Technology Assessment

Technology Assessment Program

ECG-based Signal Analysis Technologies

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ECG-based Signal Analysis Technologies

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Duke Evidence-based Practice Center

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Peer Reviewers

We wish to acknowledge individuals listed below for their review of this report. This report has been reviewed in draft form by individuals chosen for their expertise and diverse perspectives. The purpose of the review was to provide candid, objective, and critical comments for consideration by the EPC in preparation of the final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers.

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Executive Summary

Introduction

While chest pain is a common symptom of patients presenting to clinics and emergency wards, only about six percent of patients presenting to the emergency room with acute chest pain are ultimately diagnosed with myocardial infarction. Identification of which patients with chest pain are experiencing myocardial ischemia or infarction is critical, since a delay in diagnosis can impede the application of effective therapies, such as thrombolytic agents or percutaneous coronary intervention (PCI). Tests that identify patients with significant coronary artery disease (CAD) serve as a means of facilitating aggressive implementation of secondary preventive strategies. Thus, accurate diagnostic tests and protocols are imperative in order to properly triage patients presenting with chest pain.

In patients where CAD is suspected – either because of the presence of risk factors for CAD or because of symptoms that may represent manifestations of CAD (e.g., chest pain) – the standard electrocardiogram (ECG) is one of the most commonly performed tests. The ECG is nearly universally available, noninvasive, easy to perform, relatively inexpensive, and can usually be completed in less than 10 minutes. However, a resting ECG has limited sensitivity for detecting CAD.

New devices that seek to improve ECG capabilities have been proposed – specifically, devices that are potentially capable of detecting significant CAD or myocardial ischemia. An enhanced ECG-based test might demonstrate greater positive or negative predictive values, thereby limiting the harms associated with delays in treatment, or providing the diagnostic information necessary to avoid invasive diagnostic or therapeutic interventions.

The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested this report from The Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the Duke Evidence-based Practice Center (Contract No. HHSA 290-2007-10066I). The purpose of the technology assessment is to summarize the available clinical and scientific evidence on ECG-based signal analysis technologies for evaluating patients with suspected CAD. Some ECG-based technologies have been used for other purposes (e.g., detection of malignant arrhythmias), but these are not the focus of the current report. Rather, this report will concentrate on commercially available ECG-based signal analysis technologies to inform AHRQ and CMS about the utility of these emerging technologies for diagnosing CAD.

We synthesized the existing literature on these technologies in response to the following key questions:

Key Question 1:

a) What devices and methods for ECG-based signal analysis are being used or are proposed to be used for diagnosis of CAD? What is the FDA status of these devices?

b) What are considered the "gold standard" tests for the diagnosis of CAD and what are their strengths and limitations?

Key Question 2:

a) What is the evidence for inter-rater, intra-rater, intra-patient, and intra-device variability?
b) What is the evidence for diagnostic test performance compared to the reference standard used in the study? What factors (confounders) affected test sensitivity and specificity?
c) What is the evidence that ECG-based signal analysis technologies impact diagnostic decisionmaking?
d) What is the evidence that ECG-based signal analysis technologies impact patient outcomes?

Methods

We developed an analytic model based on principles from Fryback and Thornbury's hierarchical model of diagnostic efficacy that guided our research questions, search strategy, data abstraction elements, and evaluations. We conducted a systematic search of the English-language literature indexed in PubMed® and searched the U.S. Food and Drug Administration (FDA) web site, Google™, and online patents. We sought to identify devices that improved CAD diagnosis through the use of signal analysis, spectral analysis, or other forms of advanced data transformation.

The purpose of the literature review for Key Question 1 was to identify potentially relevant devices and methods, while the purpose of the literature review for Key Question 2 was to synthesize the available scientific evidence that pertains to ECG-based signal analysis technologies that are potentially applicable to the diagnosis of CAD. The general eligibility criteria included:

- Relevant device.
- Tested on outpatients at low to intermediate risk for CAD.
- Relevant outcomes reported, including performance characteristics, effects on diagnostic or treatment decisions, or effects on patient outcomes.
- N > 30.

One investigator abstracted data from each included study into an evidence table and assessed study quality; the results were then checked for accuracy by a second investigator. Since few studies met eligibility criteria, we broadened the criteria to include studies evaluating individuals at higher risk for CAD (such as inpatients or those scheduled for cardiac catheterizations). Although these studies may have had poor applicability to the target population, they provided some relevant information. Data were synthesized qualitatively and, when appropriate, using quantitative methods. We excluded from formal analysis those devices for which we could not find evidence of commercial availability.

Results

Key Question 1a – Devices and Methods for ECG-based Signal Analysis

The horizon scan identified seven potentially relevant devices, including three that use body surface mapping and one that uses mathematical signal analysis. Of the seven devices, only the PRIME ECG® by Heartscape Technologies (body surface mapping) and the 3DMP™/MCG™/ mfEMT™ by Premier Heart (mathematical signal analysis; referred to here simply as the 3DMP) are cleared for marketing by the FDA and commercially available. One body surface mapping device (Visual ECG/Cardio3KG™ by NewCardio) is commercially available but not cleared; the other devices are not commercially available.

Key Question 1b – Gold Standard Tests for Diagnosing CAD

Coronary angiography (CA) remains the best reference standard for diagnosing CAD. Through interrogation and identification of the coronary anatomy, CA is currently the best available test to identify which patients may benefit from surgical intervention, medical management, or both. Among low-risk patients who are typically not referred for CA but undergo clinical observation and/or noninvasive testing instead, several noninvasive diagnostic tests have served as an acceptable reference standard. In these patients, results from noninvasive tests have correlated with the incidence of cardiovascular events. In particular, stress tests (with or without imaging) provide clinicians with incremental risk prediction that informs management and treatment decisions. Stress tests also provide prognostically important data that have been associated with patient outcomes such as exercise capacity, hemodynamic response, and magnitude of ST-segment abnormalities.

Resting ECGs, however, are not acceptable reference standards for the diagnosis of CAD, due mainly to their low sensitivity and specificity in both symptomatic and asymptomatic patients. As a result, new technologies for diagnosing CAD are most appropriately compared to the reference standard of CA or, at the very least, acceptable noninvasive reference standards such as stress imaging. Table ES summarizes our conclusion that CA remains the preferred reference standard for the diagnosis of CAD, while exercise stress testing with imaging serves as an acceptable reference standard. Appropriate use of biomarkers is an acceptable reference standard for the diagnosis of acute myocardial infarction, but not for CAD. The standard resting 12-lead ECG is not an acceptable reference standard due to its relatively poor accuracy in diagnosing low- to intermediate-risk patients with CAD.

Table ES. Potential reference standards for CAD diagnosis

Level of reference standard	Coronary artery disease
Preferred	Coronary angiography
Acceptable	Stress testing with imaging
Unacceptable	Imaging studies without exercise or pharmacological stress Resting 12- lead ECG Stress testing with ECG
Incomplete	Biomarkers (applicable only for identifying myocardial injury)

Abbreviations: CAD = coronary artery disease; ECG = electrocardiogram

Key Question 2a – What is the evidence for inter-rater, intra-rater, intra-patient and intra-device reliability?

Two studies meeting expanded eligibility criteria evaluated the 3DMP device in subjects scheduled for cardiac catheterization. These studies evaluated test and re-test reliability in a subset of 83 subjects using a 0 to 20 severity score. Study quality was good, but the original ECG electrodes were left in place for the second recording, eliminating electrode placement as a source of variability. Of the 83 subjects, the severity score was identical across the two tests in 68 (81.9 percent). Significantly, 11 of the disagreements differed by only a single point. For one study, the authors reported that only one of the nine disagreements would have changed the overall interpretation from normal to abnormal. The data presented are not sufficient to calculate measures of chance-corrected agreement that provide a better estimate than simple agreement.

No data on reliability were identified for the other devices.

Key Question 2b – Key Question 2b: What is the evidence for diagnostic test performance compared to the criterion standard used in the study? What factors (confounders) affected test sensitivity and specificity?

The FDA-cleared PRIME ECG was evaluated in six studies involving 2345 subjects with chest pain; five of these studies also evaluated the 12-lead ECG. Subjects were recruited from emergency departments, medical wards, or mobile coronary care units (CCUs) in Ireland, settings that may serve a population with a higher risk of acute myocardial ischemia than the target population for this report. The PRIME ECG was compared to cardiac biomarkers for the presence of acute myocardial injury. A bivariate random-effects model was used to combine results. The likelihood ratio positive (LR+) was 5.0 (95 percent CI 3.5 to 6.5) and likelihood ratio negative (LR-) was 0.37 (0.30 to 0.43); studies were statistically heterogeneous.

We performed a sensitivity analysis excluding the initial study, which clearly used a different diagnostic algorithm, and a second study with a very small sample size that was disproportionately weighted in the random-effects meta-analysis. The LR+ (6.5; 95 percent CI 4.2 to 8.8) and LR- (0.33; 0.28 to 0.39) were not substantially changed; statistical heterogeneity remained significant. Using these latter estimates of test performance, an abnormal PRIME ECG test in a patient with a pretest probability for clinically significant CAD of 50 percent would yield a posttest probability of 87 percent. A normal PRIME ECG would yield a posttest probability of 25 percent. The performance characteristics of the 12-lead ECG were neither clinically nor statistically significantly different from the PRIME ECG.

For the FDA-cleared 3DMP, no studies met our inclusion criteria, but four studies enrolled subjects at high risk or with known CAD, thereby meeting expanded inclusion criteria. Using a threshold of ≥ 4.0 on the 0 to 20 severity score, the 3DMP was evaluated in 920 subjects scheduled for coronary angiography. The summary estimate for LR+ was 5.3 (95 percent CI 3.8 to 6.9) and for LR- was 0.09 (0.04 to 0.13). A single low-quality study compared the 3DMP to 12-lead ECG; the 3DMP was more sensitive (97 percent versus 75 percent) and more specific (72 percent versus 41 percent) than the ECG. For a patient with a pretest probability for clinically significant CAD of 50 percent, a 3DMP score of 4 would yield a posttest probability of 84 percent. A 3DMP score < 4 would yield a posttest probability of 8 percent. Since there were differences in the subjects and reference standard, these results are not directly comparable to the PRIME ECG, or to the 12-lead ECG results discussed above.

Key Question 2c: What is the evidence that ECG-based signal analysis technologies impact diagnostic decisionmaking?

Our search strategy did not identify any eligible studies pertinent to this question.

Key Question 2d: What is the evidence that ECG-based signal analysis technologies impact patient outcomes?

We identified a single study that addressed this question. It tested the hypothesis that individuals with ST elevation myocardial infarction (STEMI) detected only by the PRIME ECG would have similar angiographic pathology and similar mortality and morbidity rates to those with STEMI detected by standard ECG. Adults (n = 1830) presenting to 12 tertiary care emergency departments with chest pain or symptoms suspicious for acute coronary syndrome who were at moderate to high risk for adverse cardiovascular outcomes were enrolled. Subjects underwent testing with a standard 12-lead ECG and the PRIME ECG, but direct comparisons were not made. Of the 1830 subjects enrolled, 91 (4.97 percent) had STEMI by standard ECG, and 25 of the remaining 1736 patients (1.44 percent) had STEMI by PRIME ECG. A subset of those with PRIME ECG STEMI (n = 14) underwent coronary angiography which showed similar anatomy to those with STEMI by standard ECG. Clinical outcomes at 30 days did not differ significantly between those with STEMI by standard ECG versus PRIME ECG only, but sample sizes were small, and the study was not powered to detect a

clinically significant difference. These results provide preliminary data that the PRIME ECG can detect a small subset of patients without STEMI by standard ECG who have angiographic and clinical outcomes that are similar to individuals with STEMI by standard ECG.

Discussion and Conclusions

There is currently little available evidence that pertains to the utility of ECG-based signal analysis technologies as a diagnostic test among patients at low to intermediate risk of CAD who present in the outpatient setting with the chief complaint of chest pain. The limited evidence that is available demonstrates proof of concept, particularly for the PRIME ECG and 3DMP devices. Further research is needed to better characterize the performance characteristics of these devices to determine in what circumstances, if any, these devices might precede, replace, or add to the standard ECG for the diagnosis of CAD among patients who present with chest pain in the outpatient setting. The randomized controlled trial (RCT) study design is best suited for evaluating the impact that ECG-based signal analysis technologies may have on clinical decisionmaking and patient outcomes, but there are indirect approaches that might be applied to answer these questions.

Chapter 1. Introduction

Epidemiology of Coronary Artery Disease (CAD)

Cardiovascular disease remains the leading cause of mortality in the United States. An estimated one in three adults has one or more types of cardiovascular diseases, including hypertension, coronary artery disease (CAD), heart failure, stroke, and congenital defects.[1] Approximately 13 million patients have CAD. Of these individuals, approximately seven million have angina pectoris (chest pain) and have had a myocardial infarction.[1] While chest pain is a common symptom of patients presenting to clinics and emergency wards, only about six percent of patients presenting to the emergency room with acute chest pain are ultimately diagnosed with myocardial infarction.[2] Identification of which patients with chest pain are experiencing myocardial ischemia or infarction is critical since a delay in diagnosis can impede the application of effective therapies, such as thrombolytic agents or primary percutaneous coronary intervention (PCI). Tests that identify patients with significant CAD serve as a means of facilitating aggressive implementation of secondary preventive strategies. In a large national sample, only 37.6 percent of patients without known CAD referred for elective coronary angiography, most of whom had undergone prior noninvasive testing, were found to have obstructive CAD.[3] Thus, accurate noninvasive diagnostic tests and protocols are significantly important in order to properly triage patients presenting with chest pain, and currently available tests identify a relatively low proportion who will benefit from secondary prevention.

CAD vs. Ischemia vs. Infarct

A diagnosis of CAD results from the findings suggestive of atherosclerotic plaque within the coronary arteries. This plaque may or may not represent an obstruction to coronary blood flow. The build-up of atherosclerotic plaque is a progressive and diffuse process that develops within the coronary arteries. Plaque formation may begin prior to middle age, as evidenced from previous autopsy studies of young soldiers and young victims of motor vehicle accidents. CAD is believed to have a polygenetic basis, influenced by an individual's genes, as well as their susceptibility to environmental influences (such as diet and exercise). The progression and severity of CAD is associated with advancing age, such that older individuals have a higher likelihood of having CAD, even without the presence of other risk factors.

Patients with CAD may or may not present objective evidence of myocardial ischemia (defined as a mismatch between coronary blood flow and myocardial oxygen demand). Traditional observations have indicated that myocardial ischemic imbalance may begin to occur when the luminal narrowing of the coronary artery exceeds 70 percent. In a clinical setting, ischemia may trigger an episode of angina pectoris or other equivalent symptoms of reduced oxygen delivery to the myocardium (e.g., shortness of breath, epigastric discomfort, jaw or arm pain/heaviness). Stress tests (whether solely electrocardiographic or combined with imaging modalities), are

designed to qualitatively or quantitatively identify decreased regional myocardial blood flow in the distribution of its corresponding coronary artery. Patients who exhibit demonstrable ischemia on stress testing and whose symptoms are not optimally managed with medical therapy are often referred for diagnostic angiography and elective revascularization.

Prolonged ischemia may result in myocardial infarction, although infarction can also develop in nonobstructive coronary vessels as a consequence of a spontaneous atheromatous plaque rupture. The hallmark of infarction is elevation of cardiac muscle biomarker serum levels, including cardiac troponin and the creatine kinase MB isoenzyme. Elevations of cardiac troponin serve as evidence of myocardial cell death. Compared to patients without a prior myocardial infarction, patients with a history of myocardial infarction are at higher risk for future cardiac events, including recurrent infarction and death.

Diagnostic Testing and Risk Stratification for CAD

Patient history and physical examination are the starting points of a diagnostic workup for suspected CAD. Additional diagnostic testing may be indicated if such testing can support or modify (in a clinically meaningful manner) the clinician's initial risk assessment of the patient, thereby helping to clarify the appropriate management strategy. Validated risk scores have been developed for a variety of clinical settings, including the emergency department and general medical setting.[4]

Figure 1 illustrates the relationship between risk stratification and clinical decisionmaking for patients without known CAD who present with chest pain or other symptoms for which CAD-related myocardial ischemia is a possible etiology. Tests designed to diagnose CAD may not be indicated in patients who are deemed to be at very low risk, such as in the case of a healthy 22-year-old woman with atypical chest pain and no known risk factors for CAD. Similarly, a 73-year-old man with diabetes, hypertension, and a long history of tobacco use who presents with exertional substernal chest pain is likely to be treated initially for presumptive myocardial ischemia without confirmatory testing for CAD. In neither scenario would diagnostic testing be expected to move a patient across decisionmaking thresholds (indicated by the letters A and B in Figure 1).

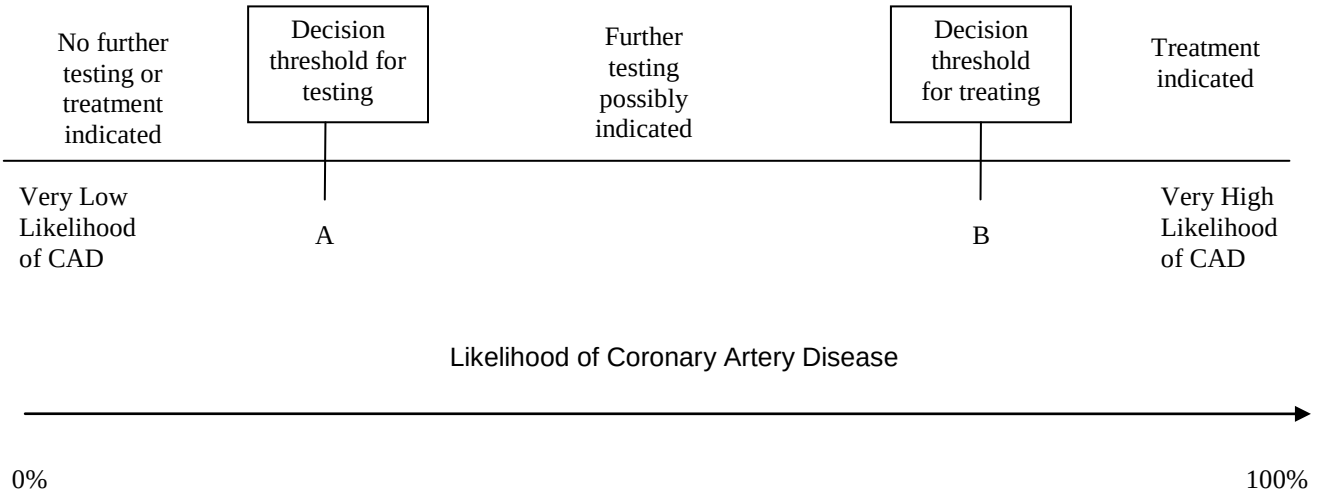

Figure 1. Decision threshold conceptual model

Noninvasive diagnostic testing may, however, be particularly informative for the large population of patients who are best categorized as having a low to intermediate risk for CAD, yet who present with chest pain or other symptoms suggestive of CAD. For this category of patients, noninvasive test results have proven to be useful for posttest decisionmaking.[5] Within this framework of pretest risk prediction, decisions regarding which diagnostic test to use, or the decision not to perform a test at all, must be made.

The Role and Limitations of the ECG in the Diagnostic Workup of CAD

In patients where CAD is suspected – either because of the presence of risk factors for CAD or because of symptoms that may represent manifestations of CAD (e.g., chest pain) – the standard ECG is one of the most commonly performed tests.[6] By providing a "snapshot" of the heart's electrocardiographic activity, the ECG allows the reader to assess the presence of myocardial infarct, ischemia, hypertrophy, or arrhythmia, as well as the risk of inherited cardiomyopathies such as long-QT syndrome or Wolff-Parkinson-White syndrome. The ECG is nearly universally available, and is noninvasive, easy to perform, relatively inexpensive, and expedient (an ECG can usually be performed in less than 10 minutes). In addition, most ECG machines are equipped with computerized diagnostic algorithms that provide an immediate preliminary interpretation, which is made available for physician over-read.

However, the ECG has several significant limitations. First, an ECG represents electrocardiographic activity at a single moment in time while the patient is at rest. This means that an ECG cannot provide information about a patient's functional capacity. Moreover, ECGs often need to be repeated as a patient's clinic condition changes.

Second, wave pattern recognition and comparison to expected normal findings are used in ECG assessment, but the final analysis is open to subjective interpretation by the reading physician. Finally, a resting ECG's diagnostic utility is limited, given that the test's estimated sensitivity for the diagnosis of CAD is low (between 12 and 70 percent depending on the population studied and criteria applied).[7,8]

Evaluating Emerging ECG-based Technologies

New devices that seek to improve ECG capabilities have been proposed – specifically, devices that are potentially capable of detecting significant CAD or myocardial ischemia. An enhanced ECG-based test might demonstrate greater positive or negative predictive values, thereby limiting the harms associated with delays in treatment (as in the example of a posterior myocardial infarction that was not evident on the 12-lead ECG), or by providing the diagnostic information necessary to avoid invasive diagnostic or therapeutic interventions.

Ideally, all new tests would be compared to the reference standard that most accurately discriminates between individuals with and without disease. Additionally, the relative advantages of a new test should be evaluated in comparison to existing technology. For example, in patients with low to intermediate risk of CAD who present with chest pain, an enhanced test might serve as a better initial diagnostic instrument. Enhanced ECG technology could be used instead of, or in addition to, the standard 12-lead ECG. Regardless of whether a new test is intended to complement or replace the standard ECG, the performance characteristics of both technologies should be evaluated relative to one or more appropriate reference standards.

Objectives of this Report

The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested this report from The Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the Duke Evidence-based Practice Center (Contract No. HHSA 290-2007-10066I). The purpose of the technology assessment is to summarize the available clinical and scientific evidence on ECG-based signal analysis technologies for evaluating patients with chest pain at low to intermediate risk for CAD. The report does not address the use of these technologies to screen asymptomatic individuals for CAD or focus narrowly on acute coronary syndrome that may present with symptoms other than chest pain. A horizon scan was performed to identify emerging technologies that noninvasively analyze electrical signals from the heart, which we have collectively termed "ECG-based signal analysis technologies. One form of signal analysis is the signal-averaged ECG which analyzes the ECG by computing the average of numerous ECG complexes. This increases the signal-to-noise ratio, allowing for the detection of small, microvolt signals. This technique is most often used in the detection of low amplitude signals at the terminal portion of the QRS complex (also known as ventricular late potentials). These late potentials may reflect inflammation, edema, fibrosis, or

infarct. A newer form of ECG-based signal analysis utilizes mathematical modeling to derive clinical indices. These indices are then compared with an empirical database to generate differential diagnoses and a heart disease severity score. Another ECG-based signal analysis technology is body surface mapping (also called body surface potential mapping) which uses up to 120 ECG electrodes to expand the measured area of electrocardiographic activity. Data collected by these electrodes are used to construct a three-dimensional representation of the thorax. Some ECG-based signal analysis technologies have been used for purposes other than detecting CAD, but these uses are not the focus of the current report. For example, we specifically excluded the use of ECG-based signal analysis technologies for measuring heart rate variability since this is aimed at predicting malignant arrhythmias. This report concentrates on commercially available ECG-based signal analysis devices to inform AHRQ and the CMS about the utility of these emerging technologies for diagnosing CAD.

Chapter 2. Methods

Key Questions

The sponsor of this report, AHRQ, identified two key questions to be addressed. The Duke Evidence-based Practice Center (EPC) research team further clarified these questions and research objectives through consultation with the AHRQ Task Order Officer assigned to the project.

At the most general level, the objectives of this report are to: (1) identify and describe devices and methods for ECG-based signal analysis that are being used, or are proposed to be used, for the diagnosis of CAD; and (2) summarize the available clinical and scientific evidence on the use of ECG-based signal analysis technologies for the diagnosis of suspected CAD in the ambulatory setting under nonprovocative conditions. These questions can be further broken down as follows:

Key Question 1:

a) What devices and methods for ECG-based signal analysis are being used or are proposed to be used for diagnosis of CAD? What is the FDA status of these devices?
b) What are considered the "gold standard" tests for the diagnosis of CAD and what are their strengths and limitations?

Key Question 2:

a) What is the evidence for inter-rater, intra-rater, intra-patient, and intra-device variability?
b) What is the evidence for diagnostic test performance compared to the reference standard used in the study? What factors (confounders) affected test sensitivity and specificity?
c) What is the evidence that ECG-based signal analysis technologies impact diagnostic decisionmaking?
d) What is the evidence that ECG-based signal analysis technologies impact patient outcomes?

Analytic Framework

We developed an analytic framework based on principles from Fryback and Thornbury's hierarchical model of diagnostic efficacy.[9] This framework proposes a multilevel evaluation of diagnostic tests, beginning with studies of reliability, progressing through diagnostic test performance, and ending with the effects on relevant patient outcomes. This analytic framework (Figure 2) guided our research questions, search strategy, data abstraction elements, and evaluations.

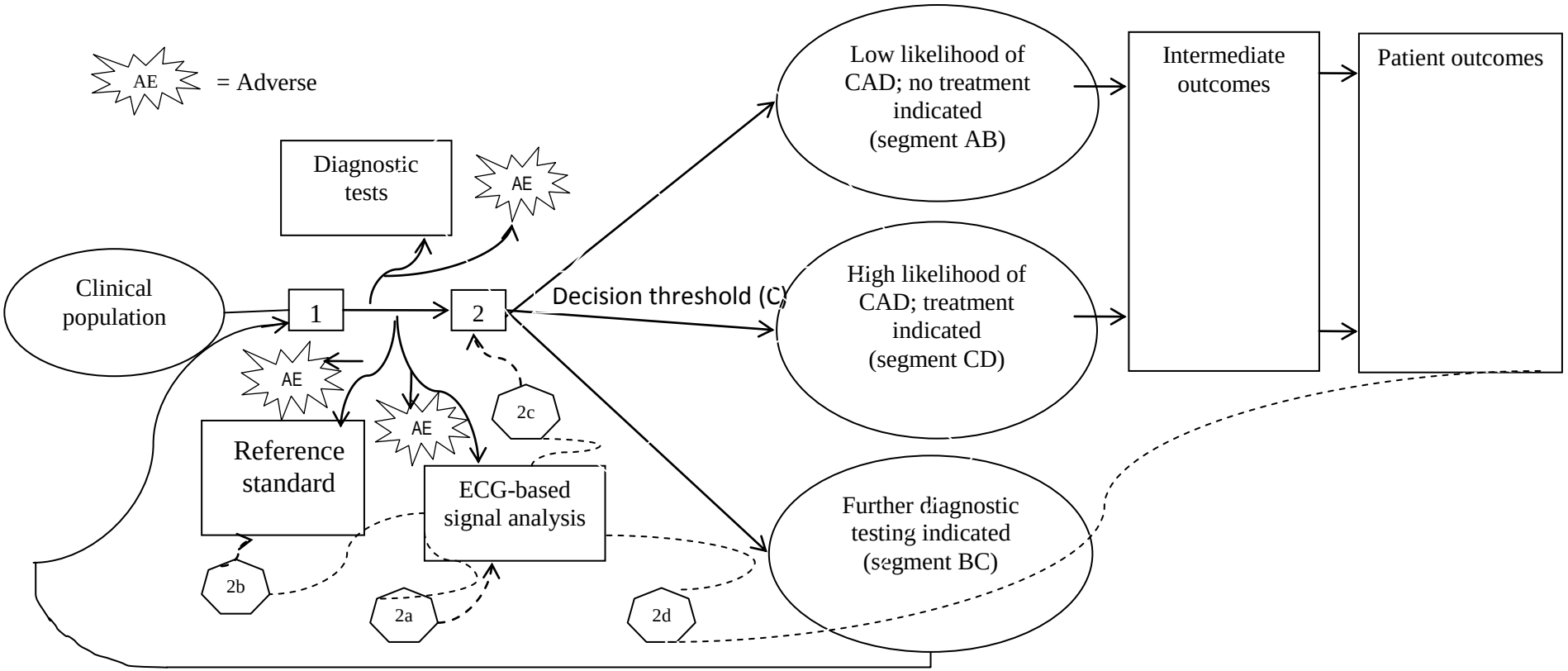

Figure 2. Analytic framework

Approach

Sources of Information and Review Methods

The sources of information consulted, as well as the review methods used by the Duke team, varied according to the key question being addressed. For Key Question 1, we conducted a comprehensive review of literature and gathered and collated information from the FDA, device manufacturers, and other relevant sources. Key Question 1 also involved summarizing information about commonly used diagnostic tests, procedures, and strategies. Both Key Question 1 and Key Question 2 required similar systematic literature search strategies, but the data extracted from the eligible studies were quite different; the purpose of the literature search for Key Question 1 was to identify potentially eligible devices or methods, while the purpose of the literature search for Question 2 was to synthesize the available scientific evidence that pertains to ECG-based signal analysis technologies that may potentially be applicable to the diagnosis of CAD in a patient without known CAD, but who presents with chest pain.

General Approach

We conducted a systematic search of the English-language literature indexed in PubMed® and a search of the U.S. Food and Drug Administration (FDA) web site, Google™, and online patents. We sought to identify devices that improved CAD diagnosis through their use of signal analysis, spectral analysis, or other forms of advanced data transformation. We specifically excluded devices that used imaging techniques such as echocardiography or coronary angiography. We identified the major categories of electrocardiography, including body surface mapping potential, phonocardiography, and magnetocardiography.

After discussions with our stakeholders, we narrowed our focus to devices that: (1) obtain and interpret information about the heart's electrical activity; (2) interpret the electrical signal in a novel way using advanced mathematics (e.g., fast Fourier transform or spatial imaging); and (3) interpret specifically for the purpose of diagnosing CAD or myocardial ischemia. We used the above-stated criteria to define ECG-based signal analysis devices for the purpose of this report.

We limited our search to named devices for which we could identify a manufacturer or distributor. We reviewed all of the studies identified that reported on any device or method that met the above-stated criteria. We excluded from formal analysis those devices for which we could not find evidence of commercial availability.

Literature Sources and Search Strategies

We devised three main strategies for gathering information. First, we searched PubMed from January 1949 to May 2009 using search terms for the specific devices identified in the horizon scan, terms for signal analysis or spectral analysis, and terms for CAD or myocardial ischemia. For studies of reliability, we added terms related to precision, test-retest reliability, and inter- or intrarater reliability. The exact search

strategies used are detailed in Appendix A. The titles and abstracts of all citations retrieved through searches of PubMed were screened by two reviewers for potential inclusion. All citations that appeared to report primary data relevant to the study question were retrieved for full-text review.

Second, we conducted an extensive search of the "gray literature" on this subject. A single investigator searched each of the general gray literature sources listed in Appendix B, including the ClinicalTrials.gov web site (www.clinicaltrials.gov), in order to identify potentially relevant devices. We were assisted in this effort by a representative of the FDA and a Duke University Medical Center librarian with expertise in gray literature searching, who suggested sources and search terms.

Finally, we contacted Drs. Mark Donahue and Mitchell Krucoff (both of Duke University Medical Center), who are experts in the field of ECG technologies, to ask if they were aware of any additional devices that should be included in our review.

Inclusion and Exclusion Screening Criteria

Titles and abstracts were screened for eligibility by two investigators and selected for full-text review if either investigator deemed the study potentially eligible. Eligibility criteria were specific to each question and are detailed in Appendix C. General eligibility criteria included:

- Relevant device.
- Tested in outpatients at low to intermediate risk for CAD.
- Relevant outcomes reported, including performance characteristics, effects on diagnostic or treatment decisions, or effects on patient outcomes.
- N > 30.

Since few studies met eligibility criteria, we broadened the criteria to include studies evaluating individuals at higher risk for CAD (such as inpatients or those scheduled for cardiac catheterizations). These expanded eligibility criteria were applied to questions 2b-2d. Although these studies may have had poor applicability to the target population, they provided some relevant information.

Data Abstraction

For eligible studies, an investigator abstracted data into an evidence table and assigned quality ratings. Abstracted data included first author, year of publication, study design, patient selection criteria and patient characteristics, information about the study device, reference tests used, device and reference test performance characteristics, and quality assessment ratings. A second investigator overread abstracted data and independently assigned quality ratings. Disagreements were resolved by consensus. Quality ratings were based on the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) instrument[10-12] and included characteristics of sample selection, adequate description of the index and reference tests, blinded interpretation of the index and reference tests, presence of incorporation and verification bias, and an assessment of

the analysis approach appropriateness (Appendix D). Appendix E presents summary evidence tables for all included studies. Appendix F provides details of the reviewers' assessment of quality for each eligible study.

Device performance was summarized using sensitivity, specificity, and likelihood ratios. A test's sensitivity describes the proportion of subjects with disease who have an abnormal test. Test specificity describes the proportion of subjects without disease who have a normal test. A likelihood ratio is a measure that may be more useful to clinicians since a simple nomogram allows posttest disease probabilities to be calculated readily. The likelihood ratio positive (LR+) describes how many times more likely it is that an abnormal test comes from a patient with disease versus a patient without disease. The likelihood ratio negative (LR-) describes how many times more likely it is that a normal test comes from a patient with disease versus a patient without disease.

When studies were conceptually homogeneous, we used random-effects bivariate meta-analysis to compute a summary estimate of performance.[13] For studies that derived a test algorithm in a training set and tested performance in a validation sample, we analyzed performance characteristics from the validation set. We evaluated statistical heterogeneity by inspecting forest plots and computing Q and I^2 statistics. Since the Q test is underpowered, we set the threshold for significant heterogeneity at $p < 0.10$. For the I^2 test, a suggested interpretation is to assign the terms low, moderate, and high to I^2 values of 25 percent, 50 percent, and 75 percent, respectively.[14]

Peer Review Process

We employed internal and external quality-monitoring checks through every phase of the project to reduce bias, enhance consistency, and verify accuracy. Examples of internal monitoring procedures include three progressively stricter screening opportunities for each article (abstract screening, full-text screening, and data abstraction); involvement of at least two individuals (an abstractor and an over-reader) in each data abstraction; and agreement of at least two clinicians on all included studies.

Our principle external quality-monitoring device was the peer-review process. Nominations for peer reviewers were solicited from several sources, including clinical content experts from the Duke Research Team and the AHRQ. The list of nominees was forwarded to the AHRQ for vetting and approval.

Chapter 3. Results

Key Question 1a: Devices and Methods for ECG-based Signal Analysis

Overview of Devices Identified

Results of the horizon scan and gray literature search are summarized in Appendix B. The horizon scan identified seven potentially relevant devices (Table 1):

Table 1. ECG-based signal analysis devices identified by the horizon scan

Device name	Manufacturer	Commercially available*	FDA cleared†	Device type
FDX-6521	Fukuda Denshi	No	No	SA
VCM-3000	Fukuda Denshi	No	No	BSM
Prime ECG®	Heartscape	Yes	Yes	BSM
Visual ECG/Cardio3KG™	New Cardio	Yes	No	BSM
3DMP™/MCG™/mfEMT™	Premier Heart	Yes	Yes	MA
Model 1200	Arrhythmia Research Technology	No	No	SA
Predictor™	Corazonix	No	Yes	SA

Abbreviations: BSM = body surface mapping; ECG = electrocardiogram; FDA = U.S. Food and Drug Administration; MA = mathematical analysis; SA = signal-averaging.
*Commercially available from a device manufacturer.
†Cleared for marketing the by FDA.

A device may be cleared for marketing by the FDA when it is determined to be substantially similar to a predicate device. Of the devices listed in Table 1, only the PRIME ECG® and 3DMP™/MCG™/mfEMT™ (referred to hereafter as the 3DMP) are currently cleared by the FDA and commercially available. Both devices received clearance for marketing for the indication of recording ECG signals. The Predictor is cleared by the FDA, but apparently no longer available. Of the four devices that are not FDA cleared, the FDX-6521 and VCM-3000 manufactured by Fukuda Denshi and the 1200 EPX by Arrhythmia Research Technology appear to be no longer commercially available; the Visual ECG/Cardio3KG™ (referred to hereafter as the Cardio3KG) manufactured by NewCardio is commercially available. The three commercially available devices include two body surface mapping devices (PRIME ECG and Cardio3KG) and one device that uses mathematical analysis (3DMP).

Body Surface Mapping Devices

The PRIME ECG utilizes a disposable vest that incorporates additional electrodes to measure electrocardiac activity from the front, back, and sides of the torso to create an “80-lead ECG.” ECG recordings showing ST segment elevation, suggestive of acute myocardial injury, are represented on a torso map to localize and demonstrate the extent of injury. Areas on the torso map corresponding to regions of myocardium demonstrating ST segment elevation are color coded red. Areas of ST depression are blue, and neutral areas are green.

The Cardio3KG extracts data from the standard 12-lead ECG to generate a three-dimensional representation of cardiac electrical activity. Without requiring additional electrodes, this device transforms 12-lead ECG information into X, Y, and Z components of the heart vector, normalizes the lead vectors, and displays virtual lead voltages on a three-dimensional model of the heart.

Mathematical Analysis Devices

The 3DMP device (also referred to as the MCG or mfEMT) utilizes ECG data from two of the 12 standard leads (leads II and V5) to perform frequency and time domain analyses. Recordings for over 82 seconds are amplified, digitized, encrypted, and sent securely over the internet to Premier Heart Datacenter, where signal analysis and mathematical transformations are performed to derive indices that, in particular patterns, may signify the presence of disease. The data are compared to a large empirical database to determine a "Final Diagnosis" and "Severity Score"; these are then securely reported back over the internet within several minutes to the requesting provider. We were unable to determine the details of the proprietary severity scoring.

Key Question 1b: Gold Standard Tests for Diagnosing CAD

Overview

Diagnostic tests for CAD can be categorized as either invasive or noninvasive. Invasive tests include cardiac catheterization with coronary angiography and postmortem autopsy. Noninvasive tests utilize technologies that permit either visualization of the heart and corresponding vasculature, or interpretation of electrical signals generated by a beating heart. With the exception of an autopsy, no invasive or noninvasive test yields a definitive diagnosis of CAD. Rather, these tests are used to infer the presence of CAD by identifying coronary artery occlusion, irregular electrical signals, abnormal heart wall motion, or damage to myocardial cells. Our discussion emphasizes the options for reference standards that might be considered in research studies to evaluate a new diagnostic technology.

Invasive Testing – Coronary Angiography

Description. Invasive coronary angiography (CA) involves the insertion and manipulation of slender catheter tubes from a percutaneously accessed arterial site (most commonly via the femoral artery) to the origin of the coronary arteries. Iodinated contrast agents are injected through these tubes, lighting up the arterial structure, and allowing x-ray images to be obtained. These images are then used in determining a diagnosis of and/or treatment for CAD. The cineangiograms are the recorded real-time X-ray images of the epicardial coronary arteries. These images are subsequently reviewed by the physician to determine the optimal management strategy for the patient. Lesions that obstruct 70 percent or more of the coronary lumen significantly restrict coronary blood flow and may cause functional obstruction (e.g., angina or angina-like symptoms). The traditional cutpoint of 70 percent obstruction is often accepted as the threshold for significant CAD and may prompt revascularization. Nevertheless, data challenging qualitative angiographic grading for revascularization on patient outcomes have recently been reported.[15]

Strengths. The current role of CA has been to aid in the identification of patients who will benefit clinically from revascularization.[16-20] CA can be used in conjunction with contrast ventriculography to determine left ventricular function. CA is the preferred reference standard for diagnosing the severity of obstruction in the coronary arteries, as noninvasive testing currently lacks the sensitivity to exclude left main or multivessel CAD, which are independently associated with poor survival.[21-23] CA is generally considered to be the best available method of diagnosing CAD.

Limitations. CA is primarily restricted to identifying the degree of major epicardial vessel luminal stenosis. Furthermore, CA cannot provide information regarding the patient's exercise capacity, hemodynamic response to exercise, or functional status. Although CA is generally considered a relatively safe procedure, serious complications (including death, myocardial infarction, and embolization) have been reported. The rate of serious complication or death associated with CA is approximately 0.1 percent.[21] Finally, of all the frequently used tests for diagnosing CAD, CA is the most expensive.

Noninvasive Testing

Noninvasive tests are often used in the workup of undifferentiated chest pain in outpatient or acute care settings to provide incremental data and refine the pretest clinical suspicion of CAD. Patients with negative (i.e., normal) findings on noninvasive tests may be triaged to prevention and clinical observation management strategies, whereas patients with positive findings may be referred for CA in order to determine the presence or absence of CAD. Supported by the literature, this approach has been used to refine the selection of patients with the highest likelihood of significant CAD and for whom revascularization may improve clinical outcomes, while at the same time minimizing unnecessary referrals for more expensive and potentially risky invasive testing. Patients with indeterminate or conflicting results on initial noninvasive testing may be triaged to either strategy (prevention and clinical observation or CA) or referred for additional testing. This determination is largely dependent upon the posttest risk assessment by the clinician.

A) Electrocardiography:

Description. The standard clinical ECG detects the electrical field generated by the ion currents in cardiac cells through detection of potential differences on the skin surface. The signal is amplified, filtered, and displayed as a recording which is then interpreted either computationally or by medical personnel.

Strengths. The ECG is inexpensive, universally available, and broadly understood across medical disciplines.

Limitations. The ECG lacks sufficiently high sensitivity for detection of CAD to be considered an adequate reference standard.[7,8,24]

B) Cardiac computed tomography:

Description. Computed tomographic angiography, or cardiac computed tomography (CCT) uses modified software and hardware to acquire images of the luminal patency of the epicardial coronary arteries after administration of an intravenous contrast agent. Once obtained, the images are reformatted and reviewed for quantitative estimation of luminal narrowing in the coronary artery. If present, luminal narrowing is suggestive of CAD.[25,26] Sensitivity is estimated to be 85 percent, and specificity 95 percent

Strengths. CCT provides noninvasive anatomical detail of both the heart and the coronary arteries. CCT can identify unrelated or unsuspected diseases, which may or may not be related to the patient's symptoms (e.g., lung mass, pulmonary embolus, or aortic dissection). Operating characteristics (sensitivity/specificity) compare well with currently used stress imaging studies.

Limitations. CCT is relatively expensive. The procedure involves radiation exposure and the administration of an intravenous contrast (thus, CCT is not appropriate for patients with renal insufficiency). The procedure does not readily identify CAD in distal segments of the coronary arteries. CCT is a relatively new technology; as such, there is limited information about how information it generates correlates with long-term clinical outcomes.

C) Biomedical markers:

Description. Patients with acute myocardial infarction demonstrate elevations of serum cardiac biomedical markers (biomarkers) such as troponin or creatinine kinase (CK-MB). These values are usually elevated within 6 to 8 hours after onset of myocardial infarction. Elevation of biomarkers carries prognostic value after myocardial infarction; testing for such elevation is, therefore, part of the standard procedure used to diagnose myocardial infarction.

Strengths. Tests of biomarkers are widely available, and results are rapidly and safely obtainable. Interpretation of findings is relatively straightforward. When measured serially, the troponin and CK-MB biomarkers carry high sensitivity (89 to 95 percent) and specificity (95 percent).[27-29] Cardiac troponin is favored, since this marker provides greater specificity than CK-MB. However, since troponin results may remain elevated for up to 10 days, CK-MB is useful in assessing the timing of acute myocardial infarction.

Limitations. Biomarkers may be elevated in conditions unrelated to myocardial infarction, so results must be interpreted in the context of clinical presentation and other available test results. Conditions unrelated to myocardial infarction that may contribute to elevated biomarkers include sepsis, pulmonary embolus, renal failure, tachycardia,

and valvular heart disease. Biomarkers have no role in screening for, or diagnosing, CAD outside of the presence of acute myocardial infarction.

Stress Testing

A) Stress testing with ECG:

Description. Exercise, when used as the stressor, can provide both diagnostic and prognostic information in patients with either suspected or known CAD. Both treadmill and bicycle protocols have been used to evaluate exercise time, intensity, and reproducibility of clinical symptoms. The standard 12-lead ECG, along with clinical symptoms and vital signs, is evaluated for changes during exercise. ECG criteria that have been standardized to suggest an abnormal test result rely on the finding of ST segment depression of 0.01mV (1 mm) that is horizontal or down-sloping on three consecutive beats. Patients unable to exercise would normally undergo a pharmacologic "stress" test in conjunction with an imaging modality (see section B, below).

Strengths. Stress testing is generally safe, widely available, well validated, and less costly compared to other forms of cardiac diagnostics. Stress testing can provide useful prognostic data. In a recent meta-analysis of the relevant studies, sensitivity and specificity were 68 percent and 77 percent, respectively, but values are lower among low-risk patients.[22] A normal exercise ECG has excellent negative predictive value.

Limitations. Stress testing is associated with relatively high rates of false-positive results in women, and it cannot be reliably interpreted in patients with a variety of different baseline ECG abnormalities. Other limitations include difficult-to-interpret results in the setting of valvular heart disease, left ventricular hypertrophy, left bundle branch block, or patients on certain heart rate lowering medications such as digoxin. Because of its low sensitivity, with correspondingly high likelihood of misclassifying patients, stress testing with ECG alone is not an adequate reference standard for CAD diagnosis.

B) Stress testing with imaging:

Description. The addition of a cardiac imaging component to the standard exercise ECG stress test is intended to improve test specificity by differentiating true-positive from false-positive ST segment depression during exercise. This is achieved through the absence of perfusion abnormalities (as in the case of myocardial perfusion imaging using single photon emission computed tomography) or left ventricular dysfunction (as in the case of stress echocardiography). Patients are typically imaged at baseline and then undergo ECG-monitored exercise, followed by imaging at peak exercise and recovery. Images are obtained for the purposes of detecting myocardial perfusion abnormalities or regional wall motion abnormalities. For single photon emission computed tomography, sensitivity is estimated to be 90 percent and specificity 72 percent.[30] Exercise echocardiography is estimated to be 81 percent sensitive and 89 percent specific using stress-induced wall motion abnormalities.[30]

Strengths. Stress testing with imaging is a well-validated diagnostic test for CAD, with a highly negative predictive value. The procedure is widely available and noninvasive. Results of stress testing with imaging can guide management and treatment recommendations. The procedure is considered an appropriate diagnostic

test in patients with known or suspect CAD who are at low to intermediate risk for cardiovascular events.[5]

Limitations. Stress testing with imaging is relatively expensive, as well as time-intensive. The procedure requires expertise in performance and interpretation. The procedure involves radiation exposure among patients injected with radiopharmaceuticals. Image quality for study interpretation may be limited in patients with suboptimal images due to attenuation artifacts from overlying soft tissue in single photon emission computed tomography, or poor echocardiographic acoustic windows in patients who are obese or who have lung disease.

Summary

The strengths and limitations of the current diagnostic tests for the evaluation of suspected CAD represent the absence of a "one-size-fits-all" approach for cardiovascular risk assessment. In accordance with clinical guideline recommendations, the selection of the appropriate test must take into account the available expertise for both test performance and accurate test interpretation, while at the same time maximizing patient safety.[31] In the research setting, we ideally want the best available reference test. Pragmatic clinical considerations, including guideline recommendations, legitimately influence this choice.

CA remains the best reference standard for diagnosing CAD.[21] Through interrogation and identification of the coronary anatomy, CA is currently the best available test to identify which patients may benefit from surgical intervention, medical management, or both. Among low-risk patients who are typically not referred for CA but undergo clinical observation and/or noninvasive testing instead, several noninvasive diagnostic tests have served as an acceptable reference standard. In these patients, results have correlated with the incidence of cardiovascular events. In particular, stress tests (with or without imaging) provide clinicians with incremental risk prediction that informs management and treatment decisions. Stress tests also provide prognostically important data which have been associated with patient outcomes such as exercise capacity, hemodynamic response, and magnitude of ST segment abnormalities.

Resting ECGs, however, are not acceptable reference standards for the diagnosis of CAD, due mainly to their low sensitivity and specificity among both symptomatic and asymptomatic patients.[24] As a result, new technologies for diagnosing CAD are most appropriately compared to the reference standard of CA or, at the very least, acceptable reference standards such as stress imaging. In some disorders (e.g., deep venous thrombosis), reference standards with only moderate performance characteristics have been coupled with longitudinal followup for subsequent events to create a more robust standard.[32,33] For CAD, a similar approach might couple noninvasive testing with longitudinal followup for coronary events or CAD diagnosis to create a composite reference standard with improved discriminate validity. Table 2 summarizes our conclusion that CA remains the preferred reference standard for the diagnosis of CAD, while exercise stress testing with imaging serves as an acceptable reference standard. Appropriate use of biomarkers is an acceptable reference standard for the diagnosis of acute myocardial infarction, but not for CAD. The standard 12-lead ECG is not an

acceptable reference standard due to its relatively poor accuracy in diagnosing low- to intermediate-risk patients with CAD.

Table 2. Potential reference standards for CAD diagnosis

Level of reference standard	Coronary artery disease
Preferred	Coronary angiography
Acceptable	Stress testing with imaging
Unacceptable	Imaging studies without exercise or pharmacological stress Resting 12-lead ECG Stress testing with ECG
Incomplete	Biomarkers (applicable only for identifying myocardial injury)

Abbreviations: CAD = coronary artery disease; ECG = electrocardiogram

Key Question 2: Evidence on the Use of ECG-based Signal Analysis Technologies for the Diagnosis of Suspected CAD

Of the seven potentially relevant devices identified by the horizon scan, only the PRIME ECG, the 3DMP, and the Cardio3KG are commercially available (Table 1). We did not identify any published studies that reported on the Cardio3KG. The focus of the following discussion will therefore be on the PRIME ECG and the 3DMP.

Key Question 2a: What is the evidence for inter-rater, intra-rater, intra-patient and intra-device reliability?

Unfortunately, no studies evaluating device reliability met our inclusion criteria. However, two studies evaluating the 3DMP device enrolled subjects scheduled for cardiac catheterization and met our expanded eligibility criteria. These studies evaluated test and re-test reliability in a subset of 83 subjects and are summarized in Table 3. Both studies were reported by the same author and compared the 3DMP device to cardiac angiography using a 0 to 20 severity score. Both studies specified a priori a severity score of 4 as abnormal. Study quality was good with two exceptions: (1) subjects were a convenience sample; and (2) selection criteria likely selected for a sample population with greater disease severity than would be seen in the population of interest in this report. Patient characteristics such as body habitus and presence of comorbid medical conditions (e.g., severe chronic obstructive pulmonary disease) that may have influenced test performance were not described. In 83 subjects, a second 3DMP test was performed, blindly interpreted, and compared to the initial test results. However, the original ECG electrodes were left in place for the second recording, eliminating electrode placement as a source of variability. Of the 83 subjects, the severity score was identical in 68 (81.9 percent), and 11 of the disagreements differed by a single point. For the 2007 study, the authors reported that only one of the nine

disagreements would have changed the overall interpretation from normal to abnormal. The data presented are not sufficient to calculate measures of chance-corrected agreement such as a kappa, phi, or intra-class correlation statistics. These measures provide a better estimate than agreement alone, by accounting for agreement that occurs simply by chance.

Table 3. Test reliability of the 3DMP*

Study	Subjects	Setting	Threshold	Reference	Outcomes
Grube et al., 2007[34]	Outpatients scheduled for CA – any indication (n = 423); mean age 61.4 (11.1); 258 men, 165 women	German Heart Center	Automatic differential diagnosis based on indices of abnormality; severity score 0-20	Cardiac angiography: = 50% obstruction in left main or > 70% obstruction in any other coronary artery	Retest reliability: 36/45 identical scores; 3/9 > 1 point difference (1 would have changed from normal to abnormal); 6/9 1 point difference
Grube et al., 2008[35]	History of prior coronary revascularization procedure, scheduled for CA (n = 172); mean age 63.9 (10); 116 men, 56 women	German Heart Center	Automatic differential diagnosis based on indices of abnormality; severity score 0-20	Cardiac angiography: = 50% obstruction in left main or > 70% obstruction in any other coronary artery	Retest reliability: 32/38 identical scores; 1/6 > 1 point difference; 5/6 1 point difference

*3DMP = Multifunction Cardiogram[sm] (FDA cleared, commercially available, Premier Heart, LLC, Port Washington, NY).
Abbreviation: CA = cardiac angiography

Key Question 2b: What is the evidence for diagnostic test performance compared to the criterion standard used in the study? What factors (confounders) affected test sensitivity and specificity?

Studies meeting inclusion criteria with FDA cleared devices. We identified studies evaluating the performance characteristics of the PRIME ECG. Six studies involving 2345 subjects with chest pain were evaluated using the PRIME ECG (Table 4); five of these studies also evaluated the 12-lead ECG. Subjects were recruited from emergency departments, medical wards, or mobile coronary care units (CCUs) in Ireland. It is unclear whether these mobile CCUs serve a chest pain population similar to that served by U.S. emergency departments, or if they tend to serve patients triaged to be at high risk for acute myocardial ischemia. A study sample with more severe CAD would be expected to bias test performance towards greater sensitivity. Although there was some uncertainty about whether these patients were truly at low to intermediate risk, we decided to treat these studies as if they were. In all but one study,[36] selection bias was minimized by enrolling subjects consecutively. The PRIME ECG interpretation appears to have evolved over time. In the initial study,[36] a regression model was developed from 28 candidate variables. In later studies, slightly different criteria (sometimes specified a priori and in other instances apparently derived from the data)

are described. The variable criteria for an abnormal PRIME ECG could lead to variable performance across studies. Furthermore, criteria derived from the observed data could overestimate accuracy. In all studies, the PRIME ECG was compared to cardiac biomarkers, which serve as a test for myocardial injury. Four studies either used a single set of biomarkers or did not specify the number of sets obtained (at least two sets, 8 hours apart, are needed for an adequate reference standard). Only one study specified that the PRIME ECG was blindly interpreted and compared to the reference standard. Similarly, only one study described the reference standard as blindly interpreted relative to the PRIME ECG. If abnormal ranges for cardiac biomarkers were prespecified, it is unlikely that interpretation would be influenced by the index test results.

Table 4. Studies evaluating performance characteristics of the PRIME ECG*

Study	Subjects	Setting	Threshold	Reference	Outcomes
Menown et al., 1998[36]	Chest pain (n = 760; 125 controls, 635 patients)	Emergency department, medical wards or mobile CCU; controls from WHO screening program	Not specified; developed from 28 variables via logistic regression	Acute MI – criteria not specified	*Training set (n = 384)* Sensitivity = 80% (132/165) Specificity = 86% (134/156) *Validation set (n = 376)* Sensitivity = 77% (123/160) Specificity = 85% (131/154)
Menown et al., 2001[37]	Ischemic type chest pain < 24 hours and 1 mm ST segment depression (n = 54)	Cardiology – via emergency department or mobile CCU	Algorithm: visual display using QRS Y ST-T isointegrals and ST60 isopotential + multivariate model	MI by chest pain > 20 minutes + abnormal biomarkers	*Training set (n = 30)* Sensitivity = 69% (11/16) Specificity = 71% (10/14) *Validation set (n = 24)* Sensitivity = 88% (7/8) Specificity = 75% (12/16) *ECG (n = 24)* Sensitivity =50% (4/8) Specificity = 88% (14/16)
McClleland et al., 2003[38]	Ischemic type chest pain (n = 103)	Cardiology – via emergency department or mobile CCU	Algorithm: QRS width and axis, QRS and ST-T isointegrals, ST0 and ST60 isopotentials	MI by chest pain > 20 minutes + abnormal biomarkers	Sensitivity = 64% (34/53) Specificity = 94% (47/50) *Physician ECG* Sensitivity = 45% (24/53) Specificity = 94% (47/50)
Navarro et al., 2003[39]	Had ECG, BSM, biomarkers (n = 379)	Cardiology – via emergency department or mobile CCU	Algorithm: epicardial - ST0 isopotential from subset of study sample	MI by abnormal biomarkers	*Body surface potential* Sensitivity = 62% (106/171) Specificity = 80% (166/208) *Epicardial potential* Sensitivity = 78% (133/171) Specificity = 80% (166/208) *Physician ECG* Sensitivity = 54% (93/171) Specificity = 97% (202/208)

Study	Subjects	Setting	Threshold	Reference	Outcomes
Owens et al., 2004[40]	Ischemic type chest pain (n = 294)	Mobile CCU	Cardiologist interpreted using ST0 maxima, ST 60 minima, and vector magnitude	MI by abnormal biomarkers	Sensitivity = 80% (146/182) Specificity = 92% (103/112) *ECG* Sensitivity = 57% (104/182) Specificity = 94% (105/112)
Owens et al., 2008[41]	Ischemic type chest pain (n = 755)	Cardiology – via emergency department or mobile CCU	Region specific ST segment elevation on isopotential map	MI by abnormal biomarkers	Sensitivity = 76% (402/529) Specificity = 92% (208/226) *ECG* Sensitivity = 49% (238/291) Specificity = 92% (208/226)

*PRIME ECG (FDA cleared; commercially available; initially Meridian Medical Technologies, Belfast – now owned by Heartscape Technologies, Columbia MD).
Abbreviations: BSM = body surface mapping; CCU = coronary care unit; ECG = electrocardiogram; MI = myocardial infarction; WHO = World Health Organization.

We used a bivariate random-effects model to combine results across the six included studies (Table 5). Studies were statistically heterogeneous for the LR+ ($Q = 25.6$, $df = 5$, $p < 0.001$) and for the LR- ($Q = 30.0$, $df = 5$, $p < 0.001$; $I^2 = 80.5$ percent). The summary estimate for the LR+ was 5.0 (CI 3.5 – 6.5) and for the LR- was 0.37 (95 percent CI 0.30 to 0.43). We performed a sensitivity analysis excluding two studies, namely, the initial study that most clearly used a different diagnostic algorithm[36] and a second study with a very small sample size that was disproportionately weighted in the random effects meta-analysis.[37] The remaining studies were heterogeneous for the LR+ ($Q = 7.1$, $df = 3$, $p = 0.07$, $I^2 = 57.6$ percent) and LR- ($Q = 11.8$, $df = 3$, $p = 0.008$, $I^2 = 74.6$ percent). The LR+ (6.5; 95 percent CI 4.2 to 8.8) and LR- (0.33; 0.28 to 0.39) were not substantially changed. Using these latter estimates of test performance, an abnormal PRIME ECG test in a patient with a pretest probability for clinically significant CAD of 50 percent, would yield a posttest probability of 87 percent. A normal PRIME ECG would yield a posttest probability of 25 percent. For the five studies that also evaluated the 12-lead ECG, we computed performance characteristics in the same manner (Table 6), excluding the study with a very small sample size.[37] There was significant heterogeneity for the LR- ($Q = 11.8$, $df = 3$, $p = 0.02$), but not for the LR+ ($Q = 7.1$, $df = 3$, $p = 0.18$). The 12-lead ECG had a summary LR+ of 8.8 (95 percent CI 5.8 to 11.7) and LR- of 0.52 (0.46 to 0.59). For a patient with a pretest probability for clinically significant CAD of 50 percent, an ECG suggesting ischemia would yield a posttest probability of 90 percent. An ECG without evidence of ischemia would yield a posttest probability of 34 percent. The 12-lead ECG had a higher LR+ (a positive test increases the likelihood of disease), but the PRIME ECG had a lower LR- (a negative test lowers the likelihood of disease). However, neither of these differences was statistically significant as judged by the overlapping confidence intervals, nor were they clinically significant as judged by the similar posttest probabilities.

All studies used myocardial injury as the reference standard and included subjects with ischemic type chest pain. Patients with ischemic type chest pain certainly form an important subgroup of the target population, but patients at lower risk for CAD (such as individuals with atypical chest pain) were not included. Applicability was also limited by the reference standard. Myocardial injury is an important outcome of interest, but clinicians are also concerned with identifying significant CAD that may affect functional status or survival prior to myocardial injury.

Table 5. PRIME ECG* performance characteristics

Author	Sample size	Sensitivity	Specificity	Likelihood ratio positive	Likelihood ratio negative
Menown et al., 1998[36]	314	76.9%	85.1%	5.2	0.27
Menown et al., 2001[37]	24	87.5%	75.0%	3.5	0.17
McClelland et al., 2003[38]	103	64.2%	94.0%	10.7	0.38
Navarro et al., 2003[39]	379	62.0%	79.8%	3.1	0.48
Owens et al., 2004[40]	294	80.2%	92.0%	10.0	0.22
Owens et al., 2008[41]	755	76.0%	92.0%	9.5	0.26
Summary (95% CI)	1869	68% (63 to 74%)	86% (83 to 90%)	5.0 (3.5 to 6.5)	0.37 (0.30 to 0.43)
Summary (95% CI; omits Menown et al., 1998[36] and Menown et al., 2001[37])	1531	70% (66 to 75%)	89% (86 to 93%)	6.5 (4.2 to 8.8)	0.33 (0.28 to 0.39)

* PRIME ECG (FDA cleared; commercially available; initially Meridian Medical Technologies, Belfast – now owned by Heartscape Technologies, Columbia MD).
Abbreviations: CI = confidence interval; ECG = electrocardiogram.

Table 6. 12-lead ECG performance characteristics

Author	Sample size	Sensitivity	Specificity	Likelihood ratio positive	Likelihood ratio negative
Menown* et al., 2001[37]	24	50%	88%	4.0	0.57
McClelland et al., 2003[38]	103	45.3%	94.0%	7.6	0.58
Navarro et al., 2003[39]	379	54.4%	97.1%	18.9	0.47
Owens et al., 2004[40]	294	57.1%	93.8%	9.1	0.46
Owens et al., 2008[41]	517	81.8%	92.0%	5.6	0.60
Summary (95% CI)	1555	61% (46 to 76%)	94% (92 to 96%)	8.8 (5.8 to 11.7)	0.52 (0.46 to 0.59)

*Not included in meta-analysis due to small sample size.
Abbreviations: CI = confidence interval; ECG = electrocardiogram.

Studies meeting expanded eligibility criteria with FDA cleared devices. For the FDA-cleared 3DMP, no studies met our full inclusion criteria, but we identified four studies that met our expanded inclusion criteria (Table 7). These four studies included subjects scheduled for coronary angiography for any indication; one enrolled subjects with a history of coronary revascularization.[35] The clinical symptoms (e.g., presence of chest pain), prior evaluation, and clinical risk score were not reported, making the clinical risk category and applicability to our population of interest uncertain; the prevalence of coronary artery disease by angiography ranged from 32 to 57 percent. These four studies included 920 subjects who were evaluated using 3DMP, and one study also evaluated the resting 12-lead ECG. Two studies were conducted in Germany, one in Southeast Asia, and one in the United States. All studies used a threshold of 4.0 on the 0 to 20 severity score to define an abnormal 3DMP test result.

Table 7. Studies evaluating performance characteristics of the 3DMP*

Study	Subjects	Setting	Threshold	Reference	Outcomes
Weiss et al., 2002[42]	Ambulatory patients scheduled for CA (n = 136); 81 male, 55 female	Westchester Medical Center	Manual and automated analyses – 6 indices integrated and compared to results from a 21,000 patient database	Cardiac angiography: > 60% obstruction in a coronary artery	Severity Score: = 4.0 Sensitivity = 93.3% (76/78) Specificity = 83% (40/58)
Grube et al., 2007[34]	Outpatients scheduled for CA – any indication (n = 423); mean age 61.4 (11.1); 258 men, 165 women	German Heart Center	Automatic differential diagnosis based on indices of abnormality; severity score 0-20	Cardiac angiography: = 50% obstruction in left main or > 70% obstruction in any other coronary artery	Severity Score: = 4.0 Sensitivity = 89% (179/201) Specificity = 81.1% (180/222) aROC = 0.843
Grube et al., 2008[35]	History of prior coronary revascularization procedure, scheduled for CA (n = 172); mean age 63.9 (10);116 men, 56 women	German Heart Center	Automatic differential diagnosis based on indices of abnormality; severity score 0-20	Cardiac angiography: = 50% obstruction in left main or > 70% obstruction in any other coronary artery	Severity Score: = 4.0 Sensitivity = 90.9% (50/55) Specificity = 88.0% (103/117)
Hosokawa et al., 2008[43]	Scheduled for CA (n = 189); mean age 61.3 (12.9); 132 male, 57 female	Cardiac catheterization lab – 5 southeast Asian countries	Automatic differential diagnosis based on indices of abnormality; severity score 0-20	Cardiac angiography: = 50% obstruction in left main or > 70% obstruction in any other coronary artery	Severity Score: = 4.0 Sensitivity = 94.8% (73/77) Specificity = 86.6% (97/112) aROC = 0.914 (0.868 to 0.961)

*3DMP = Multifunction Cardiogram^{sm} (FDA cleared, commercially available, Premier Heart, LLC, Port Washington, NY).
Abbreviations: aROC=area under the receiver operator curve; CA=coronary angiography.

We used a bivariate random-effects model to combine results across studies (Table 8). Studies were statistically heterogeneous for LR+ ($Q = 7.6$, $df = 3$, $p = 0.06$; $I^2 = 60$ percent), but not for LR- ($Q = 5.2$, $df = 3$, $p = 0.16$; $I^2 = 42$ percent). The heterogeneity could not be explained by differences in study design. The summary estimate for the LR+ was 5.3 (95 percent CI 3.8 to 6.9) and for the LR- was 0.09 (0.04 to 0.13). For a patient with a pretest probability for clinically significant CAD of 50 percent, a 3DMP score of 4 would yield a posttest probability of 84 percent. A 3DMP score < 4 would yield a posttest probability of 8 percent. The single study that evaluated the 3DMP and 12-lead ECG[42] found a higher sensitivity (97 percent, 95 percent CI 94 to100 versus 75 percent, 65 to 85) and specificity (72 percent, 61 to 84 versus 41 percent, 28 to 54) for the 3DMP. However, this study had important methodological limitations. Of 200 patients selected for study, 64 were excluded due to inadequate 3DMP tracings, and criteria for an ECG diagnosis of CAD were not specifically stated. Since there were differences in the subjects and reference standard, these results are not directly comparable to the PRIME ECG or to the 12-lead ECG results discussed above. Although these results show impressive discriminate validity, it is uncertain how the device would perform in outpatients with undifferentiated chest pain that would certainly include more individuals with mild disease (potentially lowering sensitivity) or in patients with body habitus or comorbid diseases that may decrease accuracy.

Table 8. 3DMP* performance characteristics

Author	Sample size	Sensitivity	Specificity	Likelihood ratio positive	Likelihood ratio negative
Weiss et al., 2002[42]	136	97.4%	72.4%	3.5	0.04
Grube et al., 2007[34]	423	89.1%	81.1%	4.7	0.13
Grube et al., 2008[35]	172	90.9%	88.0%	7.6	0.10
Hosokawa et al., 2008[43]	189	94.8%	86.6%	7.08	0.06
Summary estimate (95% CI)		92.9% (88.7 to 97.2%)	82.1% (75.7% to 88.4%)	5.3 (3.8 to 6.9)	0.09 (0.04 to 0.13)

*3DMP = Multifunction Cardiogram[sm] (FDA cleared, commercially available, Premier Heart, LLC, Port Washington, NY).
Abbreviation: CI = confidence interval.

Key Question 2c: What is the evidence that ECG-based signal analysis technologies impact diagnostic decisionmaking?

Our search strategy did not identify any eligible studies pertinent to this question.

Key Question 2d: What is the evidence that ECG-based signal analysis technologies impact patient outcomes?

A single, multicenter observational study evaluating the effects of the PRIME ECG on clinical outcomes was published after our search date but identified during peer review.[44] The study tested the hypothesis that individuals with ST elevation myocardial infarction (STEMI) detected only by the PRIME ECG would have similar angiographic pathology and similar mortality and morbidity rates to those with STEMI detected by standard ECG. Adults (n = 1830) presenting to 12 tertiary care emergency departments with chest pain or symptoms suspicious for acute coronary syndrome who were at moderate to high risk for adverse cardiovascular outcomes were enrolled. Based on the study population, the study met our expanded eligibility criteria and indirectly addresses effects on patient outcomes. Subjects underwent testing with a standard 12-lead ECG and the PRIME ECG, but logistical difficulties prevented a substantial number of subjects with STEMI on standard ECG from completing the PRIME ECG, thus direct comparisons were not possible. Both the PRIME ECG and standard ECG were interpreted by experts. Clinical outcomes were compared between those with STEMI by standard ECG versus those with STEMI detected only by PRIME ECG and included 30-day mortality, myocardial infarction, and rehospitalization. In effect, these analyses evaluated the value of the PRIME ECG used as an "add-on" test to the standard ECG in emergency department patients with symptoms of acute coronary syndrome.

Of the 1830 subjects enrolled, 91 (4.97 percent) had STEMI by standard ECG. Of the remaining 1736 patients, 25 had STEMI by PRIME ECG. Therefore a diagnostic strategy that used the PRIME ECG as an add-on test would detect a total of 116 subjects with STEMI (6.34 percent) versus 91 by standard ECG alone (4.97 percent), for an incremental gain of 1.43 percent more patients detected with STEMI. A subset of those with PRIME ECG STEMI (n = 14) underwent coronary angiography that showed similar anatomy to those with STEMI by standard ECG. Clinical outcomes at 30 days did not differ significantly between those with STEMI by standard versus PRIME ECG only, but sample sizes were small, and the study was not powered to detect a clinically significant difference. These results provide preliminary data that the PRIME ECG can detect a small subset of patients without STEMI by standard ECG who have angiographic and clinical outcomes that are similar to individuals with STEMI by standard ECG. A more robust design would directly compare differences in diagnostic and treatment decisionmaking (e.g., decision to admit to hospital or proceed to emergent catheterization) and clinical outcomes.

Summary

In summary, only the PRIME ECG has been evaluated in patients with acute chest pain, but it was compared to an incomplete reference standard. The reference standard used (biomarkers) detects only acute myocardial injury. This is less than ideal, since clinicians are also concerned with identifying significant CAD that may affect functional status or survival prior to myocardial injury. Although the PRIME ECG had a better LR- than the standard 12-lead ECG, the differences were not large and are unlikely to affect

current diagnostic strategies. The 3DMP has not been evaluated in the population of interest, but its reliability and test performance in subjects at high risk or with known CAD is promising. Other devices identified are either not commercially available or not FDA cleared, and there is little published literature describing their performance. The literature is not sufficient to determine if factors such as sex, body habitus, medications, and comorbid medical conditions affect test performance. Finally, we did not identify any studies evaluating the effects of these tests on clinical decisionmaking or patient outcomes. To fully assess the impact of these devices on the diagnostic strategies for patients with chest pain, test performance needs to be linked to clinically important outcomes through modeling or longitudinal studies, potentially including randomized trials.

Chapter 4. Discussion

Summary of Findings

The horizon scan identified seven ECG-based devices used to diagnose CAD or detect acute myocardial infarct. Of these devices, the PRIME ECG, the Cardio3KG, and the 3DMP appear to be commercially available at this time, with only the PRIME ECG and 3DMP having obtained FDA clearance for marketing. Our original search of the English-language literature identified only six studies that reported on performance characteristics of a single ECG-based signal analysis device (the PRIME ECG) in outpatients with chest pain. An expanded search strategy that allows for the inclusion of studies on patients at higher risk of CAD identified an additional seven studies.

The PRIME ECG appears to be the only relevant device in the published literature that has been evaluated in patients with acute chest pain, but it was compared to an incomplete reference standard that only detected acute myocardial injury. Even these studies enrolled subjects at higher risk than the target population for this report. The available published evidence suggests that the PRIME ECG demonstrates slightly more favorable performance characteristics compared to the standard ECG among patients with ischemic-type chest pain, with myocardial injury as assessed by biomarkers as the reference standard. We were unable to identify any published evidence about the performance characteristics of the PRIME ECG among the patient population of interest (e.g., persons at low to intermediate risk of CAD).

Limited published evidence suggests that the 3DMP may have adequate retest reliability, but studies are needed that fully evaluate inter-rater reliability and include electrode placement as a potential source of variability. Test performance characteristics for this device appear to be generally good, but the findings from the published studies do not apply to the target population for this report.

Limitations of Current Studies

Our search strategy did not identify any eligible studies of patients at low to intermediate risk of CAD who presented in the outpatient setting with chest pain. The evidence summarized in this report was obtained from studies that included patients recruited from urgent care or hospital settings who were generally at high risk of CAD, or who had known CAD. There is, therefore, insufficient evidence to address directly the key questions as they pertain to the patient population of interest.

The evidence summarized in this report may still be informative, however, with the caveat that selection of a patient population with high prevalence of CAD may result in a cohort of patients with higher disease severity. An enriched prevalence may affect how a test is interpreted (most likely by lowering the implicit threshold defining a positive test result). Both of these effects (higher prevalence and a tendency to lower the threshold for an abnormality) can result in an overestimate of test performance. Furthermore, potential differences in patient characteristics such as body habitus, comorbid conditions, or prevalence of conduction abnormalities, might affect test performance.

The studies identified by our search strategy reported exclusively on test performance. They did not provide direct evidence pertaining to the impact of ECG-based signal analysis technologies on decisionmaking or patient outcomes. Additional information that is lacking in the published literature but that would help in the evaluation of ECG-based signal analysis technologies includes practical considerations, such as how long it takes to administer the tests and obtain interpretable data, the training required to operate the equipment and interpret the findings, the extent of ancillary support or additional space requirements, and whether it is feasible to administer the test to certain subgroups of patients, such obese or very thin patients or patients with certain comorbid conditions. Another limitation of the current studies is that they do not allow for comparative analysis of the performance between the new devices (e.g., 3DMP versus PRIME ECG) due to the use of different reference standards and substantial diversity in study populations.

Strengths and Limitations of this Review

The strengths of our search strategy include a gray literature search to identify relevant devices. Intentionally, we did not use electronic search filters, given that filters often inadvertently exclude relevant studies. The limitations of our search strategy include: (1) an absence of standardized, widely accepted, reliable, and validated methods for searching the gray literature; (2) the fact that some of the pertinent evidence is proprietary and not accessible via manufacturers' websites, and that we did not request information from manufacturers directly; and (3) in general, identifying test accuracy studies is more difficult than identifying studies of therapeutic interventions.

We relied primarily on published studies to identify potentially relevant devices. Peer-reviewed publications, however, do not always include complete information about investigational devices or methods. We therefore had difficulty tracking the lineage of both the devices and the proprietary data transformation algorithms that are central to signal analysis technologies. We do not know if the devices or the mathematical algorithms underlying the technology have remained constant over time. This problem may be common to formal evaluations of medical devices for which potentially significant changes over time are not documented in the public record.

Future Research

Bossuyt and colleagues have proposed a framework for new test evaluation that may help guide future research pertaining to ECG-based signal averaging technologies.[45] This framework considers new diagnostic tests as either potential replacement, triage, or add-on tests. Bossuyt argues that in order to determine if a new test can replace an existing one, the diagnostic accuracy of both tests need to be compared in the same patient sample, since the sensitivity and specificity of a test can vary across subgroups. Furthermore, the new tests should be compared to existing tests using the same reference standard. The paired test evaluation that is used to determine performance characteristics has advantages over a randomized controlled trial (RCT) design, including a requirement of fewer subjects than an RCT.

ECG-based signal analysis technologies may be more accurate than the 12-lead ECG. According to the evidence summarized in this report, the PRIME ECG and 3DMP may demonstrate slightly higher sensitivity than the standard 12-lead ECG. This suggests that ECG-based signal analysis devices could potentially serve to complement the findings from standard 12-lead ECGs as "add-on" tests. Add-on tests can be used in a subgroup of patients where diagnosis needs clarification. For example, add-on tests could be used to further evaluate a patient who presents with a normal ECG, but nonetheless is having active chest pain. An add-on test may be able to help clarify whether or not such a patient is having chest pain due to cardiac etiologies that are undetected by the 12-lead ECG, or if this patient is having chest pain due to a noncardiac cause. Add-on test strategies are attractive because they are noninvasive and accurate alternatives to the standard 12-lead ECG. However, these tests are less attractive than the standard 12-lead ECG, due to the fact that they are more expensive, more time consuming for medical personnel, and currently have limited availability in clinical settings. The add-on test strategy can potentially increase the sensitivity of the existing testing standards, but possibly at the expense of specificity. Study designs that are more efficient than the fully paired evaluation can be used to evaluate this add-on strategy.

Currently available published literature on ECG-based signal analysis technologies does not provide answers to the key questions surrounding the debate over whether or not these technologies impact diagnostic decisionmaking or patient outcomes. However, these questions may best be addressed by RCTs. Depending on the specific question, a number of trial designs could be considered, including a clinical trial of test-positive patients, with clinicians randomized to disclosure of test results. Another alternative would be a trial that randomizes patients to a test strategy that uses conventional testing versus a test strategy that uses a new device. Finally, another but less direct approach, would be to link evidence on test performance to evidence on the effects of interventions (e.g., anti-anginals or PCI) in the population of interest. This final example is sometimes employed by the United States Preventive Services Task Force for evaluation of screening tests. This less direct approach is more subject to bias due to the underlying assumptions that are inherent in creating these linkages.

Summary

There is currently little available evidence that pertains to the utility of ECG-based signal analysis technologies as a diagnostic test among patients at low to intermediate risk of CAD who present in the outpatient setting with the chief complaint of chest pain. The limited evidence that is available demonstrates proof of concept, particularly for the 3DMP and PRIME ECG devices. Further research is needed to better characterize the performance characteristics of these devices to determine in what circumstances, if any, these devices might precede, replace, or add to the standard ECG in test strategies for the diagnosis of CAD in the patient population of interest. The RCT study design is best suited for evaluating the impact that ECG-based signal analysis technologies may have on clinical decisionmaking and patient outcomes, but there are indirect approaches that might be applied to answer these questions.

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Acronyms and Abbreviations

AHRQ	Agency for Healthcare Research and Quality
BSM	Body surface mapping
CA	Coronary angiography
CAD	Coronary artery disease
CCT	Cardiac computed tomography
CCU	Coronary care units
CK-MB	Creatine kinase, MB fraction
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic obstructive pulmonary disease
CP	Chest pain
ECG	Electrocardiogram
EPC	Evidence-based Practice Center
ETT	Exercise treadmill test
FDA	U.S. Food and Drug Administration
LR-	Likelihood ratio negative
LR+	Likelihood ratio positive
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomized controlled trial
ROC	Receiver operator curve
SAECG	Signal averaging electrocardiogram
STEMI	ST elevation myocardial infarction
WHO	World Health Organization

Appendix A: PubMed® Search Strategies

Search Used for Question 1a and Questions 2b-d

1	("Signal Processing, Computer-Assisted"[Mesh] OR "signal averaged" OR "signal averaging" OR "signal analysis" OR "signal processing" OR "signal interpretation" OR "spectral analysis" OR “body surface potential mapping”))	39884
2	(“Prime ECG” OR “PRIMEECG” OR “PRIME ECG” OR “3DMP/mfEMT OR “3DMP*” OR “multifunction-cardiogram” OR “multifunction cardiogram” OR “CARDx” OR “Arrhythmia research technology” OR “1200EPX” OR “fukuda denshi” OR “fdx-6521” OR “fdx 6521” OR “vcm-3000” OR “vcm 3000” OR “visual ecg”)	44
3	#1 OR #2	39902
4	(ecg OR ekg OR electrocardiogram OR electrocardiography)	174569
5	("coronary artery disease"[MeSH Terms] OR "coronary artery disease"[All Fields])	58288
6	“myocardial ischemia”[MeSH Terms] OR “myocardial ischemia”[MeSH Terms] OR (“myocardial”[All Fields] AND “ischemia”[All Fields]) OR “myocardial ischemia”[All Fields]	299759
7	#5 OR #6	311377
8	#3 AND #4 AND #7	1792
9	#8 Limits: Limits: Human, English	1361
10	#8 Limits: Review	188
11	#9 NOT #8	1239

Search Used for Question 2a

1	("Signal Processing, Computer-Assisted"[Mesh] OR "signal averaged" OR "signal averaging" OR "signal analysis" OR "signal processing" OR "signal interpretation" OR "spectral analysis" OR “body surface potential mapping”)	39884
2	(“Prime ECG” OR “PRIMEECG” OR “PRIME ECG” OR “3DMP/mfEMT OR “3DMP*” OR “multifunction-cardiogram” OR “multifunction cardiogram” OR “CARDx” OR “Arrhythmia research technology” OR “1200EPX” OR “fukuda denshi” OR “fdx-6521” OR “fdx 6521” OR “vcm-3000” OR “vcm 3000” OR “visual ecg”)	44
3	#1 OR #2	39902
4	(ecg OR ekg OR electrocardiogram OR electrocardiography)	174569
5	((((("Observer Variation"[Mesh] OR "Reproducibility of Results"[Mesh]) OR "Validation Studies "[Publication Type]) OR "Validation Studies as Topic"[Mesh]) OR (inter-rater OR intra-rater OR intra-patient OR intra-device OR validity OR relia* OR reproducib*))	478616
6	("coronary artery disease"[MeSH Terms] OR "coronary artery disease"[All Fields])	58288
7	“myocardial ischemia”[MeSH Terms) OR “myocardial ischemia”[MeSH Terms] OR (“myocardial”[All Fields] AND “ischemia”[All Fields]) OR “myocardial ischemia”[All Fields]	299759
8	#6 OR #7	311377
9	#3 AND #4 AND #5 AND #8	168
10	#6 Limits: Human, English	134

Appendix B: ECG-Based Signal Analysis Devices – Gray Literature Sources, Search Terms, and Results

Source	Search term(s)	Restrictions	Number of citations identified	Unique devices identified
General gray literature sources				
Google Advanced Search (http://www.google.com/advanced_search?hl=en)	[("ECG" OR "electrocardiogram" OR "EKG") AND ("signal averaging" OR "signal averaged" OR "signal analysis" OR "spectral")] OR "body surface mapping"	• In the title of the page • Published between April 22, 2008, and May 28, 2009 • English language	175	Procardia 7 Procardia 8 Cardiag 112.2 Cardiag 128.1 CarDx
Federal Drug Administration Searched via: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm; and http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm	Product codes: DPS, LOS, DRW, KRC, MLO, MWJ, OEY, KXN	None	592	0
Patents Searched via www.freepatentsonline.com	("cardiac" AND "spectral") AND ("electrocardiograph" OR "electrocardiogram") "body surface mapping" AND "ischemia"	None Searched May 17, 2009	1591 10,265	0
Abstracts from scientific meetings				
American Heart Association (AHA) scientific sessions website (http://scientificsessions.americanheart.org/portal/scientificsessions/ss) Abstract Archive Tool search portal (http://www.abstractsonline.com/arch/home.aspx?lookupkey=12345)	"cardiac spectral" or "body surface mapping" or "signal averaging"	Abstract Archive Tool searches across all AHA-sponsored scientific meetings through 2004	23	0

Source	Search term(s)	Restrictions	Number of citations identified	Unique devices identified
Online search of the AHA's journal *Circulation* (advanced search page: http://circ.ahajournals.org/search.dtl)	"signal analysis" or "signal averaged" or "signal averaging" or "body surface map" or "body surface mapping"	• In title or abstract • Include AHA Scientific Sessions Abstracts • July 2007 – June 2009	20	0
American College of Cardiology (ACC; http://www.acc.org/) Search page: http://content.onlinejacc.org/search.dtl	"signal averaging" or "signal averaged" or "surface mapping" or "body surface map"	• In title or abstract • All JACC journals • July 2007 – June 2009	9	0
Heart Rhythm Society (http://www.hrsonline.org/Sessions/) Search page: http://www.abstracts2view.com/hrs/	All of the words: electrocardiogram AND signal averaging or signal averaged AND spectral analysis or body surface mapping	All abstract categories 2009-2009	5	XL-ECG, Mortara Prime ECG
European Society of Cardiology (ESC; http://www.escardio.org/Pages/index.aspx) Search page: http://spo.escardio.org/abstract-book/topic.aspx	All of the words: electrocardiography, noninvasive studies, ECG and arrhythmia analysis, exercise testing in CAD, "signal", "body"	2007 and 2008	239	0
Ongoing trials				
ClinicalTrials.gov (http://www.clinicaltrials.gov/) Basic Search: http://www.clinicaltrials.gov/ct2/search	"ischemia" AND ("electrocardiograph" OR "electrocardiogram")	None Searched May 17, 2009	52	0

Appendix C: Inclusion/Exclusion Criteria

Question 2a: What is the evidence for inter-rater, intra-rater, intra-patient and intra-device variability?

- Patients: Adults with chest pain or being evaluated for myocardial ischemia/CAD
- Intervention: Commercial Device* using ECG based technology on our list of included devices (e.g. evaluates electrical waveforms with advanced analytic techniques such as computer evaluation of vectors)
- Outcome: Reliability measure (e.g., simple agreement, kappa, intraclass correlation)
- Setting: Outpatient or inpatient
- Study Design: N>30

Question 2b: What is the evidence for diagnostic test performance compared to a criterion standard?

- Patients: Adults with chest pain, at low to intermediate risk for CAD, being evaluated for myocardial ischemia/CAD
- Intervention: Commercial Device using ECG based technology on our list of included devices (e.g. evaluates electrical waveforms with advanced analytic techniques such as computer evaluation of vectors)
- Outcome: Comparison to an acceptable reference standard**
- Setting: Outpatient (to include physician offices, urgent care and ED)
- Study Design: N>30

Question 2c: What is the evidence that signal-analysis technologies impact diagnostic decisionmaking?

- Patients: Adults with chest pain, at low to intermediate risk for CAD, being evaluated for myocardial ischemia/CAD
- Intervention: Commercial Device using ECG based technology on our list of included devices (e.g. evaluates electrical waveforms with advanced analytic techniques such as computer evaluation of vectors)
- Comparator: Comparison to an alternative diagnostic test (or test strategy)
- Outcome: Further diagnostic testing
- Setting: Outpatient (to include physician offices, urgent care and ED)
- Study Design: Cross-sectional, longitudinal observational or randomized controlled trial, N>30

Question 2d: What is the evidence that signal-analysis technologies impact patient outcomes?

- Patients: Adults with chest pain, at low to intermediate risk for CAD, being evaluated for myocardial ischemia/CAD

- Intervention: Commercial Device using ECG based technology on our list of included devices (e.g. evaluates electrical waveforms with advanced analytic techniques such as computer evaluation of vectors)
- Comparator: An alternative diagnostic test (or test strategy)
- Outcome: Clinical - mortality, cardiac symptoms or function, functional status; process - therapeutic interventions
- Setting: Outpatient (to include physician offices, urgent care and ED)
- Study Design: Longitudinal observational or randomized controlled trial, N>50

Key features of relevant devices:

- Obtains and interprets electrical activity from the heart (so ECG device)
- May utilize standard 12 lead information or have fewer (e.g., 3DMP/mfEMT) or additional leads (e.g., body surface mapping)
- Transforms/interprets the electrical signal in a novel way. Data transformation into spatial imaging, or through advanced mathematics (e.g., Fast Fourier Transform) to produce new indexes are relevant.
- Is claimed to be useful for diagnosing CAD or detecting myocardial ischemia
- Is a commercially available device
- Any other device meeting these criteria

Appendix D: Quality Criteria

Sample or Study Design

- Random or consecutive sample?: yes, no, can't tell
- Selection criteria favor representative spectrum of disease?: yes, no, can't tell
  Yes = Individuals with comorbid conditions (e.g., COPD) or body habitus (e.g., obesity) that may affect index test result are not excluded. In patients with CAD, severity ranges from mild (e.g., single vessel disease) to severe (3 vessels or left main).

Reference Test

- Index test adequately described?: yes, no
  Yes = Described in enough detail to replicate with confidence
- Reference test adequately described?: yes, no
  Yes = Described in enough detail to replicate with confidence; criteria for an abnormal result (e.g. CAD, myocardial ischemia) prospectively defined and clearly stated
- Is reference test a valid reference standard?: yes, partially, no
  See definitions from question 1a
- Reference test interpreted blinded to index test result?: yes, no, can't tell
- Index test interpreted blinded to reference test result?: yes, no, can't tell
- Absence of verification bias (independence of indication for tests)?: yes, no, can't tell
  Yes = All subjects had both the index and reference test; the reference test applied was the same for index test positive and index test negative groups. Note – if eligibility criteria required that patients have both the index test and reference test, then – by definition – verification bias is absent. However, this eligibility reference makes it less likely that a random or consecutive sample was obtained.
- Absence of incorporation bias (definition of disease/abnormal by the reference standard does not include (incorporate) the index test result)?: yes, no

Analysis

- Analysis appropriate?: yes, no, partially
  Consider: a) handling of intermediate or indeterminate data; b) a priori definition of abnormal result; and c) able to calculate sensitivity/specificity, likelihood ratios, diagnostic odds ratio, ROC curve, or c statistic

Other issues to consider but not part of formal quality rating – relevant to applicability

1. Patient population: age group (Medicare, = 65 y.o); do inclusion criteria select for outpatients with low to intermediate likelihood of CAD?
2. Intervention: a) Was the index test performed or interpreted by technicians/clinician with specialized training such that the index test is likely to

perform better in their hands compared to technicians/clinicians in routine clinical care?; b) Is there any information given on the amount of time taken to administer and interpret the index test? – would have implications for real world practice?

Appendix E: Evidence Tables – Published Studies Evaluating Reviewed Devices

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
Bojovic et al., 2009[46]	**Geographical location:** Boston, MA **Study dates:** NR **Study objectives:** To compare the Visual 3Dx to the standard 12-lead ECG for detection of acute myocardial ischemia (AMI) in 2 clinical models. **Setting:** - ED - Inpatient - Hospital lab **How was coronary artery disease diagnosed?:** NA (this study focuses on ischemia, as diagnosed by ECG and SAECG)	**Sample size:** Study 1: 51 patients and 117 events Study 2: 122 patients **Age:** NR **Sex:** NR **Race/ethnicity:** NR **Comorbidities:** NR **Clinical characteristics of tested patients:** 2 clinical studies: 1) 51 patients undergoing balloon coronary artery occlusion during angioplasty. 2) 122 consecutive patients who: a) presented to the ED with chest discomfort; b) were hospitalized for suspected MI; c) developed elevated troponin I levels; and d) underwent coronary arteriography within 6 hours of admission.	**Index test (ECG-based signal analysis):** - Device name: Visual 3Dx - Manufacturer: - Device type: - Test operator: The device "transforms the ECG input into a time-variable heart vector, and normalizes each lead input to assure equal representation from all cardiac regions." ST magnitude > 0.1mv measured 80 msec after j point was the threshold for abnormal **Comparator/reference test(s):** - Standard ECG - Study 1 used occlusion by angioplasty **Other tests performed (before or after index test):** Angiography, but results not reported	**Study 1:** **1) Number (%) of patients who had index (ECG-based signal analysis) test:** 51 (100%) patients and 117 balloon occlusion events (authors use occlusion events as unit of analysis). 3Dx-Sensitivity 105/117 (not calculable)* ECG-Sensitivity 78/117 (not calculable)* **2) Number (%) of patients who had comparator test(s)**: Standard ECG: 117/117 events (100%) **3) Number (%) of patients diagnosed with <u>acute ischemia</u> based on index test:** NR. Authors interpret findings, relative to standard ECG findings, as such: "The 3Dx showed significantly better sensitivity than the standard ECG for detecting ischemia (90% vs. 67%). The sensitivity advantage was observed in each of the three coronary artery distributions." Study 2 Visual 3Dx Sensitivity 103/122 (84.4%) Specificity – not given ECG Sensitivity 80/122 (65.5%) Specificity – not given	**Comments:** - SAECG was compared to ECG without the use of gold standard. - Ischemia (as diagnosed by SAECG and ECG) is the outcome of interest. - *Study 1 used 51 patients and 117 balloon occlusions – observations not independent so can't calculate a sensitivity **Quality assessment:** Random or consecutive sample: Yes Representative sample: Yes Index test described: Yes Reference test described: Yes Valid reference standard: Yes Blinded reference test: Yes Blinded index test: Yes Absence of verification bias: Yes Absence of incorporation bias: Yes Appropriate analysis: No

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
				4) Number (%) of patients diagnosed with coronary artery disease by other means. Not applicable. Only compared ECG with SAECG in patients with known CAD. **Study 2:** **1) Number (%) of patients who had index (ECG-based signal analysis) test:** 122 (100%) **2) Number (%) of patients who had comparator test(s)**: Standard ECG: 122 (100%). Of these, 80 (65.5%) had ECG diagnosis of acute ischemia. **3) Number (%) of patients diagnosed acute ischemia based on index test:** 103 (84.4%). Authors interpret this finding, relative to standard ECG findings, as such: "This represents a 19% absolute percentage gain, and a relative 29% gain in diagnostic sensitivity for the Visual 3Dx ($p<0.01$)." **4) Number (%) of patients diagnosed with coronary artery disease by other means**. Not applicable. Only compared ECG with SAECG in patients with known CAD. **5) Possible to construct 2x2 tables?:** No **6. Other:** Primary outcome of Study 2 was the sensitivity of the first ECG for detection of acute ischemia, defined	

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
				as ST segment elevation or depression in 2 consecutive leads. Findings broken down by the 3 coronary arteries	
Grube et al., 2008[35]	**Geographical location:** Siegburg, Germany **Study dates:** 2001-2003 **Study objectives:** Compare 3DMP to coronary angiography to evaluate the device's accuracy (and sensitivity and specificity) in detecting hemodynamically relevant CAD. **Setting:** Other: Pts scheduled for angiography **How was coronary artery disease diagnosed?:** Coronary angiography	**Sample size:** 213; 41 excluded for poor ECG tracings (7) or lack of full risk factor information (34) **Analytical sample:** 172 **Age:** - Mean (SD): 63.9 ± 10 - Median: NR - Range: 35-83 **Sex:** - Male: 116 (67%) - Female: 56 (33%) **Race/ethnicity:** NR **Comorbidities:** H/o MI: 36 (17% of 213)) **Clinical characteristics of tested patients:** Convenience sample of 172 patients with h/o coronary revascularization scheduled for coronary angiography. Patients had undergone at least one coronary revascularization	**Index test (ECG-based signal analysis):** - Device name: 3DMP - Manufacturer: Premier Heart, LLC - Device type: SAECG. 2 leads. Generates a severity score from 0-20 that indicates the level of myocardial ischemia (if present) resulting from coronary disease. - Test operator: Trained trial site technician. Locally operated (presumably by any trained technician) and remotely analyzed at a central data facility. **Comparator/reference test(s):** - Cardiac catheterization **Results classified as:** 1) Nonobstructive CAD, or "negative for hemodynamically relevant CAD." 2) Obstructive CAD, or "positive for hemodynamically relevant CAD."	**1) Number (%) of patients who had index (ECG-based signal analysis) test:** 172 (100%) **2) Number (%) of patients who had comparator test(s)**: 172 (100%) had coronary angiography **3) Number (%) of patients diagnosed with coronary artery disease based on index test:** Several different cut-off scores analyzed. With a cut-off score of 4.0, 50 (29%) Dx'd with CAD **4) Number (%) of patients diagnosed with coronary artery disease by other means**: 55 (32%) Dx'd with hemodynamically relevant CAD or graft stenosis by angiography. **5) Possible to construct 2x2 tables?:** Yes **6) Other findings:** The device "accurately identified 50 of 55 (90.9%) patients as having hemodynamically relevant stenosis (sensitivity 90.9%, specificity 103/117, 88.0%)" PPV: 62.7% NPV: 97.8%	**Comments:** Very well-designed and comprehensively reported study. **Quality assessment:** Random or consecutive sample: Yes Representative sample: No (recent revascularization) Index test described: Yes Reference test described: Yes Valid reference standard: Yes Blinded reference test: Yes Blinded index test: Yes Absence of verification bias: Yes Absence of incorporation bias: Yes Appropriate analysis: Yes

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
		procedure at least 6 weeks prior to scheduled angiography.	**Other tests performed (before or after index test):** None	ROC curve reported to show score of 4 as best threshold; figure confirms Risk and demographic factors in a logistic regression model had lower PPV for coronary stenosis than did 3DMP severity score: OR 2.04 (95% CI: 0.74,5.62) vs. 73.57 (95% CI: 25.10, 215.68). **7) Retest reliability:** Retest reliability was assessed in 38 patients within 4 hr	
Grube et al., 2007[34]	**Geographical location:** Siegburg, Germany **Study dates:** 7/1/01-6/30/03 **Study objectives:** "The present study compared a new computer-enhanced, resting ECG analysis device, 3DMP, to coronary angiography to evaluate the device's accuracy in detecting hemodynamically relevant CAD." **Setting:** - Outpatient /convenience sample **How was coronary artery disease diagnosed?:** Coronary angiography, classified by performing	**Sample size:** 423 (562-17 poor ECG-122 no risk factor info) **Age**: - Mean (SD): 61.4+/-11.1 - Median: - Range: 24-89 - Other: **Sex**: - Male: 258 (61%) - Female: 165 (39%) **Race/ethnicity:** NR, presumably mostly German **Comorbidities:** Arterial HTN (62%) DM (17%) Hyperchol (61%) Smoking (38%) Obesity (43%) Family hx (29%) Peripheral artery dz	**Index test (ECG-based signal analysis):** - Device name: 3DMP - Manufacturer: Premier Heart - Device type: SAECG (resting 2 lead analysis) - Test operator: trial site technician **Threshold for severity score:** ≥ 4.0 **Comparator/reference test(s):** - Cardiac catheterization **Other tests performed (before or after index test):** None	**1) Number (%) of patients who had index (ECG-based signal analysis) test:** 423 (100%) **2) Number (%) of patients who had comparator test(s)**: 423 (100%) had cath, 201 (47.5%) had "hemodynamically relevant coronary stenosis" **3) Number (%) of patients diagnosed with coronary artery disease based on index test:** 179 of 201 (89%) **4) Number (%) of patients diagnosed with coronary artery disease by other means:** 201 (47.5%) also compared to logistic regression model of CAD RF **5) Possible to construct 2x2 tables?:** Sensitivity 179/221 (89.1%) Specificity 180/222 (81.1%) PPV 79% NPV 90%	**Comments:** -Convenience sample -Similar design to Hosokawa et al., 2008[43] **Quality assessment:** Random or consecutive sample: Yes Representative sample: Partial (patients scheduled for cardiac catheterization) Index test described: Yes Reference test described: Yes Valid reference standard: Yes Blinded reference test: Yes Blinded index test: Yes Absence of verification bias: Yes Absence of incorporation bias: Yes Appropriate analysis: Yes

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
	angiographer and independent cardiologist within 4 wks; if disagreed, discussed until agreed; nonobstruc CAD between 40-70% stenosis obstruc CAD >70$ or >50% in L Main	**Clinical characteristics of tested patients:** -44 pts (10%) had prior MI -no patients had ACS, -no pts had prior revascularization -all pts referred for cor angio for any indication -23 (5.4%) had no risk factors (RF) for CAD -216 (51%) had at least 3 RF for CAD			
Hosokawa et al., 2008[43]	**Geographical location:** Seoul, South Korea; Mount Elizabeth Med Ctr, Singapore; Tokyo, Japan; Mumbai, India; Kuala Lumpur, Malaysia **Study dates:** June 1-Oct 18, 2004 **Study objectives:** "…compared a new computer-enhancing resting ECG analysis device (multiphase functional electromyocardial tomography (mfEMT) with coronary angiography to evaluate the device's accuracy in detecting hemodynamically relevant CAD." **Setting:**	**Sample size:** 189 **Age:** 61.3+/-12.9 21-88 yrs **Sex:** - Male: 132 (70%) - Female: 57 (30%) **Race/ethnicity:** Not given, but all 4 centers in Asia **Comorbidities:** 43 (23%) had PCI at least 6 wks prior to inclusion in study; other comorbidities not provided **Clinical characteristics of tested patients:** Convenience sample at 4 institutions of patients scheduled for	**Index test (ECG-based signal analysis):** - Device name: mfEMT/3DMP - Manufacturer: Premier Heart - Device type: SAECG-two lead - Test operator: **Comparator/reference test(s):** - Standard ECG; referenced against 1978-2000 "data-gathering trials[ref20-21]" - Cardiac catheterization **Other tests performed (before or after index test):** None	**1) Number (%) of patients who had index (ECG-based signal analysis) test:** 189 (100%) **2) Number (%) of patients who had comparator test(s):** 189 (100%) with ECG **3) Number (%) of patients diagnosed with coronary artery disease based on index test:** 73 of 77 (95%) with angiography proven CAD **4) Number (%) of patients diagnosed with coronary artery disease by other means**: 77 of 189 (angiography) **5) Possible to construct 2x2 tables?:** Yes Sensitivity 73/77, 94.8% Specificity48/55, 86.6%	**Comments:** 2 of 3 authors have ties to maker **Quality assessment:** Random or consecutive sample: Yes Representative sample: Partial (patients scheduled for cardiac catheterization) Index test described: Yes Reference test described: Yes Valid reference standard: Yes Blinded reference test: Yes Blinded index test: Yes Absence of verification bias: Yes Absence of incorporation bias: Yes Appropriate analysis: Yes

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
	- Hospital lab (cath) **How was coronary artery disease diagnosed?:** Patients were referred for angiography for "any indication"; CAD was diagnosed by review of angiography; angiography performed at discretion of attg; angiographer blinded to mfEMTresults; a second independent angiographer verified the findings within 4 wks, and if disagreed, they discussed until agreement reached; nonobstructive CAD ≤ 70% stenosis; mfEMT provides a severity score, 0-20, "where a higher score indicated a higher likelihood of ischemia due to stenosis; ≥ 4.0 was considered indicative of a hemodynamically relevant stenosis > 70%	angiography for any reason; 30 patients excluded from one center "because angiograms were not available for second external review due to unforeseen legal imitations"; 3 patients excluded due to poor ECG; "patient demographics, medical history, and risk factors apart from sex and age were not recorded because they are not required for mfEMT analysis"; "poor tracing" defined in paper (excluded 3 total)			
MeClelland et al., 2003[38]	**Geographical location:** Belfast, Northern	**Sample size:** 103 **Age:**	**Index test (ECG-based signal analysis):** - Device name: PRIME	**1) Number (%) of patients who had index (ECG-based signal analysis) test:**	**Comments:** - Consecutive patients - High probability for acute myocardial

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
	Ireland **Study dates:** Dec 2001 – April 2002 **Study objectives:** Assess whether an automated body surface algorithm could improve detection of acute myocardial infarction compared with 12-lead ECG **Setting:** - Other: "presented to cardiology department via ED or mobile CCU" **How was coronary artery disease diagnosed?:** AMI by acute CP >20 minutes & cardiac troponin I >1 ug/L and/or CK-MB >25 U/L	- Mean (SD): 63.6 (12) **Sex:** - Male: 76 (74%) - Female: 27 (26%) **Race/ethnicity:** NR **Comorbidities:** Smoker: 50 (49%) DM 18 (18%) HTN 41 (40%) Prior AMI or angina pectoris: 42 (41%) **Clinical characteristics of tested patients**: Ischemic type chest pain <12 hours with or w/o ST changes. Excluded patients given fibrinolytics, GP IIb/IIIa receptor antagonists, or nitrates prior to ECG or BSM	ECG - Manufacturer: Meridian Medical Technologies - Device type: Body surface mapping - Test operator: "technician" **Comparator/reference test(s):** - Standard ECG - Other: AMI by acute CP >20 minutes & cardiac troponin I >1 ug/L and/or CK-MB >25 U/L **Other tests performed (before or after index test):** None	103 (100%) **2) Number (%) of patients who had comparator test(s):** 103 (100%) with ECG **3) Number (%) of patients diagnosed with coronary artery disease based on index test:** 53 with AMI **4) Number (%) of patients diagnosed with coronary artery disease by other means:** NA **5) Possible to construct 2x2 tables?:** Yes BSM: 34/53 with AMI ; 64% sensitive x/50 without AMI = 94% specific ECG: 17/53 with AMI = 32% sensitive 49/50 without AMI = 98% specific BSM detected AMI in all patients detected by ECG (n=17) or physician diagnosis (n=20; overlap uncertain). BSM improved sensitivity by 2% compared to ECG and 1.4% compared to physician diagnosis Of the 17 patients diagnosed by BSM and missed by ECG, 3 had anterior MI, 7 inferior MI, 7 posterior MI. Of the 10 patients diagnosed by BSM and missed by physician, 4 had inferior MI and 6 had posterior MI.	ischemia - No data given for outcome of CAD, only for ischemia - Algorithm for abnormal BSM appears to be prespecified **Quality assessment:** Random or consecutive sample: Yes Representative sample: Yes Index test described: Yes Reference test described: Yes Valid reference standard: Yes Blinded reference test: Yes Blinded index test: Yes Absence of verification bias: Yes Absence of incorporation bias: Yes Appropriate analysis: Yes

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
Menown et al., 2001[37]	**Geographical location:** NR, presumably Belfast, NI **Study dates:** NR, presumably prior to 2001, over a 17 mo period **Study objectives:** "The aim of this study was to test the hypothesis that , when compared with the 12-lead ECG, body surface mapping would improve early detection of acute myocardial infarction in patients with ST depression only on the initial 12-lead ECG either by (1) enabling the spatial detection of ST elevation, should it occur outside the conventional precordial leads; and/or enabling full spatial evaluation of multiple QRST variables" **Setting:** - ED - Hospital lab - Other: CCU **How was coronary artery disease diagnosed?:** AMI defined by presence of acute chest pain of >20 min duration, elevation of CK more than twice	**Sample size:** 54, divided into training set (30) and validation set **Age:** (Training set) - Mean (SD): 66.3 +/- 12 **Sex:** - Male: 23 (77%) - Female: 7 (23%) **Race/ethnicity:** NR **Comorbidities:** (Training set) Fam His 15 (50%) Smoking 15 (50%) Diabetes 5 (17%) Hypertension 8 (27%) Hyperlipidemia (12 (40%) Previous angina 19 (63%) Previous MI 16 (53%) Median time from pain to BSM 3.9 hours **Clinical characteristics of tested patients:** Inclusion criteria:1) onset of CP within previous 24 h, 2) presence of ≥ 1mm ST dep in 1 or more leads, 80 ms after the J point, without coexisting ST elev. Exclusion criteria: ST elv, LBBB, LVH	**Index test (ECG-based signal analysis):** - Device name: PRIME ECG - Manufacturer: Meridian Technologies - Device type: Body surface mapping (80leads) - Test operator: NR **Comparator/reference test(s):** - Standard ECG - Other: cardiac biomarkers **Other tests performed (before or after index test):** None	**1) Number (%) of patients who had index (ECG-based signal analysis) test:** 100% **2) Number (%) of patients who had comparator test(s)**: 100% (ECG and biomarkers) **3) Number (%) of patients diagnosed with coronary artery disease based on index test:** 16/30 in training set had AMI; 8/24 in validation set; so 24 out of 54 total: 61% were correctly classified via univariate prediction based on ST elev outside of the standard precordial leads, 74% by the multivariate analysis (3 variables) **4) Number (%) of patients diagnosed with coronary artery disease by other means:** univariate 12-lead ECG (ST dep >=2mm): 68%; multivariate ECG model (6 variables involving degree of ST dep): 67% **5) Possible to construct 2x2 tables?:** Sensitivity (all patients) 71% univariate, 75% multivariate; Specificity (all patients) 53% univariate, 73% multivariate	**Comments:** - Multivariate model (3 variables), not spatial detection of ST elev outside conventional 12 leads, was better than standard 12-lead ECG - Why exclude LVH- might miss large numbers of intermediate risk pts - 3.9 hours long time - N is small (too few cases for the modeling approach) **Quality assessment:** Random or consecutive sample: Yes Representative sample: Partial (excluded patients with bundle branch block) Index test described: Yes Reference test described: Yes Valid reference standard: Yes Blinded reference test: Yes Blinded index test: Yes Absence of verification bias: Yes Absence of incorporation bias: Yes Appropriate analysis: Yes

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
	the upper limit of normal	BSM's created on first presentation to the hospital			
Menown et al., 1998[36]	**Geographical location:** Belfast, Northern Ireland **Study dates:** NR, pre 1998 **Study objectives:** "It has been suggested that body-surface mapping (BSM) may be useful in patients presenting with nondiagnositc ECGS, as it enables electrocardiographic sampling in areas of the thoracic surface outside the area covered by the six conventional precordial leads…We thus evaluated the mapping system in patients with symptoms suggestive of AMI, including patients presenting with nondiagnostic ECG changes." **Setting:** - ED - Hospital lab - Other: CCU **How was coronary artery disease diagnosed:**	**Sample size:** Training set (T) 384, Validation set (V) 376 **Age:** - Mean (SD): 59.3+/-14 (T); 60.6 +/- 13 (V) **Sex :** - Male: 69% (T); 70% (V) - Female: 31% (T); 30 % (V) **Race/ethnicity:** NR **Comorbidities:** FHx 55% (T), 54% (V) Smoking 50%, 53% Diabetes 8%, 12% Hypertension 30%, 32% Hyperlipidemia 23%, 27% Previous angina 35%, 40% Previous MI 30%, 32% **Clinical characteristics of tested patients:** 635 pts with chest pain suggestive of AMI with *325* pos for AMI and *310* "abnormal ECG but not AMI" plus 125 controls without chest	**Index test (ECG-based signal analysis):** - Device name: NR - Manufacturer: ?self made - Device type: Body surface mapping - Test operator: **Comparator/reference test(s):** - Standard ECG - Cardiac catheterization "when available"- #s NR - Echocardiogram- "when available - Other: cardiac biomarkers **Other tests performed (before or after index test):** None	**1) Number (%) of patients who had index (ECG-based signal analysis) test:** 50% **2) Number (%) of patients who had comparator test(s):** 100% **3) Number (%) of patients diagnosed with coronary artery disease based on index test:** 325/760 (43%) **4) Number (%) of patients diagnosed with coronary artery disease by other means**: NR **5) Possible to construct 2x2 tables?:** Stage 1: (92%) specificity, (98%) sensitivity (T); 77.4% spec, 96% sens (V) Stage 2: : 86% spec, 80% sens (T); 131/154 (85%) spec, 123/160 (77%) sens (V) Combo of Stage 1+2: 0% sens, 84% spec (T); 82% spec, 74% sens (V)	**Comments:** - Consecutive sample **Quality assessment:** Random or consecutive sample: No (controls from epidemiologic study) Representative sample: Partial (controls without chest pain) Index test described: Yes Reference test described: No (biomarker not specified) Valid reference standard: No (biomarkers not specified) Blinded reference test: Yes Blinded index test: Yes Absence of verification bias: No (not all had biomarkers) Absence of incorporation bias: Yes Appropriate analysis: Yes

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
	Used WHO criteria to define AMI	pain; QRS and ST-T isointegrals (integration of the ECG signal from each electrode) and variables were derived to create map; the total 760 subjects were randomly assigned to the training set and validation set; multiple logistic regression was used to identify which variables best discriminated the groups; Stage 1 regression analysis was comparing the 635 pts vs the 125 controls; Stage 2 compared the 325 vs 310			
Navarro et al., 2003[39]	**Geographical location**: Belfast, Northern Ireland **Study dates:** NR **Study objectives:** To determine whether epicardial potentials using a general thoracic volume conductor model to improves detection of acute MI compared to body surface potentials and standard ECG **Setting:** - Other: cardiology department	**Sample size:** 379 **Age:** NR **Sex:** NR **Race/ethnicity:** NR **Comorbidities:** NR **Clinical characteristics of tested patients:** Consecutive patients presenting to the cardiology department via the ED or mobile CCU. Initial 12-lead ECG and 80-lead ECG prior to treatment and with CK	**Index test (ECG-based signal analysis):** - Device name: PRIME ECG - Manufacturer: Merian Medical Technologies, Belfast - Device type: Body surface mapping - Test operator: "Trained cardiac technicians" **Comparator/reference test(s):** - Standard ECG - Body surface potentials using body surface mapping - Other: Acute MI based on CK twice the upper	**1) Number (%) of patients who had index (ECG-based signal analysis) test:** 379 **2) Number (%) of patients who had comparator test(s)**: 379 **3) Number (%) of patients diagnosed with coronary artery disease based on index test:** 171 with acute MI; CAD not diagnosed **4) Number (%) of patients diagnosed with coronary artery disease by other means**: NA **5) Possible to construct 2x2**	**Comments:** - Consecutive patients - Threshold for abnormal epicardial potential was based on a subset of the study population (would increase sensitivity/specificity) - Appear very high risk for CAD, given that about 50% had acute MI **Quality assessment:** Random or consecutive sample: Yes Representative sample: Yes Index test described: Yes Reference test described: Yes Valid reference standard: No (single biomarker) Blinded reference test: Yes Blinded index test: Yes Absence of verification bias: Yes Absence of incorporation bias: Yes Appropriate analysis: Yes

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
		and/or CK-MB drawn 12 hours after sx onset. Excluded if presenting >12 hours after sx onset, had received tx (fibrinolytic, GP IIb/IIIa antagonist or nitrate) prior to ECG recording.	limit of normal, with CK-MB >= 7% of total CK **Other tests performed (before or after index test):** None	**tables?:** Yes BSM with body surface potential: Sensitivity: 106/171 (62%) Specificity: 166/208 (80%) BSM with epicardial potential Sensitivity: 133/171 (78%) Specificity: 166/208 (80%) ECG (physician interpretation): Sensitivity: 93/171 (54%) Specificity: x/208 (97%)	
Owens et al., 2008[41]	**Geographical location:** Belfast, Northern Ireland **Study dates:** Jan 2002 – June 2004 **Study objectives:** Threefold: 1) quantify performance of 12-lead ECG for acute MI, 2) ask whether additional QRST variables improve diagnostic performance, 3) compare diagnostic capability of 12-lead ECG to BSM **Setting:** - ED - Hospital - Other: mobile CCU **How was coronary artery disease diagnosed?:** CAD not diagnosed.	**Sample size:** 755 **Age:** - Mean (SD): 65 (12) AMI; 60 (12) nonAMI **Sex:** - Male: 528 - Female: 227 **Race/ethnicity: NR** **Comorbidities:** HTN 308 (40.8%) Current smoker: 259 (34.3%) DM: 110 (14.6%) Previous MI: 295 (39.1%) Previous angina pectoris: 396 (52.5%) Previous PCI: 168 (22.3%) **Clinical characteristics of tested patients:** Presented to mobile	**Index test (ECG-based signal analysis):** - Device name: Appears to be PRIME ECG - Manufacturer: NG - Device type: Body surface mapping - Test operator: NR Abnormal values for ST elevation on the ST) isopotential map were: >=2 for anterior territory; >=1mm in lateral, inferior, right ventricular and high right anterior territory; >=0.5mm in the posterior territory **Comparator/reference test(s):** - Standard ECG - Other: Acute MI diagnosed by cardiac troponin T or I increases of >=	**1) Number (%) of patients who had index (ECG-based signal analysis) test:** **2) Number (%) of patients who had comparator test(s)**: 519 with AMI by troponin + 10 with ST elevation/LVH/early repolarization – with “evolutionary changes” but negative troponin = 529 total classified as AMI **3) Number (%) of patients diagnosed with coronary artery disease based on index test:** 420 **4) Number (%) of patients diagnosed with coronary artery disease by other means**: As above **5) Possible to construct 2x2 tables?:** Yes BSM Sensitivity: 402/529 (76%) Specificity: 208/226 (92%)	**Comments:** - 1022 patients analyzed; 755 met eligibility criteria - High risk group – 70% had AMI **Quality assessment:** Random or consecutive sample: Yes Representative sample: Yes Index test described: Yes Reference test described: Yes Valid reference standard: No (uncertain biomarkers) Blinded reference test: Yes Blinded index test: Yes Absence of verification bias: Yes Absence of incorporation bias: Yes Appropriate analysis: Partial (no validation set)

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
	Acute MI diagnosed by cardiac troponin T or I increases of >= 0.1ng/ml	CCU (n=347), ED or "other medical wards to our unit" Ischemic type chest pain of <12 h duration Excluded if: pain < 20 minutes; transferred from other hospitals; treated with fibrinolytics, nitrates or GP IIb/IIIa inhibitors prior to 12 lead ECG or BSM Could not give informed consent Has BSM > 15 minutes after initial 12 lead ECG.	0.1ng/ml **Other tests performed (before or after index test):** None	Excluding subjects with LVH, LBBB, early repolarization or findings of pericarditis (755-123=632) sensitivity (76%) and specificity (93%) were not significantly changed 12-lead ECG using ACC/ESC criteria: Sensitivity: 238/291 (49%) Specificity: 208/226 (92%)	
Owens et al., 2004[40]	**Geographical location:** Belfast, Northern Ireland **Study dates:** January 2002 – January 2004 **Study objectives:** Compare the 12-lead ECG with the body surface map in the diagnosis of acute MI **Setting:** - Other: Mobile coronary care unit **How was coronary artery disease diagnosed?:** CAD not diagnosed.	**Sample size:** 294 **Age:** - Mean (SD): 62 (12) **Sex:** - Male: 209 (71%) - Female: 85 (29%) **Race/ethnicity:** NR **Comorbidities:** h/o HTN 122 (42%) smoker 97 (33%) DM 44 (15%) **Clinical characteristics of tested patients:** Ischemic type chest pain of <12 hours duration Excluded if pain < 20	**Index test (ECG-based signal analysis):** - Device name: Prime Analysis software - Manufacturer: Meridian Technologies, Belfast - Device type: Body surface mapping - Test operator: Cardiac technicians Abnormal BSM defined by ST0 (j point) maxima, ST 60 minima and vector magnitude **Comparator/reference test(s):** - Standard ECG - Acute MI by cTnt > 0.09 ng/mL or cTnI > 0.1 ng/ml- None	**1) Number (%) of patients who had index (ECG-based signal analysis) test:** 294 **2) Number (%) of patients who had comparator test(s)**: 294 biomarkers **3) Number (%) of patients diagnosed with coronary artery disease based on index test:** **4) Number (%) of patients diagnosed with coronary artery disease by other means**: Acute MI 182 by biomarkers Acute MI 103 by ECG Acute MI 146 by BSM **5) Possible to construct 2x2 tables?:** ECG – Minnesota ST elevation: sensitivity 103/182 (57%), specificity	**Comments:** - Recruited consecutively - Maps with > 6 "bad leads" were disregarded - Unclear if abnormal thresholds set a priori **Quality assessment:** Random or consecutive sample: Yes Representative sample: Yes Index test described: Yes Reference test described: Yes Valid reference standard: Yes Blinded reference test: Yes Blinded index test: Yes Absence of verification bias: Yes Absence of incorporation bias: Yes Appropriate analysis: Partial (no validation set)

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
	Acute MI diagnosed by cardiac troponin T or I increases of >= 0.1ng/ml	minutes, had received fibrinolytic therapy, nitrates or GP IIb/IIIa inhibitors prior to initial ECG or BSM, could not give informed consent or BSM >15 minutes after the 12-lead ECG	**Other tests performed (before or after index test):** None	105/112 (94%), c statistic 0.73 BSM ST0 criteria: sensitivity 146/182 (80%), specificity 103/112 (92%), c statistic 0.86 By region, BSM more sensitive to posterior and high right anterior acute MI	
Solomon and Tracy, 1991[47]	**Geographical location:** Washington, DC (Georgetown University) **Study dates:** NR **Study objectives:** Hypothesis: "chronic intermittent ischemia, as occurs in chronic stable angina, damages areas of myocardium such that electrical activity is slowed, and the SAECG from patients with CAD will differ from its appearance in those without CAD. Herein we report a prospective study utilizing SAECG as a noninvasive tool in the evaluation of patients for the presence of significant CAD." **Setting:** - Hospital lab **How was coronary**	**Sample size:** 40 (with an additional 13 patients to identify SAECG parameters to differentiate patients with and w/o CAD) **Age:** - Mean: 56 ± 11 - Range: 27 - 69 **Sex:** - Male: 29 (73%) - Female: 11 (27%) **Race/ethnicity:** NR **Comorbidities:** NR **Clinical characteristics of tested patients:** 40 consecutive patients without known CAD and with chest pain of undetermined etiology referred for cardiac catheterization **Indications for**	**Index test (ECG-based signal analysis):** - Device name: Predictor - Manufacturer: Corazonix, Oklahoma City, OK - Device type: SAECG - Test operator: NR **Comparator/reference test(s):** - Cardiac catheterization **Other tests performed (before or after index test):** ETT performed in 28 of the 40 patients (positive ETT in 18 patients, negative in 8, and indeterminate in 2). 12-lead ECG in all 40 patients. Threshold for positive SAECG result defined *a priori*: QRS threshold: ≥ 100 msec.	**1) Number (%) of patients who had index (ECG-based signal analysis) test:** 40 (100%) **2) Number (%) of patients who had comparator test(s)**: Catheterization: 40 (100%) 12-lead ECG: 40 (100%) **3) Number (%) of patients diagnosed with coronary artery disease based on index test:** QRS parameter 15 (37.5%) with positive SAECG. 13 of these had CAD on catheterization, and 2 did not have CAD on catheterization. RMS parameter 21 (52.5%) with positive SAECG. 16 of these had CAD on catheterization, and 5 did not have CAD on catheterization. LAS parameter 20 (50%) with positive SAECG. 15 of these had CAD on catheterization, and 5 did not have CAD on catheterization. **4) Number (%) of patients**	**Comments:** Exceptionally well designed, executed, and reported study. A separate patient sample (n=13) was used to identify (and subsequently test) parameters that might differentiate patients with and w/o CAD by SAECG. **Quality assessment:** Random or consecutive sample: Yes Representative sample: Partial (patients scheduled for cardiac catheterization) Index test described: Yes Reference test described: Yes Valid reference standard: Yes Blinded reference test: Yes Blinded index test: Yes Absence of verification bias: Yes Absence of incorporation bias: Yes Appropriate analysis: Yes

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
	artery disease diagnosed?:	**catheterization:** new chest pain syndrome (n=37) or asymptomatic positive ETT (n=3) Exclusions: 1) known h/o of CAD 2) h/o of MI 3) h/o of VT 4) h/o of cardiac arrest 5) h/o of congestive heart failure 6) valvular heart disease 7) bundle branch block	RMS voltages: < 50 microV LAS threshold: > 28 msec	**diagnosed with coronary artery disease by other means**. Catheterization findings: 19 patients had no significant CAD, and 21 had significant stenosis (1-vessel disease in 3, 2-vessel disease in 6, and 3-vessel disease in 12). 8 patients had regional hypokinesis. All had EF > 45%, and no patients had akinesis or dyskinesis. **5) Possible to construct 2x2 tables?:** Yes. QRS parameter Sensitivity: 13/21, 62% Specificity: 17,19, 89% PPV: 87% RMS parameter Sensitivity: 76% Specificity: 74% PPV: 75% LAS parameter Sensitivity: 71% Specificity: 74% PPV: 75% With requirement that all three parameters be present: Specificity: 95% PPV: 92% **6) Other:** Patients with CAD had significantly longer filtered QRS and LAS durations and lower root mean square voltages compared with patients w/o CAD. "The SAECG may be a useful tool in evaluating patients for the presence of CAD."	

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
				Comparison with 12-lead ECG 26 of 40 (65%) had normal ECG. SAECG was normal in 11 of these 26. CAD was present in 2 and absent in 9 (by catheterization). In patients with normal ECG and SAECG, 9 of 11 (81%) had no significant CAD. Of the 14 patients with abnormal ECG, all had nonspecific ST and wave abnormalities, and none were diagnostic of ischemia. In patients with abnormal ECG and SAECG, 7 or 10 (70%) had CAD.	
Strobeck et al., 2009[48]	**Geographical location:** US (n=136) Germany (n=751) Asia (n=189) 7 medical centers. **Study dates:** NR **Study objectives:** "To assess sensitivity and specificity of the 3DMP for the detection of relevant coronary stenosis (>70%)" Meta-analysis of 3 published trials. **Setting:** - Other: Pts scheduled for angiography **How was coronary artery disease diagnosed?:** Coronary angiography	**Sample size:** 1076 **Age:** - Mean (SD): 62 ±11.5 **Sex:** - Male: 686 (64%) - Female: 390 (36%) **Race/ethnicity:** NR **Comorbidities:** 249 had either PTCA or CABG 6 or more weeks before enrollment. **Clinical characteristics of tested patients:** Convenience sample of patients in participating medical centers who were already scheduled for coronary angiography for any indication.	**Index test (ECG-based signal analysis):** - Device name: 3DMP - Manufacturer: Premier Heart, LLC - Device type: SAECG. 2 leads. Generates a severity score from 0-20 that indicates the level of myocardial ischemia (if present) resulting from coronary disease. - Test operator: trained trial site technician. Locally operated (presumably by any trained technician) and remotely analyzed at a central data facility. **Comparator/reference test(s):** - Cardiac catheterization	**1) Number (%) of patients who had index (ECG-based signal analysis) test:** 1076 (100%) **2) Number (%) of patients who had comparator test(s):** 1076 (100%) **3) Number (%) of patients diagnosed with coronary artery disease based on index test:** 467 **4) Number (%) of patients diagnosed with coronary artery disease by other means:** 467 (43%) Dx'd with hemodynamically relevant CAD by angiography **5) Possible to construct 2x2 tables?:** Yes **6) Other** With a cut-off score of 4.0, the device	**Comments:** Meta-analysis. Duplicate data but unclear which published studies comprise the 3 samples. Excellent study. **Quality assessment:** Random or consecutive sample: Yes Representative sample: Partial (patients scheduled for cardiac catheterization) Index test described: Yes Reference test described: Yes Valid reference standard: Yes Blinded reference test: Yes Blinded index test: Yes Absence of verification bias: Yes Absence of incorporation bias: Yes Appropriate analysis: Yes

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
		This population had a demonstrated pretest risk of disease from 27.7% to 43.4%. Excluded from analysis: 30 due to angiogram results not available, and 84 due to inadequate 3DMP tracings.	Results classified as: 1) Nonobstructive CAD, or "negative for hemodynamically relevant CAD." 2) Obstructive CAD, or "positive for hemodynamically relevant CAD." **Other tests performed (before or after index test):** None	correctly classified 941 of the 1076 patients with or without relevant stenosis. Sensitivity: 91.2% Specificity: 84.6% PPV: 0.777 (Bayes Corrected) NPV: 0.942 (Bayes Corrected) Adjusted PPV: 81.9% Adjusted NPV: 92.6% ROC AUC = 0.881 (95% CI: 0.860, 0.903) Subgroup analysis showed no significant influence of sex, age, race/nationality, previous revascularization procedures, ECG morphology, or participating center on device's diagnostic performance.	
Weiss et al., 2002[42]	**Geographical location:** Valhalla, NY **Study dates:** NR **Study objectives:** To compare the 3DMP to coronary angiograms **Setting:** -Outpatient **How was coronary artery disease diagnosed?:** Coronary angiography; nonobstructive CAD=40-69% stenosis, obstructive CAD=71-100% or left main of >=50%; normal=<40%	**Sample size:** 136 **Age:** 0-40: 6 (4.4%) 40-60: 49 (36%) >60: 81 (59.6%) **Sex:** - Male: 81 (60%) - Female: 55 (40%) **Race/ethnicity:** NR **Comorbidities:** H/O MI: 29 (21.3%) H/O MI: 22 (16%) HTN: 54 (39.7%) COPD: 4 (2.9%) Renal dysfunction: 5 (3.7%) Smoking: 57 (42%)	**Index test (ECG-based signal analysis):** - Device name: 3DMP - Manufacturer: - Device type: Body surface mapping - Test operator: Abnormalities were identified by comparing the results to a 21,000-patient database **Comparator/reference test(s):** - Standard ECG - Cardiac catheterization **Other tests performed (before or after index test):**	**1) Number (%) of patients who had index (ECG-based signal analysis) test:** 92 CAD; 37 "other heart disease"; 7 normal **2) Number (%) of patients who had comparator test(s):** 136 cardiac catheterizations **3) Number (%) of patients diagnosed with coronary artery disease based on index test:** 78 based on >60% stenosis 90 based on >40% stenosis **4) Number (%) of patients diagnosed with coronary artery disease by other means**: 92 with CAD by angiography 37 with "other heart disease"	**Comments:** - 200 patients selected but only 136 analyzed; exclusions included poor tracings (so indeterminate/ intermediate results appear to have been excluded) - 57% of sample had >60% stenosis **Quality assessment:** Random or consecutive sample: No Representative sample: Partial (scheduled for cardiac catheterization) Index test described: Yes Reference test described: Yes Valid reference standard: Yes Blinded reference test: Yes Blinded index test: Yes Absence of verification bias: Yes Absence of incorporation bias: Yes Appropriate analysis: No

Study	Study Design	Patients	Index and Comparator Test Characteristics	Results	Comments/Quality Scoring
	stenosis	**Clinical characteristics of tested patients:** Patients considered for diagnostic coronary angiography based on history, physical examination, ECT, laboratory values Excluded: Contraindication to angiography h/o cardiac surgery or PCI Long-term drug abuse Pregnancy	None	7 normal **5) Possible to construct 2x2 tables?:** Difficult: sensitivity reported as 93.3% and specificity as 83% - can recreate from Table 5 by collapsing “normal” and “other OHD” results from 3DMP together vs. “CAD” results and using >40% stenosis for the reference standard sensitivity calculated as 76/78 (97.4%) and specificity 40/58 as 68.9% - from Table 5 by collapsing “normal” and “other OHD” results from 3DMP together vs. “CAD” results and using >60% stenosis for the reference standard Uncertain if for obstructive or obstructive + nonobstructive disease; abstract gives sensitivity of 96% for >=70% stenosis by angiography.	

Appendix F: Quality Assessment Ratings

	Menown et al., 1998[36]	Menown et al., 2001[37]	McClelland et al., 2003[38]	Navarro et al., 2003[39]	Owens et al., 2004[40]	Owens et al., 2008[41]
Random/consecutive sample	No, controls from epidem study	Consecutive	Consecutive	Consecutive	Consecutive	Consecutive
Appropriate selection criteria	Partial; controls without CP and normal ECG	Partial, excluded those with BBB; all had ST depression	Yes	Yes	Yes	Yes
Index test described	Yes	Yes	Yes	Yes	Yes	Yes
Reference test described	No, Biomarker not specified	Yes	Yes	Yes	Yes	Yes
Valid reference standard	No, Biomarkers not specified	Yes	Yes	No (single biomarker)	No (incomplete biomarkers)	No (uncertain biomarkers)
Blinded reference test	Can't tell	Can't tell	Can't tell	Can't tell	Yes	Can't tell
Blinded index test	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Yes
No verification bias	No, not all had biomarkers	Yes	Yes	Yes	Yes	Yes
No incorporation bias	Yes	Yes	Yes	Yes	Yes	Yes
Appropriate analysis	Yes, training & validation sets	Yes	Yes	Yes	Partial, no validation set	Partial, no validation set

	Solomon and Tracy, 1991[47]	Weiss et al., 2002[42]	Grube et al., 2007[34]	Grube et al., 2008[35]	Hosokawa et al., 2008[43]
Random/consecutive sample	Consecutive	No	Can't tell	Can't tell	Consecutive
Appropriate selection criteria	Partial, cath scheduled	Partial, cath scheduled	Partial, cath scheduled	No, recent revascularization	Partial, cath scheduled
Index test described	Yes	Yes	Yes	Yes	Yes
Reference test described	Yes	Yes	Yes	Yes	Yes
Valid reference standard	Yes	Yes	Yes	Yes	Yes
Blinded reference test	Can't tell	Yes	Yes	Yes	Yes
Blinded index test	Can't tell	Yes	Yes	Yes	Yes
No verification bias	Yes	Yes	Yes	Yes	Yes
No incorporation bias	Yes	Yes	Yes	Yes	Yes
Appropriate analysis	Yes	No	Yes	Yes	Yes

Abbreviations: BBB = bundle branch block; cath = catheterization; CP = chest pain; ECG = electrocardiogram.