# Abdominal Aortic Sonography as a Cardiovascular Disease Risk Assessment

Thesis

Presented in Partial Fulfillment of the Requirements for the Degree Master of Science in the Graduate School of The Ohio State University

By

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2022

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## Abstract

Cardiovascular disease (CVD) is a group of disorders affecting the heart and blood vessels. This insidious pathology is the leading cause of death in the United States, accounting for 868,662 deaths in 2017.[1] The prevalence of this disease is expected to increase, with 45.1% of the population expected to have some form of CVD by 2035.[1] Aside from the growing health concern, CVD is also the costliest chronic disease in the country, projected to hit 1.1 trillion dollars in total cost by 2035.[2] This information underscores the importance of advancing CVD detection and primary prevention.

Current CVD risk assessment usually relies on clinical prediction models that estimate a patient's risk of having a CVD event in the future. The most recent recommendation for assessing risk of CVD in asymptomatic populations, is the use of the pooled cohort equations (PCE) atherosclerotic cardiovascular disease (ASCVD) risk estimator.[7] Many patients who are evaluated using these clinical prediction models end up needing a more refined risk assessment to develop the most appropriate care plan. For this purpose, coronary artery calcium (CAC) scoring with computed tomography is the most widely used. While these tools are well validated, they are not without limitations. The need for new, non-invasive, accessible, relatively inexpensive, and low-risk CVD assessment tools is vital to further improve detection and prevention.

This project explored the use of abdominal aortic sonography for use as a CVD risk assessment tool. Participants provided their imaging and health data in order to both evaluate the feasibility of using sonography to assess atherosclerotic plaque burden in the abdominal aorta, and explore associations between the imaging data and traditional CVD risk factors. After developing an imaging protocol and novel grading system, abdominal aortic sonography was proven to be a reliable, and practical method of measuring atherosclerotic burden in the inferior portion of the aorta. Statistically significant moderate associations were found between sonographic measures of atherosclerosis and several traditional CVD risk factors. Abdominal aortic sonography is a practical, accessible, and relatively low cost diagnostic tool, but further research is needed to definitively prove it can be appropriate for improving risk assessment of CVD.

## Dedication

This work is dedicated to my children, Olivia and Owen. Everything I do, the person I am, and the person I strive to be, is all for them. I can only hope that one day they will grow to develop an appreciation and passion for science and knowledge, just as I have. Even if not, they will still be loved unconditionally for the rest of my days.

## Acknowledgments

I would like to express my great appreciation for my committee members, Dr. Funderburg, Dr. Evans, and Dr. Taylor. I am thankful for their help, expertise, wisdom, and feedback. I am truly appreciative for the support and motivation that has guided me along the way.

A special thank you is owed to Dr. Kevin Evans who gave me the opportunity to be shown the incredible world of research when I was welcomed into his group. Without his guidance and continued encouragement, I am certain I would not be where I am today. Not only is he a remarkable mentor and colleague, but a true friend. Thank you.

Finally, I would also like to thank my wife, Samantha. Without her support this accomplishment would not have been possible.

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Bloom IW, Evans KD, Brady AN, Stigall-Weikle AN. Preventive Health Screening for Women at Risk for Cardiovascular Disease: Targeting Women 40 to 64 Years of Age. Journal of Diagnostic Medical Sonography. 2022 August. doi:10.1177/87564793221116295. In Press.

Stigall-Weikle N, Brady AN, Yang Q, Bloom IW, Evans KD. Sonographic cardiovascular assessment of the aorta: pilot of a modified image grading system. Journal of Diagnostic Medical Sonography. 2021 May;37(3):223-30.

## Fields of Study

Major Field: Health and Rehabilitation Sciences

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# Chapter 1. Introduction

## 1.1 Overview

Cardiovascular disease (CVD) is highly prevalent among adults in the United States. So prevalent in fact, that it is the leading cause of death, accounting for approximately 868,662 deaths in 2017.[1] Despite the known threat that CVD poses, its prevalence is forecasted to increase in the years ahead. By 2035, 45.1% of the U.S. population is forecasted to have some form of CVD, which is an increase from 41.5% in 2015.[2] Apart from the human toll this disease inflicts, CVD is also the costliest chronic disease in the country. The total cost of CVD is projected to hit 1.1 trillion dollars by 2035. This is double the total cost of 555 billion that was reported in 2015.[2] Limiting the burden imposed by this insidious condition will require the development of effective research, prevention, and treatment strategies.

CVD is a group of disorders affecting the heart and blood vessels. Some of these conditions include, but are not limited to heart attack, stroke, arrhythmia, and heart valve problems.[3] Many of these CVD conditions can be attributed to a disease process known as atherosclerosis. Atherosclerosis is the narrowing of an artery that forms due to a buildup of cholesterol, blood cells, and other substances inside the arterial wall. This buildup is referred to as “plaque”. The plaque may start to form during childhood and progresses as a person ages. When calcium is deposited within the plaque, it

becomes known as “calcification”.[4] As this plaque develops, it may cause arterial wall thickening and stenosis of the blood vessel. The lesion could also rupture which may potentially lead to a thrombotic event.[5] Prevention and early detection of atherosclerosis could hold the key to reducing the number of deaths attributed to CVD.

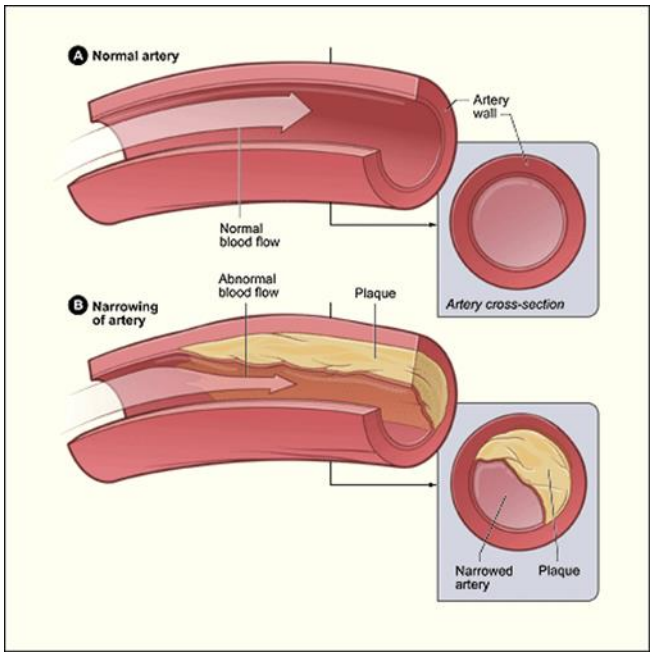


Figure 1. Atherosclerotic plaque formation causing abnormal blood flow.[4]

Many researchers and organizations have come together to develop a better understanding of CVD risk. The studies conducted have been vital in putting emphasis on the risk factors that better predict CVD. The risk factors that are currently considered significant are high blood pressure, elevated low-density lipoprotein (LDL) cholesterol, decreased high-density lipoprotein (HDL) cholesterol, elevated total cholesterol, diabetes, obesity, age, and family history.[1,6] Some lifestyle behaviors have also been noted as increasing the risk of CVD which include, lack of physical activity, poor nutrition, stress, and tobacco use.[1,6] Some of these factors, such as age and family

history, are difficult to control for medically. However, it will be important for healthcare providers to identify individuals who are at a higher risk for CVD as most of the risk factors listed are modifiable.

## 1.2 Current CVD Risk Assessment Methods

An accurate risk assessment for the future potential of CVD events is paramount to the successful management and treatment of patients who may be at intermediate or high risk. Furthermore, an accurate assessment could also protect patients at low risk from having unnecessary and costly medical procedures performed on them. The importance of a quality CVD risk assessment is underscored by the recommendation from both the American College of Cardiology (ACC) and the American Heart Association (AHA) for adults between the ages of 20 and 79 to have a CVD risk assessment and reassessment every 4 to 6 years.[7] Many CVD risk assessments have been developed and several have been widely adopted by healthcare practitioners as the result of this directive.

One of the most widely used and well-validated CVD risk assessment tools is the Framingham risk score (FRS). The FRS predicts the absolute risk of cardiac events in populations that are asymptomatic of CVD. These predictions are made from calculations based on easily obtained patient metrics such as age, sex, blood pressure, cholesterol levels, and patient history.[8] Although the FRS has been validated through extensive clinical use, it is not without its limitations. The FRS overestimates risk in certain populations and is not appropriate for use in patients with known diabetes.[9]

The most recent recommendation from the ACC and AHA for assessing risk of CVD in asymptomatic populations points to the pooled cohort equations atherosclerotic cardiovascular disease (ASCVD) risk estimator.[7] This estimator is a sex and race-specific tool that uses many of the same metrics the FRS does, in conjunction with other variables such as use of anti-hypertensive medication and diabetes status, to predict the 10-year absolute risk of ASCVD events.[10] These risk estimates can then be used to make recommendations for preventative therapies such as lifestyle modification and statin medication.[7,11] While this particular risk estimator is more broadly applicable than the FRS, it also has documented issues with overestimating risk on occasion in some populations.[10,12]

Many patients evaluated by clinical prediction models like the ones described here, often fall in to an intermediate risk category (See Appendix A for scoring tables). A borderline or intermediate risk prediction prompts the use of further non-invasive diagnostic tests to better refine the risk assessment.[7,13] The ACC/AHA guidelines have stated that coronary artery calcium (CAC) scoring, under computed tomography (CT) is currently the most useful approach to improve risk assessment in the intermediate risk populations.[7] In fact, CAC scoring has shown to outperform many other markers of CVD risk.[13] CAC scoring uses CT to detect the burden of coronary artery calcifications and quantifies it numerically. A score of 0 represents the absence of calcifications and a low risk of a CVD event. As this numerical CAC score rises, so does the risk of having a CVD event in the next 10 years (See Appendix A for scoring tables). Although very reliable, there are certainly some undeniable disadvantages to

this assessment method which include cost, and the exposure to potentially harmful ionizing radiation.[14]

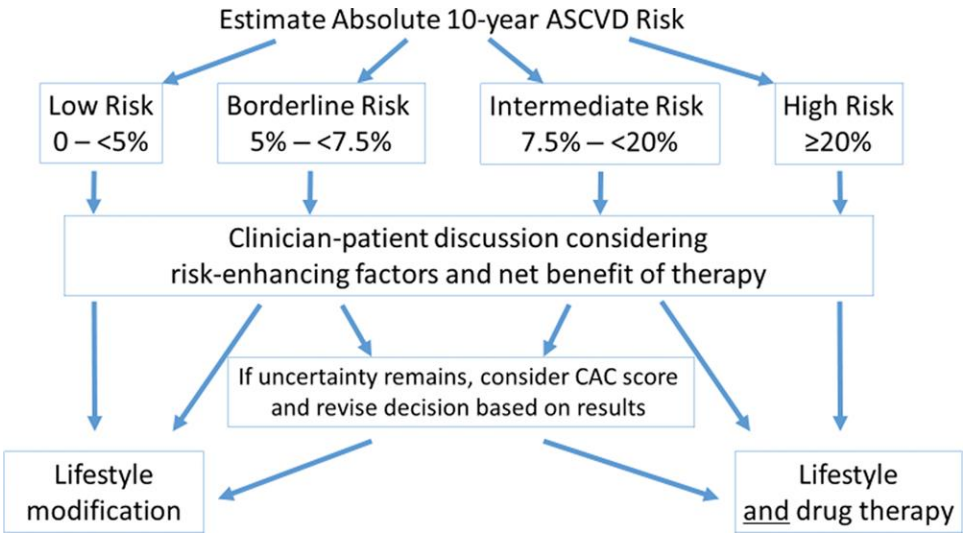


Figure 2. Current approach to risk assessment and decision making in the primary prevention of ASCVD.[15]

## 1.3 Objectives

Prevention of CVD and its associated events is a preeminent way to reduce the massive burden imposed by the disease, both globally and within the United States. Primary prevention of CVD not only decreases the chances of cardiovascular events, but has also been shown to be more cost effective when compared to secondary prevention strategies.[16] A large part of this prevention strategy is the risk assessment and stratification of individuals who are asymptomatic. As such, an incredible amount of research and resources have been used to develop and further refine the assessment techniques that are currently used in clinical practice today.

While much progress has been made in the area of CVD risk assessment and primary prevention, further empirical evidence is needed to advance risk prediction

capabilities, positively influence the prevention of CVD events, and aid in the development of individualized care plans for patients. Furthermore, new tools for CVD assessment should ideally be non-invasive, accessible, relatively inexpensive, and low-risk. Sonographic assessment of the abdominal aorta may hold the key to satisfying this very important need.

The objectives of this study are to examine current CVD risk assessments and identify gaps, develop a method for effectively documenting the atherosclerotic plaque burden of the abdominal aorta under ultrasound, and explore associations between sonographically measured abdominal aortic plaque burden and traditional risk factors. A literature search is needed to determine where research gaps may exist, identify a specific research question, and ascertain appropriate variables to explore.

# Chapter 2. Literature Review

## 2.1 Literature Review Methodology

To gain a greater understanding of CVD risk assessment practices, a literature review was conducted. The search was conducted using the PubMed database and Google Scholar search engine. The keywords and medical subject headings (MeSH) used for the search were specific to CVD, its associated risks and assessments, which included: cardiovascular disease; atherosclerosis; assessment; risk stratification; calcification; imaging; and aorta. The articles extracted for this review highlighted numerous techniques and the extreme importance of cardiovascular screening. However, this review also uncovered the need for the further research and development to enhance the current clinical standards for CVD assessment.

## 2.2 Popular CVD Risk Assessments

### 2.2.1 Cholesterol levels

CVD and the adverse events associated with it are known to be one of the deadliest pathologies. As such, it comes as no surprise that many screening methods have been tested and implemented into clinical practice. Among the first of the widely accepted CVD screening tools was the use of individual measure of blood lipids levels, specifically total cholesterol, LDL, and HDL. Several cohort studies have demonstrated that elevated levels of total cholesterol and LDL, and decreased levels of

HDL, do well in predicting premature coronary heart disease in humans.[17-19] While these studies provided an excellent foundation for CVD assessment, atherosclerotic development and CVD is known to be quite complex and there are a number of other factors that play into an individual risk of future CVD events.

2.2.2 Risk Calculators

Several risk calculators have been developed in an attempt to quantify CVD risk more holistically, rather than simply using cholesterol levels. The Framingham Risk Score is a risk assessment tool developed from the decades-long Framingham Heart study. Another such calculator is the pooled cohort equations (PCE) atherosclerotic cardiovascular disease (ASCVD) risk estimator. Both of these tools use not only patient cholesterol levels, but a multitude of other factors like blood pressure, age, and sex to calculate the 10-year risk of cardiovascular events.[8,10] Because these calculators are so widely used, their accuracy and impact has been the subject of great scrutiny.

Systematic reviews of the FRS specifically have shown mixed results. One systematic review that included 25 validation cohorts, concluded that the FRS performed well in predicting coronary events in populations from the United States, Australia, and New Zealand, but overestimated the absolute risk for Europeans.[9] Another such prospective review of 6 cohorts found that FRS prediction functions performed well in Caucasian and black populations, but would need recalibrated if it were to be used for other ethnic groups.[20] A third review of 27 different studies was much more critical of the FRS, concluding that its performance varies considerably

between populations and that there is scarce evidence supporting its use for primary prevention.[21]

The PCE ASCVD risk estimator was developed more recently than the FRS, so the body of research attempting to validate its efficacy is not quite as robust, but still substantial. One large U.S. study of 10,997 participants sought to assess calibration and discrimination of the PCE ASCVD risk estimator. This study found that, over 5 years, the observed ASCVD risks were similar to those that were predicted by the tool. The authors concluded that the ASCVD risk estimator was well calibrated to the population it was designed for, as well as having moderate to good discrimination in rank ordering individuals into appropriate risk groups.[22] Another study even compared the performance of the FRS to the PCE ASCVD tool to determine which better identified subclinical vascular disease in blacks versus whites. There were 1,231 asymptomatic individuals enrolled in this trial. The results showed that the ASCVD risk estimator not only accounted for racial differences in vascular structure and function, but was a better predictor of both subclinical and clinical CVD risk, especially in black populations.[23] Although positive results for the PCE ASCVD risk estimator were reported in the two studies described, this risk estimator does have some issues with overestimating risk. Another large study with 37,311 participants provided further evidence that the ASCVD risk estimator was well calibrated and had acceptable discrimination, but it overestimated the risk for overweight and obese individuals, particularly in the high risk groups.[10] Both in a large cohort (n= 1,672,336) and a smaller cohort (6,441) it was noted that the ASCVD risk estimator overestimated risk

across all populations and cautioned that this could adversely affect prevention and intervention decisions.[24,25]

The overestimation of risk appeared to be a trend that was reported based on the use of CVD risk calculators in studies. A systematic review and meta-analysis of 38 published studies that involved three different types of risk calculators, including the FRS and the PCE ASCVD, found that while all of them were able to discriminate comparably well, they all overestimated the 10-year risk of CVD, especially in higher risk groups.[26] This sweeping overestimation certainly has the potential to drive a patient's care plan in a manner that may not be the most advantageous for them. A recent Cochrane systematic review of 41 randomized control trials concerning the use of CVD risk estimators in primary prevention, indicated without evidence of harm, the use of these tools lead to increased prescribing of lipid-lowering and antihypertensive medications. Aside from this possibly negative finding, the review also noted a statistically significant, but modest effect on reducing CVD risk factors when CVD risk scores were provided, versus the usual care.[27]

### 2.2.3 Coronary Artery Calcium Scoring

With mixed results on the usefulness and accuracy of CVD risk calculators, it would make sense for a clinician to want to further explore an individual's true risk of having a CVD event, especially if they fell in to an intermediate risk category. It is important to refine these risk stratifications to be able to develop an appropriate care plan for a patient. For this reason, the ACC/AHA have recommended CT CAC to improve risk assessment in intermediate risk populations.[7]

CAC scoring employs CT to detect the burden of coronary artery calcifications and quantifies it numerically, with a score of 0 signifying the absence of calcific plaque. This number increases with increased calcific plaque burden. Initially, two long-term population based studies, with populations of 6,814 and 4,200, provided substantial evidence that there was a strong association between CAC and cardiovascular outcomes in asymptomatic individuals.[28,29] Since then, a large body of evidence has been produced which suggests CAC scoring is a superior method for assessing atherosclerotic disease and its risks, across many populations. More so than the use of standard risk factors, biomarkers, or other imaging techniques such as the sonographic measurement of carotid-intima-media thickness (CIMT).[30-34] A recent review of studies from the largest CAC scoring cohort assembled (n=66,636), known as the CAC consortium, confirmed that CAC is a reliable and consistent predictor of CVD across all traditional cardiovascular risk levels.[35] Figure 3 demonstrates the vast body of work surrounding the CAC consortium.[35]

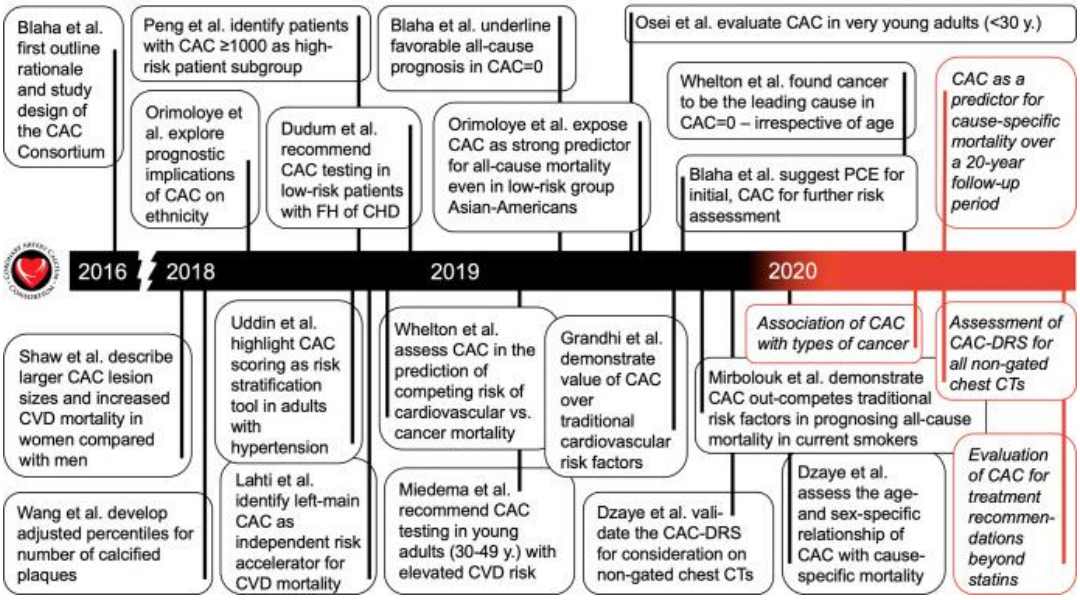


Figure 3. Timeline of studies published in the framework of the coronary artery calcium (CAC) Consortium.

While CT CAC is a well-documented tool for assessing CVD risk, it is not without some documented disadvantages. In regards to interpreting CAC scoring with CT, there are several factors that could potentially lead to inaccuracies. Patient motion, non-coronary calcium, and artifacts from adjacent structures can all lead to an incorrect CAC score.[36] CAC scoring also exposes a patient to potentially harmful ionizing radiation. Performed with modern CT equipment systems and protocols, a CAC CT involves a radiation dose of 1 to 2 millisieverts.[36,37] While this dose poses a minimal health risk from radiation exposure, it is not a zero risk. With a CAC CT, a patient may also incur some out-of-pocket costs and the potential for increased anxiety. A coronary CT typically carries a cost between $50 and $350 and is not usually covered by insurance companies. Aside from this, incidental findings on coronary CT are not uncommon, and while usually benign, often require follow up examinations.[38] These

costs, coupled with travel to a facility that has CT equipment, may be prohibitive for some, thus making CAC CT inaccessible to parts of the population.

## 2.3 Alternative Imaging Approaches

The commonly used risk assessment tools described above are well validated and have proven to be quite useful in clinical practice. However, they are not without their disadvantages and pitfalls. CVD risk calculators and CT CAC scoring are confined to estimating risk from traditional risk factors and calcific plaque burden in the coronary arteries. A sample of 2,408 patients from the population-based Rotterdam study found that increased risk of death was associated with atherosclerotic burden in many major arterial beds, not just the coronary arteries.[39] Due to this combination of factors, it would make sense that alternative blood vessels, and methods of imaging them, would be evaluated in their ability to assess CVD risk.

### 2.3.1 Ionizing Techniques

CAC CT relies on the presence of calcific plaque to determine a risk score for the patient. This could be seen as perhaps not the most appropriate measure of CVD risk, given calcium deposits within the arterial wall represent a healing process leading to plaque stabilization.[40] On the contrary, non-calcified plaques, which are not visualized with CAC CT, are more likely to rupture, leading to a CVD event.[41] Coronary computed tomography angiography (CCTA) is a newer CT modality that has the ability to visualize both calcified and non-calcified plaque, along with the extent of luminal stenosis. However, many of the techniques used to supplement CCTA with physiological data, to determine the risk of a CVD event, are still investigational.[42]

CCTA also caries all of the disadvantages stated for CAC CT, in addition to an added risk to the patient with the use of contrast media. Furthermore, CCTA has the potential to lead to increased use of invasive procedures such as percutaneous coronary angiography and revascularization.[43] This further exacerbates the risk and cost prohibition associated with CT-based risk assessment.

CT has been employed to assess the atherosclerotic burden in blood vessels outside of just the coronary arteries. O'Connor et al conducted a retrospective study of 829 asymptomatic individuals and used non-enhanced CT images to score abdominal aortic calcifications (AAC), similar to the way calcifications are scored for CAC. The predictive abilities of this AAC score was then compared to that of the FRS. The authors concluded that AAC was actually a better predictor of future CVD events than FRS.[44] This finding may not come as a great surprise given the results of previous studies that examined AAC under CT. Three different studies with a combined 600 participants have found that AAC correlates with CAC.[45-47] Alternatively, Criqui et al. found that while AAC and CAC detected by CT predict CVD events independent of one another, AAC was a stronger predictor of CVD mortality than CAC.[48]

Dual-energy X-ray absorptiometry (DXA) is another diagnostic modality that utilizes ionizing imaging, and has been used in the measurement of AAC. Measurement of AAC on DXA generally employs the use of a scoring system known as AAC-8. This scoring system assesses the length of calcifications on each of the anterior and posterior walls of the abdominal aorta, from the first lumbar vertebral body (L1) to the fourth lumbar vertebral body (L4), compared to the height of the lumbar

vertebrae. A score of 0 indicates that no calcifications were seen, while increasing scores are directly related to an increase in the sum length of calcification.[49] A representative DXA image is provided in Figure 4.[50]

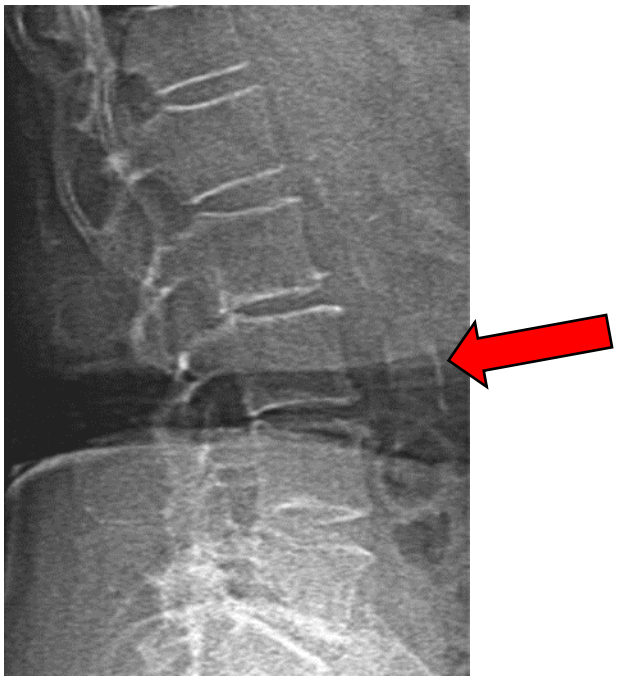

Figure 4. A lateral DXA image produced of the lumbar spine and distal abdominal aorta. Arrow indicates the aortic calcifications that are captured on the image.

A meta-analysis of 10 longitudinal studies showed that this method of measuring AAC was a strong predictor of CVD related events or death.[51] The AAC-8 scoring method derived from a DXA image can also be applied to a radiograph of the lateral lumbar spine. When this is done, similar results have been reported in that the AAC-8 score was once again an independent predictor of CVD events.[52] Measuring AAC on a DXA image has also been compared to the current gold standard of CAC CT. In a study of 106 patients, AAC score on a DXA image was found to be strongly associated

with CAC score.[50] However, these results may not apply to the general population as it was a small study that was based almost entirely on Caucasian participants.

### 2.3.2 Sonographic Techniques

Sonographic imaging offers a potentially suitable medium for assessing atherosclerosis without ionizing radiation in different vascular beds. Vascular intima-media thickness (IMT) measured by sonography is a validated surrogate marker for atherosclerosis.[53] More specifically, carotid intima-media thickness (CIMT), is a well-studied form of this type of measurement. A systematic review by Peters et al., looked at the added CVD predictive value of several different methods, where 12 of the 25 included studies involved CIMT, and found that there was significant evidence CIMT was indeed of added value in predicting CVD risk in asymptomatic individuals.[54] However, the authors did underscore the need for more research to explore the true impact of imaging of subclinical atherosclerosis on CVD risk factors and patient outcomes. A subsequent meta-analysis of 14 population-based cohorts including 45,828 individuals, attempted to determine whether or not the addition of CIMT improved the 10-year predictive ability of the FRS. This analysis established that there was a small improvement in predictive ability from CIMT, but likely not large enough to be clinically significant and therefore should not be routinely performed in the general population.[55] Conflicting results on the added value of CIMT are attributed to difference in imaging protocols, technical difficulties, and inherent variability involved with CIMT imaging.[53,55]

There is a substantial body of research exploring the utility of non-invasive measurement of atherosclerosis in the carotid arteries with ultrasound, but the same cannot be said for sonographic assessment of the aorta. In current clinical practice, ultrasound images of the abdominal aorta are used to diagnose the presence of vessel pathology such as plaque, aneurysm, endoleak, and dissection.[56] The benefits of using sonography to screen patients for abdominal aortic aneurysms (AAA), has been associated with significant increased risk of future CVD events and death.[57] However, existing methods and research for quantifying AAC sonographically are extremely limited. In a study of 1,667 Chinese patients undergoing coronary angiography, sonographic measurements of AAC were taken using a grading system originally designed for trans-esophageal echocardiogram (TEE) of the aortic arch, and were then compared to their angiography findings. In this instance abdominal aortic plaque was found to be an independent factor associated with the presence and severity of coronary artery disease.[58] There were however, quite a few limitations to this study and understandably, this study population would not be generalizable to U.S. or global populations.

## 2.4 Research Question

In summary, this literature review revealed that traditional CVD risk factors and risk calculators, while an excellent primary tool to assess risk, may not be specific enough to guide patient management, especially for asymptomatic patients who fall in an intermediate risk category. In these instances, more information is needed to refine the risk assessment. CAC CT is currently well established as the most precise tool to

perform this job. However, there are demonstrated limitations in cost, accessibility, and exposure to ionizing radiation. Other imaging methods such as CT scoring of AAC, and AAC-8 scoring with DXA and radiographs have shown results close to that of CAC scoring under CT, but those same limitations still exist. Sonographic evaluation of atherosclerotic burden could offer a more accurate, lower cost, non-ionizing alternative to the other methods described. Unfortunately, adequate research into CIMT has returned tentative results. Even though quantification of AAC has proven to be an excellent predictor of CVD risk, it has been vastly neglected as an application for sonography, thus far. Due to these demonstrated gaps in knowledge and applicable clinical tools, the research question that needed to be explored is as follows:

Can abdominal aortic sonography be an appropriate diagnostic tool for improving risk assessment of CVD?

# Chapter 3. Methods

## 3.1 Patient Population

For the purposes of this study, a convenience sample of participants aged 40-60 were recruited. These participants were recruited from a primary care physicians' office in the mid-west. Participants were excluded from the study if they were outside of the stated age range, had known history of CVD, or had known history of any other vascular pathology. A total of 48 participants were recruited for sonographic imaging of the aorta, along with demographic and biometric data collection. Each participant that wished to be included in the study signed a written informed consent along with a Health Insurance Portability and Accountability Act (HIPAA) release form before data was collected. This study was Institutional Review Board approved.

## 3.2 Data Collection

On the day of the participants' visit to the primary care clinic, sonographic assessment of the aorta was performed. Images were saved to the ultrasound device's hard drive. At a later time, these images were assessed and measurements were taken. This image analysis process is described in greater detail later, in this chapter.

Biometric data such as height and weight were obtained on the day of visit. The information collected on this day also included systolic and diastolic blood pressure, total cholesterol, low-density lipoproteins, high-density lipoproteins, and triglycerides.

This data was collected with a blood pressure cuff and blood draw, at the clinic. A chart review was also performed to collect additional biometric and demographic data for each participant. The data gleaned from the chart review included age, race, sex, diabetes status, tobacco smoking history, and current use of statin and/or anti-hypertensive medications.

Much of the collected data was utilized to generate an estimated PCE ASCVD 10-year risk score. The American College of Cardiology ASCVD risk estimator tool was used to perform this calculation. This tool uses age, sex, race, total cholesterol, HDL, systolic blood pressure, diabetes status, smoking status, and hypertension treatment status to calculate a percent risk of having a CVD event in the next 10 years. The ASCVD calculator will not generate a risk score if some values are outside of the stated constraints. These constraints are listed in Table 1.

| **Input** | **Value must be between:** |
|---|---|
| Age | 20-79 |
| Total Cholesterol | 130-320 |
| HDL | 20-100 |
| Systolic Blood Pressure | 90-200 |

Table 1. The constraints for utilizing the ASVCD risk calculator.

### 3.3 Sonographic Assessment of the Aorta

The use of sonography to assess atherosclerosis in the abdominal aorta is not well documented. In one reported study, the method used to measure and also grade plaque burden was not very robust. For this reason, both IMT and a modified grading system,

which combines measurement aspects from DXA of the abdominal aorta and trans esophageal echocardiogram (TEE) of the aortic arch, were used for this present assessment of the abdominal aorta.

### 3.3.1 Equipment

All ultrasound equipment systems and transducers were regularly validated for quality control (QC) and assurance. Transducers are checked monthly and the accuracy was confirmed with caliper placement and measurements, utilizing a QC phantom. All measures were recorded and evaluated to ensure there were minimal to no changes in equipment system's quality. A GE Logiq i (Waukesha, WI, USA) portable ultrasound laptop equipment system, with a 2- to 5-MHz curvilinear transducer, was used to collect images on all the participants. The abdominal imaging preset was used on the Logiq i, but the frequency was downshifted to 2.0 MHz, overall gain adjusted to 69, and the output power was increased to 100%. Time gain compensation and overall gain were the only adjustments made in the sonographic imaging technique. The focal zones were adjusted to a far field depth which included the aorta and the anterior surface of the vertebral bodies.

### 3.3.2 Examination

For every sonographic examination, the participants were asked to lie in the supine position. The participant's abdominal aorta was imaged from the ventral position, starting at the aortic bifurcation and continuing to the proximal abdominal aorta. These images were acquired in the sagittal, transverse, as well as oblique planes for post procedure evaluation and assessment. From the sonographic images obtained, each

region was examined for calcifications and the aortic intima-media thickness (a-IMT). This was acquired by imaging a section of the aorta and then using the equipment calipers to measure the thickness down to one tenth of a millimeter. See Figure 5 for a-IMT measurement example.

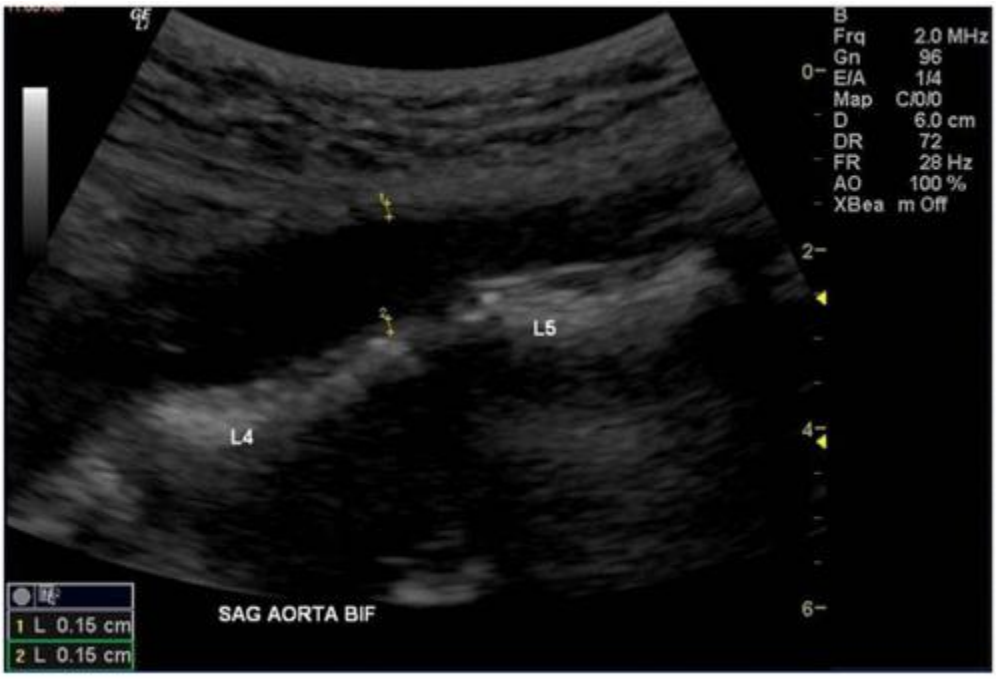


Figure 5. Sonographic measurements taken of the intima-media thickness in the sagittal mid-abdominal aorta.

3.3.3 Image Analysis

Multiple images were saved to the hard drive of the ultrasound laptop equipment system. All of the images were reviewed post-examination for analysis, measurement, and scoring. The aortic calcifications, noted sonographically, were evaluated with the DXA/TEE grading system, with only slight modifications. The DXA and TEE-based grading systems both involved reviewing the abdominal aorta image and measuring the length of calcific plaques along the walls of the aorta[49,59] (See Figure 6). The TEE-

based grading system ranks the level of CVD risk, based on the size, as well as the characteristics of the plaque. This evaluative system assigns a grade from I to V, for CVD risk[59] (see Table 2). The slight modifications to the scoring systems required terminology adjustments, allowing for it to be translated to sonography of the abdominal aorta.

| Grade | Description |
|---|---|
| I | Normal intima |
| II | Increase intimal echo density without thickening |
| IIIA | Increase intimal echo density with single atheromatous plaque ≤3mm |
| IIIB | Multiple plaques ≤3mm |
| IV | ≥1 Plaque >3mm |
| V | Mobile or ulcerated plaques |

Table 2. The abdominal aortic plaque grading system used during this study.

Unlike DXA, TEE, or radiography, sonographic images of the abdominal aorta cannot routinely capture the entire length of the vessel in one image. For this reason, an additional modification was needed so that the grading system could be broken up into three regions. These regions were defined by using the vertebrae, similar to DXA, and aortic bifurcation as landmarks (See Figure 6). Region 1 was defined as the area between the bifurcation of the aorta and the superior part of the fourth lumbar vertebrae. Region 2 was defined as the area between the superior part of the fourth lumbar vertebrae and the inferior part of the first lumbar vertebrae. Region 3 was defined as

the area above the inferior part of the first lumbar vertebrae through the twelfth thoracic vertebrae. A grade was assigned based on the above scoring system. After all regions were reviewed and scored, a total AAC grade was assigned based on the highest scores across all visualized regions. A grading sheet (See Appendix B) was used to record the data, and each image was evaluated by two researchers for QC. If any discrepancies arose, an additional researcher would make the final determination.

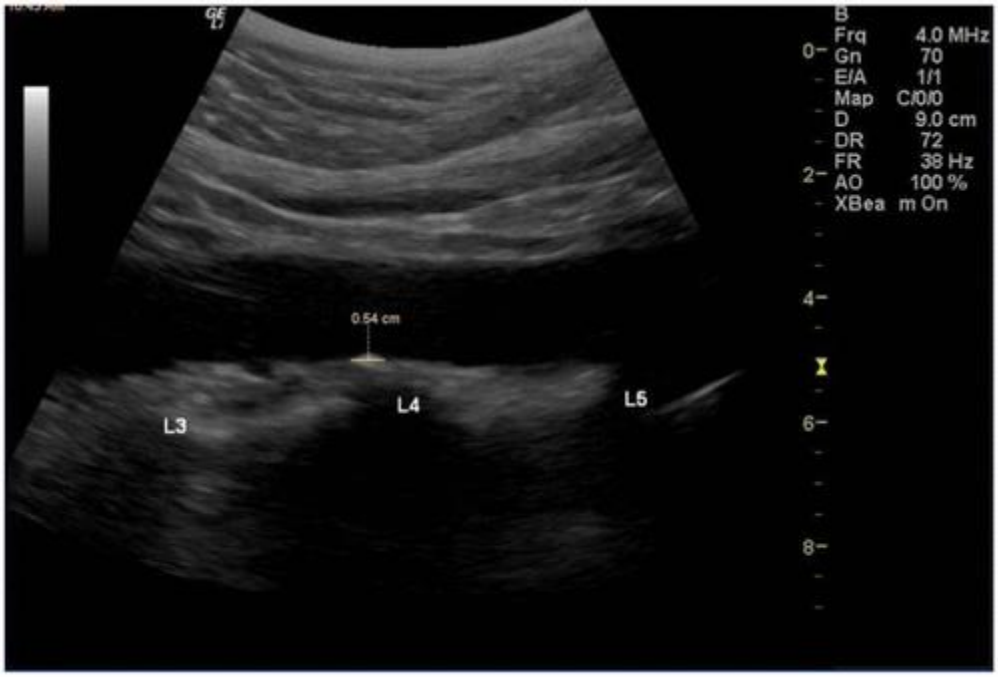


Figure 6. Sagittal sonogram of the lower abdominal aorta with vertebral bodies labelled as anatomical landmarks. A length measurement of a calcific plaque is also present.

The a-IMT manual measurements were made multiple times to obtain the mean measured thickness of the aortic wall. Anterior and posterior measurements were attempted in each of the three segments of the aorta. The posterior wall of the aorta was the most consistently measured thickness across all patients, especially in regions 1 and

2. This method of recording a posterior a-IMT was most recently reported, and these analytics were replicated.[60] The posterior a-IMT measure was obtained in the following manner. Each region was evaluated and that portion of the abdominal aorta was measured in the center of the image, perpendicular to the incident beam. Although calcific, dense vessel walls were included in these measures, large deposits of plaque or an atheroma was never part of any measures.

### 3.4 Statistical analysis

Descriptive and correlational statistics were chosen for this study. Statistical associations between the study variables were made using Spearman's correlation test. The statistical significant was set a priori with a p-value of 0.05. All statistics were performed using SPSS 25.0 (IBM Corp., 2017).

# Chapter 4. Results

The demographics, biometric data, and pertinent health histories were gathered from each patient's chart. This information was used to calculate an ASCVD 10-year risk score. Significant associations between the participants' health data and sonographic assessment of the abdominal aorta were considered in an attempt to answer the research question.

## 4.1 Demographics

A total of 48 people ranging in age from 40 to 60 years old, with a mean age of 49, agreed to participate in this study. 29 of the participants were female (60.4%) with the remaining 19 being male (39.6%). 33 participants were White (68.75%), 13 Black/African American (27.08%), 1 Hispanic (2.08%), and 1 Asian (2.08%). A summary of this demographic data is demonstrated in the table below.

| Demographic | n (%) |
|---|---|
| Age | |
| 40-45 | 19 (39.58) |
| 46-50 | 11 (22.92) |
| 51-55 | 7 (14.58) |
| 56-60 | 11 (22.92) |
| Sex | |
| Male | 19 (39.6) |
| Female | 29 (60.4) |
| Race | |
| White | 33 (68.75) |
| Black/African American | 13 (27.08) |
| Hispanic | 1 (2.08) |
| Asian | 1 (2.08) |

Table 3. The demographical breakdown of this study's participants.

4.2 Health Characteristics

Numerical values for blood pressure, total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), and triglycerides (TG) were all gathered. This numerical data was also converted to categorical values using the appropriate conversion tables from the American Heart Association (See Appendix C).[61,62] Tobacco smoking status, current statin medication use, and current anti-hypertensive medication use were also noted. 3 participants were unable to complete a blood draw which lead to the absence of their cholesterol data. The complete set of data on these variables is listed in Table 4.

| Variable | n (%) |
|---|---|
| Blood pressure (n=48) | |
| Normal | 22 (45.83) |
| Elevated | 5 (10.42) |
| High | 21 (43.75) |
| Total Cholesterol (n=45) | |
| Normal | 26 (57.78) |
| Elevated | 13 (28.89) |
| High | 6 (13.33) |
| Low-density lipoproteins (n=45) | |
| Normal | 21 (46.67) |
| Elevated | 20 (44.44) |
| High | 4 (8.89) |
| High-density lipoproteins (n=45) | |
| Adequate | 34 (75.56) |
| Low | 11 (24.44) |
| Triglycerides (n=45) | |
| Normal | 31 (68.89) |
| Elevated | 4 (8.89) |
| High | 10 (22.22) |
| Statin use (n=48) | |
| Yes | 11 (22.92) |
| No | 37 (77.08) |
| Anti-hypertensive use (n=48) | |
| Yes | 10 (20.83) |
| No | 38 (79.17) |
| Tobacco use (n=48) | |
| Never | 34 (70.83) |
| Current/Former | 14 (29.17) |

Table 4. Available health characteristics of the study population which included blood pressure, blood lipid levels, and pertinent medical history.

Much of this health data was used in combination with the demographic data to calculate a 10-year ASCVD risk score. This risk score was calculated for 43 of the 48 total participants. It was not possible to calculate the risk scores for 3 participants due to the lack of blood cholesterol data, and an additional 2 participants had total cholesterol levels below the ASCVD calculator constraints stated previously. For the

43 participants whose risk scores were able to be calculated, the percent chance of a cardiovascular event occurring within 10 years ranged from 0.1% to 17.2% with a mean risk score of 2.9%.

4.3 Sonographic Assessment Data

The participants' sonographic images of the abdominal aorta were used for grading of potential AAC, as well as measurement of the aortic intima-media thickness (a-IMT), across the three regions. Region 3 was not well visualized in a large majority of the cohort, so those particular results are not reported here. The total AAC grade for each participant ranged from the lowest grade of I (normal intima) to the highest grade of V (mobile or ulcerated plaques). The breakdown of the number of participants with each total grade is shown in the table below.

| Total AAC Grade | n (%) (*Total n=48*) |
|---|---|
| I | 2 (4.2) |
| II | 36 (75.0) |
| IIIA | 5 (10.4) |
| IIIB | 1 (2.1) |
| IV | 1 (2.1) |
| V | 3 (6.2) |

Table 5. A complete representation of the number of participants with each total AAC grade.

The posterior section of the abdominal aorta was adequately visualized more frequently in comparison to the anterior section. For this reason, posterior measurements were used for the a-IMT values. Posterior a-IMT measured in region 1 had a range of 0.7mm to 4.5mm with a mean thickness of 2.55mm. The posterior a-IMT measured in region 2 had a range of 0.0mm to 8.4mm with a mean thickness of 2.48mm.

4.4 Correlational statistics

Inferential correlational statistical analyses in the form of Spearman's rho, were used to assess possible associations between the sonographic assessment data and 10-year ASCVD risk scores. These risk scores were calculated in addition to other traditional CVD risk factors, such as blood cholesterol levels, smoking status, and blood pressure. Posterior a-IMT in both regions 1 and 2 showed a statistically significant positive association with 10-year ASCVD risk scores with correlation coefficients of .351 (p=.025) and .322 (p=.043), respectively. Tobacco use was positively associated with posterior a-IMT in region 1 (r=.357, p=.024). Lastly, statistically significant negative associations were observed between posterior a-IMT in region 1 and numerical values of total cholesterol(r=-.321, p=.038), LDL(r=-.313, p=.043), and HDL(r=-.410, p=.007). Categorical values of total cholesterol, LDL, and HDL did not show any association with a-IMT. No other significant associations involving a-IMT were observed and no significant associations between AAC grade and ASCVD risk score or other CVD risk factors were detected.

| | ASCVD risk score | Tobacco Use | Total cholesterol | Low-density lipoproteins | High-density lipoproteins |
|---|---|---|---|---|---|
| Posterior a-IMT region 1 | p=.025<br>r=.351 | p=.024<br>r=.357 | p=.038<br>r=-.321 | p=.043<br>r=-.313 | p=.007<br>r=-.410 |
| Posterior a-IMT region 2 | p=.043<br>r=.322 | p=.518<br>r=-.125 | p=.464<br>r=-.119 | p=.163<br>r=-.225 | p=.435<br>r=-.127 |

Table 6. Correlations between posterior a-IMT and traditional risk factors.

# Chapter 5. Discussion

## 5.1 Summary

A review of literature in Chapter 2 revealed the need for a more accessible tool for CVD risk refinement. A gap in the current research exploring the usefulness of abdominal aortic ultrasound as one such tool, was demonstrated. This thesis attempted to answer the research question: Can abdominal aortic sonography be an appropriate diagnostic tool for improving risk assessment of CVD? There were 29 females and 19 males (n=48) between the ages of 40 and 60, who were recruited for the study and were asymptomatic for CVD. Their demographic, biometric, and sonographic data were collected and subsequently analyzed.

### 5.1.1 Traditional CVD Risk

Demographic and health data were retrieved from each participant's medical record. Some of the individual data points collected, such as blood cholesterol levels and tobacco smoking status, are traditionally associated with CVD risk. However, much of this data was collected from the participants, in order to calculate a 10-year ASCVD risk score. Descriptive statistics were used to establish the traditional CVD risk among the participants of this study.

It has long been established that elevated levels of total cholesterol and LDL, and decreased levels of HDL, do well in predicting premature CVD.[17-19] In the 45 participants that were able to have their blood drawn to check blood cholesterol levels,

19 (42.22%) had above normal levels of total cholesterol and 24 (53.33%) had above normal levels of LDL, while 11 participants (24.44%) had less than adequate levels of HDL. Research has also shown that both current and former tobacco smokers have a significantly elevated risk of CVD relative to people who have never smoked.[63] Among this study's participants, 14 (29.17%) were found to be current or former tobacco smokers. Of the entire study cohort, 43 10-year ASCVD risk scores were able to be calculated, with a mean score of 2.9%. The ACC considers "low risk" to be any score below 5%. The large majority of participants (n=34) fell in to this "low risk" category while none were considered "high risk" which is a score of greater than 20%. The remaining participants (n=9) were in the "borderline" to "intermediate" risk category.

5.1.2 Sonographic Assessment of the Abdominal Aorta

A crucial step in answering the research question was developing and testing the usability of a novel method for measuring atherosclerotic burden in the abdominal aorta. Both a modified AAC grading system and a-IMT measurements were used to assess the abdominal aorta. These were both found to be feasible methods of assessment as sonographers were able to acquire sonographic images of the aorta and subsequently score the potential atherosclerotic burden with an AAC grade and at least one a-IMT measurement, for all 48 participants.

Region 1 and region 2 were found to be the most reliably imaged across participants. In region 3, only 13 participants of the 48 were imaged well enough to make an attempt at scoring. Due to intestinal gas and bony anatomy such as the sternum, sonographers found that this more superior portion of the abdominal aorta

suffered from the obstruction of adequate ultrasound transmission. While imaging of region 3 was part of the described methods, the spatial resolution was poor enough from this section that scorers were not confident in their assessment and this data was ultimately omitted.

### 5.1.3 Abdominal Aortic Sonography and CVD Risk Associations

Correlational statistics were used to determine the extent to which sonographically acquired AAC grading and a-IMT could detect CVD risk. While the power of these statistics could likely be increased with a greater cohort size, the findings do offer insight to how imaging of the abdominal aorta with sonography may perform as a CVD risk assessment. A moderate positive association was found to exist between the calculated ASCVD 10-year risk score and the a-IMT in both regions 1 and 2. This may suggest that a patient with greater a-IMT is at greater risk for having a CVD event within the next 10 years. Given the PCE ASCVD risk estimator tool is widely used and has been validated numerous times, this could be considered a potentially substantial finding.[10,22,23]

Another finding included a moderate association between tobacco use and a-IMT in region 1. For example, participants who were current or former smokers were also more likely to have greater a-IMT measurements in region 1. This finding is supported by other evidence that suggests smoking is associated with an increase in inflammatory markers, accelerated atherosclerosis, and increased risk for CVD.[63,64] This same statistically significant association was not replicated for smoking history and a-IMT in region 2.

Significant associations between blood cholesterol levels and a-IMT were also observed. The strongest of these associations was a negative correlation between a-IMT in region 1 and HDL. Considering levels of HDL have been confirmed to be inversely related to CVD, this negative correlation would be expected if sonographic a-IMT measurements are a potential adequate detector of CVD risk.[65] Perhaps the most peculiar significant result using correlation statistics was the moderate negative association among a-IMT and both total cholesterol and LDL. Typically, total cholesterol and LDL are thought of as having a positive relationship with atherosclerotic burden and CVD risk. In this study, the a-IMT measured using sonography did not confirm this usual association. One possible confounder that was not accounted for in this statistical analysis, and potentially the cause of this irregular finding, was the use of statin medications by some of the participants. Statins are used to lower both LDL and total cholesterol in patients with known hypercholesterolemia.[66] In this study cohort, 22.92% of the participants (n=11) were reported as currently taking this cholesterol-lowering medication. While not for certain, it could be speculated that some participants taking statins may have previously had high total cholesterol and LDL levels for an unknown amount of time, but had much lower levels of these lipids at the time of this study due to the medication. Thus, the concern for inaccurate results concerning blood lipids and a-IMT should be taken in to account. It should also be noted that no significant associations between blood lipids and a-IMT in region 2 were observed.

Measures of AAC using the modified grading system were not found to be significantly associated with any of the other variables included in this study. However, AAC grading should not be fully dismissed as a tool for CVD risk assessment given this study's smaller sample size and limited variables to which potential associations could be made. AAC grading using ultrasound was demonstrated to be easily obtainable and may still have the potential to add valuable information to a patient's overall CVD risk profile, given further investigation.

## 5.2 Clinical Implications and Future Studies

In the current practice of primary CVD risk assessment in asymptomatic individuals, there is often a need for further risk refinement after clinical prediction models are employed. Although CT CAC scoring is widely recommended and used for CVD risk refinement, the exposure to ionizing radiation, associated costs, and potential accessibility issues may not make it the most appropriate for all asymptomatic individuals. Sonography offers a promising alternative in providing a non-invasive CVD risk assessment with lower cost and without the use of ionizing radiation. Current and emerging technologies in sonography have created diagnostic ultrasound devices that are the size of a laptop computer, and more recently, introduced ultrasound transducers that can be connected directly to a tablet or cell phone. The demonstrated ease in which a sonographic assessment of atherosclerotic burden in the abdominal aorta can be made, coupled with these smaller ultrasound technologies, suggests that CVD risk assessment and refinement could be made in virtually any location, and at any time.

While the data and associations generated in this study are promising, there is not nearly enough evidence to conclude as to whether or not abdominal aortic sonography is an appropriate tool for improving risk assessment of CVD. Traditional risk assessments and refinement, like that of blood lipids, the PCE ASCVD estimator, and CAC scoring have been validated by a vast body of research and meticulously scrutinized evidence for their use. Much of the evidence validating these assessments included very large and diverse cohorts in longitudinal studies, which followed patients to set endpoints. Ideally, future studies attempting to validate the use of abdominal aortic sonography as a CVD risk assessment, would replicate this same rigorous design.

The number of variables for correlation in this study were limited. For future studies it may be useful to have more metrics to both correlate as well as compare. The observed association between a-IMT and smoking, coupled with the fact that tobacco smoking is known to increase inflammatory markers, is an interesting data point that could be explored. The role of inflammatory markers in the development of CVD has more recently been found to be significant, but is still not fully understood.[67] Future studies exploring a-IMT and AAC grading as CVD risk assessment could benefit from looking for associations with these novel inflammatory markers. Finally, comparing sonographic a-IMT or AAC grading to established risk assessments, such as PCE ASCVD score or CAC score, to see which would better predict CVD events, may be more revealing than simply looking for associations between variables.

## 5.3 Limitations

This study was conducted during the height of the COVID-19 global pandemic. This made conducting research generally more difficult than normal, and likely lead to a smaller cohort size given many patients' understandable unwillingness to spend additional time in contact with healthcare personnel. Due to the fact that much of the recruiting took place on the same day the data was gathered, participants were not able to be instructed to fast. This may have some effect on blood cholesterol levels as well as quality of the sonogram due to the absence or presence of bowel gas, particularly in the more superior portions of the abdominal aorta. Lastly, a-IMT measurements were made manually by the sonographer and not electrocardiographically gated.

## 5.4 Conclusion

The use of abdominal aortic sonography has proven to be a reliable, accessible, and practical method of measuring atherosclerotic burden in the inferior portion of the aorta. Limited research has been conducted concerning the use of this method as a CVD risk assessment tool. In this study, statistically significant associations were found between posterior a-IMT and several traditional CVD risk factors such as 10-year ASCVD risk score, tobacco smoking history, and blood cholesterol. While the results of this study are promising, additional and more robust studies are needed to definitively prove abdominal aortic sonography can be an appropriate diagnostic tool for improving risk assessment of CVD.

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Appendix A. ASCVD Risk Estimator and CT CAC scoring tables

| ASCVD 10-year Risk of cardiovascular event | Risk category |
|---|---|
| 0 to <5% | Low |
| 5 to <7.5% | Borderline |
| 7.5 to <20% | Intermediate |
| ≥20% | High |

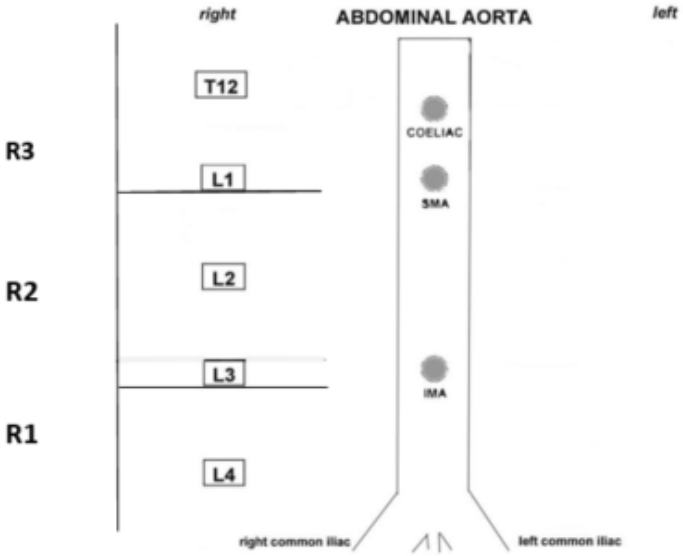
| CT Coronary artery calcium score | Risk category |
|---|---|
| 0 | Low |
| 1 to 100 | Borderline |
| 101 to 400 | Moderate |
| >400 | High |

Appendix B. AAC grading sheet based on a modified version of the DXA and TEE based grading systems.

Participant #_____

Date _____

# CVD Sonogram Worksheet




On the diagram provided, please indicate the levels where plaque was noted on the saved images, of the distal abdominal aorta.

The measurement scale is based on the thickness of the calcification, which is given a grade from I to V. These five grades are as follows: **grade I = normal intima; grade II = increased intimal echo density without thickening; grade IIIA = Increased intimal echo density with single atheromatous plaque ≤ 3 mm; grade IIIB = multiple plaques ≤ 3mm; grade IV = ≥ 1 plaque**
**>3 mm; and grade V = mobile or ulcerated plaques**

| Level of the Aorta | L5 – (L4,L3 Space) | L3 – (L2,L1 Space) | L1 – Upper Aorta |
|---|---|---|---|
| Region | Region 1 | Region 2 | Region 3 |
| Number of Calcifications | | | |
| Morphology (Smooth or Rough) | | | |
| IMT (mm) | | | |
| Intimal Calcific thickness (mm) | | | |
| Atheroma (number and thickness)(mm) | | | |
| Grade | | | |
| Total Grade | | | |
| Demonstrated on image #? | | | |

Sources: Pitsavos CE, Aggeli KI, Barbetseas JD, et al. Effects of Pravastatin on Thoracic Aortic Atherosclerosis in Patients With Heterozygous Familial Hypercholesterolemia. The American Journal Of Cardiology 1998;82:1484-1488

Appendix C. American Heart Association categorical ranges for blood cholesterol and blood pressure.

| Category | Total Cholesterol (mg/dL) | Low-density lipoproteins (mg/dL) | Triglycerides (mg/dL) |
|---|---|---|---|
| **Normal** | <200 | <100 | <149 |
| **Elevated** | 200-239 | 100-159 | 150-199 |
| **High** | ≥240 | ≥160 | ≥200 |

| Category | High-density lipoproteins (Men) (mg/dL) | High-density lipoproteins (Women) (mg/dL) |
|---|---|---|
| **Adequate** | ≥40 | ≥50 |
| **Low** | <40 | <50 |

| Category | Systolic (mm HG) | and/or | Diastolic (mm HG) |
|---|---|---|---|
| **Normal** | <120 | and | ≤80 |
| **Elevated** | 121-129 | and | ≤80 |
| **High** | ≥130 | or | >80 |