Assessment of Invasive and Non-invasive Radiological Diagnostic Procedures of Coronary Artery Disease in the Diabetic Patient

Hassan El Jesr

Lithuanian University of Health Sciences
Faculty of Medicine
Department of Radiology

Supervisor: MD PhD Antanas Jankauskas

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1. SUMMARY


The connection between coronary artery disease (CAD) and diabetes has been well-established in previous literature. The ability to detect CAD in diabetic patients has the potential to prolong their lifespan and allow them to live a better-quality life as they age. Both invasive and non-invasive diagnostic techniques are used to detect CAD in diabetic patients. Until recently, non-invasive diagnostic techniques were not considered to be as reliable in detecting early CAD as invasive tests.

Aim: To determine whether non-invasive screening techniques could be used to effectively diagnose early CAD in diabetic patients.

Objectives: 1) To determine what is considered state of the art radiological diagnostic techniques for CAD in diabetic patients. 2) To assess the clinical considerations that may affect the appropriateness of the radiologic techniques discussed for diabetic patients. 3) To assess which clinical radiological diagnostic techniques have the best chance of detecting CAD in its earliest stages. 4) To determine which criteria physicians should use when selecting radiological diagnostic techniques for diabetic patients.

Methodology: A systematic literature review was conducted. Eighty studies were used to assess the research objectives. The study used qualitative methods to explore both invasive and non-invasive techniques for detecting early CAD in diabetic patients. The study examined ultrasound techniques, coronary computed tomography (CCT), SPECT, magnetic resonance techniques, and performed a comparison of the sensitivity and specificity of these techniques for detecting early CAD. The study also explored non-invasive screening techniques such as Framingham risk score and calcium score.

Results: Until recently, invasive procedures such as IVUS were considered the gold standard for detecting early CAD. However, an examination of approximately twelve studies revealed that using ultrasound to measure intima media thickness (IMT), SPECT analysis, and CCTA were found to be effective means for early detection of CAD in diabetic patients.

Conclusions: SPECT analysis, MRI, and using ultrasound to measure IMT were found to be the most reliable techniques for the diagnosis of early-stage CAD in all types of patient groups. One of the main clinical considerations for assessing diabetic patients is that they may be at an increased risk when
subjected to invasive procedures. SPECT analysis, CCT angiography (CCTA), and using ultrasound to measure IMT were found to be the most reliable technique for detecting CAD in its early stages in diabetic patients. The criteria for selecting radiological techniques for diabetic patients is dependent on their overall health and individual risk factors for CAD. Ultrasound is recommended for diabetic patients, regardless of previous history of CAD. However, more invasive tests should use criteria based on individual patient characteristics.
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3. CONFLICT OF INTEREST

The author reports no conflicts of interest.
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4. ETHICS COMMITTEE APPROVAL

Title of Work: Assessment of Invasive and Non-invasive Radiological Diagnostic Procedures of Coronary Artery Disease in the Diabetic Patient

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5. ABBREVIATIONS LIST

AHA – American Heart Association
CAD – Coronary artery disease
CCA – Common carotid artery
CCA-max-IMT – Common carotid artery maximum intima-media thickness
CCTA – Coronary artery CT angiography
CMR – Cardiac magnetic resonance
CT – Computed Tomography
CZT – Cadmium zinc telluride
DM – Diabetes Mellitus
DM2 – Diabetes Mellitus Type 2
ECG – Electrocardiogram
GSM – Gray-scale median
ICA – Invasive coronary angiography
IMT – Intima-media Thickness
IVUS – Intravascular Ultrasonography
LAD – Left anterior descending artery
LCX – Left circumflex artery
Max-IMT – Maximum intima-media thickness
MCE – Myocardial contrast echocardiography
MRI – Magnetic Resonance Imagery
MDCT – Multi-detector computed tomography
MI - Myocardial infarction
MPI – Myocardial Perfusion Imaging
MPS - Myocardial Perfusion Scanning
NIH – National Institute of Health, United States
NTG - Nitroglycerin
PCT - Procalcitonin
PET – Positron Emission Tomography
Plaque-GSM – Plaque Gray Scale Median
PPV – Positive predictive value
PROCAM Scores - Prospective Cardiovascular Münster
QCA – Quantitative Coronary Analysis
RCA – Right coronary artery
SPECT – Single-photon Emission Computed Tomography
SPECT 2 - Single-photon Emission Computed Tomography 2
6. TERMS

Cardiac Ischemia. This condition refers to a condition that occurs when a portion of a heart becomes starved for oxygen, typically due to the blockage of its major blood vessels.

Coronary artery disease: This term refers to a condition where plaque builds up in the major blood vessels that supply the heart. These are known as the coronary arteries. This plaque builds up and causes a narrowing of the blood vessels and restricts the flow of blood. If a complete blockage occurs, it can result in damage to the heart muscle.

Computed Tomography. This is a type of imaging procedure that uses a series of x-rays to create a detailed image of the body.

Diabetes Mellitus. This refers to a condition where the body fails to respond to or produce enough of the hormone insulin to control glucose levels in the blood.

Electrocardiogram. This is a diagnostic procedure that records the electrical signals in the heart using electrodes placed on the body. This test is largely concerned with irregularities in the rhythm of the heart and is not particularly useful in producing images of the heart, such as those which are used to detect plaque build-up. This test is useful when the plaque has become so thick that it affects the functioning of the heart muscle.

Intima-media Thickness. This is a measurement of the thickness of the tunica intima and tunica media, which are the innermost layers of the walls of an artery. It can be used as a means to find CAD when the patient is still asymptomatic.

Intravascular Ultrasonography. This is a diagnostic test that uses sound to visualize the blood vessels that supply the heart. This is an invasive technique where a catheter is inserted into an artery in the groin and threaded up to the heart. A tiny ultrasound wand is attached to the top of the thin tube. This technique measures the way the sound waves reflect off of the blood vessels and transforms them into images that can be used to visualize the coronary arteries on the inside.
**Myocardial infarction.** This is commonly referred to as a heart attack. The term literally means the death of the heart. It is typically the result of one of the blood vessels that supplies the heart becoming blocked. The heart then becomes starved of oxygen and begins to die.

**Myocardial contrast echocardiography.** This diagnostic technique is used to examine the microcirculation in the heart. It uses tiny bubbles filled with gases that behave similarly to red blood cells in the circulation of the heart. It then visualizes these bubbles and constructs an image of the circulation patterns in the blood vessels surrounding the heart.

**Magnetic Resonance Imagery.** This diagnostic technique uses magnets and radio waves to construct detailed images of the body. Unlike x-rays and CT scans, an MRI does not use radiation.
7. INTRODUCTION

For patients with diabetes mellitus (DM), coronary artery disease (CAD) is a major determinant of long-term prognosis and lifespan. The connection between DM and CAD is well-established. According to Aronson et al. [1], patients with DM have a 2 to 4-fold increase in the risk of mortality from heart disease than patients without DM. The risk for cardiovascular mortality rises in patients with DM and those with a history of myocardial infarction (MI). In patients 65 years old and older with DM, over 70% will die from heart disease or stroke. As with many progressive diseases, early detection is the key to preventing mortality [3]. According to Adams et al. [3], patients with early-stage CAD are often asymptomatic, making it crucial to develop diagnostic techniques that will help catch CAD as early as possible in diabetic patients.

Screening methods for CAD include invasive and non-invasive diagnostic techniques. Diabetic patients often have risk factors which may make a particular diagnostic technique more appropriate, depending on their circumstances. This research will explore current diagnostic techniques and will discuss the merits of current invasive and non-invasive diagnostic procedures in their ability to detect CAD. This study will examine the range of diagnostic techniques available and will help physicians make more appropriate decisions regarding testing coronary artery disease their diabetic patients. The aim of this study is to compare invasive and non-invasive diagnostic techniques in terms of their ability to detect CAD in diabetic patients. It also examines the clinical considerations for the choice of a diagnostic test. It will use a systematic literature review to achieve its aims and answer the research questions. The literature review will use a qualitative approach in this comparison. It will answer the research question, “what are the best diagnostic techniques to detect CAD in patients with DM?”.
Coronary Artery Disease (CAD) is a major cause of mortality in patients with diabetes. For this reason, it is recommended that screening for CAD is a part of diabetes management. The goal of screening is to catch the development of CAD early so that it can be properly treated and does not become severe. Finding radiological techniques that can help detect CAD early on is the goal of research into diagnostic techniques. The aim of this research is to explore the state-of-the-art radiological diagnostic techniques to provide information that will help physicians provide the best screening techniques for their patients. It will compare both invasive and non-invasive diagnostic techniques in terms of their ability to detect CAD and clinical considerations for diabetic patients. It will provide a tool that physicians can use to assess various diagnostic techniques in their ability to detect CAD in patients with diabetes, as well as any clinical considerations regarding the use of the test.

The research will examine the topic with the following research objectives as the guiding principles of this research.
1. To determine what is considered state of the art radiological diagnostic techniques for CAD in diabetic patients.
2. To assess the clinical considerations that may affect the appropriateness of the radiologic techniques discussed for diabetic patients.
3. To assess which clinical radiological diagnostic techniques have the best chance of detecting coronary artery disease in its earliest stages.
4. To determine which criteria physicians should use when selecting radiological diagnostic techniques for their patient with diabetes.
9. LITERATURE REVIEW

The research methodology chosen for this study is a systematic literature review. Therefore, the literature review will provide the bulk of the information used to draw conclusions and make recommendations for the study. It will identify, critically evaluate, and synthesize empirical evidence related to the early detection of CAD in patients with DM using the most recent radiographic techniques.

The sources used for the search included Google scholar, PubMed, NIH, and Medline. An attempt was made to use the most recent articles, focusing on those that are less than ten years old. Only a few exceptions to this rule were made, such as if the literature review was considered a seminal work in the field of radiography or the screening of diabetic patients for coronary artery disease. Search strings included “coronary artery disease and diabetes,” “coronary artery disease detection,” “coronary artery disease diagnosis,” and “coronary artery disease radiography.” The goal of the search strategy was to develop an overview of the literature that was available on the research topic. Once the studies to be used were identified, they were categories according to the type of radiographic technique and its comparator. These categories form the basis for the organization of this chapter.

Screening for CAD in Patients with DM

In 1997 the American Diabetes Association published recommendations that clinicians consider a risk factor approach to the early diagnosis of CAD in symptomatic and asymptomatic diabetic patients [4]. This recommendation was aimed at reducing morbidity, mortality, and cost of treating diabetes. Since that time, clinical trials have not supported a risk factor guided approach. Techniques such as calcium scoring, non-invasive angiography with computed tomography (CT) techniques have been developed that allow the quantification of atherosclerotic burden on the patient [4]. Newer imaging methods make the connection between diabetes and cardiovascular disease even clearer. There has been some question as to whether documenting asymptomatic atherosclerosis in patients with diabetes is warranted. Deciding which patients to screen is one of the key challenges that physicians and researchers face [4]. The goal of screening is to identify patients with a high cardiac risk whose outcomes may be improved through medicals surveillance, revascularization, or factor modification [4].

Framingham Risk Score is a non-invasive screening technique to help classify a patient’s risk for CAD. Patients with diabetes are classified into low, medium, and high-risk categories using this screening
technique. Even those who are asymptomatic can fall into the intermediate cardiac risk category, which has been associated with a 10-year mortality rate of approximately 18.9% in the UK [4]. Clinical features that are associated with an increased risk for myocardial infarction are also related to other atherosclerotic vascular diseases such as renal disease, abnormal resting electrocardiogram, diabetic neuropathy, and other novel risk factors. Several non-invasive imaging techniques have been useful in diagnosing CAD. One of these is coronary calcification. This technique can estimate the degree of narrowing of individual lesions. These tests provide objective evidence of coronary artery disease, but it is unclear how this information should be used to make treatment decisions for individual patients [4].

The Framingham Risk Score is an algorithm that is used to estimate the chances of a person developing cardiovascular disease over the next ten years. It is gender specific and takes into consideration several different factors. It is designed to be used for patients between the ages of 30 and 79 years of age. It takes into consideration age, total cholesterol, high density lipoproteins (HDL), systolic blood pressure, treatment for hypertension, and smoking status [23]. The Framingham Risk Score is not 100% effective in its ability to predict patients that will get CAD in the future. This is especially true for patients with diabetes, who can develop the condition rapidly. There is a continual effort to improve the Framingham Risk Score so that it will be a more useful tool in different populations of patients.

One of these efforts to improve the diagnostic usefulness of the Framingham Risk Score involved using intima-media thickness and brachial-ankle pulse wave velocity to add more meaning to the score and the development of cardiovascular diseases. This study involved type II diabetic patients with a negative history of cardiovascular disease [24]. The study was a five-year follow-up study to determine whether these factors were predictive of the development of cardiovascular disease in this specific patient population. The selection of patients was a key reason for including it in this research study. At the end of the follow-up period, 50 coronary events and 35 strokes were recorded in the original patient population of 783. Of those, the most useful parameters were found to be age, blood pressure, higher brachial-ankle pulse wave velocity, higher intima-media thickness, and a higher overall from Framingham Risk Score. Patients with these factors were found to have higher five-year incidents of cardiac and vascular-related events than those that did not have this set of risk factors [24].

Improved risk assessment is the goal for the development of diagnostic techniques for all groups of patients, but especially those that have diabetes and an elevated risk for the development of the disease in the future. Carotid intima-media thickness has been demonstrated to be a significant predictor of cardiovascular risk in numerous studies [25]. Improving methods to measure this component of the risk more accurately will have a significant effect on the predictability of the Framingham Risk Score and its
ability to determine which patients are at higher risk for the development of cardiovascular disease and who would benefit the most from preventative therapies.

In 1998 the ADA consensus recommended exercise electrocardiography to screen high-risk patients. Recommendations by the ADA contradict those recommended by the American Heart Association, which considers coronary calcium to be of little value in individuals with low Framingham risk, but they find it an important tool for those who are in the intermediate risk category. This includes patients with diabetes [4]. Other studies have indicated that coronary artery calcium score is valuable in identifying those with a high likelihood of inducible myocardial ischemia. Those with a calcium score of <100 are at a low likelihood of ischemia. Those with a calcium score of ≤400 are at a relatively high risk for ischemia [4]. It may be noted that in certain patients with renal insufficiency and the elderly that coronary calcification may not be predictive of ischemia in these patient populations [4]. It is now recommended that for patients with calcium scores of >400 further assessment be performed using single photon emission tomography, stress echocardiography, or cardiac magnetic resonance [4].

Currently, cardiac magnetic resonance imagery, combined with cardiac computed tomography and other non-invasive techniques such as calcium screening are considered to be sufficient for ruling out probability of atherosclerosis, but only if patients are selected correctly [38]. However, at this point, it is not recommended that any of these techniques is to be relied on solely as a means to rule out atherosclerosis. The goal of developing non-invasive techniques for detecting atherosclerosis in diabetic patients is to avoid or reduce invasive techniques, for which this particular patient population is at high risk for complications [38]. While a combination of techniques including cardiac CT and coronary MRI was found to be acceptable in their predictive value when used in combination, neither one of them was found to be reliable when used alone [38].

Compared to their nondiabetic counterparts, patients with diabetes develop CAD at an accelerated rate and have a higher incidence of heart failure [5]. Unfortunately, many times the disease is not detected until it is in its advanced stages and becomes symptomatic. This raises the risk for a poor outcome. Finding ways to detect CAD in diabetic patients while it is still in its early stages can play an important role in preventing heart failure in this high-risk group [5]. Performing a coronary angiogram after the demonstration of myocardial perfusion defects by stress myocardial contrast echocardiography has been shown to accurately present findings of flow-limiting coronary artery stenosis during vasodilator tests [5]. Using this methodology, it was found that diabetic patients with risk factors of >1 are more likely to have significant CAD than those with fewer risk factors [5].
Framingham Risk Score alone does not warrant further testing for CAD. However, when combined with other non-invasive techniques, it can indicate patients who should be watched closely for the development of CAD or sent for further invasive testing techniques. The next section will explore some of the more widely used non-invasive techniques.

**Non-invasive Techniques**

Coronary computed tomography (CT) angiography is an effective way of assessing atherosclerotic plaques in the early stages of CAD. Multi-slice coronary CT angiography is a non-invasive technique that shows promise in the diagnosis of CAD in its early stages as well. These are non-invasive techniques that have improved over the years in their accuracy and sensitivity. They are now becoming the method of choice in detecting “silent” CAD before it becomes symptomatic [6]. The sensitivity of cardiac CT was reported at 82-100%, with a specificity of 78-98% [6].

In a study that used ultrasound technology, patients were asked to assess their risk for CAD [7]. Ultrasonography was performed on those that indicated at least one risk factor, and that were asymptomatic. During the study, the total plaque area and maximum plaque thickness in the carotid artery and the PROCAM scores were determined. During the course of the study, 94 of the subjects became ill. An ultrasound study revealed a Type III or IV finding. This was later confirmed using computed tomography coronary angiogram. It was found that the measurement of TBA and maximum plaque thickness by ultrasound was able to detect early-stage CAD effectively enough to predict risk [7]. In a similar study, ultrasound was compared to exercise electrocardiography (ECG) [8]. This study also measured total plaque area and maximum plaque thickness in the carotid artery along with PROCAM scores. The subjects in this study were symptomatic. The ultrasound examination was more effective in detecting coronary sclerosis than exercise ECG. The ECG was only able to find one true positive result in four patients and produced 21 false negatives. This is a 96% failure rate in the ability to accurately make a diagnosis. Of the sample population, only two had entirely smooth coronary arteries. Ultrasound was able to detect CAD in all of the population that demonstrated coronary sclerosis [8].

The goal of early detection is to try to find ways to reduce or stop CAD if it has developed. Computed tomography angiography was used to determine the benefit of using baselines and aspirin as a means to reduce mortality. It was found that mortality was reduced for those that had plaque, but not for those who did not. Aspirin was not found to reduce plaque [9]. Total plaque area and total plaque thickness were found
to be useful in the detection of early-stage CAD. Ultrasound was found to be more reliable than ECG in finding positive CAD results. The use of ultrasound will be further discussed in the following section.

**Ultrasound Measuring Intima-media Thickness**

In a study that developed a discordant system using angiography and carotid ultrasound on the same set of patients the same day, a scoring system was developed. The scoring system uses the mean far distal carotid intima-media thickness of the common carotid artery, total plaque area and maximum plaque high as measured by ultrasound. Cutoff values were determined using a characteristic curve for predicting the presence of CAD [10]. Several conclusions were drawn from the study. All three measures were significantly higher in patients with CAD. All three of these factors also correlated with an increased number of vessels that were affected. The measurement of plaque height was found to be the best factor for ruling out threshold values diagnosing CAD were 0.82 mm for carotid intima-media thickness, 25.6 mm for plaque area, and 1.5 mm for plaque height [10].

Ultrasound was used to assess subclinical arteriosclerotic lesions of the carotid and femoral bifurcations. B-mode ultrasound of these locations was able to predict 98.6% of cardiovascular events and deaths in a set of subjects over a ten-year period [11]. During this study over a five-year period measurement of carotid plaque area as measured by ultrasound was found to be a significant predictor of an increased risk of myocardial infarction, stroke, and death due to vascular events [12].

Two different approaches exist when it comes to using intima-media thickness when assessing the risk or development of cardiovascular disease. The first approach is to measure the intima-media in the vessel surrounding heart muscle itself. The second approach is to measure the intima-media thickness of the carotid artery. This approach has been shown to be a satisfactory predictor of cardiovascular risk in numerous extensive studies [25]. However, the ability of this method to predict cardiovascular risk hinges on obtaining the most accurate images possible.

Another issue with using intima-media thickness as a predictor of cardiovascular disease is which section of the carotid artery to measure. It is important to measure a section of the carotid artery that is a representative sample of plaque build-up within the blood vessels. Several studies use the common carotid artery, and others use the internal carotid artery or the carotid bulb. There were also differences in the type of measurements that were made in terms of the number of imaging angles and the number of images used to calculate the mean thickness [25]. All of these factors had an effect on the ability of intima-media thickness to predict cardiovascular risk.
Meta-analyses found that carotid artery intima-media thickness alone only improves the predictive power of the assessment minimally. However, the inclusion of the carotid bulb and internal carotid artery enhance the sensitivity of the test in predicting cardiovascular risk [25]. What this means in practical terms is that the more images from the largest sampling of the carotid artery one has, the better the predictive value. As the topic of this study is assessing asymptomatic diabetic patients in the early stages of coronary artery disease development, this becomes an important issue. In many cases, imaging facilities have a standard number of images that they take for assessment. The question is whether they are taking enough images and images from a wide enough section of the carotid artery to be useful in the prediction of CAD for patients that had beginning stage coronary artery disease.

**Factors Affecting Ultrasound for CAD**

This study suggests that images result in a better prediction of CAD of the patient [25]. However, there is a question as to whether a sufficient number of images are being taken in daily practice. The number of images taken for this study were conducted as a part of a research setting. However, when one of the factors is the expense and time needed to perform the extra imaging, the ability to take the number of images and types of images necessary for accurate assessment becomes questionable. What this means is that in daily practice, patients are not getting the number of images necessary to catch cardiovascular disease at the early stages. It leads to the question of whether standard practice in terms of the number and types of images that were taken are able to significantly improve the predictability of using intima-media thickness to predict cardiovascular disease probability in diabetic patients who are asymptomatic. It is one thing to conduct an appropriate number of images in research setting, but it is entirely another matter when it comes to daily practice and factors such as cost and time.

In another study, it was found that intima-media thickness was able to predict both coronary stenosis and coronary plaque using ultrasound techniques. However, it was also found that gender, the duration of their diabetes, the presence or absence of elevated systolic blood pressure, and the LDL/HDL ratio were all independent predictors of coronary artery stenosis and could not be taken in aggregate [26]. The study did find that adding LDL/HDL improves the prediction when using intima-media thickness ultrasound techniques.

The “intima media thickness (IMT) complex” includes the intima and the media, which is primarily smooth muscle. In the average person, approximately 97.5% of this complex consists of the media. In a person that has an atherosclerotic disease, the intima contribution to the IMT complex is higher, and only
80% of the complex is formed by the media [15]. Plaque sequence was also found to have a significant predictive value, but its value was found to be greater in women than in men [15]. Ultrasound has the ability to measure the protrusion of the intima-media into the lumen quantitatively or by a subjective estimate of the sonographer [16]. High resolution with B (brightness) mode was used to analyze the intima media thickness of the carotid bifurcation and proximal internal carotid arterial segments. In this study, it was found that CIMT measurement was not correlated to hard outcomes such as death, myocardial infarction, or death [36]. It was also noted that differences in sonography techniques and the skill of the technician were found to influence its use as a predictive device.

Although ultrasonography and the measurement of the intima-media complex and plaque thickness have proven to be useful in the assessment of CAD, ultrasonography has several limitations that may be affected by the skill of the sonographer. Compared to tests such as coronary calcium score, which is automated and easy to perform, differences in the patient’s body may have an effect on the ability to gain clear ultrasound images. Furthermore, minor changes in the angle of the imaging could affect the intima-media measurement. This would affect the measured value and the interpretation of the test [15]. The chance for human error is higher with tests such as ultrasonography and other imaging techniques that depend on the skill of the technician. However, it also has an advantage in that there are no significant side effects, devices are portable, they are quick, lower-cost, and safer than invasive techniques [15].

The advantages of ultrasonography make it an excellent choice in terms of the ability to achieve a high patient throughput rate in a cost-effective manner. However, the primary concern of this research is the accuracy of tests to predict asymptomatic CAD in diabetic patients. Therefore, concerns over the accuracy of the task take precedence over economic interests, for the purposes of this research. This would make the researcher place emphasis on the potential for error and its effect on making an accurate diagnosis when assessing ultrasonography as a diagnostic technique. Although it has been suggested that intima media thickness may not have enough clinical evidence to support it as a single clinical technique, patients with high intima media thickness scores were associated with increased atherosclerosis [35]. It has been further suggested that patients determined to have increased intima media thickness be referred for more definitive, albeit invasive, testing to confirm the findings [35].

Another challenge when using ultrasound is establishing the parameters for determining when CAD is present. One study set out to assess ultrasound parameters by comparing it to results obtained by coronary computed tomography angiography in persons with CAD [19]. The purpose of the study was to establish a relationship between results obtained by these two techniques. This study focused on carotid IMT and plaque assessment using these two techniques and compared with the number of coronary arteries affected with
any evidence of atherosclerosis and coronary artery calcification. In this study, the patients underwent both techniques on the same day. The results of the tests found that carotid plaque was found to be present in 47.6% of the subjects who had a calcium score of zero and in 80.5% of subjects with a calcium score of greater than zero. Carotid plaque that had a mean IMT value of >0.75mm was found to be associated with a calcium score of greater than zero and disease in at least one vessel. Results of the study were independent of the age and sex of subjects [19]. Carotid plaque and calcium score demonstrated good correlation in this study and were found to be predictive of CAD.

Carotid ultrasonography uses methods such as intima-media thickness and the characterization of the carotid artery using gray-scale median (GSM) to add information that is useful in the prognosis of conventional risk markers in diabetic patients [57]. In a study that involved 3,263 patients with diabetes, but who demonstrated no apparent cardiovascular disease when baseline measurements were taken, coronary ultrasound results corroborated with the first occurrence of cardiovascular disease in 488 cases [57]. These events included morbidity, CAD, stroke, and peripheral artery disease. Common carotid artery (CCA)-mean-IMT, CCA-max-IMT, Max-IMT, plaque-GSM, and the presence of low-GSM echolucent plaques were found to be reliable indicators for cardiovascular disease. Among these factors, CCA-mean-IMT, CCA-max-IMT, and Max-IMT were found to be significant predictors of CAD when combined with conventional risk factor analysis [57]. These techniques were used to develop a hazard ratio that was used for prognostic prediction within the 95% confidence interval [57].

A study involving 156 subjects without a previous incident of vascular disease were analyzed using carotid ultrasonography and coronary angiography as the primary diagnosis technique [58]. The population was then subjected to exercise echocardiography to determine if they had any exercise-induced wall motion abnormalities. In patients with greater than 50% stenosis, it was found that exercise echocardiography did not have significant sensitivity, specificity, predictive values, or efficiency to be useful in the classification of patients with CAD [58].

Using graphical analysis, a study was conducted that compared eight relevant studies in terms of design, measurement protocols, and the data that was reported [59]. The purpose of the study was to obtain a pooled estimate of the relative risk as determined by inter-media thickness differences. The study found that the relationship between IMT and risk of cardiac event was nonlinear for those with a 0.10 m IMT difference, but that it was linear for those with moderate to high IMT values [59].

In a study that used autopsy findings, the IMT of several structural members was measured and compared. The structural members included the coronary artery, cerebrovascular, thoracic aorta, abdominal aorta, and iliac artery [60]. All of these were found to be significant indicators of coronary artery disease.
The study concluded that carotid IMT was a valid method for confirming generalized presence of atherosclerosis [60].

Ultrasound was found to be an effective method for detecting early-stage CAD. Its predictive ability is enhanced through the use of risk scales. However, several factors limit the usefulness of it in predicting CAD. These include the section selected for measurement, instrumentation differences, and differences in technician skill and technique. However, overall, ultrasound is considered to be a useful tool in the detection of CAD.

**Coronary Computed Tomography**

Using non-invasive techniques, risk stratification was undergone using a combination of carotid plaque area, intima-media thickness, C-reactive protein, and coronary calcium scores [13]. Although each of these tests may enhance risk stratification alone, their predictive ability when used together had not been studied. The presence of coronary artery disease was defined as the existence of stenosis equal to or greater than 50%. The study found that carotid plaque area is the most effective and accurate in determining the likelihood of underlying CAD. The patients within this study were of varying cardiac risk degrees. When taken as a whole, carotid plaque area was superior to coronary calcium score, intima-media thickness, and c-reactive protein in predicting the likelihood of CAD [13]. The use of carotid intima-media thickness, along with the presence or absence of plaque proved to be a valuable tool in predicting the risk of CAD [14,15] and ischemic stroke [17]. This was supported by another study that used these factors. These factors were found to be significant in the prediction of the first machine stroke within a ten-year period. In this study, total plaque area was found to be a slightly stronger predictor than intima-media thickness [17, 18].

**CT Angiography**

Another test of supposedly healthy asymptomatic individuals yielded similar results using coronary CT angiography. In this study, approximately 71.7% of the sample population tested positive for CAD using this diagnostic technique, and 21.5% of the subjects had high-grade stenosis. The negative predictive value of invasive angiography was 92.9%. The negative predictive value of CTA was 99.4%. CT angiography was found to be useful in detecting both calcified and non-calcified plaque [21]. One of the most significant findings of the study was that a calcium score of zero did not necessarily exclude the presence of CAD [21].
This study demonstrated that this test method was highly accurate with the diagnosis or exclusion of CAD in patients. It also found that total coronary plaque burden and noncalcified plaque associated with an increased risk of adverse outcomes, even if only one segment is involved [21]. The study supports the use of coronary CT angiography for screening asymptomatic patients that have a high risk of CAD. They further suggested the inclusion of patients with diabetes and abnormal previous treadmill stress tests as good candidates for the screening of CAD by coronary CT angiography. This technique demonstrated the ability to detect CAD in patients who were asymptomatic. Early diagnosis and the diagnosis of asymptomatic patients are an essential contribution to the ability to manage CAD in all patient populations. However, it is especially important in high-risk groups, such as those that have diabetes mellitus. Another important finding of the study was that coronary CT angiography was a better predictor of CAD than blood calcium. It was found that in a significant portion of the sample population, even though calcium levels were found to be normal, significant CAD was still found using the imaging technique.

A typical diagnostic flow involves a pre-screening using ultrasound. This can be performed in the office of the primary care physician. If the results of the ultrasound indicate the presence of CAD, then it can be confirmed using coronary CT angiography. This is a more expensive technique than ultrasound, which is why it is used as a secondary diagnostic test instead of a primary screening tool. Ultrasound has the ability to provide adequate images for screening purposes, but it requires a more sensitive test such as coronary CT angiography, to achieve a more accurate image of the stage of CAD the patient is in. This diagnostic process hinges on the ability of the ultrasound to detect CAD and results in differing the diagnosis to a more accurate diagnostic testing. It was found that ultrasound resulted in successful referral among greater than 50% of patients with a more than 50% blockage, but it was not necessarily able to trigger a referral for patients who were asymptomatic and in the early stages of the disease [22].

For the purposes of this study, this indicates that ultrasound may not be effective in catching CAD until it has reached moderate to advanced stages. This limits the potential for successful treatment and can lead to higher mortality rates among patients with diabetes due to the rapid advancement of their CAD. This study suggests that ultrasound is not an effective means to perform a primary screening for asymptomatic patients with CAD. The current system that uses ultrasound first and then referral to more sensitive diagnostic tests will not lead to early diagnosis of CAD at a time when it is most likely to be successfully treated.

In patients that were found to have significant coronary artery disease using multi-detector CT angiography, invasive coronary angiography was performed. In 50% of the patients, the results of the multi-detector CT angiography and the invasive coronary angiography were in agreement. However, in the other
half of the patients the multi-detector CT angiography overestimated the severity of the stenosis in one or more vessels [34]. This study highlights two important issues. The first is that multidetector CT angiography has the potential for estimating the stenosis that is present in patients. The second is that invasive coronary angiography remains superior in its quantitative and qualitative diagnostic capabilities. This suggests that invasive techniques will remain state-of-the-art in terms of the ability to quantify plaque and the amount of stenosis present in a patient’s vessels. Multi-detector CT angiography may overestimate the amount of coronary artery disease present in a patient, but at least it had the ability to detect it. However, it is not known if the same results would be obtained in a patient population that had mild, rather than intermediate risk.

Coronary computed tomographic angiography (CCTA) is emerging as one of the most widely used non-invasive techniques. It was found that this technique is best for measuring the overall plaque burden, the severity of the plaque burden, distribution of the plaque burden, location, composition, and remodelling [48]. An examination of techniques found that the use of CCTA can also save costs for individuals that are not known to have CAD. It has been suggested that CCTA may be a first-line test for those symptomatic patients, but do not have any previous known CAD [48]. It was concluded that although the results of an initial study that used CCTA to detect plaques in a group of moderate risk individuals, it was not suggested that it be used as a standalone technique. The authors suggested that those that have an indication of severe CAD according to see CCTA results be referred for more invasive testing. At this point in time, the authors did not feel that important studies have been conducted to warrant the use of CCTA as a single diagnostic technique [48].

Coronary computed tomography angiography was used to detect CAD in asymptomatic middle-aged study participants. None of the participants in the study reported any symptoms of CAD and the screening was conducted as part of a general health assessment. Plaques were identified in approximately 22% of the individuals who were in supposedly good health. Five percent of subjects had significant diameter stenosis, and 2% had severe stenosis [20]. This was an important study for the purposes of this research for several reasons. First, it demonstrated that a certain portion of the population can have severe stenosis and still be asymptomatic and healthy. It also demonstrated that coronary computed tomography angiography can provide better insight about asymptomatic CAD. This technique was used to address a population that had a general risk for CAD. The population under study and this research has a significantly higher risk for CAD than the general population due to their diabetes. This study suggests that CCTA could be useful in diagnosing CAD in asymptomatic diabetic patients. However, this technique was not recommended for
screening due to potential radiation exposure. Radiation exposure is another consideration that must be accounted for when deciding to use to detect potential CAD in asymptomatic diabetic patients.

In patients presenting with erectile dysfunction and acute chest pain, but negative initial electrocardiogram, it was found that diagnostic imaging using coronary computed tomography angiography was a viable imaging technique independent of the risk factors such as age, gender, and other cardiac risk factors [81]. This technique was especially useful in high-risk coronary plaque patients with advanced stenosis. It was able to detect high-risk plaque in patients that had acute chest pain, but who had no other evidence of ischemia or infarction upon initial assessment with electrocardiography. However, its usefulness was limited in milder cases [28]. This technique improved classification in high-risk patients, but not in those with low-risk plaque features.

Once again, it comes down to a question of practicality. When a patient presents with acute chest pains and has a negative electrocardiogram, this technique may be useful in detecting high-risk plaque in patients that would have an otherwise normal heart rhythm at this point. However, the question is how many of these patients should be sent for screening. Unfortunately, this is difficult to determine until the tests have been run. Using coronary CT angiography is more expensive than electrocardiography and is certainly not practical for every patient that presents acute chest pain but has normal electrocardiography findings. This study is focused on the early diagnosis of coronary artery disease in diabetic patients. The findings of this study indicate that it might not be useful in cases that involve early plaque formation and stenosis. This means that it may not be the best diagnostic technique for predicting which diabetic patients are more likely to develop advanced cardiovascular disease in the future. It is only useful for patients that already have advanced disease. Understanding the limitations and usefulness of coronary CT angiography is an important factor in its proper use as a diagnostic technique.

In a study that compared stress testing and coronary CT angiography with invasive coronary angiography, non-invasive techniques were able to indicate the need for more invasive tests in 100% of the patients [29]. The advantage of adding stress testing to coronary CT angiography is that the stress test measures the heart function and provides information that may add value to non-invasive imaging techniques. In practice, invasive techniques are used to confirm the results of inconclusive non-invasive testing. The proper use of non-invasive imaging techniques involves developing better techniques for determining the risk of cardiovascular disease and plaque formation accurately. It is the goal to develop non-invasive tests that are accurate enough to be definitive diagnostic techniques on their own, without having to resort to more invasive techniques to confirm or rule out test results from non-invasive diagnostics.
Invasive techniques, such as invasive coronary angiography, find their most useful application in research settings to improve the accuracy of non-invasive diagnostic techniques such as coronary CT angiography. In actual practice, they are typically only reserved for cases that cannot be diagnosed using non-invasive techniques. Non-invasive techniques are more accurate in detecting advanced plaque formation and stenosis. Due to their expense, invasive techniques are often reserved when surgery is eminent. Invasive techniques are not typically used for patients that have beginning plaque formation and stenosis. Unfortunately, non-invasive techniques are less accurate in their predictive qualities for patients that do not have advanced coronary artery disease. This means that many patients with early disease may not be properly diagnosed using non-invasive techniques. Therefore, the use of invasive techniques to confirm the results and improve the sensitivity of non-invasive techniques is of significant clinical value in reducing risk of the development of coronary artery disease for diabetic patients in the future. The more sensitive non-invasive techniques become, the better their ability to predict early coronary artery disease and to prevent the development of more severe CAD. This means that patients with early disease stages will be able to obtain non-invasive techniques to prevent CAD from developing into more serious advanced stages, which is the goal of improving non-invasive techniques.

Invasive coronary angiography is typically not performed until the results from computed CT angiography have been deemed inconclusive. However, one study found that assessing coronary plaque characteristics using coronary CT angiography can improve the predictive value of more invasive techniques such as invasive coronary angiography [30]. This study contradicts the findings of other studies that consider non-invasive techniques such as coronary CT angiography to be inferior to invasive techniques such as invasive coronary angiography. However, this study suggests that non-invasive techniques have their own value in terms of diagnostic capability and that they can be used to enhance invasive techniques. In a traditional diagnostic setting, non-invasive techniques are used before invasive techniques are performed. They are typically not performed concurrently in everyday practice due to cost and practicality. Once more invasive techniques have been approved, the results of non-invasive techniques are typically considered inconsequential in terms of diagnosis, with the invasive technique taking priority. This study suggests that this practice may be in error and that non-invasive techniques have something to add to the picture of coronary artery disease development in addition to invasive techniques. Using these techniques together may help to improve the predictive value in patients with beginning coronary artery disease development. It is not known if this philosophy will be adopted by the medical community in standard practice due to cost and current practice guidelines that consider invasive techniques to be only used to determine if surgery is necessary, or the type of surgery to be performed.
In current practice, coronary CT angiography results are used to refer patients for more invasive, but more accurate techniques. The ability of non-invasive techniques to accurately predict patients who would benefit from more invasive techniques is the subject of a study that examined the usefulness of non-invasive techniques as the gate keeper for referring patients for more invasive studies [31]. It was found that for patients with more invasive coronary artery disease, the rate of referral was about 76%. However, for patients with nonsignificant coronary artery disease, only 20% were referred for more invasive techniques. Of those with more significant coronary artery disease, only 0.6% of patients required revascularization. None of those with nonsignificant CAD results were referred for revascularization. This study found that coronary CT angiography were strong and independent determinants of conclusive results involving invasive techniques and revascularization. The study concluded that CT angiography was an adequate gatekeeper to identify patients who would be most likely to benefit from revascularization and those patients who can safely avoid more invasive diagnostic testing [31]. This was at least the case for identifying those with advanced coronary artery disease. However, it says little about its ability to serve as a preventative diagnostic test for those with early stages of coronary artery disease. This study suggests that its usefulness is more significant in advanced cases than in milder cases. The goal of this research is to find ways to prevent mild cases from turning into advanced and significant plaque blockages. This study does not indicate that non-invasive techniques would be useful for this purpose.

Another study examined the use of coronary CT angiography in patients with no coronary artery disease or mild coronary artery disease. It was found that obstructive coronary artery disease was associated with higher rates of invasive coronary angiography and revascularization surgery of at least one vessel [32]. In patients with less than 50% stenosis, the risk for death is reduced when the patient’s received follow-up invasive coronary angiography. The risk for death was significantly higher when no follow-up invasive coronary angiography was performed [32]. This study indicates that referral for invasive coronary angiography in patients where less than 50% stenosis is indicated, using non-invasive tests may help to reduce the risk of death for these patients. This suggests that referral for invasive testing that is more accurate may help to improve patient outcomes for those that have mild coronary artery disease and are in the beginning stages. However, even though this may be the best for patient outcomes, it is not always practical due to financial and risk factors with individual patients. The study does indicate that it may be useful in preventing deaths and getting appropriate medical intervention for those that are in the beginning stages of coronary artery disease.
**Calcium Score**

Even though non-invasive diagnostic techniques are less expensive and pose less risk to the patient, there is a question as to whether they have sufficient predictive value for the detection of CAD in diabetic patients. For instance, the use of a multi-detector CT angiography technique combined with other diagnostic techniques have a better chance of catching early coronary artery disease than a single test alone. Coronary multi-detector CT angiography was found to rule out CAD in an intermediate-risk population [34]. It was found that this technique significantly predicted outcomes in this patient group. This non-invasive diagnostic test was also found to be useful in the establishment of baseline in comparator studies on the same patient in the future [34]. In the study, patients with normal coronary arteries and nonsignificant stenosis did not suffer any cardiac events during follow-up in the study. The combination of calcium scoring and multidetector CT angiography allowed for accurate assessment and prediction of coronary artery disease in an intermediate-risk population.

Calcium levels alone were found to have a low predictive value, especially in patients that have atypical symptoms [37]. In addition, there are several conditions that could cause a false positive in terms of the predictive value of calcium score alone. For instance, calcium may be falsely elevated in patients with a positive troponin test. In addition, not all plaques are calcified, and the calcium test will not predict noncalcified plaques [37]. Calcium test alone is not recommended for the detection of atherosclerosis in diabetic patients.

Coronary computed tomography was found to be an effective non-invasive technique for the classification of CAD in asymptomatic patients. It can accurately predict CAD in patients with advanced stages of the disease, but it was also found to have significant predictive ability in those who are in the early stages of the disease. When combined with calcium score, coronary computed tomography was found to be an effective method for predicting early CAD.

**SPECT for CAD**

Several studies have addressed the use of multiple detectors to assess the risk of coronary artery disease, particularly for patients that are in the early stages or that have mild disease development. One such study explored single photon emission computed tomography (SPECT) and coronary CT angiography (CCTA) [33]. Of the patients examined, patients with normal diabetes mellitus and normal SPECT findings were found to have advanced stenosis and a high coronary artery calcium score. Throughout the course of the study, five cardiac events occurred in patients that had normal findings on SPECT but who had abnormal
findings using coronary CT angiography. The study concluded that SPECT was not able to detect the potential for a coronary artery event when used alone [33]. It was not able to differentiate those who had a significant amount of plaque from those who did not. However, coronary CT angiography proved to be a better predictor of an actual coronary event occurring in the future. It was found that SPECT added little to the predictive ability of coronary CT angiography, and was unable to differentiate those that had a significant coronary artery risk, even in patients with advanced stenosis.

The goal of developing non-invasive techniques that can effectively predict coronary artery disease in diabetic patients is to find a way to avoid, to the extent possible, invasive techniques on diabetic patients. However, at present, no single non-invasive test was found to be predictive of atherosclerosis on its own. The standard for comparison of non-invasive tests is how well they correlate with invasive techniques such as invasive quantitative angiography and IVUS [39]. Current findings demonstrate a satisfactory agreement between non-invasive and imaging techniques included MPI, MDCT and invasive techniques that include angiography, QCA, and IVUS [39]. These non-invasive techniques were found to be sufficient in patients that had flow restricting and obstructive stenosis. Non-invasive techniques were found to be sufficient in patients who have advanced atherosclerosis [39]. One of the limiting factors is that MDCT produced a false positive result in patients where flow-limiting atherosclerosis was not present [39].

In a comparison of invasive and non-invasive techniques, it was found that non-invasive techniques are still limited in their ability to confirm or rule out atherosclerosis to any degree of certainty. Invasive techniques are still the most reliable predictor of atherosclerosis and the potential for cardiac incidents in the future [39]. Although combination techniques were found to be reliable for patients with advanced atherosclerosis, they were still limited in their ability to accurately predict coronary artery disease and those that did not have advanced states where blood flow was restricted [39]. Combination techniques came close to the predictive ability of invasive techniques, but they are still not good enough to replace them completely.

Several imaging agents emerged as superior when used with single photon emission tomography imaging [61]. The investigation compared the use of potassium, thallium, rubidium, and ammonia in the assessment of myocardial perfusion. It was found that myocardial segments showing a greater than 50% uptake, compared to normal uptake had a better outcome with revascularization and improved survival rate. SPECT was found to be a reliable method for determining coronary atherosclerosis [61]. Another study found that multi-slice row computed tomography has an advantage of detecting coronary atherosclerosis at its earliest stages, but follow-up but by SPECT can clarify the hemodynamic consequences of the anatomic findings of computed tomography [62]. This suggests that SPECT is more effective in determining the functional outcome of atherosclerosis findings.
The results of high-speed SPECT have a sensitivity of 90%, a specificity of 84%, a positive predictive value of 80% and a negative predictive value of 87%. These were significantly lower on a per vessel basis, and the technique was more effective when predicting a greater than 70% dynamic diameter stenosis in an ischemic artery [63]. A study that involved 70 consecutive patients with no known CAD used high-speed SPECT in both resting and stress states [64]. The results found that high-speed SPECT was an effective way to detect stenosis of greater than 5% in those with abnormal findings for coronary arteries [64].

Transient ischemic dilation of the left ventricle and myocardial perfusion SPECT was found to be a clinically useful marker of severe coronary artery disease [65]. The sensitivity using this technique was around 72% for patients with severe CAD [65]. A new novel camera system for high-efficiency SPECT demonstrated a sensitivity and specificity in patients with a greater than 50% stenosis at 80% and 62% [66]. In a study that involved 34 patients with stable angina, myocardial SPECT was performed using a one-day stress/rest protocol. The technique had a positive predictive value of 56.5 and the negative predictive value of 90.9% [67]. A subgroup analysis was performed on the vessel territories positive predictive value (PPV) of LAD, LCX, and RCA. It was found that the positive predictive value of LAD was significantly lower than those of LCX or RCA. The positive predictive value of LAD was 86.4%, LCX was 92.6%, and RCA was 95.7% [67]. A similar technique was also used to establish normal limits and a novel method for computation of regional functional changes between rest and post-stressed studies [68].

It was found that using SPECT myocardial perfusion imaging a significant relationship was found between myocardial ischemia and angiographic findings [69]. A direct relationship was found between the extent of coronary artery disease and increasing ischemia. In patients that did not have ischemia, only about 6% had a three-vessel left main markers of CAD. In those with greater than 10%, 10% had no significant CAD, and only 7% had a less than 50% stenosis. The study concluded that patients with a greater than 10% stenosis rarely have non-significant stenosis by angiography and patients with no or mild ischemia rarely have left main or triple vessel disease [69].

The goal of any analysis is to be able to predict the prognosis in patients with coronary artery disease. The study found that MPS showed similar power in predicting coronary disease to the corresponding visual analysis that included all clinical information on a population of 90 patients with coronary artery disease [70]. However, the ability out SPECT alone to predict coronary artery disease has been challenged.

SPECT alone was not found to be effective in detecting CAD. However, when combined with other techniques, such as coronary CT angiography the results have adequate predictive value in the detection of early-stage CAD in diabetic patients. Combination techniques were found to be more effective, as they
represent confirmatory results and support for the findings. Now, let us examine the use of Magnetic Resonance (MR) for comparison of its effectiveness in diagnosing CAD.

**Magnetic Resonance Tomography in CAD Diagnosis**

Coronary magnetic resonance is typically performed as a free breathing, three-dimensional study that examines the whole heart [40]. Several factors can influence its accuracy can influence its ability to detect the amount of CAD present. These include, the use of an appropriate pulse sequence in accordance with the magnetic field strength, preparation pulses, cardiac and respiratory gating, parallel imaging, contrast material injection, and multi-channel cardiac coils [40]. Both contrast and non-contrast techniques have been used to visualize coronary artery plaque. It was found that the contrast agent uptake by the coronary wall is nonspecific and can be associated with either inflammation or atherosclerotic plaque in patients with stable CAD [40]. This is one of the challenges associated with using MR to detect CAD in subclinical patients.

One of the key advantages stated for the use of magnetic resonance is that it does not expose the patient to radiation and can be used repetitively without exposing the patient to harm [41]. This allows it to be used for the continuous monitoring of CAD over time without concern for radiation damage. In a comparison between coronary magnetic resonance and other diagnostic tests, CMR was found to have a similar sensitivity and specificity to other tests, with the exception of CT scan. As the authors found that CT scan had better performance than MR, but in all other cases CMR proved to be at least comparable to other diagnostic techniques in the detection of CAD [41]. CMR was also found to have a sufficient negative predictive value to exclude patients from having coronary stenosis [41].

Perhaps one of the most important studies regarding this research utilized a meta-analysis of randomized controlled trials that compared the outcomes of non-invasive diagnostic modalities for coronary artery disease [42]. The study utilized patients with low-risk acute coronary syndrome. The results of the study found that among patients with low-risk acute coronary syndrome cardiovascular magnetic resonance, stress echocardiography, and exercise electrocardiograms resulted in fewer referrals for further testing using coronary angiography, as compared to those that were tested with computed tomographic angiography [42]. Another study also compared these three diagnostic methods. This group of patients experienced stable chest pain and an intermediate likelihood of CAD. In this study, computed tomographic angiography also had the highest diagnostic accuracy as compared to stress echocardiography and cardiac magnetic resonance.
Myocardial perfusion imaging was also found to have good diagnostic accuracy in this group of patients [43].

A meta-analysis that involved a comparison of computed tomography derived fractional flow reserve to invasive fractional flow reserve it was found that computed tomography derived fractional flow reserve performed superior to invasive fractional flow reserve in detecting significant coronary stenosis [44]. This study holds promise for the use of computed tomography techniques as a non-invasive means of detecting coronary artery disease. In a comparison of invasive and non-invasive techniques for detecting CAD, MDCT demonstrated a sensitivity of 96% and a specificity of 67%, when compared to QCA [45]. However, this study concluded that considerable plaque burden can be observed with MDCT, even when myocardial perfusion abnormalities are not present. They did not find that this represented a false-positive for MDCT, but that it reflects that this technique can detect atherosclerotic lesions that are not yet flow-limiting [45].

It is recognized that invasive coronary angiography is the gold standard for imaging coronary arteries, but it has been criticized in that it detects luminal stenosis but gives little information about the condition of the vessel wall or any plaques that are present [46]. In addition, it is recognized that not all lesions are functionally significant and limit the flow of blood through the arteries. It has been suggested that non-invasive techniques such as coronary calcium score, coronary CT, and an MRI of the coronary arteries provide a means of assessing the plaque burden. It is further suggested that assessing the plaque burden is likely to get more information about the function of lesions and their importance in the development of flow limiting stenosis [46].

This brings up the question of when MRI and CT are most appropriate in the assessment of CAD. The results of these studies indicate that MR and CT studies are promising as techniques for the primary diagnosis of CAD [47]. In addition, these techniques are becoming widely available and increasingly being applied in the clinical setting. However, it has also been stressed that they are not advanced enough in their predictive value to exclude CAD when used singly. It has been suggested that combining two or more non-invasive techniques will provide the best view of the presence of CAD in the patient [47]. At present, invasive coronary catheterization cannot be replaced by non-invasive techniques. However, there is promise that the number of patients who need to undergo invasive techniques can be reduced by combining two carefully selected non-invasive approaches using CT and MRI [47].

Similar results were found in the study that compared CTA and MRA. The results of the study found that neither CTA nor MRA should be used as a single diagnostic technique for CAD [49]. This study concluded that the potential benefit of non-invasive techniques was more appropriate for patients who were symptomatic and who were at immediate risk for CAD after an initial risk stratification has been performed.
One of these suggested tests for risk stratification is stress test results. The results found that patients who were at the highest risk for CAD according to stress test results were the best candidates for detection of CAD using CTA [49]. One of the greatest concerns raised was radiation protection concerns for patients who are at risk for such exposure [49]. As other authors also indicated, the authors of this study felt that CTA and MRA warranted further consideration for the detecting and characterization of CAD and plaque burden.

In a study involving an older community patient cohort, all of whom were asymptomatic, NTG-induced coronary vasodilation by MRA was found to be independently associated with advanced CAD. The connection between these results and CAD were found to be significant [50]. The authors concluded that this technique might be an effective functional measure of subclinical coronary atherosclerosis [50]. However, it may be noted that the authors were cautious in recommending this non-invasive technique as a solid diagnostic approach. As other authors have indicated regarding other non-invasive techniques, it is apparent that research is needed that involves larger sample populations and clinical trials. Even though the non-invasive techniques explored in this literature review hold promise, they cannot be recommended as diagnostic techniques, particularly for subclinical CAD, until further studies have been conducted.

The bottom line in this literature review is whether non-invasive techniques are ready for use in the diagnosis of subclinical CAD. Douglas (2008) directly asked this question. The overall conclusion was that although this new technology, or new use of old technology, holds some promise for the future in diagnosing subclinical CAD, it is not yet ready to be used as a single diagnostic technique. However, Douglas agrees with other authors that non-invasive techniques can be useful if they are used in combination, rather than separately [51]. The overall consensus is that non-invasive techniques such as CT, MRA, calcium scores, and other non-invasive techniques hold the potential for providing an accurate diagnosis when used in combination, and they hold future promise after studies have been conducted to address their accuracy. The one exception to this was CIMT. It was found that carotid plaque performed better than CIMT in the prediction of coronary events in the future [52]. For now, it appears that many of the authors are in agreement that invasive techniques are still the gold standard for diagnosis of CAD, particularly in asymptomatic patients or in the early stages of the disease process. It was found that risk stratification was a critical factor in the ability of non-invasive techniques to diagnose CAD in its early space stages.
Sensitivity and Specificity

The choice of imaging techniques for the detection of coronary artery disease in the general population varies between different countries and regions. In addition, facilities make the choice of imaging techniques based on the availability, staff knowledge, and other factors [53]. The question is which of the techniques currently available represent the best choice in terms of the ability to detect CAD in its earliest stages. A study that compared a group of 475 patients with stable chest pain and an intermediate probability of having CAD were examined using a variety of imaging techniques. These techniques were compared to the results of IVUS [53]. It was found that coronary computed tomographic angiography had the highest accuracy with a sensitivity of 91% and specificity of 92% [53]. Myocardial perfusion had acceptable accuracy with a sensitivity of 74% and a specificity of 73% [53]. Wall motion imaging had the lowest accuracy, with a sensitivity of 74% and a specificity of 73%. This study considered coronary computed tomographic angiography to be the most accurate of the methods that were compared.

Single-scan stress perfusion cardiac computed tomography (SSPCT) is used to assess hemodynamically significant CAD. The study involved 29 patients with suspected CAD [54]. These results were compared to those obtained by cardiovascular magnetic resonance myocardial perfusion imaging (CMR-MPI), and invasive coronary angiography (ICA) [54]. CT was performed using coronary calcium scan, static SPECT for both coronary artery CT angiography (CCTA) and myocardial perfusion (PCT) during adenosine infusion and late-phase scan [54]. Per-vessel sensitivity and specificity were under the receiver operating characteristic curve. The sensitivity of each of the techniques was coronary calcium scan (92%), static SPECT for coronary CT (88%), angiography (CCTA) (90%) and myocardial perfusion (90%) [54]. Comparatively, the ability of SPECT was higher than that of CCTA when used alone. The study concluded that SPECT might facilitate the detection of hemodynamically significant CAD better than CCTA in patients with greater than or equal to 50% stenosis [54].

A comparison of myocardial computed tomography perfusion and myocardial magnetic resonance was performed using a multicentre trial of 92 patients with a mean age of 63.1 years old [55]. All patients underwent both types of tests. The results for the prevalence of CAD was 39% in the sample population by CT angiography and 64% by SPECT [55]. The per-patient accuracy was 63% for CT alone and 75% for MR perfusion alone. The sensitivity for CT was 92% and 83% for MRI. The specificity of CT was 45% and 70% for MRI. When using QCA with CT and MRI, the accuracy of CT perfusion was 82%, and 74% for MRI. The sensitivity under these parameters was 90% for CT and 69% for MRI [55]. The specificity was 67% for CT and 82% for MRI using QCA alone [55]. This study is significant because it used multiple diagnostic centers, which eliminates the variables associated with technician experience and techniques.
For persons with coronary artery disease, the presence of diabetes mellitus automatically places them in the high-risk category [56]. The role of cardiac computed tomography in asymptomatic diabetics is not well understood, as compared to those who are symptomatic or have advanced disease states [56]. Assessment with CCT in patients that have diabetes mellitus, the CAD burden is a strong predictor of future health-related events [56]. Studies indicate that as the duration of time the person has diabetes increases, the prevalence of normal coronary arteries on CCT scans progressively reduces [56]. This suggests that the use of CCT can be used to predict patients with diabetes mellitus who are at an increased risk for coronary events in the future by using the number of normal arteries, versus those that are diseased as the criteria for making this prediction.

The regular screening for CAD in diabetic patients has been considered controversial due to a lack of reliable non-invasive techniques [56]. The current guidelines recommend those with abnormal ECG or rest echocardiography to be weighted by CCT [56]. However, a recent trial among asymptomatic diabetic patients used CCT to screen for CAD. It did not affect the composite rate for all causes of mortality over a four-year period [56]. However, another study found that CCT findings allowed for improved risk stratification, discrimination, and reclassification of asymptomatic diabetes patients [56]. It was found that CCT imaging of multiple vascular districts and an examination of the distribution and progression rates of CAD in these districts has a significant predictive rate in patients with diabetes mellitus and asymptomatic CAD [56]. This technique of examining a region of arteries using CCT holds promise for improving outcomes for patients with diabetes mellitus, particularly those who have been diabetic for a longer period of time, or who have poor management of the disease. This method provides an alternative to an examination of a single artery or small section of arteries in the diagnosis and the classification of CAD in asymptomatic diabetic patients.

These studies favor CT techniques for specificity and sensitivity over MRI techniques. One of the considerations in evaluating studies that compare non-invasive techniques is that there may be differences between various facilities and methods that are used. In addition, the experience of the technician and reader may affect the results of single-site studies. Different results may be obtained when evaluating different facilities and patient population.

In a study that explored the diagnostic value of CCTA, SPECT and PET involving 208 patients, the sensitivity for CCTA was 90%, 57% for SPECT, and 87% for PET analysis [71]. However, the study also found that the diagnostic accuracy was highest for PET at 85%, compared to that of CCTA at 74%, and of SPECT at 77% [71]. Although PET had the highest accuracy, for the diagnosis of CAD, it seems that there is a sacrifice in sensitivity compared to CCTA, but it performs better in this respect than SPECT. PET has
also been attributed to better spatial resolution, coincidence detection, and accurate attenuation correction [72]. A preliminary study of a novel camera approach for high-efficiency (HE) SPECT myocardial perfusion imaging (MPI) has been shown to perform similar to conventional SPECT [73]. The sensitivity of visual MPI was 86% for those with greater than 50% stenosis and 86% for those with greater than 70% stenosis [73].

MPI with SPECT is a widely used technique and can be combined with CCTA [74]. As with other studies, the CCTA was found to be able to detect a defect, but SPECT was able to determine the functional status of the vessel disease and was a better predictor of future cardiac events [74]. In a study of 205 patients with stable angina pectoris and an intermediate to high pretest likelihood of CAD, patients were evaluated using stress and rest SPECT, coronary calcium scoring, and CCTA [75]. The calcium index had a predictive value of 0.73, which was increased to 0.85 with the addition of SPECT and to 0.90 with the addition of CCTA [75]. This study demonstrates that the layering of SPECT and CCTA increases the ability to diagnose patients with suspected significant coronary artery disease [75]. While these two techniques alone are effective in diagnosing CAD, this study demonstrates that when used together, they demonstrate a relatively accurate predictive value. Another study concluded that CCTA and SPECT could be performed within several minutes of each other using the same radiation dose, eliminating the need to re-dose the patient an increase in radiation exposure [76].

Myocardial CT perfusion imaging was compared to SPECT and a diagnosis of anatomically significant coronary artery disease that was first examined using invasive coronary angiography. The study involved 381 patients who underwent rest and adenosine stress CT perfusion imaging and rest with either exercise or pharmacologic stress SPECT before and within 60 days of the coronary angiography [77]. The results of the study demonstrated that the specificity for CT perfusion imaging was 88% for patients with a greater than 50% stenosis. This is compared to 62% for SPECT. The sensitivities were comparatively 55% for CT perfusion imaging and 67% for SPECT [77].

One factor of concern is the age of SPECT cameras. A survey of hospitals with SPECT units found that the sensitivity of the instrument decreases with the age of the instrument. Moreover, those that are older require a higher dose of radiation for the detection of CAD [78]. It was recommended that SPECT detectors be replaced optimally every five years, and every ten years at a minimum to maintain their diagnostic sensitivity [78].

New technology promises to revolutionize SPECT analysis through higher sensitivity and speed while maintaining a similar specificity for CAD. CZT SPECT is an innovation that can provide ultrafast SPECT results using solid-state semiconductor detectors for nuclear myocardial perfusion imaging. The
instrument has only a three-minute scan time for stress and two-minute scan time for rest [79]. A satisfactory clinical agreement was found between CZT and SPECT. CZT showed a 96% agreement with SPECT on a per patient basis and a 96.4% agreement on a per vessel basis [79]. It was found that the CZT camera allows a more fivefold reduction in the scan time and that the clinical information is similar to that produced by SPECT MPI [79].

This technology has the potential for reducing throughput times for patients, allowing more patients to access the diagnostic techniques, while maintaining the same level of confidence in diagnosis adds traditional SPECT techniques. This represents a significant advancement in technology and the ability to diagnose CAD. This high-speed SPECT technique was found to reduce the imaging time from 16 minutes for a conventional SPECT analysis to four minutes using the high-speed technology [80]. The image quality was found to be good or higher in 94% of the cases for high-speed SPECT. It was determined that the high-speed image quality also resulted in an eight-fold increase in system sensitivity over the conventional SPECT system used.

No studies could be found that provided sensitivity and specificity information for ultrasound techniques and compared it to CT or MRI. The only comparative studies found were for CT and MRI techniques using various methods. When recommending a technique that warrants further evaluation as compared to invasive techniques, CT is the best candidate to produce reliable results and will be the most likely to detect CAD. It might be noted that the studies found involved patients with intermediate CAD and the beginning of symptoms. These particular studies may not apply to populations with early stage disease.

**Invasive Techniques**

Intravascular ultrasonography (IVUS) is an invasive technique that has the capacity for producing high-resolution images and assessing early-stage CAD. Invasive coronary angiography is considered the standard for diagnosing CAD and is a technique that has a history spanning three decades [6]. IVUS images provide three-dimensional reconstructions that provide information about the length, volume, and reference landmarks of a plaque that is being examined. It is also highly effective in identifying different types of lesions. It has excellent predictive power for soft plaque, fibrous plaque, calcific plaque, and mixed plaque lesions. This imaging technique is typically used during the placement of stents. However, this technique is expensive and requires a high level of expertise for an accurate diagnosis. For this reason, only a designated portion of the population can receive this diagnostic technique. In general, invasive techniques are more expensive than non-invasive ones, but they tend to provide more accurate results. Conventional angiography
can show the presence or absence of atherosclerotic plaques, but IVUS can provide a three-dimensional image that provides much more information about individual lesions.

IVUS is an invasive technique, but it also provides more sensitive data. In one study, this technique was used as a comparator to blood lipid profile to explore coronary plaque tissue characteristics [27]. This study found that the LDL/HDL ratio may serve as a useful positive predictor for lipid-rich plaque and vulnerability to cardiovascular disease in ischemic heart disease patients. The question is regarding the practicality and usefulness of this technique. Even though IVUS is extremely sensitive in assessing CAD, it is also invasive and more expensive. Additionally, it is not pragmatic to use IVUS as a screening technique in patients with raised LDL/HDL ratios.

One of the essential factors in this study is whether non-invasive techniques can help to predict coronary artery disease as well as invasive techniques, at least from a practical standpoint. Invasive techniques, such as invasive coronary angiography, are considered to be the most sensitive test from a diagnostic perspective. However, they are not always practical. For one, they required the patient to be sedated, and some patients may not be able to withstand anesthesia. Additionally, they are more expensive, and insurance may not be willing to pay for these tests. Invasive tests are not always practical for every patient and in actual practice are rarely used. This fact leaves physicians to depend on non-invasive diagnostic tests for the majority of their patients with suspected coronary artery disease.

IVUS is appraised to be the most accurate technique for the diagnosis of CAD. However, it has the potential for placing the patient in danger of operational risks. This is particularly true in diabetic patients with complications of uncontrolled glucose levels. For each patient, the clinician must weigh the risks of surgery and consider it the decision regarding the method chosen for the diagnosis and monitoring of CAD.

**Literature Review Summary**

This literature review examined academic research on various diagnostic techniques for the detection of coronary artery disease. The purpose of the literature review was to discover what is known about the ability of various techniques to detect mild cases of plaque build-up and stenosis early in the disease process. It was found that numerous studies have been conducted on non-invasive techniques, but there were significantly fewer studies conducted on invasive techniques such as invasive coronary angiography. It is probable that this reflects practice in terms of the number of times invasive versus non-invasive diagnostic techniques are prescribed. As non-invasive techniques are often used as a screening tool for more invasive techniques, this creates a reduced sample population size for studies that examined invasive techniques.
The results included 80 studies that examined a variety of different techniques. The techniques were using ultrasound to measure intima media thickness, magnetic resonance, CCTA, and SPECT. The study also explored screening tools such as Framingham risk score and calcium score. It compared state-of-the-art invasive techniques, such as IVUS. The sensitivity and specificity of SPECT and CCTA were found to be sufficient to be used to detect CAD in diabetic patients before it becomes symptomatic. Of these techniques, SPECT had the highest sensitivity and specificity for detecting CAD in asymptomatic patients. A majority of the studies found considered SPECT to have a sensitivity and specificity ranging between 70 and just below 100 percent. The literature review results consider SPECT, CCTA, and ultrasound to be the most effective in detecting early CAD in asymptomatic diabetic patients.
10. RESEARCH METHODS

The research method chosen for this study was a systematic literature review. Upon examination of the literature, it was found that the studies used inconsistent patient populations and techniques to make the body of literature acceptable for use in techniques such as a meta-study. The literature was identified using a search that included Google scholar, PubMed, NIH, and Medline.

Using these sources, a search for strings that included “coronary artery disease and diabetes,” “coronary artery disease detection,” “coronary artery disease diagnosis,” and “coronary artery disease radiography” revealed tens of thousands, and in some cases, hundreds of thousands of search results. However, upon further examination of the results, it was found that a majority of the search was a result-focused on techniques and methods for curing coronary artery disease, rather than diagnostic techniques. Besides, it appears that new diagnostic techniques developed around 2006 and 2007 resulted in a plethora of new research regarding the most effective diagnostic techniques. It was found that clinical diagnostic recommendations appear to have been developed around 1997 and 1998. Therefore, current recommendations and practices regarding diagnosis are based on techniques that were not in existence the last time recommendations were updated. This was a key finding of concern regarding the body of literature that was found.

At the outset of this systematic literature review, it was expected that much more recent literature would be found. However, it appears that after the initial wave of literature around 2006 and 2007, there has been little advancement in terms of diagnostic techniques. Unfortunately, this left the researcher to rely on those studies that were produced around 2006 and 2007 when advances in diagnosis were the focus of academic research. Even though from the literary standpoint, the literature is almost ten years old, it is still reflective of standard practice in terms of the diagnosis progression and referral to more expensive and invasive techniques. Although the literature is for the most part, approximately ten years old, it still reflects current practice in the medical field. Despite the fact that research may yield advanced diagnostic techniques, several factors affect their actual adoption into practice. It takes some time for technology adoption to become diffused in the medical field. State-of-the-art in terms of medical research does not necessarily reflect the state-of-the-art in actual practice. Therefore, the literature located as part of this literature review was determined to be of practical significance because it represents actual practice when it comes to the everyday diagnosis of patients.
11. DISCUSSION OF RESULTS

This literature review examined both invasive and non-invasive diagnostic techniques for the detection of early coronary artery disease. Unfortunately, a majority of the literature was found focus on patients with advanced coronary artery disease. Literature was in agreement that for patients with significant stenosis and advanced plaque development, non-invasive techniques are adequate for determining the presence of disease. Non-invasive techniques were found to be the first line of diagnosis and patients only referred for more invasive testing once positive results from non-invasive tests are achieved. Unfortunately, non-invasive testing was found to be inadequate for patients that had mild or beginning stage disease. This means that patients with mild disease are not being referred for more invasive tests, and therefore their early coronary artery disease is not being addressed.

In terms of the ability to detect early coronary artery disease, coronary CT angiography was found to be this technique that was most in agreement with more invasive tests. It was found to be the most reliable in detecting early-stage coronary artery disease. Its results for advanced age coronary artery disease were remarkable, but it was still found to be useful in terms of detecting early-stage disease. When combined with other risk factors such as coronary calcium, blood pressure, the presence of diabetes, and other risk factors on the Framingham Risk Scale, coronary CT angiography was found to be reliable in the ability to detect early-stage disease. Unfortunately, in actual practice patients with early-stage disease may not be eligible for treatment due to financial considerations, such as insurance and resources.

Ultrasound techniques are the least invasive and least expensive of the diagnostic techniques that were examined. They can easily before performed in a physician’s office. However, they were also found to be dependent on the skill of the technician and on the number of images and angles that were taken into consideration for the calculation of plaque build-up in the arteries. Ultrasound was found to be a reliable technique, but only when sufficient sites were used, and images were taken in the calculation of the mean plaque build-up. Unfortunately, this is another case where the criteria for accurate assessment are only met in the research laboratory. Physicians and diagnostic facilities are often under pressure to see as many patients as possible, which means they are limited to the amount of time they can spend with each patient. This reduces the number of images that are typically taken from the number that research has deemed adequate for proper diagnosis.

If one were to rank the ability of the diagnostic tests to detect mild coronary artery disease in diabetic patients, invasive tests such as invasive coronary angiography would have to hold the top position. They are
the most sensitive tests, but they also have several disadvantages. The first is that they may be risky for some patients due to their use of anesthesia and potential for infection. In the research setting, invasive tests were used as the comparator for assessing the accuracy of other non-invasive tests. In terms of a single diagnostic test that comes closest to invasive coronary angiography, coronary CT angiography has the most considerable amount of positive literature support.

One of the diagnostic components that were found to be lacking in the literature, and presumably, in practice is a quick and easy screening technique that can accurately predict the potential for the development of more serious coronary artery disease. Ultrasound is the most widely used diagnostic technique in actual practice, but its ability to detect early-stage disease are limited. The recommendation for more expensive and more accurate testing such as coronary CT angiography was based on the results of the ultrasound and the assessment of other risk factors. Studies that examined the use of multiple risk factors in combination with non-invasive testing demonstrated that when taken as a whole, these methods can increase the chances for early detection of coronary artery disease. However, few of them stand alone as single tests that are inexpensive and can be used as a precursory screening tool.

Unfortunately, a lack of literature and research was focused on early detection. Much of the research was focused on the screening and detection of late-stage disease that is in dire need of invasive treatment such as revascularization. A significant effort was not found to be concentrated on the prevention of advanced disease states. This is a gap that necessitates being filled by future literature, as it would be a benefit to both patients and their physicians. The treatment of the early-stage disease can often involve lifestyle changes, medications, and other methods that are much less expensive than the methods that are used in advanced stages, such as revascularization. From a social standpoint, a focus on research into developing non-invasive diagnostic techniques that can accurately assess mild coronary artery disease in its early stages would be a significant saving to the healthcare industry. It would also result in more positive outcomes for patients.

It is not practical or advisable to refer every patient who has significant risk factors for coronary artery disease to be referred for the more accurate, but invasive testing methods. These methods are only reserved for cases that are most severe and in need of the most drastic interventions. However, the conundrum that the medical field faces is that those screening techniques that are easily performed within the primary physician setting at a relatively low cost are not accurate enough to serve the intended preventative medicine purposes. They can detect advanced disease dates and trigger more invasive and accurate testing. To date, in terms of precursory screenings, the best methods were those that used multiple risk factors in combination with ultrasound or another non-invasive testing such as coronary CT
angiography. Unfortunately, risk factor screening tends to miss some patients who are asymptomatic, but who have advanced stages of the disease. The literature review found that in some patients, it was little to indicate that they were at risk for coronary artery disease, yet when more invasive tests were performed, a significant disease state was found. This is the challenge being faced by physicians in their ability to diagnose early-stage coronary artery disease. It does not always show itself using less invasive techniques for qualitative screening, but it is not practical to send every patient with one or two risk factors for the more expensive and invasive testing methods. At present, the best screening methods combine multiple techniques in addition to non-invasive techniques such as ultrasound.
12. CONCLUSION

This systematic literature review examined current state-of-the-art in terms of diagnostic methods for patients with mild or beginning stage coronary artery disease. It compared invasive and non-invasive techniques in terms of its ability to detect milder forms of the disease and for its usefulness. What was found to be missing, was a single screening technique that was quick and easy, but that resulted in a high level of accuracy. Ultrasound and multiple risk factor assessment tools are the most common initial screening tests that are performed on diabetic patients. However, these techniques are restricted by their capability to find coronary artery disease in its early stages. Though, for patients with advanced disease, they were found to be adequate and lead to further testing and treatment of the condition. Nevertheless, intima media thickness demonstrated the ability to detect early-stage CAD in diabetic patients with a higher degree of accuracy and is considered to be an adequate diagnostic method. Of the methods found, SPECT analysis was found to be the most reliable and most specific non-invasive test. This technique is often combined with CCTA for increased diagnostic power.

In reference to the objectives of the study, the following conclusions can be drawn based on the literature examined. Eighty studies were used to assess the research objective. SPECT analysis, MRI, and using ultrasound to measure intima media thickness were found to be the most reliable techniques for the diagnosis of early-stage CAD in all types of patient groups. One of the main clinical considerations for assessing diabetic patients is that they may be at an increased risk when subjected to invasive procedures. SPECT analysis, CCTA, Coronary CT angiography, and using ultrasound to measure intima media thickness were found to be the most reliable technique for detecting CAD in its early stages in diabetic patients. The criteria for selecting radiological techniques for diabetic patients is dependent on their overall health and individual risk factors for CAD. However, ultrasound is recommended for diabetic patients, regardless of previous history of CAD.
13. RECOMMENDATIONS

The critical challenge that is being faced by the medical community is that it needs to develop techniques that are fast, easy, and low cost. Furthermore, these techniques need to have a sensitivity that is beyond the level of current screening techniques. Techniques such as ultrasound and qualitative screening meet the criteria of being low-cost and easy to perform. However, they are not currently sensitive enough to detect early-stage disease. Invasive techniques that can predict and detect early-stage coronary artery disease do exist, but they are not always practical from a financial or from the point of specific patient risk factors.

The main finding of this study, for practical purposes, is that more research needs to be conducted into the development of screening techniques that have higher sensitivity, and that are inexpensive and easy to conduct. For instance, improvements in ultrasound technique may hold the answer for detecting earlier coronary artery disease in diabetic patients in the future. Additionally, it was noted that the techniques that are currently available for early detection of coronary artery disease in diabetic patients, and the general patient population are inadequate in terms of sensitivity. The future of research in this area needs to focus on not only improving the sensitivity of screening techniques, but perhaps developing more accurate tests that are less expensive, and have a higher patient throughput rate than ones currently in existence.
14. REFERENCES


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