottish population (Dhinger & Vasan, 2012). Cardiovascular risk scores developed in Britain (Hippisley-Cox, et al., 2007), Scotland (Woodward et al., 2007), and China (Zhang, Attia, D’Este, Yu, & Wu, 2005) have not been formally tested in the United States (Dhinger & Vasan, 2012).

**Chapter Summary**

The literature review synthesizes known racial disparity in the prevalence of cardiovascular risk factors. A large percentage of prior research studies have been comprised of predominately white study populations. Given the high and often differential prevalence of cardiovascular risk factors among blacks and Hispanics, their inclusion in cardiovascular research is critical. The underrepresentation of non-white participants hinders the acquisition of knowledge to formulate adequate cardiovascular prevention that is fully applicable across races. The Heart SCORE population included nearly equal number of white and black participants.
Applying the Heart SCORE population to the Framingham Risk Score, Reynolds Risk Score for women, Reynolds Risk Score for men, and the Pooled Cohort Risk Equation models is expected to contribute to the knowledge of cardiovascular risk among white and black men and women.

The search for new risk factors is an important component of cardiovascular research. The examination of any incremental value to risk prediction model may be ascertained. Therefore, the inclusion of the variables carotid intima media thickness (CIMT), peripheral artery tonometry (PAT) and vasa vasorum (VV) to cardiovascular risk models may provide additional knowledge leading to optimal management of intermediate risk patients.

Additionally, the application of a population that was not used to derive the risk score permits an additional assessment of risk model performance. The application of the Heart SCORE population to the Framingham risk score, Reynolds Risk Score for women, Reynolds Risk Score for men, and Pooled Cohort Risk Equations provides new information and knowledge. The Pooled Cohort Risk Equations is the newest of the cardiovascular risk scores used in this research. The application of a novel population is especially informative.
CHAPTER 3: METHODS

Chapter 3 details the quantitative research methodology of this large prospective cohort study, including the following topics: research design, sample, measures of study variables, the plan for data management and analysis, and ethical protections for participants.

Study Design

Heart Strategies Concentrating On Risk Evaluation (Heart SCORE) is a longitudinal prospective cohort study conducted over a ten year time period. Secondary data analysis using the Heart SCORE dataset permits examination of extensive information about cardiovascular risk factors to identify scientific areas that might need further research, as well as to examine important current clinical questions. These activities can be achieved within a short time and with minimal resources. The use of this comprehensive dataset for novel research aims yielded new information on cardiovascular risk and risk stratification, consistent with the intent for which this study was initially conceived and was subsequently carried out.

Secondary Analysis

For this secondary analysis, permission from the Heart SCORE investigators at the University of Pittsburgh to conduct a secondary data analysis was requested and granted. A committee member for this research was involved in Heart SCORE research at the University of Pittsburg. Heart SCORE data was accessed from the online Heart SCORE database using a passcode protected site. With the given permissions and passcode, Dr. Kevin Kip obtained a de-identified dataset which was copied and provided to the primary investigator for analysis. The original de-identified datasets and subsequent analysis files are included on password-protected
computers of Dr. Kip and the primary investigator Johanna Wilson. No other persons on the research committee had copies or access to the de-identified datasets or subsequent analyses files for this research study.

**Protection of Human Subjects**

Prior to its initiation, the Heart SCORE study was submitted and approved by the University of Pittsburgh Institutional Review Board. The current research for secondary data analyses was submitted and approved by the University of South Florida Institutional Review Board. From the parent study (Pittsburgh), participants responded to a recruitment letter, advertisement or public announcement regarding the Heart SCORE study and called the recruitment office. Recruiters then explained the study to interested persons. These persons were then invited to a study visit where informed consent was signed, eligibility was confirmed, and they met with a research coordinator and/or co-investigator. All participants were provided with a copy of their signed informed consent. The initial meeting included detailed review of the study description including all measures to be completed and schedule of follow-up.

**Study Setting**

**Primary Research Site**

All Heart SCORE data collection and research activities were conducted at the University of Pittsburgh Medical Center (UPMC) Cardiovascular Institute in Pittsburgh, PA. Participants were assigned a study identification number to preserve anonymity. All information related to the study was stored in a locked files at the UMPC Medical Center and on a password-protected secure server.

**Heart SCORE recruitment.** Heart Strategies Concentrating On Risk Evaluation (Heart SCORE) is a multi-faceted community-based participatory research program designed to address
cardiovascular disease (CVD) by improving risk stratification, identifying racial disparities, and evaluating a multidisciplinary community-based intervention program to decrease CVD risk in high-risk populations (Kip et al., 2005). The Heart SCORE study is still ongoing with long-term data collection in progress for the cohort of 2,000 participants who were enrolled from western Pennsylvania. By study design, there is nearly equal representation of White and Black subjects. The a priori specified recruitment goals included enrollment of 2000 participants (~50% black), including 800 participants at low Framingham risk, 1,000 participants at intermediate or high Framingham risk, and 200 participants with established cardiovascular disease.

Subject eligibility criteria included age 45 to 75 years, residence in the greater Pittsburgh metropolitan area (~50 mile radius), an ability to undergo baseline and annual follow-up visits, and absence of known comorbidities expected to limit life expectancy to less than five years.

Recruitment procedures included targeted mailings by zip code, advertisements, referrals, and direct promotion through community organizations. This included recruitment from community-based blood pressure and lipid screening programs, educational seminars at places of worship, and community centers. There was purposeful emphasis on recruitment of traditionally underserved and high-risk communities, which was achieved through partnerships with the Cardiovascular Institute at the University of Pittsburgh, Metro-Urban Institute Office of Applied Religion (MUI-OAR) of the Pittsburgh Theological Seminary, the Urban League of Pittsburgh, and other community-based and academic partners. Additional details of the Heart SCORE study have been published (Kip et al., 2005).

**Heart SCORE data collection.** The current research study leverages use of information provided by the wealth of data captured from the Heart SCORE study. Demographic, clinical and biological variables were extracted from the Heart SCORE dataset. At the baseline visit, the
detailed demographic variables, of age, gender, race, and ethnicity were obtained from Heart SCORE participants via self-report (Appendix A). Race and ethnicity were classified utilizing categories defined by the U.S. Census Bureau and were collected via self-report. Measures of social economic status were obtained via self-report items regarding educational attainment and annual household income (Appendix B). Physical examination included vital signs and anthropometric measures and was measured continuously throughout the study.

Blood pressure was measured using a standard protocol, as previously described by Aiyer, et al., (2007). Diabetes mellitus was defined as fasting glucose ≥126 mg/dL or a reported history of previously diagnosed diabetes treated with diet, oral agents, and/or insulin. Hypertension was defined as a systolic blood pressure of ≥140 mmHg, diastolic pressure of ≥90 mmHg, history of physician-diagnosed hypertension, or current use of anti-hypertensive medication.

At the baseline visit, fasting blood samples were drawn into tubes containing EDTA by venipuncture. Serum total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were obtained using the vertical automated profile (VAP) (Atherotech, Inc., Birmingham, AL, USA). Fasting plasma insulin levels were determined using an immunoenzymatic method (Abbott, Abbott Park, IL, USA) and fasting glucose concentrations were measured by glucose oxidase method.

Following the baseline examination, a summary of the subject’s risk factor profile, based on the NCEP ATP-III ("Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III)," 2001) and JNC7 (Chobanian et al., 2003) guidelines, were provided to their primary care physician. Subjects who did not have an
established relationship with a healthcare provider were referred to family practitioners or general internists, including the Metro Family Practice, Inc. (MFPI, Wilkinsburg, PA), a 501(c)(3) comprehensive primary care organization that provides healthcare for uninsured patients (Kip et al., 2005).

**Cardiovascular Disease Risk Factors**

Biological measures of cardiovascular risk were obtained by laboratory assessments of blood pressure to assess the presence of hypertension, and by a fasting blood sample to obtain glucose concentrations in order to evaluate the metabolic syndrome (Appendices C, D, and E). Total cholesterol, low-density lipoprotein and high-density lipoprotein, cholesterol, and triglyceride level were collected (Appendix E) in addition to high sensitivity C-reactive protein (hs-CRP) collected at the baseline evaluation. The risk factors collected by self-report included smoking cessation, having taken blood pressure medication in the last 48 hours, history of coronary artery disease, and family history of coronary artery disease (Appendices F, G, and H).

Different cardiovascular risk factors are used to calculate a Framingham Risk Score, Reynolds Risk Score for women, Reynolds Risk Score for men and Pooled Cohort Risk Score. Cardiovascular risk factors of age, sex, total cholesterol, high-density lipoprotein, systolic blood pressure, blood pressure treatment, diabetes mellitus, and smoking are utilized to calculate a Framingham Risk Score. The Reynolds Risk Scores are calculated with the appropriate sex for each risk score in addition to age, total cholesterol, high-density lipoprotein, low-density lipoprotein, systolic blood pressure, smoking, and high sensitivity C-reactive protein. Age, total cholesterol, high-density lipoprotein, systolic blood pressure, blood pressure treatment and smoking are used to calculate the Pooled Cohort Risk Score. These cardiac risk factors used to predict an individual’s risk for cardiac events over ten years are specified for each cardiovascular
risk score. The predicted cardiac events known as cardiovascular risk model outcomes are also specific to the cardiovascular risk score.

**Cardiovascular Risk Model Outcomes**

The Framingham Risk Score, Reynolds Risk Scores and Pooled Cohort Risk Score predict different cardiovascular risk model outcomes. The 2008 Framingham Risk Score outcomes include: MI, stroke, death due to stroke, death due to coronary heart disease (CHD), and heart failure. For the Reynolds Risk Scores (women and for men), outcomes used include revascularization, MI, death due to coronary heart disease, stroke and death due to stroke. The Pooled Risk Score Equations aimed to assess risk for an initial atherosclerotic cardiovascular disease (ASCVD) event: nonfatal myocardial infarction or coronary heart disease, (CHD) death, or fatal or nonfatal stroke (Goff et al., 2014). Analysis within the present study used cardiovascular risk model outcomes that were consistent across all three cardiovascular risk scores.

**Heart SCORE Cardiovascular Events**

Heart SCORE follow-up cardiovascular events were collected over the course of the study period. Follow-events include: death, myocardial infarction, stroke (Acute Ischemic Stroke (AIS), stroke (not AIS), cardiac failure/congestive heart failure; revascularization (Coronary Artery Bypass Graft (CABG) or Percutaneous Coronary Intervention (PCT), arrhythmia, other vascular events (Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Peripheral Artery Disease (Peripheral Artery Disease) (Appendices I and J).

Throughout the entire follow-up period, cardiovascular events experienced by Heart SCORE study subjects were diligently monitored and classified through an adjudication board. In August of 2014, the number of adjudicated events experienced by the participants was
updated in Heart SCORE database. A total of 222 adjudicated events occurred. These events were used in the statistical analysis to determine the calibration and discrimination of the cardiovascular risk scores.

Table 4. Heart SCORE events for Framingham Risk Score, Reynolds Risk Scores and Pooled Cohort Risk Equations Risk Score Outcome

<table>
<thead>
<tr>
<th>Risk score outcome</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI (non-fatal)</td>
<td>MI</td>
</tr>
<tr>
<td>MI Death</td>
<td>MI Death</td>
</tr>
<tr>
<td>Stroke (non-fatal)</td>
<td>Stroke &amp; AIS</td>
</tr>
<tr>
<td>Stroke Death</td>
<td>Stroke Death, AIS Death</td>
</tr>
<tr>
<td>Revascularization</td>
<td>PCI &amp; CABG</td>
</tr>
</tbody>
</table>

Note. MI=myocardial infarction, AIS= Acute Ischemic stroke, CHF= Congestive Heart Failure, PCI= Percutaneous Coronary Intervention, CAGB= Coronary Artery Bypass Graft

Heart SCORE Novel Cardiovascular Risk Factors Data Collection

With its emphasis on better quantifying cardiovascular risk, Heart SCORE included 3 relatively novel measures that serve as surrogates for atherosclerosis and cardiovascular risk. These included measures of carotid intima-media thickness, endothelial function by use of peripheral arterial tonometry, and vasa vasorum, as described below. Carotid ultrasound imaging, pulse amplitude tonometry, and non-linear ultrasound were used to obtain biological measures of the novel cardiovascular risk factors. As these were conducted after the initiation of Heart SCORE, their data collection forms were not included in the original study forms.

Carotid intima media thickness. Carotid artery imaging was carried out using a GE VIVID7 (General Electric Corp.) ultrasound imaging system and a 7MHz linear array vascular ultrasound probe. The ultrasound beam was adjusted to obtain longitudinal scans of the carotid arteries to visualize two parallel echogenic lines corresponding to the 5 blood-intima and media-adventitia interfaces on the posterior wall. End-diastolic images were recorded using electrocardiographic gating. Software on the GE VIVID 7 was used to calculate intima-media
thickness (IMT) using automated edge detection to locate the lumen-intima and media-adventitia echo boundaries at subpixel resolution. 29 MT was averaged over 70-100 individual measurements taken along a 1-cm segment of the common carotid artery beginning 0.5 cm from the carotid bifurcation along the far wall of the distal common carotid artery. Significant carotid intima-media thickness (CIMT) was defined as maximal CIMT>1 mm in either the right or left carotid artery, as previously described by others (Spence, 2006). A subset of Heart SCORE participants (n = 739) who received CIMT assessment were used for this research.

**Peripheral arterial tonometry.** Endothelial function was measured via a (Reactive Hyperemia) (RH)–PAT index. The RH protocol consists of a 5 min baseline measurement, after which a blood pressure cuff on the test arm was inflated to 60 mmHg above baseline systolic blood pressure or at least 200 mmHg for 5 min. Occlusion of pulsatile arterial flow was confirmed by reduction of the PAT tracing to zero. After 5 minutes, the cuff was deflated, and the PAT tracing was recorded for a further 6 min. The ratio of the PAT signal after cuff release compared with baseline was calculated through a computer algorithm automatically normalizing for baseline signal and indexed to the contra lateral arm. The calculated ratio reflects the Reactive Hyperemia Index (RHI). The natural logarithmic scaled RHI (L_RHI) was calculated from the same ratio between the digital pulse volume during RH and baseline Framingham Risk Score (FRS). A PAT measurement was obtained in 1,382 of the 2,000 Heart SCORE participants

**Vasa vasorum.** Prior to the conducting vasa vasorum assessment in Heart SCORE, which is very new clinical technique, a preclinical study to validate the use of carotid ultrasound for quantification using serial evaluations of adventitial vasa vasorum was conducted on 20 New Zealand white rabbits. The rabbits were fed a high-fat diet for 3 weeks. After the initial week of feeding, bilateral femoral artery stenosis were induced by balloon injury. Non-linear ultrasound
imaging (10 MHz) was performed at 2, 4, and 6 weeks post-injury during intravenous microbubble injection using destruction-replenishment to quantify blood velocity (Beta) and volume as peak video intensity. At baseline and 2, 4, and 6 weeks post-injury (n=5 rabbits per group), both femoral arteries were sectioned (40 vessels) and stained to identify endothelium. Adventitial vasa vasorum were quantified by counting the number of stained micro vessels. Plaque size was measured from histology. Histologic results from this experiment demonstrated that atherosclerotic plaque progressed over 6 weeks (p<0.0001), with near total occlusion by 6 weeks (98±3% luminal stenosis). Total number of adventitial neovessels overlying the atherosclerotic plaques (i.e., vasa vasorum) of these vessels significantly increased from baseline (P<0.0001). In the rabbits allowed to survive for 6 weeks and in whom serial CU imaging was performed at 0, 2, 4, and 6 weeks, there was a progressive increase in peak video intensity over time (p<0.0001), suggesting that neovascularization parallels atherosclerosis progression.

On the basis on this emerging use of measurement of vasa vasorum, a total of 581 (out of 2,000) subjects in Heart SCORE underwent carotid ultrasound measurement of both carotid arteries to quantify adventitial vasa vasorum. Peak video intensity in the arterial wall after microbubble contrast injection was measured in these subjects. The normalized to peak luminal video intensity were measuring using the methods tested in the rabbit model. This information was not published, but available through the Heart SCORE study.

The measures pulse amplitude tonometry (PAT), carotid intima media thickness (CIMT) and vasa vasorum (VV) were implemented part-way into the Heart SCORE study, and not all participants had these measure completed. Importantly, the Heart SCORE data set permits the linking of these variable with other measures, such as baseline, 1-year, 2-year assessment, etc., using the variables which indicate the date these measures were taken “PAT date”, “IMT date”,
and “VV date”. Therefore, the variables from the follow up assessment completed closest to these variables will be selected. The Heart SCORE participants were enrolled from June 2003 – October 2006. Pulse Amplitude Tonometry (PAT) measurements were obtained in January of 2004 until October of 2006. Participants completed the carotid intima media thickness (CIMT) measurement and/or vasa vasorum (VV) measurement in January 2008 until April 2011.

### Statistical Analysis

#### Overview

Baseline characteristics of Black and White participants were compared using chi-squared tests for categorical variables and student’s t test or Wilcoxon Rank Sum Test for continuous variables. Variable normality was assessed for all continuous variables and those with skewed distributions were log-transformed to approximate normal distribution, before application of the t-test or fitting regression models. Multicolinearity of covariates (independent variables) was examined to avoid model over fitting. For evaluating performance of the individual risk scores, a survival analysis approach was used with Cox proportional hazards regression as the primary multivariable method. All observations were equally weighted in the analysis.

The most common method for deriving cardiovascular risk score model fit statistics to assess risk score performance with the C-statistic/aROC (area under the receiver operating curve) and Hosmer-Lemeshow X² are based on logistic regression (Chamnan, et al. 2009). Logistic regression assesses the proportion of new cases that develop in a time period. However it does not take into account subjects lost to follow up or who withdraw. Survival analysis (Cox regression) assesses the hazard rate, which is the number of new cases/events per population at risk per unit of time of events (SAS, 1999). As referenced above, logistic regression ignores the
time-dependent nature of cardiovascular risk assessment modeling and the impact of loss to follow-up. Pencina and D’Agostino (2004) and Chambless and Diao (2006) recommended the performance of a risk score estimated from survival data in the presence of censoring (Chamnan, et al., 2009). In longitudinal research studies (such as Heart SCORE), investigators follow participants for a set time period or until a pre-specified endpoint (event) is reached. Participants often withdraw from the study or reach the endpoint prior to the end of the specified follow up time. Logistic regression does not adjust address participant withdraw or occurrence of a premature event/endpoint (Boston University, 2016). Censoring is used in Cox regression analysis to include participants who withdraw and those with a premature event/endpoint.

In Cox proportional regression model several covariates (risk factors) are considered simultaneously to examine survival time (Tabachnick & Fidell, 2007). Assumptions of Cox proportional hazard models include constant relative risk during the study period, and a multiplicative relationship between predictors and hazards (Boston University, 2016). The hazard ratio is the total number of observed events in to independent group comparisons (SAS, 1999). An assumption of the Cox proportional regression hazard model is the independent survival time function (time until an event) for each participant in the sample. An individual survival function as opposed to one fixed survival function for the study population permits the comparison of the survival functions of the subpopulations (e.g. black males, white females). The hazard rate (the risk of suffering the event of interest given that the individual survived to the specific time point) can be assessed for the subpopulations (SAS, 1999).

**Cardiovascular Risk Model Performance**

For this research cardiovascular risk model performance (calibration and discrimination) were not assessed using the Harrell’s C-statistic or the Hosmer-Lemeshow $X^2$ produced by
logistic regression. Instead, the focus was on the use of survival analysis methods of visual examination of plots of calibration.

**Discrimination.** Discrimination analysis was used to assess the ability of the cardiovascular risk scores to assign a higher risk score to those who experienced the cardiovascular event or myocardial infarction (MI), death, stroke, Acute Ischemic Stroke (AIS), or revascularization (coronary artery bypass grafting or percutaneous coronary intervention compared to those who did not experience a CVD event. The cardiovascular risk scores assigned to each woman and man were split into quintiles for the Framingham Risk Score, Reynolds Risk Score for women, Reynolds Risk Score for men, and Pooled Cohort Risk Equations. The cardiovascular risk scores of the participants who experienced the cardiovascular events were also split into quintiles of risk. A Wilcoxon Rank Sum Test was conducted for statistical significance of discrimination ability of the overall cardiovascular risk scores, and discrimination ability by race and gender. Discrimination was visually assessed with the box plots of the Wilcoxon Rank Sum test for the risk cardiovascular risk.

**Calibration.** Calibration reflects prediction accuracy. A well-calibrated risk score assigns the correct probability of an event at all levels of predicted risk (Royston and Altman, 2013). The ability of the respective cardiovascular risk scores to accurately predict the risk of a cardiovascular event in 10 years across the all levels of predicted cardiovascular risk was assessed. The predicted risk scores of the Framingham Heart Score, Reynolds Risk Score, and Pooled Cohort Risk Equations) were divided into quintiles. The mean predicted risk score was calculated for each quintile.

The cardiovascular risk scores of the individuals who experienced the cardiovascular event were divided into quintiles for each of the cardiovascular risk scores. The mean observed
risk score was calculated for each quintile. The average follow up time for the Heart SCORE participants was eight years. Therefore, in order to adjust for the average follow up time of less than 10 years, the observed mean risk score of each quintile was divided by 0.8. Calibration was assessed visually with the comparison of the mean predicted risk scores and mean observed risk scores for the quintiles for each cardiovascular risk score.

**Specific Aims**

**Aim 1.** The first aim was to examine the overall predictive utility of the Framingham cardiovascular risk score, Reynolds Risk Score for Women, Reynolds Risk Score for Men and the Pooled Cohort Risk Equations using methods of calibration and discrimination. A Framingham Risk score, Reynolds Risk Score for Women, Reynolds Risk Score for Men and the Pooled Cohort Risk Equations was calculated using respective publicized risk algorithms (Appendices J, K and L) These scores served as the primary independent variable (in separate models) in relation to risk of incident cardiovascular disease events modeled by use of Cox regression analysis. Thus, three cardiovascular risk scores were calculated for each woman and man in the HeartSCORE population.

**Aim 2.** The second aim was to examine the overall predictive utility by race of the Framingham Risk score, Reynolds Risk Score for Women, Reynolds Risk Score for Men and the Pooled Cohort Risk Equations using methods of calibration and discrimination. The analytic approach for this aim parallels that for Aim #1. However, analyses were stratified by race to examine whether the different risk scores appear to perform differently when stratified by race.

**Aim 3.** The third aim was to assess the predictive utility of the Framingham Risk score, Reynolds Risk Score for Women, Reynolds Risk Score for Men and the Pooled Cohort Risk Equations with the inclusion of the variables carotid intima media thickness (CIMT), pulse
amplitude tonometry (PAT), and/or vasa vasorum (VV). From Aims 1 and 2, the relative performance of the individual risk scores was estimated overall and by race and gender. The next step was to examine whether performance of these risk scores were significantly improved by the addition of the three “novel” cardiovascular disease risk measures. The models (overall and stratified by race and gender) included the individual risk score derived from the published algorithms. Then, the variables CIMT, PAT and/or VV were forced into separate models to assess the extent to which they provided unique predictive value when modeling the risk of CVD outcomes. For all Cox regression models fit, the assumption of proportional hazard ratios was examined and found to be satisfactory. Additionally with the inclusion of the novel risk factors, the Akaike Information Criterion (AIC) (Akaike, 1973) was calculated to examine the net improvement in model and risk score performance with respect to risk of CVD outcomes. The AIC was founded on Shannon’s Information Theory (1948) and evaluates the goodness of fit of the model, and the complexity of the model. A lower AIC indicates a better model fit. Estimates of model fit can be compared between models so long as the same subjects are used in each model.

**Chapter Summary**

A secondary data analysis of the longitudinal study Heart SCORE was selected for this study. This chapter has presented the details of the study design, target population, recruitment, target population, research setting, variables, and statistical analysis. Statistical analyses to address the research aims for this research included descriptive statistics, t-tests, Wilcoxon Rank Sum Tests, and Cox regression analysis. Of key emphasis was the comparison of published risk score models in relation to risk of cardiovascular disease outcomes within Heart SCORE, including stratification by race and gender, and examination of incremental value of the variables.
carotid intima media thickness (CIMT), pulse amplitude tonometry (PAT) and/or vasa vasorum (VV) to the risk scores. Additionally data collection methods, human protection strategies, and ethical considerations were also presented for this study. The results of the study are discussed in Chapter 4.
CHAPTER 4: RESULTS

Introduction

This chapter provides a descriptive summary of the study participants and the results of a secondary data analysis of the Heart SCORE dataset (a longitudinal prospective cohort study conducted over ten years). The data set consisted of 1,949 participants of the total 2,000 Heart SCORE participants. Black and white participants were included in the sample for statistical analysis. All statistical analyses were conducted using Statistical Analysis System software version 9.4 (Citation).

Variable normality was assessed prior to baseline analysis of the baseline characteristics. Normality constraints included skewness and kurtosis that were less 2.0. All baseline variables met the assumptions of normality with the exception of triglycerides and high-sensitivity C-reactive protein. Baseline characteristics of cardiac risk factors of Black and White participants were compared using chi-squared tests for categorical variables and student’s t test or Wilcoxon Rank Sum Test for continuous variables. Variables that failed to meet the assumption of normality were log-transformed to approximate normal distribution prior to the application of the t-test.

Participant Characteristics

The overall mean age of the study participants was 59 ± 7.50. The mean age of white men was 60 ± 7.68 and white women was 59 ± 7.24. The mean age of black men was 58 ± 7.3 and black women was 57 ± 7.64, consistent with the overall mean. White participants were
overall nominally older and more educated than black participants. Having had some college (less than a formal degree) was most prevalent among black participants (43%) as well the total sample of participants. Having earned an advanced degree was most prevalent among white participants (32.2%) and was the second most prevalent amount of education for the entire sample (see Table 5). Overall, income was higher among white Heart SCORE participants compared to black participants in Heart SCORE.

**Participant Cardiovascular Risk Factors**

According to table 4.2, hypertension (Stage I and II) was more prevalent among black participants (56.1%) compared to white participants (38.4%). Hypertension was the most prevalent among black men (61.3%) and black women (53.3%) compared to white men (43.3%) and women (35.5%). Overall the men (60.3%) in Heart SCORE were more hypertensive than the women (38.5). A BMI greater than 30 was more prevalent in black females (59.2%) compared to white females (30.2%). Being overweight and/or obese was also most prevalent among black women (59.2%) and black men (50.1%)

Only 214 of 1,944 participants (11.0%) responded that they currently smoked. Smoking was more prevalent among blacks (55.7%) compared to whites (38.4%) and was most prevalent among black females. (8.6%). However, more men (60.3%) were current smokers. According to the data collected in Heart SCORE, blacks had a greater prevalence of the cardiovascular risk factors of hypertension, being overweight and/or obese, and smoking.

Variables meeting the assumptions of normality were compared by race and gender with application of the chi-squared tests for categorical variables and student’s *t*-test for continuous variables. The Wilcoxon Rank Sum Test was applied to the variables high-sensitivity C-reactive protein and triglycerides that violated the assumptions of normality.
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<th>White</th>
<th>n (%)</th>
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<td>45 to 55 years</td>
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<td>41.9</td>
<td>341</td>
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<td>56 to 65 years</td>
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<tr>
<td>Married (LiveLike)</td>
<td>369</td>
<td>43.2</td>
<td>817</td>
<td>74.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Separated</td>
<td>51</td>
<td>6</td>
<td>6</td>
<td>0.5</td>
<td></td>
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</tr>
<tr>
<td>Divorced</td>
<td>236</td>
<td>27.6</td>
<td>136</td>
<td>12.4</td>
<td></td>
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</tr>
<tr>
<td>Widowed</td>
<td>89</td>
<td>10.4</td>
<td>62</td>
<td>5.7</td>
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<td></td>
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<tr>
<td>Never married</td>
<td>96</td>
<td>11.2</td>
<td>69</td>
<td>6.3</td>
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</tr>
<tr>
<td><strong>Employment status</strong></td>
<td>1949</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-time</td>
<td>398</td>
<td>46.7</td>
<td>469</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part-time</td>
<td>87</td>
<td>10.2</td>
<td>199</td>
<td>18.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>305</td>
<td>27</td>
<td>230</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>137</td>
<td>16.1</td>
<td>118</td>
<td>10.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Income</strong></td>
<td>1761</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; $10,000</td>
<td>79</td>
<td>10</td>
<td>29</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$10,000 – &lt; $20,000</td>
<td>145</td>
<td>18.4</td>
<td>71</td>
<td>7.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$20,000 – &lt; $40,000</td>
<td>257</td>
<td>32.7</td>
<td>248</td>
<td>25.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$40,000 – &lt; $80,000</td>
<td>247</td>
<td>31.4</td>
<td>338</td>
<td>34.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$80,000+</td>
<td>59</td>
<td>7.5</td>
<td>288</td>
<td>29.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note. HS=high school; Live Like= living like you were married; < = Less Than.*
Table 6. Prevalence of Cardiovascular Risk Factors by Race and Gender

<table>
<thead>
<tr>
<th></th>
<th>White n (%)</th>
<th>Black n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td><strong>B/P Classification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>18(6.9)</td>
<td>105(17.7)</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>83(31.8)</td>
<td>172(29)</td>
</tr>
<tr>
<td>HTN Stage I</td>
<td>110(42.1)</td>
<td>207(34.9)</td>
</tr>
<tr>
<td>HTN Stage II</td>
<td>50(19.2)</td>
<td>109(18.4)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>32(12.4)</td>
<td>57(9.7)</td>
</tr>
<tr>
<td>25–30</td>
<td>97(37.6)</td>
<td>182(31.1)</td>
</tr>
<tr>
<td>30–35</td>
<td>76(29.5)</td>
<td>169(28.8)</td>
</tr>
<tr>
<td>35–40</td>
<td>35(13.6)</td>
<td>99(16.9)</td>
</tr>
<tr>
<td>40+</td>
<td>18(7)</td>
<td>79(13.5)</td>
</tr>
<tr>
<td><strong>Current Smoker</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1944</td>
<td>38(48.1)</td>
<td>51(37.5)</td>
</tr>
<tr>
<td><strong>Hx Hyperlipid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1919</td>
<td>90(34.7)</td>
<td>258(44.1)</td>
</tr>
<tr>
<td><strong>Hx Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1939</td>
<td>43(16.5)</td>
<td>96(16.2)</td>
</tr>
<tr>
<td><strong>Hx HTN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1946</td>
<td>156(59.8)</td>
<td>328(55.4)</td>
</tr>
<tr>
<td><strong>Family Hx Female CAD</strong></td>
<td>1865</td>
<td>57(23.6)</td>
</tr>
<tr>
<td><strong>Family Hx Male CAD</strong></td>
<td>1837</td>
<td>51(21.3)</td>
</tr>
</tbody>
</table>

*Note. B/P = blood pressure; HTN = hypertension; BMI = body mass index; Hyperlipid = hyperlipidemia; HX = history; CAD = coronary artery disease.*
Table 7. *t* test and Wilcoxon Rank Sum Test of Cardiovascular Risk Factors ($M \pm SD$)

<table>
<thead>
<tr>
<th>Factor</th>
<th><em>n</em></th>
<th>Male</th>
<th>Female</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Black</td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td>Age</td>
<td>1943</td>
<td>58.49(7.30)</td>
<td>60.12(7.68)</td>
<td>57.99(7.64)**</td>
</tr>
<tr>
<td>BMI</td>
<td>1928</td>
<td>30.86(5.80)</td>
<td>29.36(5.47)</td>
<td>32.52(6.77)**</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1905</td>
<td>63.86(11.12)</td>
<td>60.45(9.76)</td>
<td>64.90(10.64)**</td>
</tr>
<tr>
<td>Systolic</td>
<td>1947</td>
<td>143.81(18.85)</td>
<td>134.96(17.30)</td>
<td>140.0(20.62)**</td>
</tr>
<tr>
<td>Diastolic</td>
<td>1947</td>
<td>85.56(11.17)</td>
<td>80.45(9.42)</td>
<td>82.11(9.88)**</td>
</tr>
<tr>
<td>TC</td>
<td>1949</td>
<td>195.01(41.70)</td>
<td>202.9(38.02)</td>
<td>214.90(44.22)*</td>
</tr>
<tr>
<td>LDL</td>
<td>1937</td>
<td>131.90(37.56)</td>
<td>138.10(32.27)</td>
<td>142.70(38.98)*</td>
</tr>
<tr>
<td>HDL</td>
<td>1931</td>
<td>50.84(12.31)</td>
<td>49.87 (12.01)</td>
<td>61.40(14.28)</td>
</tr>
<tr>
<td>PAT</td>
<td>1382</td>
<td>1.80(.54)</td>
<td>2.11(.58)</td>
<td>1.97(.66)**</td>
</tr>
<tr>
<td>CIMT</td>
<td>739</td>
<td>.89(.18)</td>
<td>.84(.17)</td>
<td>.81(.16)*</td>
</tr>
<tr>
<td>VV</td>
<td>581</td>
<td>.92(.37)</td>
<td>.93(.33)</td>
<td>.89(.32)</td>
</tr>
<tr>
<td>Trigl</td>
<td>1955</td>
<td>116.04(71.66)</td>
<td>136.48(80.84)</td>
<td>106.21(55.49)**</td>
</tr>
<tr>
<td>Hs-CRP</td>
<td>1729</td>
<td>3.36 (8.32)</td>
<td>1.94(3.97)</td>
<td>4.64(8.25)**</td>
</tr>
</tbody>
</table>

Note. TC = total cholesterol; LDL = low-density lipoprotein; HDL = high-density lipoprotein; PAT = peripheral arterial tonometry; CIMT = carotid intima media thickness; VV = vasa vasorum; Trigl = triglycerides; HsCRP = high-sensitivity C-reactive protein.

*p < .05. **p < .001.
The overall mean age of the study population was $59 \pm 7.5$. White men and white women were nominally older (about 2 years) compared to black men ($t(667) = 2.74, p < .006$) and black women ($t(1278) = 3.61, p < .001$), respectively. White men and women, as well as black men and women, had on overall mean BMI indicative of being overweight or obese according to the standards set by the World Health Organization. The mean BMI of black men and black women was significantly higher compared to those of white men ($t(656) = -3.34, p < .001$) and white women ($t(1170) = -11.80, p < .001$).

The findings of the non-traditional cardiovascular risk factors of high-sensitivity C-reactive protein (HsCRP), carotid intima media thickness (CIMT), peripheral arterial tonometry (PAT), and vasa vasorum (VV) generally indicated overall higher risk for blacks as compared to whites. The mean Hs-CRP level was highest among black females and was significantly higher compared to the mean Hs-CRP level of white females women ($Z = 6.37, p < .001$). Black men also had significantly higher Hs-CRP levels compared to white men ($Z = 3.75, p < .001$). Similarly, black men and women had higher mean values of carotid intima media thickness compared to white men ($t(273) = -2.03, p = 0.04$) and white women ($t(462) = -2.88, p = .004$). In addition, white men and white women had higher (better) mean peripheral arterial tonometry values (a measure of endothelial function) compared to black men ($t(523) = 5.87, p < .001$) and black women ($t(834.99) = 4.40, p < .001$). These findings indicate that for non-traditional CVD risk factors, both black men and black females tended to present with less favorable values compared to white men and white females.

**Participant Cardiovascular Events**

According to Table 8, the participants experienced a total of 158 cardiovascular events using the composite endpoint of death/MI/AIS/stroke/PCI/CABG. Blacks had a greater incidence
of death or MI (6.3%) compared to whites (3.5%). There were no cardiovascular events in which white males had the lowest incidence. There was no cardiovascular event in which white females had the highest rate of incidence. More blacks (9.7%) experienced the cardiovascular events of death, myocardial infarction, acute ischemic stroke, stroke, percutaneous coronary intervention or coronary artery bypass graft than whites (6.8%). Black males (16%) had the highest overall prevalence and white females (3.9%) the lowest. Men in Heart SCORE (13.4%) had more than two times the incidence of this cardiovascular event composite compared to women (5.3%).

**Table 8.** Heart SCORE Cardiovascular Events by Race and Gender

<table>
<thead>
<tr>
<th>Factor</th>
<th>Black Male (n = 261)</th>
<th>Black Female (n = 593)</th>
<th>White Male (n = 408)</th>
<th>White Female (n = 687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>26(10)</td>
<td>18(3)</td>
<td>22(5.4)</td>
<td>10(1.5)</td>
</tr>
<tr>
<td>MI</td>
<td>5(1.9)</td>
<td>8(1.3)</td>
<td>7(1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>4(1.5)</td>
<td>7(1.1)</td>
<td>8(1.9)</td>
<td>5(0.7)</td>
</tr>
<tr>
<td>AIS</td>
<td>3(1.1)</td>
<td>5(0.8)</td>
<td>6(1.4)</td>
<td>4(0.5)</td>
</tr>
<tr>
<td>PCI</td>
<td>7(2.6)</td>
<td>12(2.0)</td>
<td>14(3.4)</td>
<td>10(1.4)</td>
</tr>
<tr>
<td>CABG</td>
<td>4(1.5)</td>
<td>4(0.6)</td>
<td>5(1.2)</td>
<td>2(0.2)</td>
</tr>
<tr>
<td>PCI or CABG</td>
<td>11(4.2)</td>
<td>14(2.3)</td>
<td>19(4.6)</td>
<td>12(1.7)</td>
</tr>
<tr>
<td>Death or MI</td>
<td>29(11.1)</td>
<td>25(4.2)</td>
<td>29(7.1)</td>
<td>10(1.4)</td>
</tr>
<tr>
<td>Death, MI, or AIS</td>
<td>36(13.7)</td>
<td>34(5.7)</td>
<td>40(9.8)</td>
<td>19(2.7)</td>
</tr>
<tr>
<td>Death, MI, or Stroke</td>
<td>33(12.6)</td>
<td>30(5.0)</td>
<td>36(8.8)</td>
<td>15(2.1)</td>
</tr>
<tr>
<td>Death, MI, PCI, or CABG</td>
<td>38(14.5)</td>
<td>35(5.6)</td>
<td>42(10.2)</td>
<td>22(3.2)</td>
</tr>
<tr>
<td>Death, MI, AIS, Stroke,</td>
<td>42(16.0)</td>
<td>41(6.9)</td>
<td>48(11.7)</td>
<td>27(3.9)</td>
</tr>
</tbody>
</table>

*Note. Total n = 1605; MI = myocardial infarction; AIS = acute ischemic stroke; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft.*

**Research Aims**

**Specific Aim 1**

Examine the overall predictive utility of the Framingham Cardiovascular Risk Score, Reynolds Risk Score for Women, Reynolds Risk Score for Men and the Pooled Cohort Risk Equations using methods of calibration and discrimination.
Cardiovascular risk scores. The Heart SCORE participants with a history of diabetes (n=393) were excluded from analysis and did not receive a Framingham Risk Score, Reynolds Risk Score or a Pooled Cohort Risk Score. According to the Reynolds Risk Score algorithm, a Hemoglobin A₁C (glycated hemoglobin test) blood level was required to calculate a Reynolds Risk Score for diabetic men and women. The Heart SCORE study was a community based research study. Therefore, a finger stick method was used to determine current blood glucose levels, as opposed to measurement of an actual Hemoglobin A₁C level, which determines the average blood glucose level over a 2 to 3 month time period. Thus, non-diabetic Heart SCORE participants (n=1,605) with data on cardiovascular risk factors (age, total cholesterol, high-density lipoprotein, systolic blood pressure, treatment or no treatment of hypertension, smoking status, family history, and high-sensitivity C-reactive protein) required for calculating the three risk scores were included in the analyses.

Table 9. Heart SCORE Non-Diabetic Mean Cardiovascular Risk Scores of the Reynolds Risk Score, Framingham Risk Score, and Pooled Risk Score by Race and Gender

<table>
<thead>
<tr>
<th></th>
<th>RRS</th>
<th>FRS</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Overall</td>
<td>1597</td>
<td>6.70</td>
<td>7.20</td>
</tr>
<tr>
<td>Black men</td>
<td>190</td>
<td>11.97</td>
<td>8.29</td>
</tr>
<tr>
<td>White men</td>
<td>352</td>
<td>11.31</td>
<td>8.58</td>
</tr>
<tr>
<td>Black women</td>
<td>447</td>
<td>4.58</td>
<td>5.27</td>
</tr>
<tr>
<td>White women</td>
<td>608</td>
<td>3.94</td>
<td>4.50</td>
</tr>
</tbody>
</table>

Note. RRS = Reynolds risk score; FRS = Framingham risk score; Pooled = pooled cohort risk equation.

Among all Heart SCORE participants, the mean predicted cardiovascular risk score calculated by the Framingham Risk Score (13.65) was much higher than the corresponding mean risk scores derived from the Reynolds Risk Score (6.7) or the Pooled Cohort Risk Score (9.07) (Table 9). The Framingham Risk Score predicted higher 10-year risk of CVD across all subgroups including blacks (M = 14.11, SD = 9.99), whites (M = 13.35, SD = 9.73), males (M =
20.22, \(SD = 11.19\), and females \((M = 13.65, SD = 9.84)\). The corresponding Pooled Cohort Risk Scores for blacks was \((M = 10.47, SD = 7.63)\) and for whites was \((M = 8.14, SD = 7.3)\).

Table 10. Heart SCORE Non-Diabetic Mean Ratio of Cardiovascular Risk Scores of the Reynolds Risk Score, Framingham Risk Score, and Pooled Risk Score by Race and Gender

<table>
<thead>
<tr>
<th></th>
<th>RRS/FRS</th>
<th>CI 95%</th>
<th>RRS/Pooled</th>
<th>CI 95%</th>
<th>Pool FRS</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>.44</td>
<td>.43, .45</td>
<td>.74</td>
<td>.73, .76</td>
<td>.63</td>
<td>.62, .64</td>
</tr>
<tr>
<td>Black Men</td>
<td>.54</td>
<td>.51, .57</td>
<td>.82</td>
<td>.78, .87</td>
<td>.68</td>
<td>.65, .72</td>
</tr>
<tr>
<td>White Men</td>
<td>.54</td>
<td>.52, .56</td>
<td>.92</td>
<td>.89, .95</td>
<td>.60</td>
<td>.58, .62</td>
</tr>
<tr>
<td>Black women</td>
<td>.34</td>
<td>.33, .36</td>
<td>.51</td>
<td>.49, .54</td>
<td>.71</td>
<td>.69, .73</td>
</tr>
<tr>
<td>White women</td>
<td>.34</td>
<td>.33, .36</td>
<td>.71</td>
<td>.69, .73</td>
<td>.53</td>
<td>.51, .55</td>
</tr>
</tbody>
</table>

Note. \(n=1597\). RRS = Reynolds risk score; FRS=Framingham risk score; Pooled Score = pooled cohort risk equation; CI = confidence interval.

The Reynolds Risk Score predicted the lowest cardiovascular risk for blacks \((M= 6.78, SD = 7.16)\) compared to whites \((M = 6.64, SD = 7.23)\). Consistent with the Framingham Risk Score and Reynolds Risk Score the Pooled Risk Score had a higher predicted mean risk for men \((M = 13.10, SD = 8.04)\) than women \((M = 7.00, SD = 6.32)\). The Reynolds Risk Score had the lowest predicted risk for males \((M=11.54, SD = 8.48)\) and females \((M= 4.21, SD = 4.85)\).

Thus, the three cardiovascular risk scores generated varied cardiovascular risk prediction. The Framingham Risk Score assigned all black and white Heart SCORE participants with the highest cardiovascular risk of the three cardiovascular risk scores. The Reynolds Risk Score assigned the lowest cardiovascular risk to the Heart SCORE participants, which, on average, was roughly half the value of the Framingham Risk Score (table 4.6). Using the Framingham Risk Score as the comparison metric (the denominator), risk scores ratios across race and gender subgroups for the Reynolds Risk Score ranged from 0.34 to 0.54. Corresponding risk score ratios across race and gender subgroups for the Pooled Risk Score ranged from 0.53 to 0.71 (table 4.6). Thus, in terms of absolute risk prediction of future CVD, rates were highest for the Framingham Risk Score, intermediate for the Pooled Risk Score, and lowest for the Reynolds Risk Score.
Specific Aim 2

Examine the overall predictive utility by race of the Framingham Cardiovascular Risk Score, Reynolds Risk Score for Women, Reynolds Risk Score for Men, and the Pooled Cohort Risk Equations using methods of calibration and discrimination.

**Discrimination and calibration.** The Heart SCORE sample (n = 1768) was used to assess discrimination and calibration of the Framingham Risk Score, Reynolds Risk Score for Women, Reynolds Risk Score for Men, and the Pooled Cohort Risk Equations. It was optimal to use all the available data for this portion of the analysis. Diabetic participants are historically at higher risk according to the cardiovascular risk models, and therefore, most likely to experience a cardiovascular event. Therefore, inclusion of diabetic participants was optimal for accurate assessment of discrimination and calibration of the cardiovascular risk scores. The cardiovascular events used in the analyses (as a composite endpoint) were the occurrence of a death, myocardial infarction (MI), stroke, Acute Ischemic Stroke (AIS), or revascularization (coronary artery bypass grafting or percutaneous coronary intervention).

**Discrimination analysis.** The ability of the cardiovascular risk scores to discriminate between individuals who will and will not experience a cardiovascular event was assessed. In concept, a cardiovascular risk score should assign higher predicted risk scores to individuals who subsequently experience the outcome of interest, meaning the composite endpoint of death, myocardial infarction (MI), stroke, Acute Ischemic Stroke (AIS), or revascularization (coronary artery bypass grafting or percutaneous coronary intervention in the present study. Likewise, lower cardiovascular risk scores should be assigned to individuals who do not experience a cardiovascular event. The results of the Wilcoxon Rank Sum Test conducted to determine statistical significance of discrimination ability of the three cardiovascular risk scores overall and
by race and gender are presented in tables 4.7, 4.8 and 4.9. Additionally, discrimination was visually assessed with the box plots of the Wilcoxon Rank Sum tests of the Framingham Risk Score (see figures 1 - 5), Reynolds Risk Scores for women (see figures 6 - 10), and Pooled Cohort Risk Equations (see figures 11 - 15). Overall, the three cardiovascular risk scores demonstrated strong evidence of being able to discriminate between individuals who ultimately did and did not experience a cardiovascular event (see Tables 11–13) and by race and gender.

**Table 11.** Mean Framingham Risk Scores for Heart SCORE Participants Who Did and Did Not Experience the Composite Cardiovascular Event of MI, Death, Stroke, AIS, or Revascularization

<table>
<thead>
<tr>
<th></th>
<th>$n$</th>
<th>$M$</th>
<th>$SD$</th>
<th>$Mdn$</th>
<th>5%</th>
<th>95%</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1768</td>
<td>14.54</td>
<td>10.77</td>
<td>11.65</td>
<td>3.37</td>
<td>36.77</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>154</td>
<td>24.31</td>
<td>14.22</td>
<td>21.02</td>
<td>6.25</td>
<td>54.56</td>
<td></td>
</tr>
<tr>
<td><strong>Black male</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>213</td>
<td>22.59</td>
<td>12.43</td>
<td>20.16</td>
<td>7.57</td>
<td>46.60</td>
<td>.0003</td>
</tr>
<tr>
<td>Yes</td>
<td>41</td>
<td>30.80</td>
<td>15.67</td>
<td>29.10</td>
<td>10.06</td>
<td>61.23</td>
<td>.0001</td>
</tr>
<tr>
<td><strong>White male</strong></td>
<td></td>
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<tr>
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<td>356</td>
<td>20.07</td>
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<td>16.88</td>
<td>6.55</td>
<td>46.80</td>
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</tr>
<tr>
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<td>47</td>
<td>26.24</td>
<td>10.84</td>
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<td>45.48</td>
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</tr>
<tr>
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</tr>
<tr>
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<td>10.07</td>
<td>2.89</td>
<td>31.32</td>
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<td>24.37</td>
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<td>12.76</td>
<td>4.68</td>
<td>30.83</td>
<td>.001</td>
</tr>
</tbody>
</table>

As depicted in figure 1 and listed in table 4.7, the FRS showed strong capacity to discriminate between participants who did and did not experience the primary composite cardiovascular outcome (death, myocardial infarction (MI), stroke, percutaneous coronary intervention (PCI), or coronary bypass grafting (CABG) ($p < .0001$). The median value was
14.51 for participants who did not experience the CVD composite outcome versus a median value of 24.31 for those who did.

**Figure 1.** Distribution of Framingham risk scores for participants who did or did not experience the primary composite cardiovascular outcome.

**Figure 2.** Distribution of Framingham risk scores for Black male participants who did or did not experience the primary composite cardiovascular outcome.
In comparison to the overall results for the FRS, the discrimination results were similar among black men (Figure 2, \( p = .0003 \)). The median value was 22.59 for participants who did not experience the CVD composite outcome versus a median value of 30.80 for those who did.

![Distribution of Wilcoxon Scores for FRAMINGHAM_RISK_SCORE](image)

**Figure 3.** Distribution of Framingham risk scores for White male participants who did or did not experience the primary composite cardiovascular outcome.

When compared to the overall results for the FRS, the discrimination results were similar among white men (Figure 3, \( p < .0001 \)). The median value was 20.07 for participants who did not experience the CVD composite outcome versus a median value of 26.24 for those who did.

In comparison to the overall results for the FRS and results for men, the discrimination results were similar among black females (Figure 4, \( p < .0001 \)). The median value was 12.81 for participants who did not experience the CVD composite outcome versus a median value of 21.49 for those who did.
Figure 4. Distribution of Framingham risk scores for Black female participants who did or did not experience the primary composite cardiovascular outcome.

Figure 5. Distribution of Framingham risk scores for White female participants who did or did not experience the primary composite cardiovascular outcome.
In comparison to the overall results for the FRS and results for men and black females, the discrimination results were similar among white females (Figure 4, p = .0007). The median value was 10.34 for participants who did not experience the CVD composite outcome versus a median value of 14.96 for those who did.

**Table 12.** Reynolds Risk Scores for Heart SCORE participants with and without the cardiovascular event of MI, Death, Stroke, AIS, or Revascularization

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>M</th>
<th>SD</th>
<th>Mdn</th>
<th>5%</th>
<th>95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>1508</td>
<td>6.26</td>
<td>6.88</td>
<td>3.95</td>
<td>.62</td>
<td>19.05</td>
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</tr>
<tr>
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<td>108</td>
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<td>10.93</td>
<td>1.41</td>
<td>26.73</td>
<td>&lt;.0001</td>
</tr>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
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<td>15.84</td>
<td>8.78</td>
<td>13.76</td>
<td>5.30</td>
<td>26.54</td>
<td>.002</td>
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<td></td>
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<tr>
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<td>8.08</td>
<td>2.22</td>
<td>29.81</td>
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<td>2.71</td>
<td>8.03</td>
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<td>12.96</td>
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<td>25</td>
<td>10.26</td>
<td>9.36</td>
<td>7.14</td>
<td>1.34</td>
<td>32.78</td>
<td>&lt;.0001</td>
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<tr>
<td><strong>White female</strong></td>
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<td>0.54</td>
<td>11.34</td>
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<td>4.78</td>
<td>5.25</td>
<td>0.85</td>
<td>15.07</td>
<td>.002</td>
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</tbody>
</table>

As depicted in figure 6 and listed in table 4.8, the RRS showed strong capacity to discriminate between participants who did and did not experience the primary composite cardiovascular outcome (death, myocardial infarction (MI), stroke, percutaneous coronary intervention (PCI) or coronary bypass grafting (CABG) (p < .0001). The median value was 6.26 for participants who did not experience the CVD composite outcome versus a median value of 13.02 for those who did.
Figure 6. Distribution of Reynolds risk score participants who did or did not experience the primary composite cardiovascular outcome.

Figure 7. Distribution of Reynolds risk score Black male participants who did or did not experience the primary composite cardiovascular outcome.
In comparison to the overall results for the RRS, the discrimination results were similar among black men (Figure 7, p = .002). The median value was 11.27 for participants who did not experience the CVD composite outcome versus a median value of 15.84 for those who did.

![Distribution of Wilcoxon Scores for REYNOLDS_RISK_SCORE](image)

**Figure 8.** Distribution of Reynolds risk score White male participants who did or did not experience the primary composite cardiovascular outcome.

When compared to the overall results for the RRS, the discrimination results were similar among white men (Figure 8, p < .0001). The median value was 10.81 for participants who did not experience the CVD composite outcome versus a median value of 16.07 for those who did.

In comparison to the overall results for the RRS and results for men, the discrimination results were similar among black females (Figure 9, p < .0001). The median value was 4.74 for participants who did not experience the CVD composite outcome versus a median value of 10.26 for those who did.
Figure 9. Distribution of Reynolds risk score Black female participants who did or did not experience the primary composite cardiovascular outcome.

Figure 10. Distribution of Reynolds risk score White female participants who did or did not experience the primary composite cardiovascular outcome.
In comparison to the overall results for the RRS and results for men and black females, the discrimination results were similar among white females (Figure 10, \( p = .0014 \)). The median value was 3.88 for participants who did not experience the CVD composite outcome versus a median value of 6.68 for those who did.

**Table 13.** Pooled Cohort Risk Equation Scores for Heart SCORE participants with and without the cardiovascular event of MI, Death, Stroke, AIS, or Revascularization

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>M</th>
<th>SD</th>
<th>Mdn</th>
<th>5%</th>
<th>95%</th>
<th>p</th>
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<td>Overall</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<td>10.03</td>
<td>8.93</td>
<td>7.49</td>
<td>1.08</td>
<td>28.54</td>
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<td>12.62</td>
<td>15.76</td>
<td>3.07</td>
<td>43.86</td>
<td>&lt;.0001</td>
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<td>9.04</td>
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<td>33.20</td>
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<td>21.68</td>
<td>7.03</td>
<td>47.70</td>
<td>.0002</td>
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<td>8.03</td>
<td>0.89</td>
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<td>7.43</td>
<td>7.98</td>
<td>1.52</td>
<td>26.03</td>
<td>.003</td>
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</table>

As depicted in figure 11 and listed in table 4.9, the Pooled Cohort Risk Equations showed strong capacity to discriminate between participants who did and did not experience the primary composite cardiovascular outcome (death, myocardial infarction (MI), stroke, percutaneous coronary intervention (PCI) or coronary bypass grafting (CABG) (\( p < .0001 \)). The median value was 10.03 for participants who did not experience the CVD composite outcome versus a median value of 18.70 for those who did.
Figure 11. Distribution of pooled cohort risk equation participants who did or did not experience the primary composite cardiovascular outcome.

Figure 12. Distribution of pooled cohort risk equation Black male participants who did or did not experience the primary composite cardiovascular outcome.
In comparison to the overall results for the Pooled Cohort Risk Equations, the discrimination results were similar among black men (Figure 12, $p = .0002$). The median value was 15.85 for participants who did not experience the CVD composite outcome versus a median value of 22.95 for those who did.

Figure 13. Distribution of pooled cohort risk equation White male participants who did or did not experience the primary composite cardiovascular outcome.

When compared to the overall results for the Pooled Cohort Risk Equations, the discrimination results were similar among white men (Figure 13, $p < .0001$). The median value was 12.89 for participants who did not experience the CVD composite outcome versus a median value of 18.72 for those who did.

In comparison to the overall results for the Pooled Cohort Risk Equations and results for men, the discrimination results were similar among black females (Figure 14, $p < .0001$). The median value was 10.71 for participants who did not experience the CVD composite outcome versus a median value of 20.18 for those who did.
Figure 14. Distribution of pooled cohort risk equation Black female participants who did or did not experience the primary composite cardiovascular outcome.

Figure 15. Distribution of pooled cohort risk equation White female participants who did or did not experience the primary composite cardiovascular outcome.
In comparison to the overall results for the Pooled Cohort Risk Equations and results for men, the discrimination results were similar among white females (Figure 15, p = .0015). The median value was 6.06 for participants who did not experience the CVD composite outcome versus a median value of 9.65 for those who did.

Thus, in summary, all 3 risk scores demonstrated strong evidence of being able to discriminate among individuals who ultimately did and did not experience the CVD composite outcome of interest. This occurred across gender and race subgroups, and irrespective of the fact that absolute predicted rates of CVD varied substantially across the three risk scores.

**Calibration analysis.** The predicted risk scores of the Framingham Heart Score, Reynolds Risk Score, and Pooled Cohort Risk Equations) were divided into quintiles. The mean predicted risk score was calculated for each quintile. The cardiovascular risk scores of the individuals who experienced the composite cardiovascular event of interest were divided into quintiles for each of the cardiovascular risk scores. The mean observed risk score was calculated for each quintile. The calibration of the Framingham Risk Score (see figures 16-20), Reynolds Risk Score (see figures 21-25), and Pooled Cohort Risk Equations (see figures 26-30) were assessed. Specifically, the degree of concordance among the mean predicted risk scores and mean observed risk scores for the quintiles for each cardiovascular risk score was assessed.

As depicted in figures 16-20, the Framingham risk score consistently overestimated the 10-year risk of a cardiovascular event across race and gender. Ten year cardiovascular risk was consistently overestimated across the low, intermediate and high quintiles of risk as compared to the observed risk. Thus, the Framingham Risk score demonstrated relatively poor precision in predicting 10-year cardiovascular risk scores across race and gender. The 10-year predicted cardiovascular risk predictions from the Reynolds Risk Scores demonstrated markedly better
precision when compared to the observed cardiovascular risk overall and across race and gender. Indeed, there was remarkable consistency among predicted vs. observed rates of CVD in white males. In black males, risk was slightly under predicted at the higher risk quintile as well as one of the lower risk quintiles. Ten year cardiovascular risk was also under predicted in the higher quintile of risk in black females and over predicted in white females. Risk was also under predicted in the lowest quintiles of risk in black females. Overall there was variation in the accuracy of risk prediction in the lower quintiles of cardiovascular risk. However, in aggregate, the Reynolds Risk Scores appeared to predict future CVD risk with reasonable precision by both gender and race. Overall, the Pooled Cohort Risk Equations overestimated 10-year risk of a cardiovascular event across race and gender (see figures 26 - 30). This degree of overestimation was lower than that of the Framingham Risk Score (previous figures 16-20). For black females and white females, the Pooled Cohort Risk Equation over estimated risk in higher risk quintiles. Risk was underestimated in the intermediate risk quintile for black and white males. Predicted 10-year cardiovascular risk was inconsistent in the lower risk quintiles. Interestingly, predicted 10-year cardiovascular risk was overestimated for white males in the low risk quintiles. Thus, results for the Pooled Cohort Risk Equations indicated marginal precision across quintiles.
Figure 16. Framingham risk score overall predicted risk and observed risk for the primary composite cardiovascular outcome.

Figure 17. Framingham risk score predicted risk and observed risk for the primary composite cardiovascular outcome in Black males.
Figure 18. Framingham risk score predicted risk and observed risk for the primary composite cardiovascular outcome in White males.

Figure 19. Framingham risk score predicted risk and observed risk for the primary composite cardiovascular outcome in Black females.
Figure 20. Framingham risk score predicted risk and observed risk for the primary composite cardiovascular outcome in White females.

Figure 21. Reynolds risk score overall predicted risk and observed risk for the primary composite cardiovascular outcome.
**Figure 22.** Reynolds risk score predicted risk and observed risk for the primary composite cardiovascular outcome in Black males.

**Figure 23.** Reynolds risk score predicted risk and observed risk for the primary composite cardiovascular outcome in White males.
**Figure 24.** Reynolds risk score predicted risk and observed risk for the primary composite cardiovascular outcome in Black females.

**Figure 25.** Reynolds risk score predicted risk and observed risk for the primary composite cardiovascular outcome in White females.
Figure 26. Pooled cohort risk equations overall predicted risk and observed risk for the primary composite cardiovascular outcome.

Figure 27. Pooled cohort risk equations predicted risk and observed risk for the primary composite cardiovascular outcome in Black males.
Figure 28. Pooled cohort risk equations predicted risk and observed risk for the primary composite cardiovascular outcome in White males.

Figure 29. Pooled cohort risk equations predicted risk and observed risk for the primary composite cardiovascular outcome in Black females.
Figure 30. Pooled cohort risk equations predicted risk and observed risk for the primary composite cardiovascular outcome in White females.
Specific Aim 3

Assess the predictive utility of the Framingham cardiovascular risk score, Reynolds Risk Score for women, Reynolds Risk Score for Men and the Pooled Cohort Risk Equations with the inclusion of the variables carotid intima media thickness (CIMT), pulse amplitude tonometry (PAT), and/or vasa vasorum (VV).

Table 14. Cox Regression Analysis of the Framingham Risk Score, Reynolds Risk Scores, and Pooled Cohort Risk Scores by Race and Gender in Heart SCORE

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>$n$</th>
<th>HR</th>
<th>95% CI</th>
<th>AIC</th>
<th>$p$</th>
</tr>
</thead>
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<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Framingham</td>
<td>1922</td>
<td>1.27</td>
<td>[1.22, 1.33]</td>
<td>2177.92</td>
<td>&lt;.0001</td>
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<tr>
<td>Reynolds risk</td>
<td>1616</td>
<td>1.40</td>
<td>[1.30, 1.50]</td>
<td>1497.03</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Pooled</td>
<td>1918</td>
<td>1.35</td>
<td>[1.28, 1.42]</td>
<td>2166.71</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Black Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Framingham</td>
<td>254</td>
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<td>[1.08, 1.30]</td>
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<td>.0002</td>
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<tr>
<td>Reynolds risk</td>
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<td>.01</td>
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<tr>
<td>Pooled</td>
<td>250</td>
<td>1.30</td>
<td>[1.15, 1.46]</td>
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<td>&lt;.0001</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Framingham</td>
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<td>[1.06, 1.27]</td>
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</tr>
<tr>
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<td>[1.11, 1.43]</td>
<td>434.17</td>
<td>.0003</td>
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<tr>
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<td>[1.12, 1.41]</td>
<td>530.69</td>
<td>&lt;.0001</td>
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<td>Black Females</td>
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<td></td>
</tr>
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<td>[1.20, 1.43]</td>
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<td>[1.36, 1.95]</td>
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<tr>
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<td>[1.21, 1.43]</td>
<td>468.46</td>
<td>&lt;.0001</td>
</tr>
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<td>White Females</td>
<td></td>
<td></td>
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<tr>
<td>Framingham</td>
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<td>[1.13, 1.58]</td>
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<td>681</td>
<td>1.36</td>
<td>[1.13, 1.64]</td>
<td>326.86</td>
<td>.0008</td>
</tr>
</tbody>
</table>

Note. HR = hazard ratio; CI = confidence interval; AIC = Akaike information criteria; Framingham= Framingham risk score; Reynolds Risk = Reynolds risk score; Pooled = Pooled cohort risk equation.

Without consideration of any of the novel risk factors, and based on the total population, table 4.10 provides hazard ratio estimates for the three risk scores in relation to future cardiovascular risk. Overall, hazard ratio estimates ranged from a low of 1.27 for Framingham
Risk Score to a high of 1.40 for the Reynolds Risk Score. Moreover, the AIC value was lowest (best) for the Reynolds Risk Score in terms of assessment of model fit. Similar results were observed by race and gender.

Table 15. Framingham Risk Scores, Reynolds Risk Scores, Pooled Cohort Risk Scores with inclusion of novel risk factors of PAT, CIMT, or VV for Heart SCORE participants

<table>
<thead>
<tr>
<th>Model</th>
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<th>95% CI</th>
<th>AIC</th>
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<td>1. Framingham</td>
<td>1396</td>
<td>1.25</td>
<td>[1.18, 1.32]</td>
<td>1516.06</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>2. FRS + PAT</td>
<td>1.24</td>
<td>[1.17, 1.32]</td>
<td>1517.56</td>
<td>&lt; .0001</td>
<td></td>
</tr>
<tr>
<td>PAT</td>
<td>0.89</td>
<td>[0.69, 1.51]</td>
<td></td>
<td>.48</td>
<td></td>
</tr>
<tr>
<td>1. Framingham</td>
<td>733</td>
<td>1.34</td>
<td>[1.22, 1.47]</td>
<td>554.23</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>2. FRS + CIMT</td>
<td>1.33</td>
<td>[1.20, 1.47]</td>
<td>556.08</td>
<td>&lt; .0001</td>
<td></td>
</tr>
<tr>
<td>CIMT</td>
<td>1.38</td>
<td>[0.27, 6.94]</td>
<td></td>
<td>.69</td>
<td></td>
</tr>
<tr>
<td>1. Framingham</td>
<td>576</td>
<td>1.38</td>
<td>[1.23, 1.54]</td>
<td>392.19</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>2. FRS + VV</td>
<td>1.38</td>
<td>[1.23, 1.54]</td>
<td>392.47</td>
<td>&lt; .0001</td>
<td></td>
</tr>
<tr>
<td>VV</td>
<td>1.72</td>
<td>[0.81, 3.67]</td>
<td></td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>2. RRS + PAT</td>
<td>1.39</td>
<td>[1.28, 1.52]</td>
<td>1091.06</td>
<td>&lt; .0001</td>
<td></td>
</tr>
<tr>
<td>PAT</td>
<td>0.76</td>
<td>[0.52, 1.11]</td>
<td></td>
<td>.16</td>
<td></td>
</tr>
<tr>
<td>1. Reynolds Risk</td>
<td>638</td>
<td>1.39</td>
<td>[1.20, 1.61]</td>
<td>383.02</td>
<td>.0001</td>
</tr>
<tr>
<td>2. RRS + CIMT</td>
<td>1.29</td>
<td>[1.09, 1.52]</td>
<td>381.00</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>CIMT</td>
<td>6.91</td>
<td>[1.08, 44.1]</td>
<td></td>
<td>.04*</td>
<td></td>
</tr>
<tr>
<td>1. Reynolds Risk</td>
<td>498</td>
<td>1.47</td>
<td>[1.25, 1.72]</td>
<td>258.46</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>2. RRS + VV</td>
<td>1.47</td>
<td>[1.25, 1.72]</td>
<td>260.45</td>
<td>&lt; .0001</td>
<td></td>
</tr>
<tr>
<td>VV</td>
<td>0.93</td>
<td>[0.29, 2.97]</td>
<td></td>
<td>.91</td>
<td></td>
</tr>
<tr>
<td>1. Pooled Risk</td>
<td>1366</td>
<td>1.31</td>
<td>[1.22, 1.40]</td>
<td>1514.49</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>2. PRS + PAT</td>
<td>1.31</td>
<td>[1.19, 1.45]</td>
<td>1515.78</td>
<td>&lt; .0001</td>
<td></td>
</tr>
<tr>
<td>PAT</td>
<td>0.88</td>
<td>[0.65, 1.18]</td>
<td></td>
<td>.40</td>
<td></td>
</tr>
<tr>
<td>1. Pooled Risk</td>
<td>732</td>
<td>1.51</td>
<td>[1.35, 1.68]</td>
<td>543.34</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>2. PRS + CIMT</td>
<td>1.49</td>
<td>[1.33, 1.67]</td>
<td>544.87</td>
<td>&lt; .0001</td>
<td></td>
</tr>
<tr>
<td>CIMT</td>
<td>1.76</td>
<td>[0.35, 8.74]</td>
<td></td>
<td>.48</td>
<td></td>
</tr>
<tr>
<td>1. Pooled Risk</td>
<td>575</td>
<td>1.55</td>
<td>[1.35, 1.78]</td>
<td>386.21</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>2. PRS + VV</td>
<td>1.54</td>
<td>[1.34, 1.77]</td>
<td>386.75</td>
<td>&lt; .0001</td>
<td></td>
</tr>
<tr>
<td>VV</td>
<td>1.71</td>
<td>[0.75, 3.92]</td>
<td></td>
<td>.20</td>
<td></td>
</tr>
</tbody>
</table>

Note. HR = hazard ratio; CI = confidence interval; AIC = Akaike information criteria; FRS = Framingham risk score; PAT = peripheral arterial tonometry; CIMT = carotid intima media thickness; VV = vasa vassorum; RRS = Reynolds risk score; PRS = Pooled cohort risk equation.
The hazard ratios for the three risk scores are presented in tables 4.11 (including addition of novel risk factors), and based on the participants with the risk factors to compute all three cardiovascular risk scores. As seen, the hazard ratios range from a low of 1.25 for the Framingham Risk Score to a high of 1.39 for the Reynolds Risk Score (p < 0.0001 for all risk scores). In nested models that added either peripheral arterial tonometry (PAT), carotid artery intima media thickness (CIMT), or vasa vasorum (VV), the risk score estimates were only nominally attenuated. This is further reflected in nearly identical AIC values for the index model and addition of novel risk factors. An exception was the Reynolds Risk Score model where CIMT was independently associated with future cardiovascular risk (HR = 6.91, p = .04).

The hazard ratios for the three risk scores for black participants are presented in table 4.12. As seen, they range from a low of 1.26 for the Framingham Risk Score to a high of 1.64 for the Reynolds Risk Score (p < .05 for all risk scores). In nested models that added either peripheral arterial tonometry (PAT), carotid artery intima media thickness (CIMT), or vasa vasorum (VV), the risk score estimates were only nominally attenuated. This is further reflected in nearly identical AIC values for the index model and addition of novel risk factors. There was no novel risk factor that was independently associated with future cardiovascular risk among black participants.

The hazard ratios for the three risk scores among white participants are presented in tables 4.13, and based on the participants with the risk factors to compute all three cardiovascular risk scores. As seen, the hazard ratios range from a low of 1.20 for the Framingham Risk Score to a high of 1.57 for the Pooled Cohort Risk Equations score (p < 0.05 for all risk scores). In nested models that added either peripheral arterial tonometry (PAT), carotid artery intima media thickness (CIMT), or vasa vasorum (VV), the risk score estimates were only nominally...
Table 16. Framingham Risk Scores, Reynolds Risk Scores, Pooled Cohort Risk Scores with inclusion of novel risk factors of PAT, CIMT, or VV for Black Heart SCORE participants

<table>
<thead>
<tr>
<th>Model</th>
<th>n</th>
<th>HR</th>
<th>95% CI</th>
<th>AIC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Framingham</td>
<td>557</td>
<td>1.26</td>
<td>[1.16, 1.38]</td>
<td>622.79</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>2. FRS + PAT</td>
<td></td>
<td>1.26</td>
<td>[1.15, 1.37]</td>
<td>624.08</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>PAT</td>
<td></td>
<td>0.82</td>
<td>[.50, .32]</td>
<td></td>
<td>.41</td>
</tr>
<tr>
<td>1. Framingham</td>
<td>249</td>
<td>1.48</td>
<td>[1.26, 1.73]</td>
<td>195.01</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>2. FRS + CIMT</td>
<td></td>
<td>1.48</td>
<td>[1.26, 1.74]</td>
<td>196.93</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>CIMT</td>
<td></td>
<td>0.70</td>
<td>[0.06, 8.35]</td>
<td></td>
<td>.78</td>
</tr>
<tr>
<td>1. Framingham</td>
<td>201</td>
<td>1.43</td>
<td>[1.19, 1.71]</td>
<td>137.04</td>
<td>.0001</td>
</tr>
<tr>
<td>2. FRS + VV</td>
<td></td>
<td>1.43</td>
<td>[1.19, 1.72]</td>
<td>138.94</td>
<td>.0001</td>
</tr>
<tr>
<td>VV</td>
<td></td>
<td>0.77</td>
<td>[.15, 3.98]</td>
<td></td>
<td>.76</td>
</tr>
<tr>
<td>1. Reynolds Risk</td>
<td>427</td>
<td>1.51</td>
<td>[1.30, 1.77]</td>
<td>400.97</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>2. RRS + PAT</td>
<td></td>
<td>1.51</td>
<td>[1.29, 1.77]</td>
<td>402.06</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>PAT</td>
<td></td>
<td>0.75</td>
<td>[.41, 1.37]</td>
<td></td>
<td>.35</td>
</tr>
<tr>
<td>1. Reynolds Risk</td>
<td>198</td>
<td>1.63</td>
<td>[1.25, 2.11]</td>
<td>104.50</td>
<td>.0002</td>
</tr>
<tr>
<td>2. RRS + CIMT</td>
<td></td>
<td>1.59</td>
<td>[1.19, 2.12]</td>
<td>104.02</td>
<td>.001</td>
</tr>
<tr>
<td>CIMT</td>
<td></td>
<td>11.45</td>
<td>[.62, 209.12]</td>
<td></td>
<td>.10</td>
</tr>
<tr>
<td>1. Reynolds Risk</td>
<td>160</td>
<td>1.64</td>
<td>[1.20, 1.23]</td>
<td>70.50</td>
<td>.001</td>
</tr>
<tr>
<td>2. RRS + VV</td>
<td></td>
<td>1.83</td>
<td>[1.25, 2.67]</td>
<td>65.50</td>
<td>.001</td>
</tr>
<tr>
<td>VV</td>
<td></td>
<td>0.07</td>
<td>[.00, 3.40]</td>
<td></td>
<td>.18</td>
</tr>
<tr>
<td>1. Pooled Risk</td>
<td>554</td>
<td>1.29</td>
<td>[1.17, 1.43]</td>
<td>624.42</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>2. PRS + PAT</td>
<td></td>
<td>1.29</td>
<td>[1.16, 1.43]</td>
<td>625.50</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>PAT</td>
<td></td>
<td>0.80</td>
<td>[.49, 1.28]</td>
<td></td>
<td>.35</td>
</tr>
<tr>
<td>1. Pooled Risk</td>
<td>248</td>
<td>1.59</td>
<td>[1.34, 1.88]</td>
<td>189.96</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>2. PRS + CIMT</td>
<td></td>
<td>1.59</td>
<td>[1.34, .88]</td>
<td>191.95</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>CIMT</td>
<td></td>
<td>1.13</td>
<td>[.08, 14.86]</td>
<td></td>
<td>.92</td>
</tr>
<tr>
<td>1. Pooled Risk</td>
<td>200</td>
<td>1.54</td>
<td>[1.26, 1.87]</td>
<td>133.85</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>2. PRS + VV</td>
<td></td>
<td>1.54</td>
<td>[1.26, 1.88]</td>
<td>135.81</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>VV</td>
<td></td>
<td>0.84</td>
<td>[.16, 4.37]</td>
<td></td>
<td>.83</td>
</tr>
</tbody>
</table>

Note. HR = hazard ratio; CI = confidence interval; AIC = Akaike information criteria, FRS = Framingham risk score; PAT = peripheral arterial tonometry; CIMT = carotid intima media thickness; VV = vasa vassorum; RRS = Reynolds risk score; PRS = Pooled cohort risk equation.
Table 17. Framingham Risk Scores, Reynolds Risk Scores, Pooled Cohort Risk Scores With Inclusion of Novel Risk Factors of PAT, CIMT, or VV for White Heart SCORE Participants

<table>
<thead>
<tr>
<th>Model</th>
<th>n</th>
<th>HR</th>
<th>95% CI</th>
<th>AIC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Framingham</td>
<td>812</td>
<td>1.20</td>
<td>[1.14, 1.33]</td>
<td>738.31</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>2. FRS + PAT</td>
<td></td>
<td>1.24</td>
<td>[1.14, 1.34]</td>
<td>740.30</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PAT</td>
<td></td>
<td>1.02</td>
<td>[0.69, 1.51]</td>
<td></td>
<td>.90</td>
</tr>
<tr>
<td>1. Framingham</td>
<td>484</td>
<td>1.29</td>
<td>[1.14, 1.46]</td>
<td>294.07</td>
<td>&lt;.0001</td>
</tr>
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<td></td>
<td>1.25</td>
<td>[1.09, 1.44]</td>
<td>295.30</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CIMT</td>
<td></td>
<td>2.68</td>
<td>[0.31, 23.18]</td>
<td>.37</td>
<td></td>
</tr>
<tr>
<td>1. Framingham</td>
<td>375</td>
<td>1.35</td>
<td>[1.16, 1.56]</td>
<td>211.67</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>2. FRS + VV</td>
<td></td>
<td>1.36</td>
<td>[1.17, 1.58]</td>
<td>210.87</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>VV</td>
<td></td>
<td>2.19</td>
<td>[0.98, 4.90]</td>
<td>.05*</td>
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</tr>
<tr>
<td>1. Reynolds Risk</td>
<td>729</td>
<td>1.36</td>
<td>[1.22, 1.52]</td>
<td>574.22</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>2. RRS + PAT</td>
<td></td>
<td>1.36</td>
<td>[1.22, 1.52]</td>
<td>575.84</td>
<td>&lt;.0001</td>
</tr>
<tr>
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<td></td>
<td>.86</td>
<td>[0.54, 1.38]</td>
<td>.54</td>
<td></td>
</tr>
<tr>
<td>1. Reynolds Risk</td>
<td>440</td>
<td>1.33</td>
<td>[1.11, 1.61]</td>
<td>236.99</td>
<td>.0001</td>
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<tr>
<td>2. RRS + CIMT</td>
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<td>1.22</td>
<td>[0.98, 1.53]</td>
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<td>2. RRS + VV</td>
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<td>1.42</td>
<td>[1.17, 1.72]</td>
<td>168.22</td>
<td>.0003</td>
</tr>
<tr>
<td>VV</td>
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<td>1.36</td>
<td>[0.44, 4.20]</td>
<td>.59</td>
<td></td>
</tr>
<tr>
<td>1. Pooled Risk</td>
<td>812</td>
<td>1.31</td>
<td>[1.19, 1.45]</td>
<td>737.44</td>
<td>&lt;.0001</td>
</tr>
<tr>
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<td>1.31</td>
<td>[1.19, 1.45]</td>
<td>739.41</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PAT</td>
<td></td>
<td>.97</td>
<td>[0.66, 1.42]</td>
<td>.87</td>
<td></td>
</tr>
<tr>
<td>1. Pooled Risk</td>
<td>484</td>
<td>1.43</td>
<td>[1.23, 1.66]</td>
<td>291.51</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>2. PRS + CIMT</td>
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<td>1.39</td>
<td>[1.18, 1.64]</td>
<td>292.45</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CIMT</td>
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<td>3.10</td>
<td>[0.38, 24.98]</td>
<td>.28</td>
<td></td>
</tr>
<tr>
<td>1. Pooled Risk</td>
<td>200</td>
<td>1.55</td>
<td>[1.26, 1.91]</td>
<td>209.97</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>2. PRS + VV</td>
<td></td>
<td>1.57</td>
<td>[1.26, 1.94]</td>
<td>209.35</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>VV</td>
<td></td>
<td>2.29</td>
<td>[0.93, 5.64]</td>
<td>.07</td>
<td></td>
</tr>
</tbody>
</table>

Note. HR = hazard ratio; CI = confidence interval; AIC = Akaike information criteria; FRS = Framingham risk score; PAT = peripheral arterial tonometry; CIMT = carotid intima media thickness; VV = vasa vassorum; RRS = Reynolds risk score; PRS = Pooled cohort risk equation.
attenuated. This is further reflected in nearly identical AIC values for the index model and addition of novel risk factors. The exception was the Framingham Risk Score model where VV was borderline independently associated with future cardiovascular risk (HR = 2.19, 95% CI [.98 – 4.90], p = .05). Similarly, for examination of the Pooled Cohort Risk Score, there was a suggestion of VV being independently associated with future risk of CVD (HR = 2.29, 95% CI [0.93 – 5.64], p = .07).

**Chapter Summary**

The analyses to address the three specific aims of this study yielded four main findings. First, the overall predicted 10-year absolute risk according to the Framingham Risk Score, Reynolds Risk Scores, and Pooled Cohort Risk Equations varied substantially across the three measures. Second, this pattern of substantial risk variation held true across race and gender. Third, despite large variation in estimates of absolute risk of future CVD, the cardiovascular risk score equations were all strongly associated with future cardiovascular risk. Specifically, individuals with low occurrence of a cardiovascular event tended to have low risk scores, and individuals with higher occurrence of a cardiovascular event tended to have higher scores. Lastly, despite the examination of novel risk factors to improve risk prediction, such novel risk factors did not significantly improve 10-year cardiovascular risk prediction.
CHAPTER 5: DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

This final chapter includes a synthesis of the results from the study with discussion of the findings, conclusions, and implications for nursing and future research recommendations. The purpose of this research study was an assessment and comparison of the Framingham Risk score, Reynolds Risk scores, and the Pooled Cohort Risk Equation scores with respect to ability to predict cardiovascular events in a diverse ethnic population.

This research was guided by three aims:

1. Examine the overall predictive utility of the Framingham Cardiovascular Risk Score, Reynolds Risk Score for Women, Reynolds Risk Score for Men, and the Pooled Cohort Risk Equation using methods of discrimination and calibration.

2. Examine the overall predictive utility by race of the Framingham Cardiovascular Risk Score, Reynolds Risk Score for Women, Reynolds Risk Score for Men, and the Pooled Cohort Risk Equation using methods of discrimination and calibration.

3. Assess the predictive utility of the Framingham Cardiovascular Risk Score, Reynolds Risk Score for Women, Reynolds Risk Score for Men, and the Pooled Cohort Risk Equation with the inclusion of the variables carotid intima media thickness (CIMT), pulse amplitude tonometry (PAT), and/or vasa vasorum (VV).

Study Summary

A secondary data analysis of data from the Heart Strategies Concentrating on Risk Evaluation (Heart SCORE) was conducted. Heart SCORE is longitudinal prospective cohort study conducted over a ten year time period. The demographic, clinical history, and biological
variables were extracted from the Heart SCORE dataset. The prevalence of demographic variables overall and by race was illustrated by percentages and means and standard deviations. Statistical testing of the prevalence of cardiovascular risk factors by race was performed by use of chi-square tests, t-tests, and Wilcoxon Rank Sum Tests. The occurrence of cardiovascular events of the Heart SCORE participants were collected over the ten-year study period. Incidence rates of cardiovascular events overall and by race and gender were calculated.

To examine the overall predictive utility of the Framingham Cardiovascular Risk Score, Reynolds Risk Score for Women, Reynolds Risk Score for Men, and the Pooled Cohort Risk Equation, the three risk scores were calculated using their published algorithms. The mean risk scores for black men, black women, white men, and white women were compared. Calibration of the cardiovascular risk scores was assessed by examining the degree of concordance among mean predicted risk scores and mean observed risk scores. The distributions of cardiovascular risk scores of participants who did and did not experience the composite cardiovascular endpoint of interest (death, myocardial infarction (MI), death, stroke, Acute Ischemic Stroke (AIS), or revascularization) were compared by use of Wilcoxon Rank Sum Tests. These analyses examined the extent to which the three risk scores were able to discriminate future cardiovascular risk, overall and by race and gender. The predictive utility of the Framingham Cardiovascular risk score, Reynolds Risk Score for Women, Reynolds Risk Score for Men, and the Pooled Cohort Risk Equation with the inclusion of the variables carotid intima media thickness (CIMT), pulse amplitude tonometry (PAT), and/or vasa vasorum (VV) was evaluated with the use of Cox regression modeling.
Conclusions and Discussion

There were four main findings from this research. First, using three well-established methods for estimating future cardiovascular risk, the overall predicted 10-year absolute risk estimates varied substantially across the three measures. Second, this pattern of substantial risk variation held true across race and gender. Third, despite large variations in absolute risk predictions, the cardiovascular risk score equations were strongly associated with future cardiovascular risk. Individuals with low occurrence of a cardiovascular event tended to have low risk scores, and individuals with a higher occurrence of a cardiovascular event tended to have higher scores. Lastly, despite the examination of novel risk factors to improve risk prediction, such novel risk factors did not significantly improve 10-year cardiovascular risk prediction.

The Framingham Risk Score, Reynolds Risk Scores, and Pooled Cohort Risk Equation Risk Score generated highly variable overall cardiovascular risk predictions. The Framingham Risk Score assigned all Heart SCORE participants with the highest cardiovascular risk of the three cardiovascular risk scores. These findings are consistent with findings in the literature (DeFilips et al., 2015; Goff et al, 2013). The Reynolds Risk Score assigned the lowest cardiovascular risk to the Heart SCORE participants. The variation in predicted cardiovascular risk of the Framingham Risk score and the Reynolds Risk Score for women was also consistent with findings in the literature (DeFilipps et al., 2015; Tattersall et al., 2012). The Pooled Cohort Risk Equation predicted a higher overall cardiovascular risk compared to the Reynolds Risk Scores for women and men and a lower overall risk when compared to the Framingham Risk Scores. The application of the Pooled Cohort Risk Equation indicates variation in overall cardiovascular risk prediction when compared to the Framingham Risk Score and Reynolds Risk
Score for women (Preis & Kristensen, 2015). Looking at the range of future cardiovascular risk predictions form these risk scores, Framingham predictions were highest and Reynolds Risk Score predictions were the lowest.

The substantial risk variation held true across race and gender when comparing the cardiovascular risk scores. The ratio of mean cardiovascular risk scores indicated a largest variation in predicted cardiovascular risk among white men (.54 - .92) and the smallest among black men (.54 - .82). Black and white women had the same range of variation (.34 - .71), (.34 - .71). Predicted 10-year cardiovascular risk was dependent upon which of the three risk scores was calculated overall and across race and gender. The substantial variation in predicted risk is a known limitation of cardiovascular risk prediction (Goff et al, 2013; Preiss & Kristensen, 2015).

Despite large variations in absolute risk predictions, the cardiovascular risk score equations all showed strong association with future cardiovascular risk. Individuals with the lowest scores tended to be at the lowest risk of a cardiovascular event, and vice versa. The Framingham Risk Score, Reynolds Risk Scores, and Pooled Cohort Risk Equations were able to successfully discriminate among Heart SCORE participants at low or high risk for the clinically relevant composite cardiovascular endpoint consisting of death, myocardial infarction (MI), stroke, Acute Ischemic Stroke (AIS), or revascularization (coronary artery bypass grafting or percutaneous coronary intervention). Additionally, the three risk scores discriminated among white and the black Heart SCORE participants of both genders. DeFillips et al., (2015) found all three risk scores had good discrimination across race and gender. In the findings from Ridker et al., the Reynolds Risk Score for men and a traditional risk model (age, blood pressure, smoking, total cholesterol, and high-density lipoprotein), which was similar to the Framingham Risk Score discriminated well (Ridker et al., 2008). In the development of the Reynolds Risk Score for
women, Ridker et al., (2007) found the RRS had better discrimination for women compared to
FRS. These findings are similar to the findings of discrimination in this study. In this study, the
Pooled Cohort Risk Equation was found to have adequate discrimination. However, the Pooled
Cohort Risk Equation was found to poorly discriminate in external cohorts (Munter et al., 2014).
Importantly, the statistical method of Wilcoxon Rank Sum Tests to assess discrimination of the
three risk scores in this study was not Harrell’s C-statistic, which used to assess discrimination in
the studies above. Additionally, when assessing the discrimination of these three cardiovascular
risk scores, it is important to recognize that each was developed to predict different
cardiovascular events/endpoints. Thus, at least some variation in measures of discrimination and
calibration may be expected to occur across the three risk scores.

A well-calibrated risk score assigns the correct probability of an event at all levels of
predicted risk (Royston & Altman, 2013). The ability of the three cardiovascular risk scores to
accurately predict the risk of a cardiovascular event in 10 years across the quintiles of predicted
cardiovascular risk (risk quintiles) was assessed. The risk scores evaluated portend a 10-year risk
estimate, however, the mean follow up in Heart SCORE participants was 8 years. Therefore, an
adjustment procedure was used to estimate (interpolate) 10-year risk. Calibration of the
Framingham Risk Score was consistent across race and gender. The discordance among
predicted risk and observed risk indicated overestimation of predicted risk across race and
gender. The overestimation of cardiovascular risk from Framingham risk scores was consistent
with other findings in the literature (Cook et al., 2012; DeFilips et al., 2015; Goff et al., 2013).
An overestimation of risk in non-white populations is a well-known finding in Framingham risk
score research (Goff et al., 2013; Mendis, 2010; Payne, 2012). The Reynolds Risk Scores
performed reasonably well in estimating overall 10-year predicted cardiovascular risk. The
strongest concordance between the predicted and observed risk was in the intermediate risk quintile. Risk was somewhat under predicted at the highest risk quintile for blacks compared to whites. This important finding is partially consistent with previous research demonstrating poor calibration of cardiovascular risk prediction among blacks (Goff et al., 2013). The Pooled Cohort Risk Equations were developed to address the disparity in cardiovascular risk prediction among black men and women. However, the findings of this study indicate overall over estimation of risk across race and gender. Additionally, the Pooled Cohort Risk Equations under predicted risk in black men and women at the quintile of lowest risk. Cardiovascular risk was underestimated in the intermediate quintile of risk in black men and whites. These findings of over prediction are consistent with the over prediction in the cohorts used to develop the risk score and validation cohorts (DeFilipps et al., 2015; Munter et al., 2014; Preis & Kristensen, 2015). The findings from this study of under prediction in the lowest quintile and intermediate quintile of risk among men indicate variation in cardiovascular prediction that may warrant further investigation.

Despite the examination of novel risk factors to potentially improve risk prediction, novel risk factors did not significantly improve 10-year cardiovascular risk prediction. With the minor exception of the Reynolds Risk Score model where CIMT was independently associated with overall future cardiovascular risk, there was little indication of any appreciable improvement in model performance with the addition of novel risk factors. In the Framingham Risk Score model, the association between vasa vasorum and future cardiovascular risk in white participants was borderline and added a very small improvement in mode performance. Whereas this lack of new information may seem discouraging, it is also not entirely unexpected. Specifically, the three risk scores evaluated in this study are based on decades of previous research and intensive searches
aimed at optimizing the predictive ability of the respective algorithms. The present analysis corroborates the utility of these efforts ant the risk scores in use, and underscores the challenge in finding novel risk factors that may appreciably improve upon these algorithms.

**Implications of Findings**

In summary, the purpose of this research study was to assess and compare the Framingham Risk score, Reynolds Risk scores, and the Pooled Cohort Risk Equation scores with respect to their ability to predict cardiovascular events in a diverse ethnic population (Heart SCORE). Identification and measurement of cardiovascular risk is essential to beginning treatment so as to avoid future cardiac events (Lloyd Jones, 2010). The use of cardiovascular risk scores remains the foundation for risk stratification to guide clinical management as well as early detection (Wachira & Stys, 2013). Clinicians have access to several cardiovascular risk scores in practice settings. While having several risk scores with different risk factors may provide more information, it does not imply accuracy of the cardiovascular risk score used to calculate a given individual’s cardiovascular risk. The results of this research indicate there is a high degree of variation among the predicted cardiovascular risk scores (despite the similarity in risk factors used to calculate predicted risk). Moreover, the accuracy of the predicted cardiovascular risk score may vary depending on the race and sex of the patient. The finding of discordance among predicted 10-year cardiovascular risk and observed cardiovascular risk among the Framingham Risk Score (in particular), Reynolds Risk Score and Pooled Cohort Risk Equations score is consistent with the cardiovascular risk research. An additional consideration is these discordances in cardiovascular risk scores can also be interpreted with the notion that risk assessment of cardiovascular disease is an inexact science, and risk and outcome should be looked at as multifactorial (Preiss & Kristensen, 2015).
Investigation of the awareness and perception of clinicians regarding variation in predicted cardiovascular risk from different cardiovascular risk scores is recommended. Additionally, clinicians’ awareness and perception of the accuracy of cardiovascular risk prediction is important as it pertains to race and gender.

For most patients under normal circumstances, it is recommended for clinicians to apply the current guidelines (ACC/AHA) in addition to their clinical judgment and circumstances of the individual (Preiss & Kristensen, 2015). The current guidelines recommend the Pooled Cohort Risk Equations to predict atherosclerotic cardiovascular disease risk (Goff et al., 2013). However, in the present study, the Reynolds Risk Scores (for women and men) demonstrated the best precision when compared to the observed cardiovascular risk overall and across race and gender compared to the Framingham Risk Score and the Pooled Cohort Risk Score. Based on this finding, the data support use of the Reynolds Risk Score in the clinical arena. Importantly, providing the patient with their predicted 10-year cardiovascular risk according to the Framingham Risk Score (which consistently provided higher risk estimates compared to the Reynolds Risk Score) in conjunction with the Reynolds Risk Score will provide a range of estimates of 10-year cardiovascular risk.

Clinical management is guided by stratified predicted cardiovascular risk in men over 55 years of age and women over 65 years of age with multiple cardiovascular risk factors (Lloyd Jones, 2010). Cardiovascular risk scores stratify younger adults under the age of 45 as having a lower cardiovascular risk due to overall less cardiovascular risk burden. The inclusion of young adult participants in cardiovascular risk research may provide more knowledge on the predicted risk of individuals stratified at lower or intermediate risk, as well as the accuracy of cardiovascular risk score used to predict risk.
As indicated by previous cardiovascular research, the majority of the cohorts used to
study cardiovascular risk are not racially or ethnically diverse (Goff et al., 2013). Racial and
ethic populations have higher rates of cardiovascular disease and related risk factors (Ski, King-
Shier, & Thompson, 2013). The inclusion of racially and ethnically diverse samples in
cardiovascular research is warranted to address the high rate of cardiovascular disease.

The risk factors used to predict cardiovascular risk in the Framingham Risk score,
Reynolds Risk scores, and the Pooled Cohort Risk Score are strongly associated with
cardiovascular risk. Research incorporating novel risk factors of biological measurement, such as
carotid intima media thickness, peripheral arterial tonometry, and vasa vasorum, including their
potential role in cardiovascular research, has been endorsed by the American College of
Cardiology and American Heart Association (Go et al., 2014). However, in the present analysis,
these variables provided little to no independent predictive value. Thus, inclusion of the novel
risk factors of CIMT, PAT, and VV in cardiovascular research score stratification does not
appear to be warranted at this time, pending results from other studies that might attest to their
clinical, predictive value.

Study Strengths

The Heart SCORE dataset included a large array of demographic, clinical, and biological
measures collected on each participant. The study included a sample comprised of 43.8% black
participants (n=854) to allow comparative analyses by race. A lack of accurate cardiovascular
risk assessment in black individuals was addressed when developing the Pooled Cohort Risk
Equation. This study provided additional information for application of the Pooled Cohort Risk
Equations to the Heart SCORE population to assess the performance of this risk score in black
men and women. As recommended by the current American College of Cardiology and
American Heart Association guidelines, this research included the Pooled Cohort Risk Equation previously developed to assess the risk of stroke as a cardiovascular event/endpoint. Thus, the present study appears to be unique in simultaneously evaluating three well-established cardiovascular risk score algorithms using a common cardiovascular endpoint, and conducting analyses by gender and race.

**Study Limitations**

Although this research study involved assessment of novel cardiovascular risk factors and assessment of CVD risk in a diverse population, the study was subjected to several limitations. The three cardiovascular risk scores were developed to predict different events/endpoints. The events/endpoints of this study differed from those of which they were created to predict, and thus, may have affected model performance. Additionally, when performing a secondary analysis, the data used are limited by only those data collected in the primary research study. This limitation became apparent when diabetic participants had to be excluded from analysis of participants with the components for all three cardiovascular risk scores. Similarly, one risk score required the Hemoglobin A1C values which were not collected in Heart SCORE. Furthermore, diabetics comprised only 4.5% of the total sample used in these analyses. This was a small representation of at risk population with a known need for cardiovascular risk assessment.
REFERENCES


Center for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division for Heart Disease and Stroke Prevention. (2014). High blood pressure. From http://www.cdc.gov/bloodpressure/


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139


APPENDICIES

Appendix A: Heart Score Demographics

1. Age in Years: 
   (45 to 74 to be study eligible) * Up to their 75th BD, Not Including

2. Comorbidity expected to limit life expectancy to less than 5 years: Yes ☐ No ☐

3. Inability to undergo baseline or annual follow-up visits: Yes ☐ No ☐

4. Pregnancy: Yes ☐ No ☐
   Ineligible for HBCT

5. Final eligibility status: Eligible ☐ Ineligible ☐

6. Gender: Male ☐ Female ☐

7. Ethnicity: Hispanic or Latino ☐ Non-Hispanic or Latino ☐
   Defined as: (Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin)

8. Race (Select only one irrespective of ethnicity): 
   American Indian or Native Alaskan ☐ Native Hawaiian or Pacific Islander ☐
   Asian ☐ White ☐
   Black or African-American ☐ Other ☐

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Appendix B: Heart SCORE Social Economic Status and Education

1. Date of Birth: [mm/dd/yyyy]

2. Are you presently legally married? [Yes/No]

3. Do you currently live with your spouse or partner? [Yes/No]

4. Have you become divorced within the past 12 months? [Yes/No]

5. Have you become widowed within the past 12 months? [Yes/No]

6. Work Status: (during the past 3 months)
   - Working Full-time
   - Working Part-time
   - On Long-term Sick Leave
   - Homemaker
   - Retired
   - Disabled
   - Unemployed / Looking for Work
   - Temporarily Laid Off
   - Other

7. Highest Level of School Completed: (Fill in only one circle)
   - None or Some Grade School
   - Grade School
   - Some High School
   - High School Diploma
   - Some College, No Degree
   - Vocational or Tech School
   - Associate (2 year) Degree
   - Bachelors Degree
   - Masters Degree
   - Doctoral Degree
   - Other Advanced Degree

8. Annual Income: (fill in only one circle)
   - Less than $10,000
   - $10,000 to <$20,000
   - $20,000 to <$40,000
   - $40,000 to <$80,000
   - $80,000 or More
Appendix C: Heart SCORE Blood Pressure Data

Participant ID # [ ] [ ] [ ]
Date Form Completed [ ] / [ ] / 20 [ ]

Visit Schedule:
- 24 Months (2 yr)
- 36 Months (3 yr)
- 48 Months (4 yr)
- 60 Months (5 yr)
- 72 Month (6 yr)
- 84 Month (7 yr)
- 96 Month (8 yr)
- 108 Month (9 yr)
- 120 Month (10 yr)
- Other

3 a. Weight Type
- HeartScore
- Verbal
- Certified PCP
- Home Scale
- Certified Other
- Other

1. Date of Physical Exam [ ] / [ ] / 20

2. Weight (centimeters, no decimals) [ ] [ ] [ ]

3. Weight (kilograms, no decimals) [ ] [ ] [ ]

4. Waist Circumference (centimeters, no decimals) [ ] [ ] [ ]

5. Hip Circumference (centimeters, no decimals) [ ] [ ] [ ]

6. Has the participant gained or lost more than 5 kg (-10 lbs) in the past 3 months?
- No
- Yes, Loss Unintentional
- Yes, Gain Unintentional
- Yes, Loss Intentional
- Other

7. Site caliper measurements (in centimeters, no decimals)

**FEMALES**
- 7a. Tricep [ ] [ ] [ ]
- 7b. Iliac Crest [ ] [ ] [ ]
- 7c. Thigh [ ] [ ] [ ]

**MALES**
- 7a. Pectoral [ ] [ ] [ ]
- 7b. Abdomen [ ] [ ] [ ]
- 7c. Thigh [ ] [ ] [ ]

8. Resting Pulse (beats per minute – no decimals) [ ] [ ] [ ]

9. Sitting Systolic Blood Pressure (mmHg - no decimals) [ ] [ ] [ ]

10. Sitting Diastolic Blood Pressure [ ] [ ] [ ]

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date last modified-05/18/2009 Page 1 of 1

11. Blood Pressure Classification:
- Normal: Systolic <120 and Diastolic <80
- Pre-Hypertension 120-139 or 80-89
- Stage 1 Hypertension 140-159 or 90-99
- Stage 2 Hypertension ≥160 or ≥100
- Normal
- Prehypertensive
- Hypertensive Stage 1
- Hypertensive Stage 2

Note: Use the highest systolic BP

11047 51
Appendix D: Heart SCORE Blood Pressure Medication

Heart Score

Date of Test

Time of Test (military)

Visit Schedule:
- 24 Month (2 yr)
- 36 Month (3 yr)
- 48 Month (4 yr)
- 60 Month (5 yr)
- 72 Month (6 yr)
- 84 Month (7 yr)
- 96 Month (8 yr)
- 108 Month (9 yr)
- 120 Month (10 yr)
- 132 Month (11 yr)
- 144 Month (12 yr)
- 156 Month (13 yr)
- 168 Month (14 yr)
- 180 Month (15 yr)
- 192 Month (16 yr)
- 204 Month (17 yr)
- 216 Month (18 yr)
- 228 Month (19 yr)
- 240 Month (20 yr)
- Other

Medications taken within the past 48 hours (that may impact RA results):

1. Anti-Hypertensive
   - Yes
   - No

2. Are the RA test readings acceptable?
   - Yes
   - No

3. Lipid-Lowering
   - Yes
   - No

4. Aspirin
   - Yes
   - No

5. Anti-Angina/Ischemia Agent
   - Yes
   - No

6. Oral Hypoglycemic Agent
   - Yes
   - No

7. Insulin
   - Yes
   - No

8. Corticosteroid
   - Yes
   - No

9. NSAID
   - Yes
   - No

10. Anti-depressive agent
    - Yes
    - No

11. Anti-anxiety drug
    - Yes
    - No

12. Psychotropic drug
    - Yes
    - No

13. Estrogen
    - Yes
    - No

14. Estrogen and Progesterone
    - Yes
    - No

15. Sleep Medications
    - Yes
    - No

16. C-Pap or Bi-Pap
    - Yes
    - No

Test results:
- Heart Rate (bpm)
- Brachial Artery Diameter (mm)

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Appendix E: Heart SCORE Glucose and Lipids

Form No 9
Form Name LAB  v.4

Date of Blood Draw:

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**Participant ID #**

Date Form Completed:

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<td>20</td>
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**NOTE:** The blood draw should occur on the same day as the Brachial Artery (BA) test since the BA form collects data on which medications have been taken in the past 48 hours.

**Visit Schedule:**
- 24 Month (2 yr)  
- 36 Month (3 yr)  
- 48 Month (4 yr)  
- 60 Month (5 yr)  
- 72 Month (6 yr)  
- 84 Month (7 yr)  
- 96 Month (8 yr)  
- 108 Month (9 yr)  
- 120 Month (10 yr)  
- Other

**OTHER INTERNALLY DETERMINED LAB MEASURES:**

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<th>Total Cholesterol (mg/dL)</th>
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<tbody>
<tr>
<td>&gt; 500 = 501</td>
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<td>&lt;100 = 99</td>
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<table>
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<tr>
<th>HDL cholesterol (mg/dL)</th>
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<tr>
<td>(&gt;100= 101)</td>
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<tr>
<td>&lt;15 =14</td>
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<table>
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<tr>
<th>Glucose Fasting (mg/dL)</th>
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<td>49 =&lt;50</td>
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<tr>
<td>&gt; 500 =501</td>
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<tr>
<th>LDL (mg/dL)</th>
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<table>
<thead>
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<th>Triglycerides (mg/dl)</th>
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<tbody>
<tr>
<td></td>
<td>&gt; 650 = 651</td>
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<table>
<thead>
<tr>
<th>Creatinine (mg/dl)</th>
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<table>
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<tr>
<th>Urinary albumin (g/dL)</th>
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**date last modified-05/18/2009**

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Appendix F: Heart SCORE Smoking Status

Heart Score

Form No. 11
Form Name OTHER LIFESTYLE

Date Form Completed

Visit Schedule:
- 24 Month (2 yr)
- 30 Month (2.5 yr)
- 36 Month (3 yr)
- 42 Month (3.5 yr)
- 48 Month (4 yr)
- 54 Month (4.5 yr)
- 60 Month (5 yr)
- 66 Month (5.5 yr)
- 72 Month (6 yr)
- 78 Month (6.5 yr)
- 84 Month (7 yr)
- 90 Month (7.5 yr)
- 96 Month (8 yr)
- 102 Month (8.5 yr)
- 108 Month (9 yr)
- 114 Month (9.5 yr)
- 120 Month (10 yr)
- Other

1. Smoking Status:
- Current Smoker
- Former Smoker
- Never Smoker

ia. If current smoker, are you willing to quit? Yes No

ib. If current smoker, have you tried previous cessation treatments within the past 3 months? Yes No

If yes, have you tried any of the following smoking cessation treatments:
- Practical Counseling Yes No
- Bupropion (Wellbutrin) Yes No
- Nicotine Replacement Therapy Yes No

Smoking Cessation Program Yes No
Other Yes No

2. During the past 3 months, have you consumed an average of ≥ 1 alcoholic beverage per week? Yes No

Answers must be in whole numbers (no symbols)
2a. On Average, number of 12 oz bottle/cans of beer consumed per week
2b. On Average, number of 4 oz glasses of wine consumed per week
2c. On Average, number of 1.5 oz shots of hard liquor or mixed drinks per week

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Appendix G: Heart SCORE Family History of Cardiac Event

Form No. 4

Form Name: DEMO AND MEDICAL HISTORY

9. How hard is it for you to pay for the very basics like food, housing, medical care, & heating?
   ○ Very hard
   ○ Somewhat hard
   ○ Not very hard at all
   ○ Don't know

10. Primary Method of Insurance: (Fill in only one circle)
   ○ Medicare
   ○ Medicaid
   ○ Other Public (e.g. VA)
   ○ Private (e.g. HMO, Blue Cross)
   ○ None / Self Pay

11. If Female, Menopausal Status: (Fill in only one circle)
   ○ Pre-Menopause
   ○ Peri-Menopause
   ○ Post-Menopause
   ○ Surgical Menopause
   ○ Hysterectomy, No Ovaries Removed

12. If Female, Hormone use in the past 3 months: (Fill in only one circle)
   ○ None
   ○ Estrogen / Progesterone
   ○ Estrogen Only
   ○ Other HRT

13. QOL: In General, Would you say that your health is:
   ○ Excellent
   ○ Very Good
   ○ Fair
   ○ Poor
   ○ Good

Family History of CAD/Sudden Death:

14. Before Age 55 in Male First Degree Relative: ○ Yes ○ No ○ Unknown
15. Before Age 65 in Female First Degree Relative: ○ Yes ○ No ○ Unknown

Has a physician or other health care provider ever told you that you have any of the following conditions:

16. History of Hypertension: ○ Yes ○ No

16a. If Yes, Previous Drug Therapy: ○ Yes ○ No
## Appendix I: Heart SCORE Follow-Up Events

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<tr>
<td>Visit Schedule: (fill in only one circle)</td>
</tr>
<tr>
<td>○ 24 Month (2 yr)</td>
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<tr>
<td>○ 30 Month (2.5 yr)</td>
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<tr>
<td>○ 36 Month (3 yr)</td>
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<td>○ 42 Month (3.5 yr)</td>
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<td>○ 90 Month (7.5 yr)</td>
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<tr>
<td>○ 96 Month (8 yr)</td>
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<tr>
<td>○ 102 Month (8.5 yr)</td>
</tr>
<tr>
<td>○ 108 Month (9 yr)</td>
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</table>

**Events:** Since the last follow-up assessment or since study entry, has the subject experienced any of the following?

1. **Death**
   - [ ] Yes
   - [ ] No
   - Date (First occurrence)

   If yes, fill out form 27 SAE and form #23 Study Closure

2. **Any in-patient hospitalization**
   - [ ] Yes
   - [ ] No
   - Date of First Occurrence

   - **2a. For Unstable Angina**
     - [ ] Yes
     - [ ] No
     - Positive test result
   - **2b. For Acute Ischemic Syndrome**
     - [ ] Yes
     - [ ] No
     - Positive test result
   - **2c. For Other CVD condition**
     - [ ] Yes
     - [ ] No
     - Positive test result
   - **2d. Non Cardiac Condition**
     - [ ] Yes
     - [ ] No

3. **Out-patient hospitalization (i.e. day surgery)**
   - [ ] Yes
   - [ ] No
   - Date (First Occurrence)

4. **Documented MI**
   - [ ] Yes
   - [ ] No
   - Date of First Occurrence

5. **Suspected MI**
   - [ ] Yes
   - [ ] No
   - Date of First Occurrence

6. **Chest pain or shortness of breath requiring non-hospital physician assessment**
   - [ ] Yes
   - [ ] No
   - Date of First Occurrence

7. **Diagnostic cardiac catheterization**
   - [ ] Yes
   - [ ] No
   - Date of First Occurrence

8. **Percutaneous Coronary Intervention (PCI)**
   - [ ] Yes
   - [ ] No
   - Date of First Occurrence

Check when scanned
Form No. 21
Form Name FOLLOW UP EVENT

Date __/__/____

9. Coronary bypass surgery (CABG)  ☐ Yes  ☐ No
   If yes, fill out form #27, serious adverse event

10. Cerebrovascular accident (stroke)  ☐ Yes  ☐ No
    If yes, fill out form #27, (serious adverse event)

11. Carotid stent or surgery  ☐ Yes  ☐ No
    If yes, fill out form #27, (serious adverse event)

12. Non-coronary vascular surgery  ☐ Yes  ☐ No

13. New onset/diagnosed malignancy  ☐ Yes  ☐ No
    If yes, fill out form #27, (serious adverse event)

14. Current primary method of insurance
    ☐ Medicare  ☐ Private(e.g. HMO, Blue Cross)
    ☐ Medicaid  ☐ None/Self-Pay
    ☐ Other Public(e.g. VA)

    If address or phone has changed, provide the new changes here.

    ___________________________________________________________
    ___________________________________________________________
    ___________________________________________________________

Comments:

    ___________________________________________________________
    ___________________________________________________________
    ___________________________________________________________

Via Mail / Interviewer Initials [ ] [ ]

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Appendix J: Framingham Cardiovascular Risk Score

Table J1. Regression Coefficients and Hazard Ratios—Primary Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta^a</th>
<th>p</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong> (10-year Baseline Survival: So(10) = 0.88936)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log of age</td>
<td>3.06117</td>
<td>&lt;.0001</td>
<td>21.35</td>
<td>(14.03, 32.48)</td>
</tr>
<tr>
<td>Log of Total cholesterol</td>
<td>1.12370</td>
<td>&lt;.0001</td>
<td>3.08</td>
<td>(2.05, 4.62)</td>
</tr>
<tr>
<td>Log of HDL cholesterol</td>
<td>-0.93263</td>
<td>&lt;.0001</td>
<td>0.40</td>
<td>(0.30, 0.52)</td>
</tr>
<tr>
<td>Log of SBP if not treated</td>
<td>1.93303</td>
<td>&lt;.0001</td>
<td>6.91</td>
<td>(3.91, 12.20)</td>
</tr>
<tr>
<td>Log of SBP if treated</td>
<td>1.99881</td>
<td>&lt;.0001</td>
<td>7.38</td>
<td>(4.22, 12.92)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.65451</td>
<td>&lt;.0001</td>
<td>1.92</td>
<td>(1.65, 2.24)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.57367</td>
<td>&lt;.0001</td>
<td>1.78</td>
<td>(1.43, 2.20)</td>
</tr>
</tbody>
</table>

| **Women** (10-year Baseline Survival: So(10) = 0.95012)          |        |         |              |              |
| Log of age                | 2.32888| <.0001  | 10.27       | (5.65, 18.64) |
| Log of Total cholesterol  | 1.20904| <.0001  | 3.35        | (2.00, 5.62)   |
| Log of HDL cholesterol    | -0.70833| <.0001  | 0.49        | (0.351, 0.691) |
| Log of SBP if not treated | 2.76157| <.0001  | 15.82       | (7.86, 31.87)  |
| Log of SBP if treated     | 2.82263| <.0001  | 16.82       | (8.46, 33.46)  |
| Smoking                   | 0.52873| <.0001  | 1.70        | (1.40, 2.06)   |
| Diabetes                  | 0.69154| <.0001  | 2.00        | (1.49, 2.67)   |

^b The 10-year risk for women can be calculated as $1 - 0.95012^{\exp(\beta X - 26.1931)}$ where $\beta$ is the regression coefficient and $X$ is the level for each risk factor; the risk for men is given as $1 - 0.88936^{\exp(\beta X - 23.9802)}$

^a Estimated regression coefficient
Appendix K: Reynolds Risk Scores

Reynolds Risk Score for Women

10-year cardiovascular disease risk (%) = \([1 - 0.98634(\exp(0.0799\text{_age} - 3.137\text{_natural\ logarithm (systolic blood pressure)} - 0.180\text{_natural\ logarithm (high-sensitivity C-reactive protein)} - 1.382\text{_natural\ logarithm (total cholesterol)} - 1.172\text{_natural\ logarithm (high-density lipoprotein cholesterol)} - 0.134\text{_hemoglobin A1c (\% if diabetic)} - 0.818\text{_(if current smoker)} - 0.438\text{(if family history of premature myocardial infarction)})]\] x 100%

Reynolds Risk Score Men

10-year cardiovascular disease risk (%) = \([1 - 0.8990 (\exp(4.385\text{x\ natural\ logarithm(age)} + 2.607\text{x\ natural\ logarithm(systolic\ blood\ pressure)} + 0.963\text{x\ natural\ logarithm(total\ cholesterol)} - 0.772\text{x\ natural\ logarithm(high-density\ lipoprotein\ cholesterol)} + 0.405\text{(if\ current\ smoker)} + 0.102\text{x\ natural\ logarithm(high-sensitivity\ C-reactive\ protein)} + 0.541\text{(if\ parental\ history\ of\ premature\ myocardial\ infarction)})]\) x 100%
### Table L.1.

Equation Parameters of the Pooled Cohort Equations for Estimation of 10-Year Risk for Hard ASCVD* and Specific Examples for Each Race and Sex Group

<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>African American</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Coefficient</strong></td>
<td><strong>Individual Example Value</strong></td>
</tr>
<tr>
<td>Ln Age (y)</td>
<td>–29.799</td>
<td>4.01</td>
</tr>
<tr>
<td>Ln Age Squared</td>
<td>4.884</td>
<td>16.06</td>
</tr>
<tr>
<td>Ln Total Cholesterol</td>
<td>13.540</td>
<td>5.36</td>
</tr>
<tr>
<td>Ln Age×Ln Total</td>
<td>–3.114</td>
<td>21.48</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ln HDL-C (mg/dL)</td>
<td>–13.578</td>
<td>3.91</td>
</tr>
<tr>
<td>Ln Age×Ln HDL-C</td>
<td>3.149</td>
<td>15.68</td>
</tr>
<tr>
<td>Log Treated Systolic BP</td>
<td>2.019</td>
<td>–</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log Age×Log Treated</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Systolic BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log Untreated Systolic BP</td>
<td>1.957</td>
<td>4.79</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log Age×Log Untreated</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Systolic BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Smoker (1=Yes, 0=No)</td>
<td>7.574</td>
<td>0</td>
</tr>
<tr>
<td>Log Age×Current Smoker</td>
<td>–1.665</td>
<td>0</td>
</tr>
</tbody>
</table>

*ASCVD: Atherosclerotic Cardiovascular Disease

Example: 55 years of age with total cholesterol 213 mg/dL, HDL-C 50 mg/dL, untreated systolic BP 120 mm Hg, nonsmoker, and without diabetes
### Table L1 (continued)

<table>
<thead>
<tr>
<th>Diabetes (1=Yes, 0&gt;No)</th>
<th>0.661</th>
<th>0</th>
<th>0</th>
<th>0.874</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual Sum</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.874</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean (Coefficient×Value)</td>
<td>N/A</td>
<td>N/A</td>
<td>-29.18</td>
<td>N/A</td>
<td>N/A</td>
<td>86.61</td>
</tr>
<tr>
<td>Baseline Survival</td>
<td>N/A</td>
<td>N/A</td>
<td>0.9665</td>
<td>N/A</td>
<td>N/A</td>
<td>0.9533</td>
</tr>
<tr>
<td>Estimated 10-Y Risk for hard ASCVD</td>
<td>N/A</td>
<td>N/A</td>
<td>2.1%</td>
<td>N/A</td>
<td>N/A</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

**Men** (Example: 55 years of age with total cholesterol 213 mg/dL, HDL-C 50 mg/dL, untreated systolic BP 120 mm Hg, non-smoker, and without diabetes)

<table>
<thead>
<tr>
<th>Log Age (y)</th>
<th>12.344</th>
<th>4.01</th>
<th>49.47</th>
<th>2.469</th>
<th>4.01</th>
<th>9.89</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Total Cholesterol (mg/dL)</td>
<td>11.853</td>
<td>5.36</td>
<td>63.55</td>
<td>0.302</td>
<td>5.36</td>
<td>1.62</td>
</tr>
<tr>
<td>Log Age×Log Total Cholesterol</td>
<td>-2.664</td>
<td>21.48</td>
<td>-57.24</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Log HDL-C (mg/dL)</td>
<td>-7.990</td>
<td>3.91</td>
<td>-31.26</td>
<td>-0.307</td>
<td>3.91</td>
<td>-1.20</td>
</tr>
<tr>
<td>Log Age×Log HDL-C</td>
<td>1.769</td>
<td>15.68</td>
<td>27.73</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Log Treated Systolic BP (mm Hg)</td>
<td>1.797</td>
<td>-</td>
<td>-</td>
<td>1.916</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Log Untreated Systolic BP (mm Hg)</td>
<td>1.764</td>
<td>4.79</td>
<td>8.45</td>
<td>1.809</td>
<td>4.79</td>
<td>8.66</td>
</tr>
<tr>
<td>Current Smoker (1=Yes, 0&gt;No)</td>
<td>7.837</td>
<td>0</td>
<td>0</td>
<td>0.549</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Log Age×Current Smoker</td>
<td>-1.795</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Diabetes (1=Yes, 0&gt;No)</td>
<td>0.658</td>
<td>0</td>
<td>0</td>
<td>0.645</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Individual Sum</td>
<td>60.69</td>
<td>18.97</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (Coefficient×Value)</td>
<td>N/A</td>
<td>N/A</td>
<td>61.18</td>
<td>N/A</td>
<td>N/A</td>
<td>19.54</td>
</tr>
<tr>
<td>Baseline Survival</td>
<td>N/A</td>
<td>N/A</td>
<td>0.9144</td>
<td>N/A</td>
<td>N/A</td>
<td>0.8954</td>
</tr>
</tbody>
</table>

*Note. Table retrieved May 5, 2014, from http://circ.ahajournals.org.*
The hypothetical profile provided in Table 5 (the "Individual Example Value" column) is identical for each race and sex group and is based on the overall sample mean. The profile assumes an individual 55 years of age (for which the $\ln(Age)=4.01$), with a total cholesterol of 213 mg/dL, HDL-C of 50 mg/dL, and an untreated systolic BP of 120 mm Hg. This individual is not a current smoker and does not have diabetes. For the equations, the values for age, lipids, and systolic BP are log transformed. Interactions between age and lipids or age and systolic BP use the natural log of each variable (e.g., $\ln(Age)=\ln(Total\ Cholesterol)$).

Calculation of the 10-year risk estimate for hard ASCVD can best be described as a series of steps. The natural log of age, total cholesterol, HDL-C, and systolic BP are first calculated with systolic BP being either a treated or untreated value. Any appropriate interaction terms are then calculated. These values are then multiplied by the coefficients from the equation ("Coefficient" column of Table A) for the specific race-sex group of the individual. The "Coefficient×Value" column in the table provides the results of the multiplication for the risk profile described above.

The sum of the "Coefficient×Value" column is then calculated for the individual. For the profile shown in Table A, this value is shown as "Individual Sum" for each race and sex group.

The estimated 10-year risk of a first hard ASCVD event is formally calculated as 1 minus the survival rate at 10 years ("Baseline Survival" in Table A), raised to the power of the exponent of the "Coefficient×Value" sum minus the race and sex specific overall mean "Coefficient×Value" sum; or, in equation form:

$$1 - S_{10} e^{(\text{IndivSum}-\text{MeanSum})}$$

Using White men as an example:

$$1 - 0.9144 e^{(60.69 - 61.13)}$$

equates to a 5.3% probability of a first hard ASCVD event within 10 years.

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; and HDL-C, high-density lipoprotein cholesterol.

**Figure L1.** Estimating an individual’s 10-year risk for incident hard ASCVD.
Appendix M: Institutional Review Board Approval

2/2/2015

Kevin Kip, Ph.D. College of Nursing 12901 Bruce B. Downs Blvd., MDC 22 Tampa, FL 33612-4766

RE: Expedited Approval for Initial Review

IRB#: Pro00002213

Title: Secondary Data Analyses of the Heart Strategies Concentrating on Risk Evaluation (Heart SCORE) Limited Dataset

Study Approval Period: 1/31/2015 to 1/31/2016

Dear Dr. Kip:

On 1/31/2015, the Institutional Review Board (IRB) reviewed and APPROVED the above application and all documents outlined below.

Approved Item(s): Protocol Document(s): Kip Protocol for Secondary Data Analyses Univeristy of Pittsburgh Protocol for Main Study

It was the determination of the IRB that your study qualified for expedited review which includes activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the categories outlined below. The IRB may review research through the expedited review procedure authorized by 45CFR46.110 and 21 CFR 56.110. The research proposed in this study is categorized under the following expedited review category:

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or (b) from other adults and children, considering the age,
weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Your study qualifies for a waiver of the requirements for the informed consent process as outlined in the federal regulations at 45 CFR 46.116 (d) which states that an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent provided the IRB finds and documents that (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

As the principal investigator of this study, it is your responsibility to conduct this study in accordance with IRB policies and procedures and as approved by the IRB. Any changes to the approved research must be submitted to the IRB for review and approval by an amendment.

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,

E. Verena Jorgensen, M.D., Chairperson USF Institutional Review Board

V. Jorgensen MD