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Systematic Review of ECG-based Signal Analysis Technologies for Evaluating Patients With Acute Coronary Syndrome

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Systematic Review of ECG-based Signal Analysis Technologies for Evaluating Patients With Acute Coronary Syndrome

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Remy R. Coeytaux, M.D., Ph.D.
Philip J. Leisy, B.S.
Galen S. Wagner, M.D.
Amanda J. McBroom, Ph.D.
Cynthia L. Green, Ph.D.
Liz Wing, M.A.
R. Julian Irvine, M.C.M.
Gillian D. Sanders, Ph.D.

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Peer Reviewers

We wish to acknowledge the 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.

Ethan Balk, M.D., M.P.H.
Associate Director, Tufts Evidence-based Practice Center
Tufts Medical Center
Boston, MA 02111

W. Kenneth Haisty Jr., M.D.
Cardiologist
Wake Forest Baptist Medical Center
Winston-Salem, NC 27157

Humberto J. Vidaillet, M.D.
Cardiologist
Marshfield Clinic
Marshfield, WI 54449

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Structured Abstract

Objectives: To summarize the clinical and scientific evidence for commercially available ECG-based signal analysis technologies used or proposed to be used to evaluate patients at low to intermediate risk for coronary artery disease (CAD) who have chest pain or other symptoms suggestive of acute coronary syndrome (ACS).

Data Sources: Searches of gray literature sources, MEDLINE®, EMBASE®, and the Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects.

Review Methods: We conducted a systematic search of English-language literature to identify published evidence for ECG-based technologies that may improve the diagnosis of CAD and/or ACS through signal analysis or other forms of advanced data transformation. For inclusion, a technology had to be (1) a physical device that obtains and interprets information about the electrical activity of the heart in ways that are different from the standard 12-lead ECG, (2) cleared for marketing by the U.S. Food and Drug Administration (FDA) and commercially available in the United States with feasible implementation, (3) tested in patients at low to intermediate risk for CAD who have a clinical presentation consistent with ACS, and (4) reported in a peer-reviewed, published study that reports performance characteristics, effects on diagnostic or treatment decisions, or effects on patient outcomes. Reviewers worked in pairs to extract data, assess applicability, and evaluate the quality of each study. We used a bivariate random-effects generalized linear regression model to compute summary estimates of sensitivity and specificity.

Results: We identified eight commercially available, FDA-cleared ECG-based devices proposed for use to diagnose CAD or detect ACS. Of these, published evidence meeting inclusion criteria was available for only two devices: PRIME ECG and LP 3000. PRIME ECG test performance was reported in 10 studies. Meta-analysis of eight of these studies determined a 68.4 percent sensitivity (95% CI, 35.1 to 89.7) and 91.4 percent specificity (CI, 83.6 to 95.7) for the PRIME ECG in detecting MI (with all but one study using elevated cardiac biomarkers as the reference standard) compared with 40.5 percent sensitivity (CI, 19.6 to 65.5) and 95.0 percent specificity (CI, 87.9 to 98.0) for the standard 12-lead ECG. Differences in test performance between the PRIME ECG and 12-lead ECG are not statistically significant as judged by the overlapping confidence intervals. A single study of LP 3000 demonstrated that QRS prolongation on the signal-averaging ECG was associated with a sensitivity and specificity of 70 percent and 89 percent, respectively, compared with 56 percent and 89 percent for ST changes detected by 12-lead ECG. The improved sensitivity of the signal-averaging ECG versus the 12-lead ECG in that study was statistically significant ($p<0.01$).

Conclusions: Existing research is largely insufficient to confidently inform the appropriate use of ECG-based signal analysis technologies in diagnosing CAD and/or ACS. Further research is needed to better describe 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 to identify clinically significant CAD in the patient population of interest. To fully assess the impact of these devices on diagnostic strategies for patients with chest pain, test

performance needs to be linked to clinically important outcomes through modeling or longitudinal studies.

Contents

Figures

Tables

Executive Summary

Introduction

Coronary artery disease (CAD) is one of the leading causes of mortality in the United States.[1] One of the most common manifestations of clinically significant CAD is chest pain resulting from cardiac ischemia or myocardial infarction (MI). While chest pain is a common symptom of patients presenting to clinics and emergency departments, only about 6 percent of patients presenting to the emergency room with acute chest pain are ultimately diagnosed with MI.[2] Identifying which patients with chest pain are experiencing acute ischemic heart disease is critical since a delay in diagnosis can impede the application of effective therapies such as thrombolytic agents or primary percutaneous coronary intervention (PCI). The most reliable diagnostic test for CAD is coronary angiography, but exercise or pharmacological stress tests can also help identify patients with clinically significant CAD.

Patients who present for medical attention with chest pain or other symptoms that suggest acute ischemia or infarction are often considered to have acute coronary syndrome (ACS). ACS typically serves as a "working diagnosis" for patients suspected of having ischemic heart disease, pending the establishment or ruling out of specific diagnoses.[2] The first and potentially most important test typically administered in the workup of a patient with symptoms suggestive of ACS is the standard, resting 12-lead electrocardiogram (ECG). Typically, the ECG will indicate ST elevation myocardial infarction (STEMI), or it will be normal or nondiagnostic. If the ECG indicates STEMI, the patient will most likely be taken directly to coronary angiography without additional testing. In contrast, a normal or nondiagnostic ECG result does not rule out the possibility of acute ischemia or infarction, so further testing is usually indicated if the clinical presentation suggests ischemic heart disease. Patients without ST elevation on the initial ECG who are ultimately found via further testing (e.g., elevated cardiac biomarkers, stress testing, or other tests) to have had an MI are diagnosed as having had non-ST elevation myocardial infarction (NSTEMI). Patients without ST elevation on the initial ECG who subsequently show evidence (e.g., by stress testing) of reversible myocardial ischemia are usually given the diagnosis of unstable angina. In sum, patients without ST elevation whose clinical presentation suggests a cardiac etiology are typically considered to have ACS.

Although the standard ECG is critically important in the initial evaluation of patients with ACS, it is limited in its ability to correctly identify all patients with acute ischemic heart disease. False-positive test results are likely to lead to further testing or initiation of treatment, or both, whereas false-negative test results may lead to adverse outcomes associated with delay or withholding of potentially life-saving interventions. New devices that seek to improve on the standard ECG's capabilities in the evaluation of patients presenting with chest pain have been developed. An enhanced ECG-based test that allows a patient with ACS to be accurately identified could potentially limit the myocardial damage associated with delays in administering acute reperfusion treatment (by improving on the standard ECG's true-positive rate), while possibly minimizing the use of potentially harmful invasive testing among patients who do not have clinically significant CAD (by improving on the standard ECG's false-positive rate). The

test performance and diagnostic accuracy efficacy of these technologies as well as their impact on clinical decisionmaking and patient outcomes, however, is uncertain.

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 290-2007-10066-I). The purpose of this technology assessment is to summarize the clinical and scientific evidence for commercially available ECG-based signal analysis technologies used to evaluate patients with chest pain or other symptoms suggestive of ACS among patients at low to intermediate risk for CAD. Although some ECG-based technologies have been used for other purposes (e.g., detecting malignant arrhythmias), these are not the focus of the current report—as defined in our inclusion/exclusion criteria. Rather, this report focuses on patients who do not meet STEMI or STEMI-equivalent criteria on the standard 12-lead ECG.

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

KQ 1:

a. What devices and methods for ECG-based signal analysis are used, or proposed to be used, for diagnosis of CAD and/or acute coronary syndrome (with or without chest pain) in outpatient settings (including physician offices, urgent care, and emergency departments) in patients at low to intermediate risk? What is the U.S. Food and Drug Administration (FDA) status of these devices?
b. What are considered the "gold standard" tests for the diagnosis of CAD and/or acute coronary syndrome (with or without chest pain) in patients at low to intermediate risk, and what are their strengths and limitations?

KQ 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) affect 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 used a two-step searching approach to systematically identify devices and literature relevant to this review. First, potentially relevant technologies were identified through a search of gray literature sources, including the U.S. FDA Web site, Google™, www.freepatentsonline.com, www.clinicialtrials.gov, and the abstracts of various scientific meetings, and a targeted review of selected relevant journal websites (Appendix A) . From this body of data, we sought to identify devices that may improve the diagnosis of CAD and/or ACS through the use of signal analysis, spectral analysis, or other forms of advanced data transformation. Second, terms for devices identified through the gray literature scan or prior knowledge from previous work[3] were added to detailed strategies developed to search English-

language literature indexed in PubMed, Embase, and Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects from database inception through November 18, 2011 (Appendix B). Searches conducted in these databases were designed to identify peer-reviewed publications presenting evidence regarding test performance, decisionmaking, or patient outcomes. The reference list of a similar review conducted in 2010[3] was manually hand-searched and cross-checked against our library of search results, and additional citations retrieved for screening.

Two investigators independently reviewed titles, abstracts, and full-text articles against pre-specified criteria to determine eligibility. The general eligibility criteria for our review included:

- A relevant device must be a physical device (i.e., not simply computer software) that obtains and interprets information about the electrical activity of the heart in ways that are different from the standard 12-lead ECG.
- The device must have been approved or cleared for marketing by the U.S. FDA.
- The device must be commercially available in the United States.
- Implementation of the device in most medical facilities must be feasible.
- The device must be tested in patients at low to intermediate risk for CAD who have a clinical presentation consistent with ACS.
- The study must report relevant outcomes including performance characteristics compared with an acceptable reference standard, effects on diagnostic or treatment decisions, or effects on patient outcomes.

We excluded studies that reported data only from patients known to have ST elevation by standard ECG, or studies that did not report data separately for patients with and without ST elevation at the time of the initial ECG. We excluded studies that included patients under 18 years of age, if data for the patients 18 years and older were not presented separately. We also excluded studies that included a previously scheduled coronary angiogram as an eligibility criterion for patients; the rationale for this exclusion was that a patient population preselected for coronary angiography is likely to include a relatively high proportion of individuals at high risk for CAD or ischemic heart disease—and as such does not represent the target population for this report. We excluded devices for which we could not find evidence of commercial availability. A complete table of study inclusion and exclusion criteria is presented in Appendix C.

To aid in standardization of data collection from included studies, investigators received data abstraction instructions directly on each form created specifically for this project. We designed these forms to collect the data required to evaluate eligibility criteria for inclusion in this review, test characteristics, and effects on outcomes of interest. One investigator abstracted data from each included study and assessed study quality and applicability; the results were then reviewed for accuracy by a second investigator. Data were synthesized qualitatively and, when appropriate, using quantitative methods.

Investigators assessed the quality of each study according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool,[4-6] including characteristics of sample selection, adequate description of the index and reference tests, blinded interpretation of the index and reference tests, and presence of verification bias (Appendix D). To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of Good, Fair, and Poor based on the study's adherence to well-accepted standard methodologies (such as QUADAS) and adequate reporting standards (refer to Table D-1 in Appendix D).

Device performance was summarized using sensitivity, specificity, and likelihood ratios. Test 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 readily calculated. The positive likelihood ratio describes how many times more likely it is that an abnormal test comes from a patient with disease versus a patient without disease. The negative likelihood ratio describes how many times more likely it is that a normal test comes from a patient with disease versus a patient without disease. The posttest probabilities for negative and positive results were calculated on the basis of assumed prevalence and positive and negative likelihood ratios obtained from the meta-analysis. A positive likelihood ratio greater than 10 and a negative likelihood ratio less than 0.1 imply strong effects, whereas a likelihood ratio close to 1 implies no effect. Positive and negative likelihood ratios with corresponding confidence intervals for each diagnostic method were calculated from the mean logit-sensitivity and mean logit-specificity and their corresponding standard errors.

When studies were conceptually homogeneous, we used a bivariate random-effects generalized linear regression model to compute summary estimates of sensitivity and specificity with 95 percent confidence intervals.[7] A random-effects model assumes that variability is a result of sampling errors as well as the true differences between studies and provides a meta-analytic modeling approach for pooling sensitivity and specificity, while accounting for possible correlation between sensitivities and specificities of the studies included.[8] For studies that derived a test algorithm in a training set and tested performance in a validation set, 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.[9]

Results

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

The combined gray and published literature searches identified eight potentially relevant devices that are available for purchase in the United States and have been cleared for marketing by the FDA, including four that use signal averaging, one that uses body surface mapping, one that uses mathematical analysis, and two that use high-frequency QRS analysis. The names of the eight devices and their manufacturers are as follows: Predictor® and Model 1200 EPX™ by Arrhythmia Research Technology; MAC® 5000 by GE Medical; LP 3000 by Fidelity Medical; the PRIME ECG® by Heartscape Technologies; 3DMP™/MCG™/mfEMT™ by Premier Heart; CardioSoft® by NASA; and HyperQ™ by Biological Signal Processing.

Key Question 1b—Gold Standard Tests

Coronary Artery Disease

Current guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) maintain that coronary angiography remains the best reference standard for diagnosing CAD.[10] Through interrogation and identification of the coronary anatomy, coronary angiography is the best available test to identify which patients may benefit from surgical or percutaneous intervention, medical management, or both. Among low-risk patients who are typically not referred for coronary angiography but who 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.

According to the ACC/AHA consensus guideline, the standard, resting 12-lead ECG is not an acceptable reference standard for the diagnosis of CAD.[11] The standard ECG detects electrocardiac signals emitted by myocardial cells, but it cannot directly detect the presence of atherosclerotic plaques in the coronary arteries. Consequently, the standard ECG demonstrates poor accuracy in diagnosing patients at low to intermediate risk for CAD. New technologies for diagnosing CAD are therefore most appropriately compared to the reference standard of coronary angiography or, at the very least, acceptable noninvasive reference standards such as stress imaging. Appropriate use of biomarkers, on the other hand, is an acceptable reference standard for the diagnosis of acute MI but not of CAD. Table ES-1 summarizes how current guidelines[10-15] maintain that coronary angiography remains the preferred reference standard for the diagnosis of CAD, while exercise stress testing with imaging serves as an acceptable reference standard.

Acute Coronary Syndrome

ACS is a term commonly used to describe the clinical presentation that includes acute onset of chest pain or other symptoms that suggest myocardial ischemia or infarction. ACS typically serves as a working diagnosis for such patients, pending the establishment or ruling out of specific diagnoses. As such, there is no gold standard test for ACS. The standard ECG serves as one of the most important tests in the initial evaluation of patients who present with symptoms suggestive of ACS, but additional clinical and laboratory information is required to accurately differentiate patients with and without acute ischemic heart disease. Elevations in serum biomarkers such as creatine kinase (CK) MB fraction or troponin-I may indicate ischemia or infarct of the myocardium and may be used as an acceptable but imperfect reference standard for the diagnosis of ACS (Table ES-1).

Table ES-1. Potential reference standards for diagnosing CAD[a] or ACS

Reference Standard	Level of Acceptability
CAD	
Coronary angiography	Preferred
Stress testing with imaging	Acceptable
Imaging studies without exercise or pharmacological stress • Resting 12-lead ECG • Stress testing with ECG	Unacceptable
ACS	
Biomarkers (applicable only for identifying myocardial injury)	Acceptable

[a]Based on current guidelines.[10-15]
Abbreviations: ACS=acute coronary syndrome; CAD=coronary artery disease; ECG=electrocardiogram

Key Question 2a—Evidence for Variability by Rater, Patient, or Device

Our search strategy did not identify any eligible studies that reported information about intra-rater, intra-patient, or intra-device variability. We identified a single fair-quality study that evaluated the inter-rater variability of the PRIME ECG body surface mapping (BSM) device. This study involved 150 eligible patients with acute chest pain who underwent both standard ECG and PRIME ECG testing in an emergency department setting. Complete data were available for 135 patients. Emergency physicians and BSM experts interpreted the BSM readings as either "negative" (for normal readings) or "positive" (for abnormal readings). Of these 135 readings, emergency physicians and BSM experts agreed on 52 (39%) of the negative test result readings and 63 (47%) of the positive test result readings. Fifteen (11%) BSM tests were interpreted as negative by emergency physicians but positive by BSM experts, and 5 (4%) BSM tests were interpreted as positive by emergency physicians but negative by BSM experts. This corresponds to a kappa statistic of 0.63 (95% confidence interval [CI], 0.53 to 0.72).

Key Question 2b—Evidence for Test Performance

We identified 11 studies represented by 14 articles that evaluated the test performance of 2 eligible devices. The PRIME ECG was evaluated in 10 studies involving patients with chest pain recruited from emergency departments, medical wards, or mobile coronary care units; 8 of these studies also evaluated the 12-lead ECG. Some of the patients were treated in mobile coronary care units in Ireland, and as such may have been at high risk for CAD, thereby resulting in a study population that may be at higher overall risk for CAD 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 of nine of these studies after excluding one study that was a subset of other studies and as such had duplicate data. The sensitivity and specificity were 71.1 percent (95% CI, 45.6 to 87.8) and 90.2 percent (CI, 83.2 to 94.4), respectively. Studies were statistically heterogeneous for the positive likelihood ratio ($Q=122.9$, $df=9$, $p<0.001$; $I^2=92.7\%$) and the negative likelihood ratio ($Q=314.9$, $df=9$, $p<0.001$;

I^2=97.1%). The summary estimate for the positive likelihood ratio was 6.3 (CI, 3.3 to 12.1) and for the negative likelihood ratio was 0.30 (CI, 0.16 to 0.56).

We performed a sensitivity analysis excluding two studies, namely, the first in a series of studies in which a different diagnostic algorithm was used [16], and a second study with a very small sample size that was disproportionately weighted in the random effects meta-analysis.[17]. The standard errors of the effect measures are determined by two factors—the number of subjects and the measure of interest in the compared groups. These factors in turn determine the weight given to a study in the meta-analysis. If one or both factors differ (are outliers) from the other studies included, the results can be overestimated or underestimated.[18] The sensitivity and specificity for the remaining studies were 68.4 percent (CI, 35.1 to 89.7) and 91.4 percent (CI, 83.6 to 95.7), respectively. The remaining studies were heterogeneous for the positive likelihood ratio (Q=122.1, df=7, p<0.001, I^2=94.3%) and negative likelihood ratio (Q=277.4, df=7, p<0.001, I^2=97.5%). The positive likelihood ratio (6.7; CI, 2.8 to 15.9) and negative likelihood ratio (0.31; CI, 0.14 to 0.69) 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 87.0 percent. A normal PRIME ECG would yield a posttest probability of 23.7 percent. The performance characteristics of the 12-lead ECG were not statistically significantly different from the PRIME ECG.

One other eligible device, the LP 3000, was evaluated by one study included in this report. The LP 3000 signal averaging system was compared to a 12-lead ECG in 126 consecutive patients referred to a hospital for a first episode of typical angina. The LP 3000 system was found to have a sensitivity and specificity of 70 percent and 89 percent, respectively, compared with 56 percent and 89 percent for ST changes detected by 12-lead ECG. The improved sensitivity of signal averaging ECG relative to 12-lead ECG was statistically significant (p<0.01).

Key Question 2c—Evidence for Impact on Diagnostic Decisionmaking

Our search did not identify any eligible studies providing evidence that the use of, or findings from, ECG-based technologies other than the standard 12-lead ECG had an impact on the decisions or actions of patients or health care providers.

Key Question 2d—Evidence for Impact on Patient Outcomes

We identified a single, good-quality study that addressed this question among a population of patients at moderate to high risk for CAD. The multicenter, prospective, cohort-blinded Optimal Cardiovascular Diagnostic Evaluation Enabling Faster Treatment of Myocardial Infarction (OCCULT MI) trial evaluated the PRIME ECG among 1830 adults at moderate to high risk for adverse cardiovascular outcomes who presented to a tertiary care emergency department with chest pain or symptoms suspicious for ACS. The primary aim of this study was to test the hypothesis that individuals with 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. A preplanned secondary analysis compared outcomes of patients with STEMI to patients without STEMI. Among the 1514 patients with available outcome data, ST elevation detected by the PRIME ECG was associated with increased mortality (odds ratio [OR] 11.2; 95%

CI, 1.8 to 67). ST elevation on a standard 12-lead ECG, however, was not predictive of adverse outcomes in this population.

We identified a fair-quality study that collected information about the impact of testing on patient outcomes but did not report those outcomes. That study collected information obtained from patients through the course of their hospital stay and after discharge (such as repeat visit to the emergency department with chest pain or ischemic symptoms, recurrent MI, catheterization, revascularization, or death). These patient outcomes, however, where not reported in the published paper.

Discussion

Currently, there is little evidence for the utility of ECG-based signal analysis technologies as a diagnostic test among patients at low to intermediate risk for CAD who present in the outpatient setting with the chief complaint of chest pain or other symptoms suggestive of ACS. Most devices identified by our gray literature search did not appear to have published articles describing their performance among the target population for this report. The literature was not sufficient to determine if factors such as sex, body type, medications, and comorbid medical conditions affected test performance.

All but one of the included studies were rated as fair quality, primarily because of the difficulty in blinding decisionmakers from available and pertinent data that may have influenced the course of evaluation or treatment of patients with ACS. The OCCULT MI study was rated as good quality because the investigators successfully minimized bias introduced by health care providers and because they used study-adjudicated diagnoses as the reference standard.

The limited available evidence demonstrates proof of concept, particularly for the PRIME ECG device, and it suggests that the sensitivity of body surface mapping and signal averaging devices is higher compared with standard ECG for identifying patients with ACS who have either ischemic heart disease or CAD. However, this evidence is limited by the use of incomplete reference standards in the published studies, including elevated biomarkers for detecting acute ischemic heart disease.

Further research is needed to better describe 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 to identify patients with clinically significant CAD in the patient population of interest. 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.

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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 individuals in the United States have CAD. Of these, approximately 7 million have angina pectoris (chest pain) and have had a myocardial infarction (MI).[1] While chest pain is a common symptom of patients presenting to clinics and emergency wards, only about 6 percent of patients presenting to the emergency room with acute chest pain are ultimately diagnosed with MI.[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 important in order to properly triage patients presenting with chest pain. Currently available tests identify a relatively low proportion of patients who will benefit from secondary prevention.

CAD Versus Ischemia Versus Infarction

A diagnosis of CAD results from findings suggestive of atherosclerotic plaque in the coronary arteries. This plaque may or may not create an obstruction to coronary blood flow. The buildup of atherosclerotic plaque is a progressive and diffuse process that develops in the coronary arteries. Plaque formation may begin prior to middle age and may be asymptomatic, 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 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 the corresponding coronary artery. Patients who exhibit ischemia on stress testing and whose symptoms are not optimally managed with medical therapy are often referred for diagnostic coronary angiography and then elective revascularization if indicated. Prolonged

ischemia may result in MI, 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. Elevation of cardiac troponin serves as evidence of myocardial cell death. Compared with patients without a prior MI, patients with a history of MI are at higher risk for future cardiac events, including recurrent infarction and death.

Acute Coronary Syndrome (ACS)

Acute coronary syndrome (ACS) is a term commonly used to describe the clinical presentation that includes acute onset of chest pain or other symptoms that suggest myocardial ischemia or infarction. ACS typically serves as a "working diagnosis" for patients suspected of having ischemic heart disease, pending the establishment or ruling out of specific diagnoses.[2]

The first, and potentially most important, test typically administered in the workup of a patient with symptoms suggestive of ACS is the standard, resting 12-lead ECG. Typically, the ECG will indicate ST elevation myocardial infarction (STEMI) or be normal or nondiagnostic. If the ECG indicates STEMI, the patient will most likely be taken directly to coronary angiography, and patient outcomes would not be expected to improve with further testing. A normal or nondiagnostic ECG result does not rule out the possibility of acute ischemia or infarction, so further testing is usually indicated. Patients without ST elevation on the initial ECG who are ultimately found via further testing (e.g., elevated cardiac biomarkers, stress testing) to have undergone MI are diagnosed as having had non-ST elevation myocardial infarction (NSTEMI). Patients without ST elevation on the initial ECG who subsequently show evidence (e.g., by stress testing) of reversible myocardial ischemia are usually ascribed the diagnosis of unstable angina. Patients with the clinical presentation of acute-onset chest pain or other symptoms suggesting a cardiac etiology without ST elevation on initial ECG may continue to be considered to have ACS, pending the results of further testing.

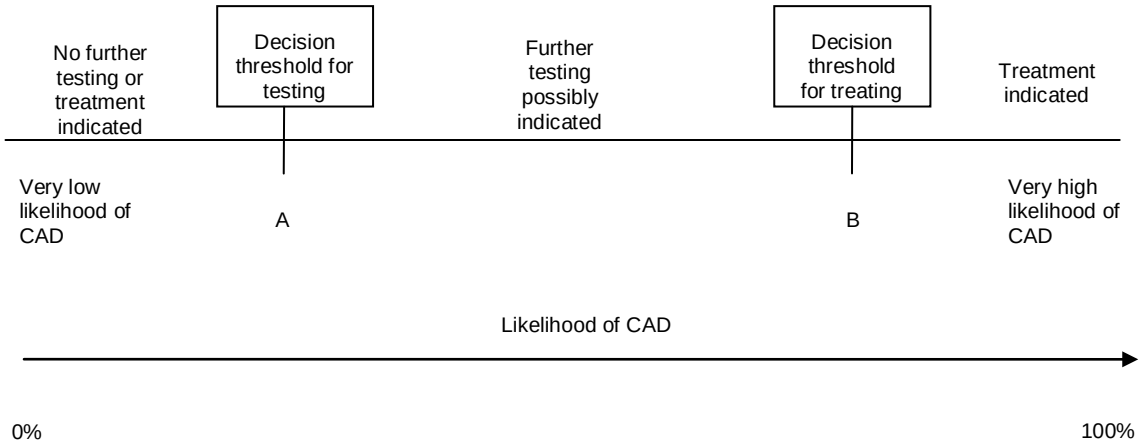
Patients who present with symptoms suggestive of ACS and who have a nondiagnostic or normal resting ECG fall into one of two categories: (1) they are experiencing myocardial ischemia or infarction (the ECG was falsely negative) or (2) their symptoms are not caused by acute ischemic heart disease. Patients with a false-negative ECG represent the population for which improvement on diagnostic performance of the resting ECG is likely to have the greatest potential for benefit. These patients are at high risk for not receiving potentially life-saving and highly time-sensitive treatments. Patients with a false-positive ECG may also potentially benefit from a more accurate, noninvasive test than the resting ECG by avoiding the need for subsequent invasive testing or possibly harmful treatment. The potential harms associated with undiagnosed and untreated ischemic heart disease, however, are generally considered greater than the potential harms associated with further workup and treatment of patients with false-positive ECGs.

Diagnostic Testing and Risk Stratification for CAD

CAD is an important risk factor for the development of ischemic heart disease. It follows, therefore, that risk stratification for the presence of CAD may help improve both the accuracy of diagnosis and the timely treatment of ischemic heart disease among patients with ACS. 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



Abbreviation: CAD=coronary artery disease

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 ACS. For this category of patients, represented by the space between A and B in Figure 1, noninvasive test results have proven useful for posttest decisionmaking.[4] 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.

Recently published guidelines[5] propose three diagnostic classifications of patients who present with symptoms suggestive of ACS, based on findings from an initial resting ECG: (1) STEMI (including patients with presumed new left bundle branch block), (2) unstable angina or NSTEMI, and (3) nondiagnostic ECG. For the purpose of this report, we considered patients with STEMI or STEMI-equivalent (defined as ST depression occurring in precordial leads V_1–V_4, indicating ST elevation on the left ventricular posterior wall opposite to the interventricular septum) to be at high risk for both CAD and ischemic heart disease. The target population for the purpose of this report excludes these high-risk patients and focuses, rather, on patients with symptoms suggestive of ACS at low to intermediate risk for CAD, including patients with a clinical presentation and initial ECG findings consistent with unstable angina or NSTEMI as well as patients with a nondiagnostic resting ECG at time of presentation.

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

In patients where CAD or ACS 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 reading physician to assess the signs suggestive of acute ischemia, hypertrophy, arrhythmia, history of MI, or 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 5 minutes). Also, most ECG machines are equipped with computerized diagnostic algorithms that provide an immediate preliminary interpretation, which is made available for physician review.

However, the standard ECG has several significant limitations. First, an ECG represents electrocardiographic activity at a single moment in time while the patient is at rest. As such, ECGs often need to be repeated as a patient's clinical condition changes. Second, although wave-pattern recognition and comparison with expected normal findings are used in ECG assessment, the final analysis is open to subjective interpretation by the reading physician. Finally, a resting ECG's diagnostic utility is severely limited in the diagnosis of CAD, with an estimated sensitivity between 12 and 70 percent depending on the population studied and criteria applied.[7,8] Nevertheless, despite its limited utility in the diagnosis of CAD, the standard ECG is perhaps the single most useful test in the initial evaluation of a patient with ACS because it can rapidly identify patients who are likely to be experiencing acute myocardial ischemia.

Evaluating Emerging ECG-based Technologies

New devices that seek to improve ECG capabilities in the evaluation of patients with chest pain have been proposed—specifically, devices that are potentially capable of detecting myocardial ischemia or identifying patients who may have significant CAD, myocardial ischemia, or MI. 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 MI that was not evident on the 12-lead ECG), or by providing the diagnostic information necessary to avoid invasive diagnostic or therapeutic interventions. Access to an enhanced ECG-based test—if proven to be more accurate than the standard 12-lead ECG—might also impact decisionmaking of health care providers at institutions that do not have onsite cardiac catheterization facilities.

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 with existing technology. For example, in patients with low to intermediate risk for CAD who present with symptoms suggestive of ACS, an enhanced test might serve as a better initial diagnostic instrument than a standard ECG alone. 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 290-2007-10066-I). The purpose of this technology assessment is to summarize the clinical and scientific evidence for commercially available ECG-based signal analysis technologies used to evaluate patients with chest pain at low to intermediate risk for CAD, or with a clinical presentation consistent with ACS. This report does not address the use of these technologies to evaluate patients at high risk for CAD—defined for the purpose of this report as generally meeting accepted criteria for STEMI.

We did a gray literature search to identify emerging technologies that noninvasively analyze electrical signals from the heart, which we have collectively termed "ECG-based signal analysis technologies." One example of such a technology is the signal-averaged ECG, which analyzes the ECG by computing the average of numerous ECG complexes. Signal averaging 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). Late potentials may reflect inflammation, edema, fibrosis, or infarct.

Another example of ECG-based signal analysis technology is body surface mapping (BSM), 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. A more recent form of ECG-based signal analysis uses 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. 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 or tests aimed at predicting malignant arrhythmias. This report focuses on commercially available ECG-based signal analysis devices to inform AHRQ and CMS about the utility of these emerging technologies for the diagnosis and management of individuals at low to intermediate risk for CAD who present with acute-onset chest pain or other symptoms suggestive of ACS.

Methods

Key Questions

The sponsor of this report identified two key questions (KQs) to be addressed. The EPC research team further clarified these questions and research objectives through consultation with the AHRQ Task Order Officer assigned to the project and representatives from CMS.

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

KQ 1:

a. What devices and methods for ECG-based signal analysis are used, or proposed to be used, for diagnosis of CAD and/or acute coronary syndrome (with or without chest pain) in outpatient settings (including physician offices, urgent care, and emergency departments) in patients at low to intermediate risk? What is the U.S. Food and Drug Administration (FDA) status of these devices?
b. What are considered the "gold standard" tests for the diagnosis of CAD and/or acute coronary syndrome (with or without chest pain) in patients at low to intermediate risk, and what are their strengths and limitations?

KQ 2:

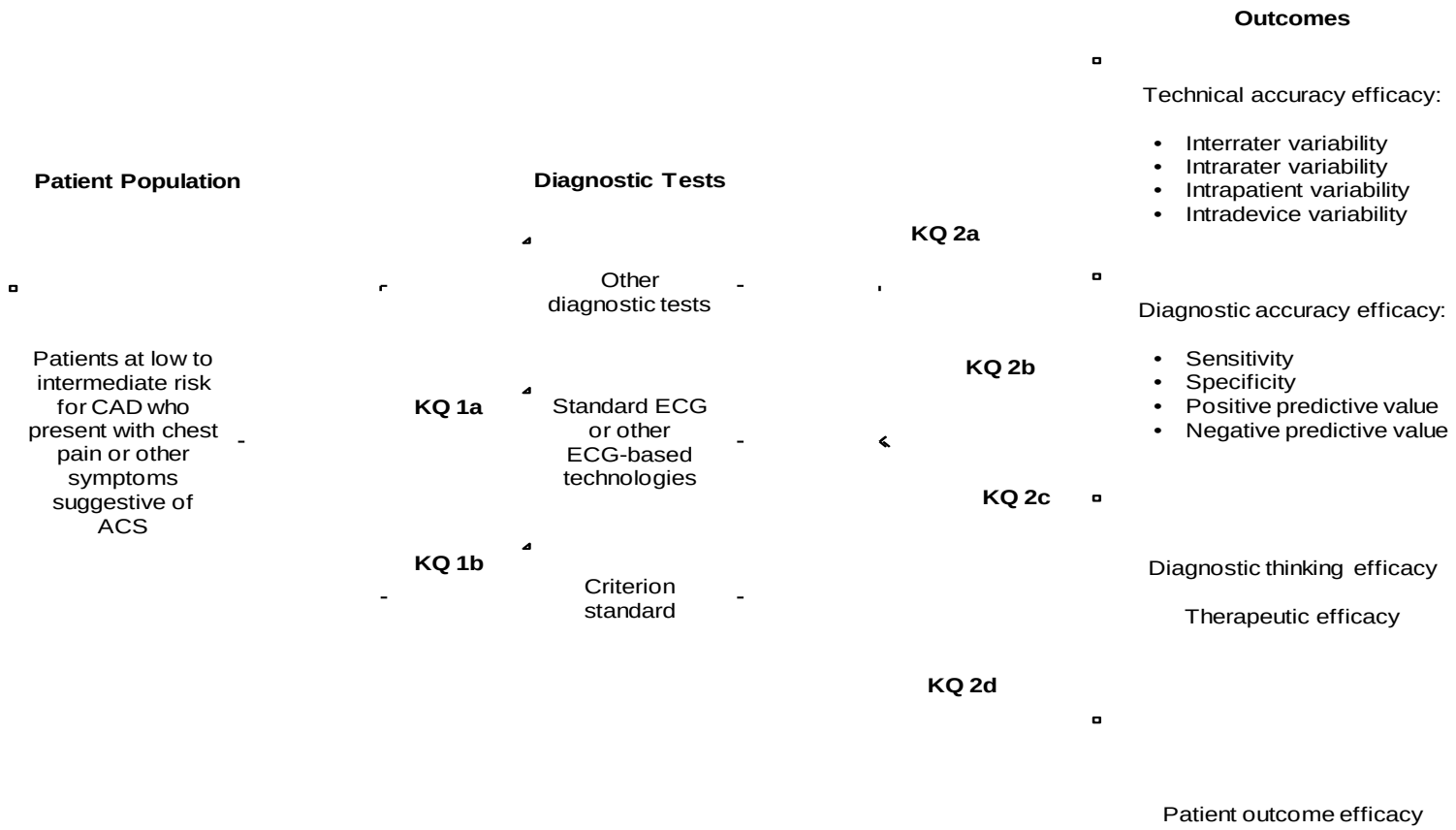
a. What is the evidence for inter-rater, intra-rater, intra-patient, and intra-device variability?
b. What is the evidence for diagnostic test performance compared to the reference standard used in the study? What factors (confounders) affect test sensitivity and specificity?
c. What is the evidence 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 variability, progressing through diagnostic test performance, and ending with the effects on relevant patient outcomes. This analytic framework, shown in Figure 2, guided our research questions, search strategy, data abstraction elements, and evaluations.

Our analytic framework defines the target population as patients at low to intermediate risk for CAD who present with chest pain or other symptoms suggestive of ACS. Diagnostic tests depicted in the framework include the standard 12-lead ECG, other ECG-based technologies, a criterion standard such as coronary angiography, or other diagnostic tests. Potential outcomes evaluated include technical accuracy efficacy, diagnostic accuracy efficacy, diagnostic thinking efficacy, and patient outcome efficacy. Patient outcomes include catheterization laboratory findings, clinical outcomes of mortality, cardiac symptoms, function and functional status, and therapeutic interventions.

Figure 2. Analytic framework



Abbreviations: ACS=acute coronary syndrome; CAD=coronary artery disease; ECG=electrocardiogram; KQ=key question

Approach

Sources of Information and Review Methods

The sources of information as well as the review methods used by the EPC varied according to the KQ being addressed. Both KQs 1 and 2 required systematic literature search strategies, but the data collected from the two strategies were quite different. For KQ 1, we conducted a comprehensive review of the published and gray literature and gathered and collated information from the FDA, device manufacturers, and other relevant sources (see search strategies provided in Appendix A). KQ 1 also involved summarizing information about commonly used diagnostic tests, procedures, and strategies. For KQ 2, we searched published, peer-reviewed literature to synthesize the available scientific evidence pertaining 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 or who has a clinical presentation suggestive of ACS.

Process for Study Selection

We conducted a systematic search of the English-language literature indexed in PubMed®, Embase, and the Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects, and a search of gray literature sources including the U.S. FDA Web site, Google™, online journal websites, professional society conference abstracts, www.clinicaltrials.gov, and www.freepatentsonline.com. We sought to identify devices that improved the diagnosis of CAD and/or ACS through the use of signal analysis, signal averaging, spectral analysis, or other forms of advanced data transformation. We specifically excluded devices that used imaging techniques such as echocardiography or coronary angiography as well as technologies that did not analyze electrocardiographic information. We initially included magnetocardiography in our published literature search strategy but later excluded this technology on the grounds that it involves more than the application of a single device and is not readily available at most medical facilities. We identified the major categories of electrocardiography, including body surface potential mapping, mathematical analysis of ECG signals, and vectorcardiography.

After discussions with representatives from CMS, 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 mathematical manipulation of data (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 our inclusion criteria. We excluded devices for which we could not find evidence of commercial availability.

Literature Search Strategies

We devised two main strategies for gathering information. First, 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 A including the ClinicalTrials.gov Web site

(www.clinicaltrials.gov) in order to identify potentially relevant devices. Next, we searched English-language articles indexed in PubMed, Embase, and the Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects through November 18, 2011, using search terms for the specific devices identified in the gray literature search, terms for signal analysis or spectral analysis, and terms for CAD, myocardial ischemia, and ACS. The exact search terms are detailed in Appendix B. The reference list of a similar review conducted in 2010[10] was manually hand-searched and cross-checked against our library of search results, and additional citations retrieved for screening. The titles and abstracts of all citations retrieved 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.

Inclusion and Exclusion 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:

- A relevant device must be a physical device (i.e., not simply computer software) that obtains and interprets information about the electrical activity of the heart in ways that are different from the standard 12-lead ECG.
- The device must have been approved or cleared for marketing by the U.S. FDA.
- The device must be commercially available in the United States.
- Implementation of the device in most medical facilities must be feasible.
- The device must be tested in patients at low to intermediate risk for CAD who have a clinical presentation consistent with ACS.
- The study must report relevant outcomes including performance characteristics, effects on diagnostic or treatment decisions, or effects on patient outcomes such as death, subsequent medical or surgical interventions, and health-related quality of life.

We excluded studies that reported data only from patients known to have ST elevation by standard ECG, or studies that did not report data separately for patients with and without ST elevation at the time of the initial ECG. We excluded studies that included patients under 18 years of age, if data for the patients 18 years and older were not presented separately. We also excluded studies that included a previously scheduled coronary angiogram as an eligibility criterion for patients; the rationale for this exclusion criterion is that a patient population preselected for coronary angiography is likely to include a relatively high proportion of individuals at high risk for CAD and ischemic heart disease—and as such does not represent the target population for this report.

Data Abstraction

To aid in standardization of data collection, investigators received data abstraction instructions directly on each form created specifically for this project with the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada). We designed these forms to collect the data required to evaluate eligibility criteria for inclusion in this review, test characteristics, and effects on outcomes of interest. For eligible studies, an investigator abstracted data 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 reviewed 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) tool[11-13] and included characteristics of sample selection, adequate description of the index and reference tests, blinded interpretation of the index and reference tests, and presence of verification bias (Appendix D). To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of Good, Fair, and Poor based on the study's adherence to well-accepted standard methodologies (such as QUADAS) and adequate reporting standards (Table D-1 in Appendix D).

Data Analysis

Device performance was summarized using sensitivity, specificity, and likelihood ratios. Test 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 readily calculated. The positive likelihood ratio (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 negative likelihood ratio (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.[14] A random-effects model assumes that variability is a result of sampling errors as well as the true differences between studies and provides a meta-analytic modeling approach for pooling sensitivity and specificity, while accounting for possible correlation between sensitivities and specificities of the studies included.[15] For studies that derived a test algorithm in a training set and tested performance in a validation set, 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.[16]

Peer Review Process

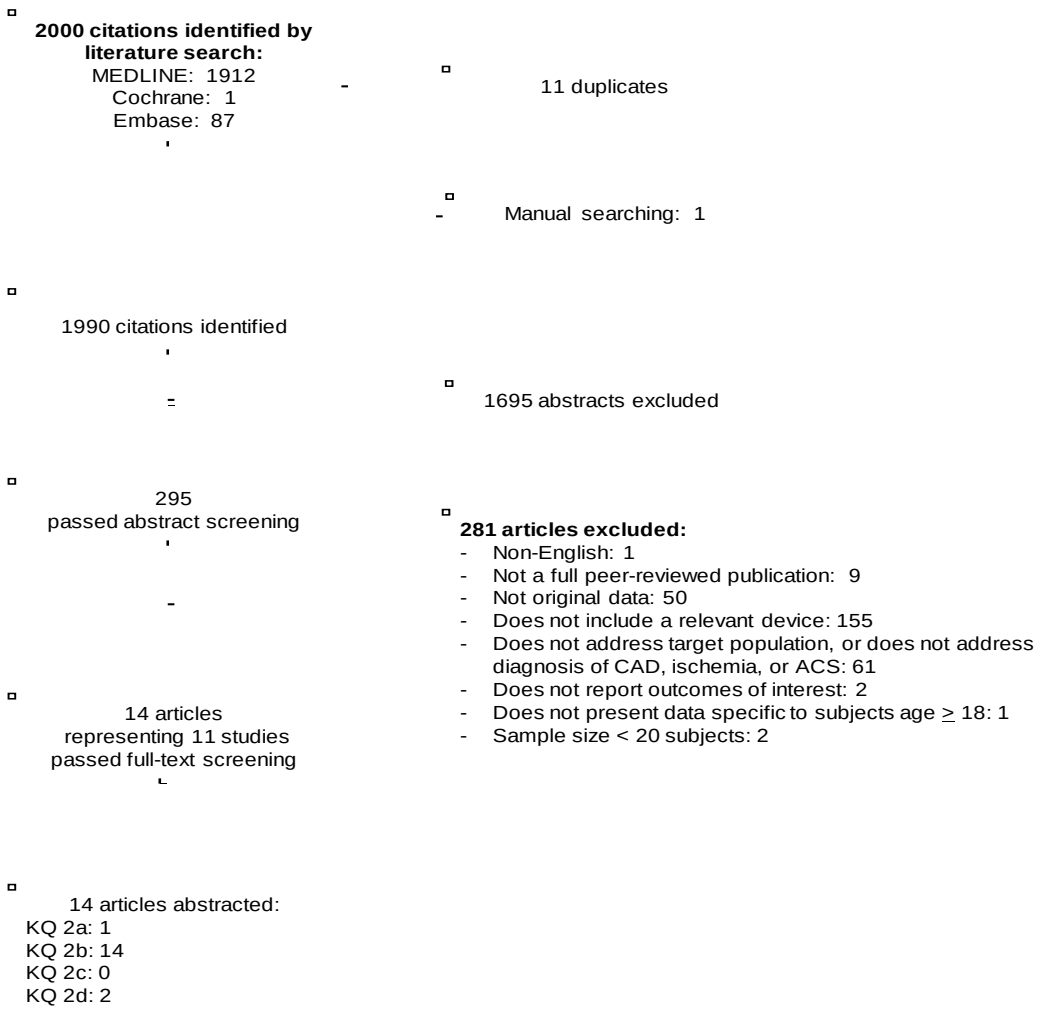
We employed internal and external quality-monitoring checks through every phase of the project to reduce bias, enhance consistency, and verify accuracy. Examples of internal monitoring procedures include three progressively stricter screening opportunities for each article (abstract screening, full-text screening, and data abstraction); involvement of at least two individuals (an abstractor and a second investigator) in each data abstraction; and agreement of at least two investigators 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 EPC and AHRQ. The list of nominees was forwarded to AHRQ for vetting and approval. A list of peer reviewers is in the Preface of this report.

Results

Figure 3 shows the flow of literature through the literature search and screening process for Key Question 2 (literature search not applicable to Key Question 1). Of the 2000 citations identified by our database searches, 11 were duplicates. After applying inclusion and exclusion criteria at the title-and-abstract level, 295 full-text articles were retrieved and screened. Of these, 281 were excluded at the full-text screening stage, with 14 articles (representing 11 unique studies) remaining for data abstraction.

Figure 3. Literature flow diagram for Key Question 2



Abbreviations: ACs=acute coronary syndrome; CAD=coronary artery disease; KQ=key question

Analysis for KQ 1

KQ 1a—Devices and Methods for ECG-based Signal Analysis

The gray literature search identified seven potentially relevant devices. We subsequently identified one additional device (the LP 3000 system) through our search of the published literature. These eight potentially relevant devices, all of which are available for purchase in the United States, are listed in Table 1. A device may be cleared for marketing by the FDA when it is determined to be substantially similar to an established device. Of the devices listed in Table 1, 8 have been cleared for marketing by the FDA: Predictor® and Model 1200 EPX™ by Arrhythmia Research Technology; MAC® 5000 by GE Medical; LP 3000 by Fidelity Medical; the PRIME ECG® by Heartscape Technologies; 3DMP™/MCG™/mfEMT™ by Premier Heart; CardioSoft® by NASA; and HyperQ™ by Biological Signal Processing. We identified several published articles that evaluated the test performance of the 3DMP and the Predictor; however, these studies are not included in this report because the devices were not administered to patients at low to intermediate risk being evaluated for ACS.

Table 1. ECG-based signal analysis devices identified by the gray literature search

Device Name	Manufacturer	FDA Cleared	Device Type
Predictor	Corazonix (now Arrhythmia Research Technology)	Yes	SA
Model 1200 EPX	Arrhythmia Research Technology	Yes	SA
MAC 5000	GE Medical	Yes	SA
LP 3000	Fidelity Medical	Yes	SA
PRIME ECG	Heartscape	Yes	BSM
3DMP/MCG/mfEMT	Premier Heart	Yes	MA
CardioSoft	NASA	Yes	HF-QRS
HyperQ (stress ECG)	Biological Signal Processing	Yes	HF-QRS

Abbreviations: BSM=body surface mapping; ECG=electrocardiogram; FDA=U.S. Food and Drug Administration; HF-QRS=high-frequency QRS; MA=mathematical analysis; SA=signal averaging

Body Surface Mapping Devices

Electrocardiographic BSM is an electrocardiographic technique that uses multiple electrocardiography leads (generally 80 or more) to detect cardiac electrical activity.[17] An example of a commercially available BSM device is the PRIME ECG, which uses 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. This colorimetric torso images are intended to help a health care provider rapidly scan the heart for significant abnormalities. A potential disadvantage of recording and analyzing data from many points on the body, however, is that this requires accurate interpretation of additional information. Some of this additional information may be useful (the "signal"), but some may be uninterpretable or unhelpful ("noise").

Mathematical Analysis and Signal Averaging Devices

A variety of devices have been developed that use mathematical modeling to derive clinical indices from electrocardiac activity detected by a standard ECG. For example, the 3DMP device utilizes ECG data from 2 of the 12 standard leads (leads II and V5) to perform frequency and time-domain analyses. Recordings for more than 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.

Another example of a device that uses mathematical analysis is the LP 3000 system, which derives standard X, Y, and Z leads from a 12-lead ECG at 2 different time points. Signals are amplified, averaged, and filtered with a bidirectional filter at frequencies of 40 to 250 Hz. The filtered leads are then combined into a vector magnitude. The magnitude of the difference in filtered QRS duration—between a recording obtained when a patient is symptomatic and when a patient is asymptomatic—is used to identify patients who appear to demonstrate a significant alteration in QRS duration, and who are therefore at high risk for ischemic heart disease.[18,19]

High Frequency QRS Devices

The standard 12-lead ECG waveforms are typically measured in the frequency range up to 100 Hz. High frequency QRS (HF-QRS) electrocardiography uses a higher sampling rate, signal averaging, and filters to monitor frequencies from 150–250 Hz.[20] Examples of HF-QRS devices are the CardioSoft and the HyperQ.

Vectorcardiography

Vectorcardiography typically uses four or five electrodes to measure the direction and magnitude of the electrical field vector of the heart. In vectorcardiography, data recorded from surface leads on the body generate three mathematically weighted orthogonal tracings: X, Y, and Z. These in turn provide three-dimensional information on voltage and special orientation of the summation vector of the surface potential that does not require a qualitative evaluation by an expert and which allows spatial analysis of beat-to-beat variability.[21]

KQ 1b—Gold Standard Tests

Tests for Diagnosing CAD

Diagnostic tests for CAD can be categorized as either invasive (e.g., coronary angiography via cardiac catheterization) or noninvasive. Noninvasive tests utilize technologies that permit either visualization of the heart and corresponding vasculature or interpretation of electrical signals generated by a beating heart. Coronary angiography can be used to detect the presence of CAD by identifying coronary artery occlusion, while noninvasive tests are used to infer the presence of CAD or ischemic heart disease by irregular electrical signals, abnormal heart wall motion, or damage to myocardial cells. Coronary angiography is universally accepted as diagnostic of clinically significant CAD.

Our discussion emphasizes the options for reference standards that might be considered in research studies to evaluate a new technology to aid in the diagnosis and management of patients suspected of having clinically significant CAD and/or ischemic heart disease.

Invasive Testing

Coronary angiography. Invasive coronary angiography 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.[22]

Strengths and limitations of coronary angiography. The current role of coronary angiography has been to aid in the identification of patients who will benefit clinically from revascularization.[23-27] Coronary angiography can be used in conjunction with contrast ventriculography to determine left ventricular function. According to a consensus guideline from the ACC/AHA, coronary angiography is the preferred reference standard for diagnosing the severity of obstruction in the coronary arteries since noninvasive testing currently lacks the sensitivity to exclude left main or multivessel CAD, which are independently associated with

poor survival.[28-30] Coronary angiography is generally considered to be the best available method of diagnosing CAD.

Coronary angiography is primarily restricted to identifying the degree of major epicardial vessel luminal stenosis. Furthermore, it cannot provide information regarding the patient's exercise capacity, hemodynamic response to exercise, or functional status. Although coronary angiography 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 coronary angiography is approximately 0.1 percent.[29] Finally, of all the frequently used tests for diagnosing CAD, coronary angiography 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 coronary angiography in order to confirm 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 on the posttest risk assessment by the clinician.

ECG. 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 and limitations of ECG. ECG is inexpensive, universally available, and broadly understood across medical disciplines. However, ECG lacks sufficiently high sensitivity for detection of CAD to be considered an adequate reference standard.[7,8,31]

Cardiac computed tomography (CCT). 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.[32,33] Sensitivity is estimated to be 97 to 99 percent and specificity 88 to 93 percent for the diagnosis of CAD by 64-detector CCT.[34]

Strengths and limitations of CCT. 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. However, 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 it correlates with long-term clinical outcomes.

Biomarkers. Patients with acute MI 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 MI. Elevation of biomarkers carries prognostic value after MI; serial testing for such elevation is, therefore, part of the standard procedure used to diagnose MI.

Strengths and limitations of biomarkers. 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%) and specificity (95%).[35,36] 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.

However, biomarkers may be elevated in conditions unrelated to MI, so results must be interpreted in the context of clinical presentation and other available test results. Conditions unrelated to MI 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 MI.

Stress testing with ECG. 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 following section).

Strengths and limitations of stress testing with ECG. Stress testing is generally safe, widely available, well validated, and less costly compared with other forms of cardiac diagnostic tests. 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 were lower among low-risk patients.[28] A normal exercise ECG has excellent negative predictive value.

However, 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.

Stress testing with imaging. 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 differentiation 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.[37] Exercise echocardiography is estimated to be 81 percent sensitive and 89 percent specific using stress-induced wall motion abnormalities.[37]

Strengths and limitations of stress testing with imaging. 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.[4] However, stress testing with imaging is relatively expensive as well as time-intensive. The procedure requires expertise in performance and interpretation. Also, it 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.

Tests for Diagnosing ACS

ACS is a term that is commonly used to describe the clinical presentation that includes acute onset of chest pain or other symptoms that suggest myocardial ischemia or infarct. ACS typically serves as a working diagnosis for such patients, pending the establishment or ruling out of specific diagnoses.[2] There is no gold standard test for ACS. The standard ECG serves as one of the most important tests in the *initial* evaluation of patients who present with symptoms suggestive of ACS, but additional clinical and laboratory information is required to accurately differentiate patients with and without acute ischemic heart disease. Elevations in serum biomarkers such as creatine kinase (CK) MB fraction or troponin-I may indicate ischemia or infarct of the myocardium and may be used as an imperfect reference standard for the diagnosis of ACS.

Summary for KQ 1

The strengths and limitations of the current diagnostic tests for the evaluation of suspected CAD and/or ACS 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.[38] In the research setting, we ideally want the best available reference test. Pragmatic clinical considerations, including guideline recommendations, legitimately influence this choice.

According to the ACC/AHA consensus guideline, coronary angiography remains the best reference standard for diagnosing CAD.[29] Through interrogation and identification of the coronary anatomy, angiography is currently the best available test to identify which patients may benefit from surgical or percutaneous intervention, medical management, or both. Among low-risk patients who are typically not referred for coronary angiography but who 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 that have been associated with patient outcomes such as exercise capacity, hemodynamic response, and magnitude of ST segment abnormalities.

Table 2 summarizes our findings that, according to current guidelines,[29-32,34,35] coronary angiography 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 ACS but not of CAD. The standard 12-lead ECG is not an acceptable reference standard due to its poor accuracy in diagnosing CAD. In contrast, there is no gold standard diagnostic test for ACS, which is an "umbrella" term that serves primarily as a working diagnosis, pending results from further testing. In this context, the standard ECG provides critically important data that informs both the diagnosis and management of patients with ACS. Finally, elevated biomarkers such as CK-MP or troponin-I may be considered an acceptable, but imperfect, reference standard.

Table 2. Potential reference standards for diagnosing CAD[a] or ACS

Reference Standard	Level of Acceptability
CAD	
Coronary angiography	Preferred
Stress testing with imaging	Acceptable
Imaging studies without exercise or pharmacological stress • Resting 12-lead ECG • Stress testing with ECG	Unacceptable
ACS	
Biomarkers (applicable only for identifying myocardial injury)	Acceptable

[a]Based on current guidelines.[29-32,34,35]
Abbreviations: CAD=coronary artery disease; ECG=electrocardiogram

Analysis for KQ 2

Of the eight potentially relevant devices identified by the gray and published literature searches, only the PRIME ECG and the LP 3000 system were evaluated in published studies that met our inclusion criteria. We did not identify any studies meeting our eligibility criteria that reported on the Predictor, Model 1200 EPX, MAC 5000, 3DMP, CardioSoft, or HyperQ. We identified several published articles that evaluated the test performance of the 3DMP or the Predictor, but these studies did not meet inclusion criteria because the study population comprised patients with a high risk for CAD. We excluded two publications that evaluated the Procardio 5.0 because this device is neither FDA approved nor commercially available. The following sections are therefore restricted to analysis of PRIME ECG (10 studies) and LP 3000 (1 study).

KQ 2a—Evidence for Variability by Rater, Patient, or Device

Our search strategy did not identify any eligible studies that reported information on intra-rater, intra-patient, or intra-device variability. We identified a single fair-quality study that evaluated the inter-rater variability of the PRIME ECG device.[39] This study involved 150 eligible patients who presented to an emergency department at times when both an emergency physician trained in BSM test interpretation and a clinical study assistant trained in the operation of the PRIME ECG were on duty. Study patients were administered both a standard ECG and a PRIME

ECG test. Twenty-eight faculty or resident emergency physicians participated in this study; each had previously completed a 4-hour training session during which basic electropathophysiology, BSM device application, beat marker placement, and BSM interpretation were reviewed. All study physicians successfully passed an exam upon completion of the training session. The study also engaged three experts in BSM test interpretation. Standard ECG and PRIME ECG were provided electronically to these experts, none of whom had knowledge of patients' clinical or laboratory data. Each BSM test was read by two expert raters. Discordant interpretations among the experts were adjudicated by a third.

Emergency physicians and BSM experts were charged with assigning each BSM reading into one of five categories: (1) normal, (2) nonspecific, (3) abnormal, (4) ischemia, or (5) infarction. The first two categories were considered to be a negative test result, and the latter three categories represented a positive test result. Of the 135 BSM tests interpreted by an expert reviewer, there was agreement between the emergency physicians and BSM experts on 52 (39%) for negative test result readings and 63 (47%) positive test result readings. Fifteen (11%) BSM tests were interpreted as negative by emergency physicians but positive by BSM experts, and 5 (4%) BSM tests were interpreted as positive by emergency physicians but negative by BSM experts. This result corresponds to a kappa statistic of 0.63 (95% CI, 0.53 to 0.72).

KQ 2b—Evidence for Test Performance

We identified 11 studies (represented by 14 articles) that evaluated the performance characteristics of a commercially available BSM or signal averaging ECG device (Table 3). All studies were prospective cohort studies, nine of which recruited consecutive patients. Ten studies (13 articles) evaluated the PRIME ECG BSM device.[39-51] and one study evaluated the LP 3000 signal averaging ECG system.[18] Ten of the eleven studies were considered fair quality because of (1) lack of details about the patient populations, (2) insufficient reporting of the methods and results, or (3) potential bias from lack of blinding by key study personnel.[18,39-49] One study, the Optimal Cardiovascular Diagnostic Evaluation Enabling Faster Treatment of Myocardial Infarction (OCCULT MI) trial, was considered good quality.[50,51] Of note, funding or material support for the PRIME ECG studies appeared to be linked to the manufacturer for all included studies of this device. This does not appear to be the case for the study of the LP 3000 system. We did not identify eligible studies that evaluated test performance or outcomes associated with the other eligible ECG-based signal averaging devices listed in Table 1 among patients that represented the target population for the purpose of this report. While screening articles for eligibility to meet inclusion criteria for this review, we separately looked for studies that addressed a population of asymptomatic patients. As noted previously, addressing use of these technologies in asymptomatic patients was not the purpose of this review. Surveying the availability of data for asymptomatic patients was a secondary interest of the research team and did not affect the inclusion/exclusion criteria used to identify evidence for the populations considered in this report. However, we think it worth noting that in the course of this additional task, we did not find any published studies that evaluated an ECG-based signal averaging device for the diagnosis of CAD and/or ACS in asymptomatic individuals.

Table 3 summarizes performance characteristics of the 11 studies included in this review.

Table 3. Performance characteristics of PRIME ECG and LP 3000 devices

Study ID	Included in Meta-analysis?	Study Quality	N Subjects	Setting	Threshold	Reference	Outcomes
PRIME ECG							
Menown et al., 1998[40]	Yes	Fair	Chest pain (n=314)	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	Sensitivity=77% (123/160) Specificity=85% (131/154)
Menown et al., 2001[41]	Yes	Fair	Ischemic-type chest pain<24 hours and 1 mm ST segment depression (n=24)	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	Sensitivity=88% (7/8) Specificity=75% (12/16) *ECG* Sensitivity=50% (4/8) Specificity=88% (14/16)
Mcclelland et al., 2003[42]	Yes	Fair	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) *ECG* Sensitivity=45% (24/53) Specificity=94% (47/50)
Maynard et al., 2003[47]	No	Fair	Ischemic-type chest pain (n=56) in the presence of left bundle branch block. Includes patients at high risk who were administered fibrinolytic therapy.	Acute medical cardiology unit in a tertiary hospital	Reversal of image	MI by abnormal biomarkers	Sensitivity=67% (12/18) Specificity=71% (27/38)

Study ID	Included in Meta-analysis?	Study Quality	N Subjects	Setting	Threshold	Reference	Outcomes
Carley et al., 2005[46]	Yes	Fair	Ischemic-type chest pain, only low/moderate risk patients (n=211)	Emergency department at a university-affiliated teaching hospital	NR	MI by standard ECG criteria, abnormal biomarkers, or autopsy	Sensitivity=18% (3/17) Specificity=87% (169/194) *ECG* Sensitivity=0% (0/17) Specificity=96% (186/194)
Owens et al., 2006[49] and Navarro et al., 2003[43]	Yes	Fair	Ischemic-type chest pain (n=427). Combined training and validation sets.	Cardiology via emergency department or mobile CCU	Algorithm: epicardial – ST0 isopotential from subset of study sample	MI by abnormal biomarkers	Physician-read BSM Sensitivity=75% (154/205) Specificity=91% (202/222) *ECG* Sensitivity=60% (123/205) Specificity=99% (220/222)
Owens et al., 2008[45] and Owens et al., 2004[44]	Yes	Fair	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=45% (238/529) Specificity=92% (208/226)

Study ID	Included in Meta-analysis?	Study Quality	N Subjects	Setting	Threshold	Reference	Outcomes
Fermann et al., 2009[39]	Yes	Fair	Ischemic-type chest pain (n =150)	Emergency department at an urban tertiary care hospital	NR. Data reported for both any abnormality on index test and abnormalities not known to be old. We report results of any abnormality on ECG or PRIME ECG test	Three separate criteria: (1) MI by abnormal biomarkers or >70% stenosis or abnormal noninvasive testing or CABG (2) MI by abnormal biomarkers or >70% stenosis or abnormal noninvasive testing or CABG or discharge diagnosis of MI or ACS (3) MI by abnormal biomarkers or >70% stenosis or abnormal noninvasive testing or CABG or discharge diagnosis of MI or ACS or postdischarge event	<u>Criteria 1:</u> Sensitivity=63% Specificity=60% *ECG* Sensitivity=53% Specificity=63% <u>Criteria 2:</u> Sensitivity=64% Specificity=59% *ECG* Sensitivity=59% Specificity=65% <u>Criteria 3:</u> Sensitivity=40% Specificity=60% *ECG* Sensitivity=60% Specificity=66%
O'Neil et al., 2010[50] and Hoekstra et al., 2009[51]	Yes	Good	Chest pain or symptoms suspicious for ACS <u>without</u> STEMI (n=1513)	High-volume tertiary care center emergency departments in United States	Core laboratory with cardiologists and emergency physicians blinded to clinical results and test readings	MI: final diagnosis of NSTEMI or UA, with any elevated troponin ACS: according to the ACC/AHA guideline for the diagnosis of ACS	<u>MI</u> Sensitivity=19% (40/206) Specificity=94% (1227/1307) *ECG* Sensitivity=11% (22/206) Specificity=96% (1260/1307) <u>ACS</u> Sensitivity=12% (50/408) Specificity=94% (1035/1105) *ECG* Sensitivity=7% (29/408) Specificity=96% (1065/1105)

Study ID	Included in Meta-analysis?	Study Quality	N Subjects	Setting	Threshold	Reference	Outcomes
Ornato et al., 2009[48]	Yes	Fair	Patients suspected of having ACS (n=589)	Emergency departments	ST J-point elevation of prespecified magnitude and location	2 separate criteria: (1) elevated CK-MB (2) elevated troponin	<u>Criteria 1 (n=364):</u> Sensitivity=100% (22/22) Specificity=96% (330/342) *ECG* Sensitivity=73% (16/22) Specificity=97% (332/342) <u>Criteria 2 (n=225):</u> Sensitivity=93% (26/28) Specificity=95% (187/197) *ECG* Sensitivity=61% (17/28) Specificity=96% (189/197)
LP 3000							
Michaelides et al., 1999[18]	No	Fair	Typical angina (n=126)	Hospital in Greece	QRS prolongation >5 msec	CAD by coronary angiography	Sensitivity=69% (75/108) Specificity=89% (16/18) *ECG* Sensitivity=56% (60/108) Specificity=89% (16/18)

Abbreviations: ACC=American College of Cardiology; AHA=American Heart Association; BSM=body surface mapping; CAD=coronary artery disease; CCU=cardiac care unit; ECG=electrocardiogram; MI=myocardial infarction; msec=millisecond; WHO=World Health Organization

PRIME ECG Device

Of the 10 eligible studies evaluating the test performance of the PRIME ECG BSM device, 6 were conducted by a research group in Belfast, Ireland. These investigators published 8 eligible articles from 1998 to 2008 on sequential series of consecutive patients with ischemic-like chest pain as they presented to a 24-hour physician-manned mobile coronary care unit (cardiac ambulance), the emergency department, or medical wards in Northern Ireland.[40-45,47,49] Excluding one study[47] of a subsample of 56 patients recruited from 1995 to 1999 with left bundle branch block, which may have included data reported in another eligible publication, and excluding data obtained from patients that contributed to training sets in preparation for validation datasets, this series of articles appears to represent a total of 2274 patients recruited from 1995 to 2004. It was unclear whether these mobile coronary care units in Ireland served a population with chest pain similar to the population served by U.S. emergency departments, or if the units tended 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 toward greater sensitivity.

Because the PRIME ECG device algorithm is evolving, the interpretation methods and potentially the accuracy of the device may have changed over time. In the initial study published in 1998,[40] 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) were described. In one study of the PRIME ECG, the authors stated, "We acknowledge that the performance of the algorithm used in this study is disappointing, particularly in terms of specificity, and we are currently developing an algorithm to improve specificity whilst maintaining sensitivity."[43]

The changing criteria for an abnormal PRIME ECG result could lead to variable performance across our included studies. Furthermore, criteria derived from the observed data could overestimate accuracy. In all studies, the PRIME ECG was compared to cardiac biomarkers, which served as a test for myocardial injury. Some studies either used a single set of biomarkers or did not specify the number of sets obtained. Three studies specified that the PRIME ECG was blindly interpreted and compared to the reference standard. 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.

One study from this research group included in this report involved 56 patients who presented with chest pain suggestive of acute MI in the presence of left bundle branch block on the initial ECG.[47] These patients were among the consecutive patients admitted to the acute medical cardiology unit included in the early published articles by the research group in Belfast, Ireland. This subset of patients was recruited between September, 1995, and November, 1999. At that time, the standard of care included initiating thrombolytic therapy in patients with left bundle branch block when acute MI was suspected. The PRIME ECG was administered before or within 15 minutes of administering thrombolytic therapy among the patients in this series who were treated with thrombolytics. In this sample of 56 patients, the sensitivity and specificity of the PRIME ECG in identifying acute MI as diagnosed by elevated biomarkers was 67 percent and 71 percent, respectively. A positive PRIME ECG test result—defined as loss of mirror image reversal in the comparison of QRS and ST-T isointegral maps—was associated with a significantly higher risk of having an acute MI (odds ratio [OR] 4.9; 95% CI, 1.5 to 16.4; p=0.007). We excluded this study and its data from our meta-analysis because of the likelihood

of duplicate data and because the other studies used different criteria for defining a positive result in patients with left bundle branch block, in which ST elevation on the ECG was not a valid indicator of acute MI.

The research group from Ireland contributed data to another study included in this report,[48] along with data from consecutive patients recruited from emergency departments in two hospitals in the United States and one in England. A total of 647 adults from these 4 recruitment sites who presented to the emergency department within 12 hours of onset of symptoms consistent with or suggestive of acute MI or unstable angina met inclusion criteria and consented to participate. Of these, 589 patients with standard ECG, PRIME ECG, and biomarker data were included in the analysis. Test performance was calculated for both the standard ECG and the PRIME ECG compared with elevated CK-MB enzymes (n=364) and to elevated troponin levels (n=225) for diagnosing acute MI. With CK-MB enzyme elevation as the gold standard, the sensitivity and specificity for the PRIME ECG was 100 percent and 97 percent, respectively, compared with 73 percent and 97 percent for the standard ECG. With troponin elevation as the gold standard, the sensitivity and specificity were 93 percent and 95 percent, respectively, for the PRIME ECG and 61 percent and 96 percent for the standard ECG.

We identified two eligible articles from the multicenter, prospective, cohort-blinded OCCULT MI trial.[50,51] This study evaluated the PRIME ECG among 1830 adults at high to moderate risk for adverse cardiovascular outcomes who presented to a tertiary care emergency department in the United States with chest pain or symptoms suspicious for ACS. Results were reported separately for patients who ultimately received a study-adjudicated diagnosis of STEMI (n=91), NSTEMI or unstable angina (n=206), or non-MI ACS (n=408). Most of the patients who ultimately received a study-adjudicated diagnosis of STEMI had ST elevations on ECG at presentation and as such were known to be high risk for CAD prior to administration of the PRIME ECG. Therefore, since our report focuses on patients at low to intermediate risk for CAD with symptoms suggestive of ACS, we report only the data from patients in this study who ultimately received a study-adjudicated diagnosis of NSTEMI, unstable angina, or ACS. Among the NSTEMI or unstable angina patients, sensitivity and specificity were 19.4 percent (95% CI, 14.6 to 25.4) and 93.9 percent (CI, 92.4 to 95.1), respectively, for the PRIME ECG and 10.7 percent (CI, 7.1 to 15.7) and 96.4 percent (CI, 95.2 to 97.3), respectively, for the 12-lead ECG. Among the ACS patients, sensitivity and specificity were 12.3 percent (CI, 9.4 to 15.8) and 93.7 percent (CI: 92.1 to 95.0), respectively, for the PRIME ECG and 7.1 percent (CI, 5.0 to 10.0) and 96.4 percent (CI, 95.1 to 97.3), respectively, for the 12-lead ECG. This is the only study included in our report that evaluated the test performance of the PRIME ECG for both NSTEMI and ACS patients; for consistency, we used the sensitivity and specificity data among the NSTEMI sample in our meta-analysis reported below.

A study that involved 150 patients with ischemic-type chest pain recruited from an emergency department at an urban tertiary care hospital was conducted in the United States.[39] Three separate sets of criteria were used to define MI or ACS: (1) abnormal biomarkers or greater than 70 percent coronary artery stenosis by cardiac catheter evaluation or abnormal noninvasive testing or revascularization, (2) in addition to first criteria, a diagnosis of MI or ACS at time of discharge from the hospital, and (3) in addition to the first and second criteria, a postdischarge event, defined as a repeated visit to the emergency department with chest pain or ischemic symptoms, recurrent MI, catheterization, revascularization, or death. Sensitivity and specificity for the PRIME ECG were 63 percent and 59 percent for the first criteria, 64 percent and 59 percent for the second criteria, and 40 percent and 60 percent for the third criteria. In

comparison, sensitivity and specificity for the 12-lead ECG were 53 percent and 63 percent for the first criteria, 59 percent and 65 percent for the second criteria, and 60 percent and 66 percent for the third criteria. The first criteria is most similar to the gold standard for diagnosis of acute MI used in the other studies in this report; for this reason, we included the sensitivity and specificity estimates with the first criteria as the gold standard in our meta-analysis, reported below.

The last of the eligible studies on the PRIME ECG device included in this report involved 211 patients with ischemic-type chest pain who were specifically identified at time of enrollment to be of low or moderate risk for CAD.[46] Patients were recruited from the emergency department at a university-affiliated teaching hospital in Manchester, England. MI was defined by standard ECG criteria, abnormal cardiac biomarkers, or autopsy. In this population, the sensitivity of the PRIME ECG was 18 percent and the specificity 87 percent, respectively, compared with zero percent and 95 percent for the standard ECG.

LP 3000 Signal Averaging System

The one eligible study we identified that evaluated a signal averaging ECG device was conducted in Greece and published in 1999.[18] This study was a prospective cohort study with coronary angiography as the criterion for diagnosing clinically significant CAD. In this study, 126 consecutive patients referred to a hospital for a first period of typical angina underwent both standard ECG and testing with the LP 3000 signal averaging ECG system. All patients also underwent coronary angiography. The signal averaging ECG test was considered positive in the presence of QRS prolongation of more than 5 milliseconds. QRS prolongation on the signal averaging ECG was associated with a sensitivity and specificity of 70 percent and 89 percent, respectively, compared to 56 percent and 89 percent for ST changes detected by 12-lead ECG. The improved sensitivity of signal averaging ECG relative to 12-lead ECG was statistically significant ($p<0.01$).

Meta-Analysis for KQ 2b

Device performance was summarized using sensitivity, specificity, and likelihood ratios. Test 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 (LR) is a measure that may be more useful to clinicians since a simple nomogram allows posttest disease probabilities to be readily calculated. The positive likelihood ratio (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 negative likelihood ratio (LR-) describes how many times more likely it is that a normal test comes from a patient with disease versus a patient without disease. The posttest probabilities for negative and positive results were calculated on the basis of assumed prevalence and LR+ and LR- obtained from the meta-analysis. A LR+ greater than 10 and LR- less 0.1 imply strong effects, whereas an LR close to 1 implies no effect. Positive and negative LRs with corresponding CIs for each diagnostic method were calculated from the mean logit-sensitivity and mean logit-specificity and their corresponding standard errors.

When studies were conceptually homogeneous, we used a bivariate random-effects generalized linear regression model to compute summary estimates of sensitivity and specificity with 95 percent confidence intervals.[14,52,53] A random-effects model assumes that variability is a result of sampling errors as well as the true differences between studies. Also, it provides a meta-analytic modeling approach for pooling sensitivity and specificity while accounting for possible correlation between sensitivities and specificities of the studies included.[15] For studies that derived a test algorithm in a training set and tested performance in a validation set, 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.[16] The mean sensitivity and mean specificity of each diagnostic method were compared using a paired Z-test. A P-value ≤ 0.05 was considered statistically significant. Analyses were performed with software (SAS, version 9.1, SAS Institute, Cary, NC; Excel, version 5.0, Microsoft, Bedford, WA; and Comprehensive Meta-Analysis version 2.0, Englewood, NJ).

We used a bivariate random-effects model to combine results across the 10 included PRIME ECG studies (Table 4). The sensitivity and specificity were 71.1 percent (95% CI, 45.6 to 87.8) and 90.2 percent (CI, 83.2 to 94.4), respectively. Studies were statistically heterogeneous for the LR+ ($Q=122.9$, $df=9$, $p<0.001$; $I^2=92.7\%$) and for the LR- ($Q=314.9$, $df=9$, $p<0.001$; $I^2=97.1\%$). The summary estimate for the LR+ was 6.3 (CI, 3.3 to 12.1) and for the LR- was 0.30 (CI, 0.16 to 0.56). Using these 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 86.3 percent. A normal PRIME ECG would yield a posttest probability of 23.1 percent (Figure 4). To summarize PRIME ECG diagnostic performance, each pair of true positive rates (sensitivity) and false positive rates (1-specificity) is shown with a summary receiver operating characteristic (SROC) curve as a way to display variations in threshold for test positivity (Figure 5).[54]

We performed a sensitivity analysis excluding two studies, namely, the initial study that most clearly used a different diagnostic algorithm[40] and a second study with a very small sample size that was disproportionately weighted in the random-effects meta-analysis.[41] The standard errors of the effect measures are determined by two factors—the number of subjects and the measure of interest in the compared groups. These factors in turn determine the weight given to a study in the meta-analysis. If one or both of these factors differ (are outliers) from the other studies included, the results can be overestimated or underestimated.[55] The sensitivity and specificity for the remaining studies were 68.4 percent (CI, 35.1 to 89.7) and 91.4 percent (CI, 83.6 to 95.7), respectively. The remaining studies were heterogeneous for the LR+ ($Q=122.1$, $df=7$, $p<0.001$, $I^2=94.3\%$) and LR- ($Q=277.4$, $df=7$, $p<0.001$, $I^2=97.5\%$). The LR+ (6.7; CI, 2.8 to 15.9) and LR- (0.31; CI, 0.14 to 0.69) were not substantially changed. Using these 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 87.0 percent. A normal PRIME ECG would yield a posttest probability of 23.7 percent.

For the 10 studies that evaluated the 12-lead ECG, we computed performance characteristics in the same manner (Table 5). The sensitivity and specificity were 43.1 percent (95% CI, 25.8 to 62.2) and 94.4 percent (CI, 88.4 to 97.4), respectively. There was significant heterogeneity for both the LR+ ($Q=89.8$, $df=9$, $p<0.001$; $I^2=90.0\%$) and LR- ($Q=209.5$, $df=9$, $p<0.001$; $I^2=95.7\%$).

The 12-lead ECG had a summary LR+ of 7.2 (CI 3.2 to 16.3) and LR- of 0.57 (0.44 to 0.74). Using these estimates of test performance, in a patient with a pretest probability for clinically significant CAD of 50 percent, a standard 12-lead ECG suggesting ischemia would yield a posttest probability of 87.8 percent. A standard 12-lead ECG without evidence of ischemia would yield a posttest probability of 36.3 percent (Figure 4). To assess standard 12-lead ECG diagnostic performance, each pair of true positive rates (sensitivity) and false positive rates (1-specificity) is shown with an SROC curve (Figure 5).

We performed a sensitivity analysis excluding the study with a very small sample size and the study not evaluating PRIME ECG performance.[18,41] The sensitivity and specificity for the remaining studies were 40.5 percent (95% CI, 19.6 to 65.5) and 95.0 percent (CI, 87.9 to 98.0), respectively. The remaining studies were heterogeneous for the LR+ ($Q=89.7$, $df=7$, $p<0.001$, $I^2=92.2\%$) and LR- ($Q=195.4$, $df=7$, $p<0.001$, $I^2=96.4\%$). The LR+ (7.0; CI 3.0 to 6.7) and LR- (0.61; 0.48 to 0.78) were not substantially changed. Using these latter estimates of test performance, in a patient with a pretest probability for clinically significant CAD of 50 percent, a standard 12-lead ECG suggesting ischemia would yield a posttest probability of 88.2 percent. A standard 12-lead ECG without evidence of ischemia would yield a posttest probability of 36.7 percent.

The 12-lead ECG had a slightly 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, using a paired Z-test, neither the LR+ nor the LR- was statistically significant when comparing diagnostic methods, $p<0.21$ and $p<0.08$, respectively.[56]

A bivariate meta-regression by time analysis was used to determine if the sensitivities and specificities changed over time. For the PRIME ECG, both sensitivity and specificity decreased slightly but not significantly as time increased ($p<0.81$). However, for the standard ECG, both sensitivity and specificity slightly increased but not significantly as time increased ($p<0.47$).

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 patients with acute ischemic heart disease prior to myocardial injury.

Figure 4. Posttest probabilities as a function of prevalence for PRIME ECG and standard 12-lead ECG

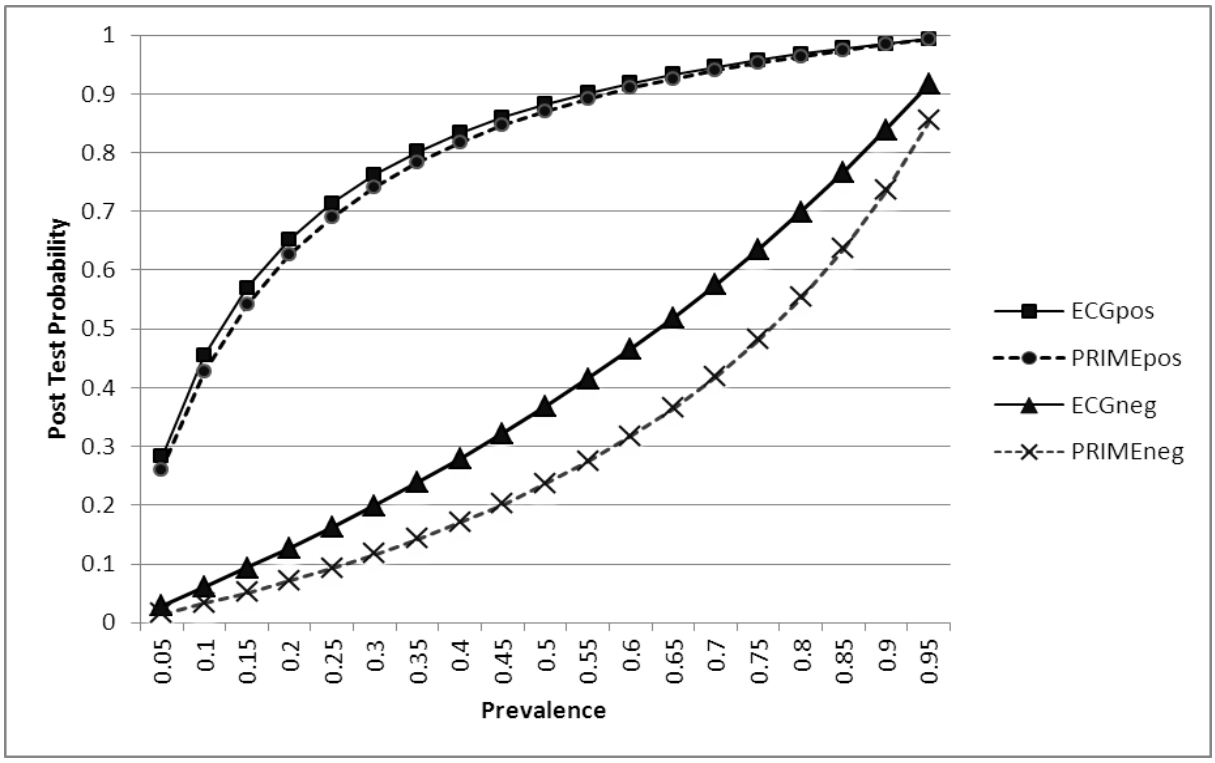


Figure 5. Summary receiver operating characteristic curves for Prime ECG and standard 12-lead ECG.

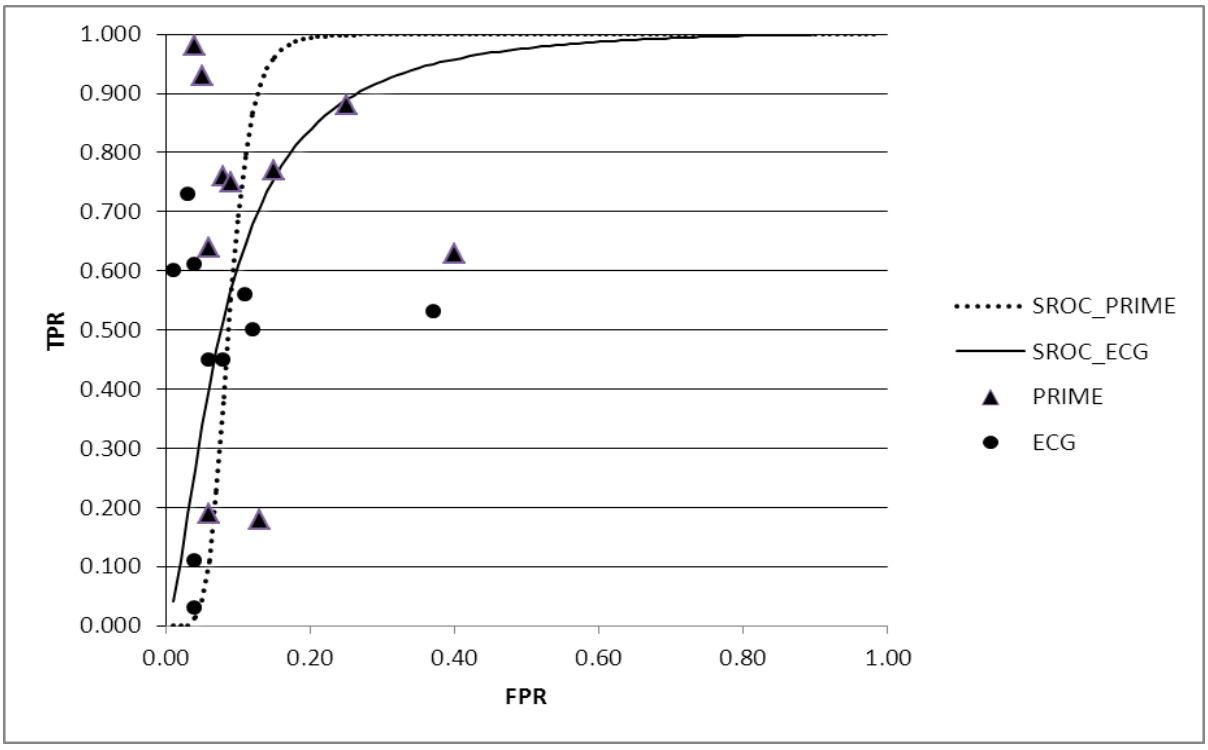


Table 4. PRIME ECG performance characteristics

Study ID	Sample Size	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio
Menown et al., 1998[40]	314	76.9%	85.1%	5.1	0.27
Menown et al., 2001[41]	24	87.5%	75.0%	3.5	0.17
Mcclelland et al., 2003[42]	103	64.2%	94.0%	10.7	0.38
Maynard et al., 2003[47]	56	66.7%	71.1%	2.3	0.47
Carley et al., 2005[46]	211	17.6%	87.1%	1.4	0.94
Owens et al., 2006[49] and Navarro et al., 2003[43]	427	75.1%	91.0%	8.3	0.27
Owens et al., 2008[45] and Owens et al., 2004[44]	755	76.0%	92.0%	9.5	0.26
Ornato et al., 2009[48]					
CK-MB	364	100.0%	96.5%	26.8	0.02
Troponin	225	92.9%	94.9%	18.3	0.08
Fermann et al., 2009[39]	150	63.4%	59.6%	1.6	0.61
O'Neil et al., 2010[50] and Hoekstra et al., 2009[51]	1513	19.4%	93.9%	3.2	0.86
Summary (95% CI) *Omits Maynard et al., 2003[47]	4086	71.1% (45.6% to 87.8%)	90.2% (83.2% to 94.4%)	6.3 (3.3 to 12.1)	0.30 (0.16 to 0.56)
Summary (95% CI) **Omits Maynard et al., 2003,[47] Menown et al., 1998,[40] and Menown et al., 2001[41]	3748	68.4% (35.1% to 89.7%)	91.4% (83.6% to 95.7%)	6.7 (2.8 to 15.9)	0.31 (0.14 to 0.69)

*One of the 11 studies[47] was omitted from the meta-analysis because it included patients with left bundle branch block.
**Three studies were omitted because of the presence of bundle branch block in patients,[47] use of a different algorithm,[40] and a very small sample size that was disproportionately weighted in the random-effects meta-analysis.[41]
Abbreviations: CI=confidence interval; CK-MB=creatine kinase-MB fraction; ECG=electrocardiogram

Table 5. 12-lead ECG performance characteristics

Study ID	Sample Size	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio
Menown et al., 2001[41]	24	50.0%	87.5%	4.0	0.57
Mcclelland et al., 2003[42]	103	45.3%	94.0%	7.5	0.58
Carley et al., 2005[46]	211	0.0%	95.9%	0.64	1.0
Owens et al., 2006[49] and Navarro et al., 2003[43]	427	60.0%	99.1%	66.6	0.40
Owens et al., 2008[45] and Owens et al., 2004[44]	755	45.0%	92.0%	5.6	0.60
Ornato et al., 2009[48]					
CK-MB	364	72.7%	97.1%	24.9	0.28
Troponin	225	60.7%	95.9%	15.0	0.41
Fermann et al., 2009[39]	150	52.7%	63.2%	1.4	0.75
O'Neil et al., 2010[50] and Hoekstra et al., 2009[51]	1513	10.7%	96.4%	3.0	0.93
Michaelides et al., 1999[18]	126	55.6%	88.9%	5.0	0.50
Summary (95% CI)	3898	43.1% (25.8% to 62.2%)	94.4% (88.4% to 97.4%)	7.2 (3.2 to 16.3)	0.57 (0.44 to 0.74)
Summary (95% CI) *Omits Menown et al., 2001[41]	3874	42.4% (23.6% to 63.8%)	94.7% (88.3% to 97.7%)	7.5 (3.1 to 18.4)	0.57 (0.43 to 0.75)
Summary (95% CI) **Omits Menown et al., 2001[41] and Michaelides et al., 1999[18]	3748	40.5% (19.6% to 65.5%)	95.0% (87.9% to 98.0%)	7.0 (3.0 to 6.7)	0.61 (0.48 to 0.78)

*One of the 11 studies[41] was omitted from the meta-analysis because it included patients with left bundle branch block.
**Two studies were omitted because of small sample size[41] and no evaluation of PRIME ECG performance.[18]
Abbreviations: CI=confidence interval; CK-MB=creatine kinase-MB fraction; ECG=electrocardiogram

KQ 2c—Evidence for Impact on Diagnostic Decisionmaking

Our search did not identify any eligible studies that provided evidence that the use of, or findings from, ECG-based technologies other than the standard 12-lead ECG had an impact on the decisions or actions of patients or health care providers.

KQ 2d—Evidence for Impact on Patient Outcomes

We identified two studies represented by three articles that collected data on long-term patient outcomes. The multicenter, prospective, cohort-blinded OCCULT MI trial[50,51] evaluated the PRIME ECG among 1830 adults at high to moderate risk for adverse cardiovascular outcomes who presented to a tertiary care emergency department with chest pain or symptoms suspicious for ACS. The primary aim of this good-quality study was to test the hypothesis that individuals with STEMI detected only by the PRIME ECG would have similar angiographic pathology and similar mortality and morbidity rates compared with individuals with STEMI detected by standard ECG. A preplanned secondary analysis compared outcomes of patients with STEMI with those without STEMI. Among the 1513 patients with available outcome data, ST elevation detected by the PRIME ECG was associated with increased mortality (OR 11.2; 95% CI, 1.8 to 67). ST elevation on a standard 12-lead ECG, however, was not predictive of adverse outcomes in this sample of patients. There are at least two interpretations of these findings: (1) the PRIME ECG device correctly identified patients that had a false-negative ECG, or (2) a positive test result on the PRIME ECG device may influence clinical decisionmaking in a way that results in harm, relative to the standard ECG. Implications of this finding on the need for further research are discussed in the Future Research section that follows.

We identified a fair-quality study that collected information about the impact of testing on patient outcomes but did not report those outcomes. That study collected information obtained from patients through the course of their hospital stay and after discharge (such as repeat visits to the emergency department with chest pain or ischemic symptoms, recurrent MI, catheterization, revascularization, or death). These patient outcomes, however, were not reported in the published paper.

Summary for KQ 2

In summary, we found two ECG-based signal analysis devices for which there were English-language, peer-reviewed studies of patients at low to intermediate risk for CAD who present with acute-onset chest pain or other symptoms suggestive of ACS. These devices were the PRIME ECG and the LP 3000 signal averaging system. Only one study reported inter-rater variability data. This study demonstrated that attending and resident emergency physicians had reasonably good agreement with experts in BSM interpretation in identifying negative versus positive findings on the BSM device after undergoing a 4-hour training session. Nine studies used elevated biomarkers as the criterion standard for comparing the test performance of the PRIME ECG relative to the standard ECG. One study, the OCCULT MI trial, evaluated both test performance and prognostic utility of the PRIME ECG relative to the standard ECG, using a comprehensive criterion standard that resulted in study-adjudicated diagnoses of MI or ACS. Meta-analysis of the 8 studies that evaluated the PRIME ECG demonstrated 68.4 percent sensitivity (95% CI, 35.1 to 89.7) and 91.4 percent specificity (CI, 83.6 to 95.7) for detecting MI (with all but one study using elevated cardiac biomarkers as the reference standard). Meta-

analysis of the same eight studies that evaluated the 12-lead ECG demonstrated 40.5 percent sensitivity (CI, 19.6 to 65.5) and 95.0 percent specificity (CI, 87.9 to 98.0) for detecting MI. The 12-lead ECG had a slightly 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, using a paired Z-test, neither the LR+ nor the LR- was statistically significant when comparing diagnostic methods, $p<0.21$ and $p<0.08$, respectively.

The study that compared the LP 3000 with the standard ECG to identify patients with clinically significant CAD used coronary angiography as the criterion standard. Results from this study suggest that the LP 3000 may have higher sensitivity and specificity than the standard ECG for identifying patients with ACS who have clinically significant CAD.

We did not identify any studies that directly assessed the impact of ECG-based signal analysis devices on clinical decisionmaking. We identified two studies that collected long-term outcome data, but one of them did not report those findings. The one study that reported long-term patient outcomes found that, among 1513patients who did not have STEMI, ST elevation detected by the PRIME ECG was associated with increased mortality (OR 11.2; 95% CI, 1.8 to 67). ST elevation on a standard 12-lead ECG, however, was not predictive of adverse outcomes in this sample of patients.

Discussion

Summary of Findings

The combined gray and published literature searches identified 11 commercially available ECG-based devices used or proposed to be used to diagnose CAD or to detect ACS. Of these, 8 are FDA cleared for marketing. Our search of the English-language literature identified 11 studies represented by 14 articles that reported on performance characteristics of one BSM device (PRIME ECG) and one signal averaging ECG device (LP 3000) in patients at low to intermediate risk for CAD who presented with chest pain or other symptoms suggestive of ACS.

The PRIME ECG has been evaluated in 10 studies by 3 different groups of investigators. Seven of these studies enrolled subjects that may have been at higher risk than the target population for this report, and nine compared the PRIME ECG to an incomplete reference standard that detects only acute myocardial injury. A single large, good-quality study[50,51] estimated the sensitivity and specificity of the PRIME ECG in the diagnosis of MI and ACS in patients at low to intermediate risk for CAD who presented with symptoms suggestive of ACS.

The available published evidence suggests that the PRIME ECG device may demonstrate higher sensitivity than the standard 12-lead ECG for identifying patients with ischemic-type chest pain, with myocardial injury as assessed by biomarkers as the reference standard. The 95-percent confidence interval of the estimates of sensitivity for these two tests overlaps, such that the observed differences are not statistically significant. The magnitude of the difference in sensitivity (68% for the PRIME ECG versus 41% for the standard ECG) is, however, likely to be clinically significant. These findings do not provide compelling evidence of a real difference in test performance for these two tests, but it is possible that study heterogeneity or small sample sizes, or both, contribute to the wide and overlapping 95 percent confidence intervals, thereby obscuring a real difference that could be clinically meaningful. There does not, however, appear to be a real difference in specificity between the two tests.

The OCCULT MI trial demonstrated that, among patients with symptoms suspicious for ACS who did not present with STEMI, the PRIME ECG provided a significant increase over the 12-lead ECG for MI or ACS, but the specificity was lower and there was no difference between the two tests in the negative or positive likelihood ratios. The authors concluded that the PRIME ECG provides early risk stratification information that identifies patients at high risk for MI, ACS, and adverse clinical outcomes. Our search identified a single eligible study for the LP 3000 signal averaging ECG that suggested this device demonstrates better sensitivity than the resting 12-lead ECG in identifying which patients with acute chest pain have underlying CAD.

Applicability of Current Studies

Eight of the eleven studies included in this report had potentially significant limitations that may affect the applicability of the findings to the target population of patients at low to intermediate risk for CAD who present for medical care with symptoms suggestive of ACS. Six studies were conducted exclusively in Ireland[40-45,47,49] among a population that included patients treated in a mobile cardiac care unit, which suggests a patient population at higher risk, on average, than patients at low to intermediate risk who present to outpatient or emergency facilities in the United States. Furthermore, the PRIME ECG algorithm appears to have evolved over the 10-year span of these articles, thereby limiting the applicability of the findings from the earlier studies. Two other studies also were conducted in European countries (England[46] and Greece[18]) in settings or among patient populations that may not be equivalent to those typically found in the United States. The remaining three studies[39,48,50,51] have the highest applicability because they included patients recruited in the United States and included patients who represent the target population for the purpose of this report.

Strengths and Limitations of This Review

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

We relied primarily on published studies to identify evidence for 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.[57] 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 needs 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. Most of the studies included in this report employed this study design. With the exception of the OCCULT MI trial, which used study-adjudicated diagnosis informed by several different sources, however, none of the studies used a fully adequate reference test. Elevated biomarkers alone serve as an incomplete reference

standard and cannot readily differentiate acute MI from reversible ischemia. Similarly, coronary angiography, which was used as the reference standard in two of the included studies, is considered the criterion standard for CAD but cannot by itself identify patients with acute ischemic heart disease.

Replication of the OCCULT MI study potentially could provide important information about the relative value of an ECG-based signal analysis device relative to the standard ECG to inform decisionmaking and improve patient outcomes among patients with ACS. The OCCULT MI study demonstrated that that among patients who were not ultimately diagnosed as having STEMI, ST elevation detected by the PRIME ECG was associated with increased mortality, whereas ST elevation on a standard 12-lead ECG was not predictive of adverse outcomes in this sample of patients. There are at least two interpretations of these findings: (1) the PRIME ECG correctly identified patients that had a false-negative ECG, or (2) a positive test result on the PRIME ECG may influence clinical decisionmaking in a way that results in harm, relative to the standard ECG. Further study is needed to confirm or investigate this finding, and more research along these lines may provide useful information about the tradeoff between improving the false-negative rate of resting ECG versus initiating further testing or treatment for patients with ACS who have a normal (or nondiagnostic) ECG test result and a positive test result on a body surface mapping device.

Other lines of research could evaluate patients and settings where ECG-based signal analysis technology might be most beneficial, or could investigate whether an ECG-based signal analysis device could serve to complement the findings from standard 12-lead ECGs as "add-on" tests. Add-on tests could 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 who nonetheless is having active chest pain. An add-on test may be able to help clarify whether such a patient is having chest pain due to cardiac etiologies that are undetected by the 12-lead ECG, or chest pain due to a noncardiac cause. Add-on tests are attractive because they offer noninvasive, accurate alternatives to the standard 12-lead ECG. However, add-on tests are less attractive in 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 could be used to evaluate this add-on strategy. The OCCULT MI study may serve as a good example of this type of study.

The available published literature on ECG-based signal analysis technologies does not provide answers to the key questions surrounding debate about whether these technologies have an impact on 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 using conventional testing versus one that uses a new device. Finally, a less direct approach would be to link evidence on test performance to evidence on the effects of interventions (e.g., antianginals or percutaneous coronary intervention) in the population of interest. This final example is sometimes employed by the U.S. Preventive Services Task Force for evaluating screening tests. This less direct approach is more subject to bias due to the underlying assumptions that are inherent in creating such linkages.

To date, the existing literature among the target population for this report is limited to 10 studies of one body surface mapping device and 1 study of a signal averaging device. Additional research is needed to evaluate the utility of other ECG-based signal analysis devices among patients at low to intermediate risk of CAD in the evaluation of ACS or among subgroups of patients. ECG-based signal analysis devices might, for example, provide new and useful information for patients with left bundle branch block or other physiological processes that interfere with the ability of the standard ECG to detect acute ischemic heart disease. Patients who have a nondiagnostic or normal ECG at presentation but whose clinical presentation is suggestive of ischemic heart disease constitute an especially vulnerable population that may benefit from an add-on ECG-based test. Future research is needed to evaluate the role of ECG-based signal analysis devices for improving the ability of noninvasive, easily and quickly administered bedside tests to identify which patients are appropriate candidates for urgent treatment or further treatment.

Summary and Conclusions

Currently, a paucity of evidence exists about the utility of ECG-based signal analysis technologies as a diagnostic test among patients at low to intermediate risk for CAD who present in the outpatient setting with the chief complaint of chest pain or with symptoms suggestive of ACS. Most devices identified by our gray literature search did not appear to have published articles describing their performance among the target population for this report. The literature was not sufficient to determine if factors such as sex, body habitus, medications, and comorbid medical conditions affected test performance.

The limited available evidence demonstrates proof of concept, particularly for the PRIME ECG device, and it suggests that the sensitivity of BSM and signal averaging devices is higher compared with standard ECG for identifying patients with ACS who have either ischemic heart disease or CAD. However, this evidence is limited by the use of incomplete reference standards in the published studies, including elevated biomarkers for detecting acute ischemic heart disease.

Further research is needed to better describe 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 to identify patients with clinically significant CAD in the patient population of interest. 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.

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Abbreviations and Acronyms

ACS	acute coronary syndrome
AHRQ	Agency for Healthcare Research and Quality
BSM	body surface mapping
CAD	coronary artery disease
CCT	cardiac computed tomography
CCU	cardiac care unit
CI	confidence interval
CK-MB	creatine kinase-MB fraction
CMS	Centers for Medicare and Medicaid Services
ECG	electrocardiogram
EPC	Evidence-based Practice Center
FDA	U.S. Food and Drug Administration
KQ	key question
LR+	positive likelihood ratio
LR-	negative likelihood ratio
MI	myocardial infarction
NSTEMI	non-ST elevation myocardial infarction
PCI	percutaneous coronary intervention
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
ROC	receiver operating characteristic
SA	signal averaging
STEMI	ST elevation myocardial infarction
WHO	World Health Organization

Appendix A: Gray Literature Search Strategy

Table A-1. Gray literature sources, search terms, and results

Source	Search terms	Restrictions	Number of Citations Identified	Unique Devices Identified
General gray literature sources				
Google search www.google.com	("ECG" OR "electrocardiogram" OR "EKG") AND [("signal averaging" OR "signal averaged" OR "signal analysis" OR "spectral") OR ("body surface mapping") OR ("body surface potential mapping") OR ("body surface potential map") OR ("mathematical analysis")] NOT (3DMP, MCG, mfEMT)	• In the title of the page • Published between May 1, 2009, and May 25, 2011 • English language	689	• Cardiag 112.2 • Cardiag 128.1 • Corazonix Predictor System • CarDx • CardioSoft, CardiaMax • Cardioscape 3.0 • Visual 3Dx • Procardio 8 • Cardiologic/Vascular explorer • Pagewriter Xli (Philips) • Megacart Recording Device (Siemens-Elema AB) • Lux-32/Lux-192 • ActiveTwo System (Biosemi) • CMI-Magnetocardiograph (Magiscan) • MCG07 (MaGIC) • 83-SQUID MCG/MEG • 31-channel biomagnetometer (Philips) • MC-6400 (Hitachi) • MAG12 (Marquette)
	("magnetocardiography" AND (ischemia OR ACS OR CAD) NOT CardioMag)	• Anywhere on the page • Published between Jan 1, 2000, and Jun 8, 2011 • English language	988	
	("HF-QRS" OR "HF QRS" or "HFQRS" OR "cardiogoniometry)	• Anywhere on the page • Published between Jan 1, 2000, and Jun 8, 2011 • English language	123	
Food and Drug Administration (FDA) documents searched via: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm	Product codes: DPS and DRW	Posted between Jan 1, 2007, and May 25, 2011	71	• Easi ECG (Philips) (DRW) - 2004 • PRIME ECG
Patents advanced search via: www.freepatentsonline.com	("cardiac" AND "spectral") AND ("electrocardiograph" OR "electrocardiogram")	• Previous 20 years • Word stemming on • US Patents only • Search performed June 8, 2011	1057	0
	"body surface mapping" AND "ischemia"		42	0

Source	Search terms	Restrictions	Number of Citations Identified	Unique Devices Identified
Online search of all AHA journals via 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" OR "mathematical analysis" OR "magnetocardiography" OR "HF-QRS" OR "HF QRS" OR "HFQRS OR "cardiogoniometry"	• In title or abstract • Published between Jul 2007 and May 2011 • All AHA journal titles and abstracts	32	0
Online search of all journals of the 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" OR "magnetocardiography" OR "HF-QRS" OR "HF QRS" OR "HFQRS" OR "cardiogoniometry" "mathematics analysis" OR "mathematical analysis" AND (ischemia OR CAD)	• In title or abstract • All JACC journals • Published between Jul 2007 and May 2011	35	• MAC 5000 (GE Medical) • CARTO system (Biosense-Webster): electroanatomical voltage mapping
Abstracts from professional society meetings				
American Heart Association (AHA) Abstract Archive tool search portal: http://www.abstractsonline.com/arch/home.aspx?lookupkey=12345	"cardiac spectral" OR "body surface mapping" OR "signal averaging" OR "mathematical analysis" OR "magnetocardiography" OR "HF-QRS" OR "HF QRS" OR "HFQRS" OR "cardiogoniometry"	Abstract Archive tool searches across all AHA-sponsored scientific meetings through 2006	56	• VCM 3000
Heart Rhythm Society Annual Scientific Sessions: http://www.hrsonline.org/Sessions/ Search page: http://www.abstracts2view.com/hrs/	All of the words: ("electrocardiogram" AND ("signal averaging" OR "signal averaged") OR "spectral analysis" OR "body surface mapping") OR "magnetocardiography" OR "HF-QRS" OR "HF QRS" OR "HFQRS" OR "cardiogoniometry"	All abstract categories 2007 to 2011	38	0

Source	Search terms	Restrictions	Number of Citations Identified	Unique Devices Identified
European Society of Cardiology (ESC) Congress Abstracts: http://www.escardio.org/Pages/index.aspx Search page: http://spo.escardio.org/abstract-book/topic.aspx	Any of the following: "signal-averaged", "body surface", "electrocardiograph", "ECG", "magnetocardiography", "HF-QRS", "HF QRS", "HFQRS", "cardiogoniometry"	2007 to 2010	279	• Active2 (BioSemi) • BioSemi Mark-6 • Nijegen 64-lead system • CardioMapp (Prucka Engineering Inc, Houston, TX) • FP-705 LP (Fukuda Denshi, Tokyo) • 120 lead BSPM • Vectorcardiogram: Frank Lead System
trial registry				
ClinicalTrials.gov: http://www.clinicaltrials.gov/ Basic Search: http://www.clinicaltrials.gov/ct2/search	"ischemia" AND ["electrocardiograph" OR "electrocardiogram") OR "signal-averaged" OR "body surface mapping" OR "magnetocardiography" OR "HF-QRS" OR "HF QRS" OR "HFQRS" OR "cardiogoniometry"]	• None • Search performed May 26, 2011	94 • Magnetocardiograph by CardioMag	• HyperQ • Micro T wave alternans detection devices

Abbreviations: BSPM=body surface potential mapping

Appendix B: Search Terms

Table B-1. PubMed search (November 18, 2011)

Set	Terms	Results
1	("acute coronary syndrome"[MeSH Terms] OR "acute coronary syndrome"[All Fields]) OR ("myocardial ischemia"[MeSH Terms] OR "myocardial ischemia"[All Fields] OR (("myocardium"[MeSH Terms] OR "myocardium"[All Fields] OR "myocardial"[All Fields]) AND ("ischaemia"[All Fields] OR "ischemia"[MeSH Terms] OR "ischemia"[All Fields])) OR ("coronary disease"[MeSH Terms] OR "coronary artery disease"[MeSH Terms]) OR "coronary artery disease"[All Fields])	349665
2	"electrocardiography"[MeSH Terms] OR "electrocardiography"[All Fields] OR "ecg"[All Fields] OR "ekg"[All Fields] OR "electrocardiogram"[All Fields]	189506
3	"Signal Processing, Computer-Assisted"[Mesh] OR "signal averaged"[All Fields] OR "signal averaging"[All Fields] OR "signal analysis"[All Fields] OR "signal processing"[All Fields] OR "signal interpretation"[All Fields] OR "spectral analysis"[All Fields] OR "body surface potential mapping"[All Fields] OR "body surface map"[All Fields] OR "body surface mapping"[All Fields]	59800
4	(((cardiag[All Fields] AND 112.2[All Fields]) OR (cardiag[All Fields] AND 128.1[All Fields]) OR (lux[All Fields] AND 32[All Fields]) OR (LUX[All Fields] AND 192[All Fields]) OR (parma[All Fields] AND 219[All Fields]) OR (Prime[All Fields] AND ("electrocardiography"[MeSH Terms] OR "electrocardiography"[All Fields] OR "ecg"[All Fields])) OR (Procardio[All Fields] AND 8[All Fields]) OR (VCM[All Fields] AND 3000[All Fields]) OR (Visual[All Fields] AND ("electrocardiography"[MeSH Terms] OR "electrocardiography"[All Fields] OR "ecg"[All Fields])) OR cardio3kg[All Fields]) OR (3DMP[All Fields] AND MCG[All Fields]) OR MultiFunction-CardioGram[All Fields] OR (hyperQ[All Fields] OR (cardiologic[All Fields] AND ("Explorer (Kansas City)"[Journal] OR "Explorer (Hayward)"[Journal] OR "explorer"[All Fields])) OR (("blood vessels"[MeSH Terms] OR ("blood"[All Fields] AND "vessels"[All Fields]) OR "blood vessels"[All Fields] OR "vascular"[All Fields]) AND ("Explorer (Kansas City)"[Journal] OR "Explorer (Hayward)"[Journal] OR "explorer"[All Fields]))) OR ((31[All Fields] AND channel[All Fields] AND biomagnetometer[All Fields]) OR (83[All Fields] AND ("decapodiformes"[MeSH Terms] OR "decapodiformes"[All Fields] OR "squid"[All Fields]) AND (mcg[All Fields] AND meg[All Fields])) OR (("Clin Microbiol Infect"[Journal] OR "cmi"[All Fields]) AND 2409[All Fields]) OR (("Clin Microbiol Infect"[Journal] OR "cmi"[All Fields]) AND Magnetocardiograph[All Fields]) OR (("Mod Churchm"[Journal] OR "mc"[All Fields]) AND 6400[All Fields])) OR ((fdx[All Fields] AND 6521[All Fields]) OR (MAC[All Fields] AND 5000[All Fields]) OR (MAG[All Fields] AND 12[All Fields])) OR (((model[All Fields] AND 1200[All Fields]) OR (mcg[All Fields] AND 7[All Fields])) AND (("electrocardiography"[MeSH Terms] OR "electrocardiography"[All Fields] OR "ecg"[All Fields]) OR ("electrocardiography"[MeSH Terms] OR "electrocardiography"[All Fields] OR "ekg"[All Fields]) OR ("electrocardiography"[MeSH Terms] OR "electrocardiography"[All Fields] OR "electrocardiogram"[All Fields]) OR ("electrocardiography"[MeSH Terms] OR "electrocardiography"[All Fields]) OR ("magnetocardiography"[MeSH Terms] OR "magnetocardiography"[All Fields])))) OR (3DMP[All Fields] OR (("arrhythmias, cardiac"[MeSH Terms] OR ("arrhythmias"[All Fields] AND "cardiac"[All Fields]) OR "cardiac arrhythmias"[All Fields] OR "arrhythmia"[All Fields]) AND ("research"[MeSH Terms] OR "research"[All Fields]) AND ("technology"[MeSH Terms] OR "technology"[All Fields])) OR 1200EPX[All Fields] OR (fukuda[All Fields] AND denshi[All Fields]))	2899
5	#1 AND #2 AND (#3 OR #4)	2354
6	#1 AND #2 AND (#3 OR #4) limits: English	1969
7	Animals[mh] NOT Humans[mh]	3616211
8	#6 NOT #7	1834
9	"magnetocardiography"[MeSH Terms] OR "magnetocardiography"[All Fields] OR cardiogoniometry[All Fields] OR (high[All Fields] AND "frequency"[All Fields] AND QRS[title/abstract])	914
10	#1 AND #2 AND (#3 OR #4 OR #9) limits: English	2055
11	#10 NOT #7	1912

Table B-2. Embase search (November 18, 2011)

Set	Terms	Results
1	'acute coronary syndrome'/exp OR 'acute coronary syndrome' OR 'coronary artery disease'/exp OR 'coronary artery disease' OR 'silent myocardial ischemia'/exp OR 'silent myocardial ischemia' OR 'heart muscle ischemia'/exp OR 'heart muscle ischemia'	260820
2	'electrocardiogram'/exp OR 'electrocardiogram' OR 'electrocardiography monitoring'/exp OR 'electrocardiography monitoring' OR 'ecg'/exp OR ecg OR 'ekg'/exp OR ekg OR 'electrocardiography'/exp OR electrocardiography	259395
3	'cardiag 112.2':ab OR 'cardiag 128.1':ab OR 'lux 32':ab OR 'lux 192':ab OR 'parma 219':ab OR 'prime ecg':ab OR 'procardio 8':ab OR 'vcm 3000':ab OR 'visual ecg':ab OR 'cardio3kg':ab OR 'cardx':ab OR mfemt:ab OR 'multifunction-cardiogram':ab OR cardiamax:ab OR cardiosoft:ab OR hyperq:ab OR 'cardiologic explorer':ab OR 'vascular explorer':ab OR '31 channel biomagnetometer':ab OR '83 squid':ab OR 'cmi 2409':ab OR 'cmi magnetocardiograph':ab OR 'mc 6400':ab OR 'squid magnometer':ab OR 'fdx 6521':ab OR 'mac 5000':ab OR 'mag 12':ab OR 'model 1200':ab OR primeecg:ab OR 3dmp:ab OR 'arrhythmia research technology':ab OR 1200epx:ab OR 'fukuda denshi':ab OR 'mcg 7':ab	128
4	'spectral analysis':ti OR 'spectral analysis':ab	13775
5	'signal averaged':ti OR 'signal averaging':ti OR 'signal analysis':ti OR 'signal processing':ti OR 'signal interpretation':ti OR 'body surface potential mapping':ti OR 'body surface map':ti OR 'body surface mapping':ti OR 'signal averaged':ab OR 'signal averaging':ab OR 'signal analysis':ab OR 'signal interpretation':ab OR 'body surface map':ab OR 'body surface mapping':ab OR 'signal processing':ab OR 'body surface potential mapping':ab	9465
6	'signal processing'/exp	48964
7	'magnetocardiography':ti OR cardiogoniometry:ti OR 'magnetocardiography':ab OR 'cardiogoniometry':ab OR 'high frequency qrs':ti OR 'high frequency qrs':ab OR 'magnetocardiography'/exp	772
8	#3 OR #4 OR #5 OR #6 OR #7	68739
9	#1 AND #2 AND #8	777
10	#1 AND #2 AND #8 AND [humans]/lim AND [english]/lim	548
11	#1 AND #2 AND #8 AND [humans]/lim AND [english]/lim AND [embase]/lim NOT [medline]/lim	87

Table B-3. Cochrane library search (November 18, 2011)

Set	Terms	Results
1	(acute coronary syndrome):ti,ab,kw or (coronary artery disease):ti,ab,kw or (myocardial ischemia):ti,ab,kw	10785
2	MeSH descriptor **Acute Coronary Syndrome** explode all trees	409
3	MeSH descriptor **Coronary Artery Disease** explode all trees	2103
4	MeSH descriptor **Myocardial Ischemia** explode all trees	19050
5	#1 OR #2 OR #3 OR #4	21953
6	(signal averaged):ti,ab,kw or (signal averaging):ti,ab,kw or (signal analysis):ti,ab,kw or (signal processing):ti,ab,kw or (signal interpretation):ti,ab,kw	2100
7	(spectral analysis):ti,ab,kw or (body surface potential mapping):ti,ab,kw or (body surface map):ti,ab,kw or (body surface mapping):ti,ab,kw	844
8	"cardiag 112.2" OR "cardiag 128.1" OR "lux 32" OR "lux 192" OR "parma 219" OR "prime ecg" OR "procardio 8" OR "vcm 3000" OR "visual ecg" OR "cardio3kg" OR "cardx" OR mfemt OR "multifunction-cardiogram" OR cardiamax OR cardiosoft OR hyperq OR "cardiologic explorer" OR "vascular explorer" OR "31 channel biomagnetometer" OR "83 squid" OR "cmi 2409" OR "cmi magnetocardiograph" OR "mc 6400" OR "squid magnometer" OR "fdx 6521" OR "mac 5000" OR "mag 12" OR "model 1200" OR primeecg OR 3dmp OR "arrhythmia research technology" OR 1200epx OR "fukuda denshi": OR "mcg 7"	9
9	MeSH descriptor **Signal Processing, Computer-Assisted** explode all trees	762
10	#6 OR #7 OR #8 OR #9	2895
11	MeSH descriptor **Electrocardiography** explode all trees	7042

Set	Terms	Results
12	(ecg):ti,ab,kw or (ekg):ti,ab,kw or (electrocardiogram):ti,ab,kw or (electrocardiology):ti,ab,kw	5473
13	#10 AND (#11 OR #12)	519
14	#5 AND #10 AND (#11 OR #12) **** Cochrane reviews= 0 / Other reviews=1 / Clinical Trials= 122 / Economic evaluations= 1**	126**
15	Limited to Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects	1

Appendix C: Inclusion and Exclusion Criteria

Table C-1. Summary of inclusion and exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	• Symptomatic patients at low to intermediate risk ("symptomatic" defined as any symptom that gives the diagnosing physician suspicion of ACS/CAD/ischemia) • Population can include both symptomatic and asymptomatic patients if data for symptomatic patients were reported separately • Population can include both high-risk and low-to-intermediate risk patients if data for low-to-intermediate risk patients were reported separately • Patients all ≥18 years of age, or if some patients <18, data for patients ≥18 must be presented separately	• Study addresses only asymptomatic or high-risk patients • Sample size <20 patients
Devices	• Obtains and interprets electrical activity from the heart (ECG-based) • Utilizes standard 12-lead information or has additional leads (e.g., body surface mapping) • Transforms/interprets electrical signal in a novel way. Data transformation into spatial imaging or through advanced mathematics (e.g., Fast Fourier Transform) to produce new indexes that are relevant • Claimed to be useful for diagnosing CAD, ACS, or detecting myocardial ischemia • Commercially available in the United States • Has received FDA approval or clearance for marketing	• Purpose of device use in the study is only to detect arrhythmias. • Does not address diagnosing CAD, ischemia, or ACS

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Outcomes	• Performance characteristics of the device • Effects on diagnostic or treatment decisions • Effects on patient outcomes of interest: o catheterization laboratory findings o clinical outcomes of mortality o cardiac symptoms o function and functional status o therapeutic interventions	None
Setting	• Implementation of the device in most medical facilities must be feasible • Studies that occur in the catheterization laboratory may be included if all other criteria are met	Implementation of the device requires facilities that are not typically available in most medical facilities in the United States
Publications	• English language articles • Peer-reviewed, full-length publication of original data (relevant followup studies and subgroup analyses meet criteria for inclusion)	• Articles not published in English, or not peer-reviewed • Not original data (e.g., editorials, letters to the editor, opinion pieces). Systematic reviews and meta-analyses were excluded from abstraction but were hand-searched as potential sources of additional material if relevant to the topic.

Abbreviations: ACS=acute coronary syndrome; CAD=coronary artery disease; ECG=electrocardiogram; FDA=U.S. Food and Drug Administration

Appendix D: Quality Assessment Criteria and Ratings

Quality Assessment of Diagnostic Accuracy Studies (QUADAS) Tool

For each question answer Yes, No, or Unclear. A user's guide explaining each question and how to score your responses is available in the 2003 QUADAS article here: http://www.biomedcentral.com/1471-2288/3/25

1. Was the spectrum of patients representative of the patients who will receive the test in practice?
2. Were selection criteria clearly described?
3. Is the reference standard likely to correctly classify the target condition?
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
6. Did patients receive the same reference standard regardless of the index test result?
7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?
8. Was the execution of the index test described in sufficient detail to permit replication of the test?
9. Was the execution of the reference standard described in sufficient detail to permit its replication?
10. Were the index test results interpreted without knowledge of the results of the reference standard?
11. Were the reference standard results interpreted without knowledge of the results of the index test?
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
13. Were uninterpretable/ intermediate test results reported?
14. Were withdrawals from the study explained?

Additional quality criteria considered

15. Were patients selected as a random or consecutive sample?
16. Was the first author funded by the manufacturer of the device?
17. Does the abstractor have concerns about conflict of interest (COI)?

Please describe any other study quality assessments not covered in the above questions.

Overall Assessment of Study Quality

Assign the study an overall quality rating based on the following definitions:

Good (low risk of bias). No major features that risk biased results. RCTs are considered a high study design type, but studies that include consecutive patients representative of the intended sample for whom diagnostic uncertainty exists may also meet this standard. A "good" study avoids the multiple biases to which medical test studies are subject (e.g. use of an inadequate reference standard, verification bias), and key study features are clearly described, including the comparison groups, measurement of outcomes, and the characteristics of patients who failed to actual state (diagnostic or prognosis) verified.

Fair (moderate risk of bias). Susceptible to some bias, but flaws not sufficient to invalidate the results. The study does not meet all the criteria required for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

Poor (high risk of bias). Significant flaws that imply biases of various types that may invalidate the results. The study has significant biases determined a priori to be major of "fatal" (i.e. likely to make the results either uninterpretable or invalid).

Quality Rating:

___ Good ___ Fair ___ Poor

If the study is rated as "Fair" or "Poor," provide rationale for decision.

Table D-1 presents the summary rating and results for the overall quality rating, the 14 QUADAS questions, and an additional 3 questions considered during the review.

Table D-1. Quality assessment for the 11 included studies (14 articles)

Study ID	Overall Quality Rating	Patient Representation	Selection Criteria	Reference Standard	Time Interval	Sample for Verification	Reference test uniformly applied	Reference test independently performed	Index Test Replicability	Reference Test Replicability	Index Test Blinded Interpretation	Reference Test Blinded Interpretation	Clinical Data Availability	Uninterpretable or Intermediate Test Reporting	Study Withdrawal Description	Random or Consecutive Sample	Author Funded by Manufacturer	Conflict of Interest
Carley et al., 2005	Fair	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y
Fermann et al., 2009	Fair	Y	Y	N	Y	U	N	Y	Y	Y	Y	Y	Y	N	N	Y	N	N
Maynard et al., 2003	Fair	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	U	N
McClelland et al., 2003	Fair	Y	U	U	Y	Y	Y	Y	U	U	U	U	Y	U	Y	U	U	Y
Menown et al., 1998	Fair	Y	N	N	Y	Y	U	Y	Y	N	U	U	Y	U	Y	N	N	N
Menown et al., 2001	Fair	N	Y	N	N	Y	Y	Y	Y	Y	U	U	Y	N	Y	Y	N	N
Michaelides et al., 1999	Fair	N	Y	Y	Y	Y	Y	Y	Y	N	U	U	Y	Y	Y	Y	U	U
O'Neil et al., 2010 and Hoekstra et al., 2009	Good	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Ornato et al., 2009	Fair	N	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	U	Y	Y	U	U
Owens et al., 2008 and Owens et al., 2004	Fair	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
Owens et al., 2006 and Navarro et al., 2003	Fair	N	Y	U	Y	Y	Y	U	Y	Y	Y	Y	Y	N	Y	Y	U	U

Abbreviations: N=No; U=Unclear; Y=Yes

Reference List of Included Studies

Carley SD, Jenkins M, Mackway Jones K. Body surface mapping versus the standard 12 lead ECG in the detection of myocardial infarction amongst emergency department patients: a Bayesian approach. Resuscitation. 2005;64(3):309-14. PMID: 15733759.

Fermann GJ, Lindsell CJ, O'Neil BJ, et al. Performance of a body surface mapping system using emergency physician real-time interpretation. Am J Emerg Med. 2009;27(7):816-22. PMID: 19683110.

Hoekstra JW, O'Neill BJ, Pride YB, et al. Acute detection of ST-elevation myocardial infarction missed on standard 12-Lead ECG with a novel 80-lead real-time digital body surface map: primary results from the multicenter OCCULT MI trial. Ann Emerg Med. 2009;54(6):779-788 e1. PMID: 19766352.

Maynard SJ, Menown IB, Manoharan G, et al. Body surface mapping improves early diagnosis of acute myocardial infarction in patients with chest pain and left bundle branch block. Heart. 2003;89(9):998-1002. PMID: 12923008.

Mcclelland A, Owens C, Menown IB, et al. Comparison of the 80-lead body surface map to physician and to 12-lead electrocardiogram in detection of acute myocardial infarction. Am J Cardiol. 2003;92(3):252-7. PMID: 12888126.

Menown IB, Allen J, Anderson J, et al. ST depression only on the initial 12-lead ECG: early diagnosis of acute myocardial infarction. Eur Heart J. 2001;22(3):218-27. PMID: 11161933.

Menown IB, Patterson R, MacKenzie G, et al. Body-surface map models for early diagnosis of acute myocardial infarction. J Electrocardiol. 1998;31 Suppl:180-8. PMID: 9988026.

Michaelides AP, Dilaveris PE, Psomadaki ZD, et al. QRS prolongation on the signal-averaged electrocardiogram versus ST-segment changes on the 12-lead electrocardiogram: which is the most sensitive electrocardiographic marker of myocardial ischemia? Clin Cardiol. 1999;22(6):403-8. PMID: 10376179.

Navarro C, Owens C, Riddell J, et al. The use of calculated epicardial potentials improves significantly the sensitivity of a diagnostic algorithm in the detection of acute myocardial infarction. J Electrocardiol. 2003;36 Suppl:127-32. PMID: 14716613.

O'Neil BJ, Hoekstra J, Pride YB, et al. Incremental benefit of 80-lead electrocardiogram body surface mapping over the 12-lead electrocardiogram in the detection of acute coronary syndromes in patients without ST-elevation myocardial infarction: Results from the Optimal Cardiovascular Diagnostic Evaluation Enabling Faster Treatment of Myocardial Infarction (OCCULT MI) trial. Acad Emerg Med. 2010;17(9):932-9. PMID: 20836773.

Ornato JP, Menown IB, Peberdy MA, et al. Body surface mapping vs 12-lead electrocardiography to detect ST-elevation myocardial infarction. Am J Emerg Med. 2009;27(7):779-84. PMID: 19683104.

Owens C, McClelland A, Walsh S, et al. Comparison of value of leads from body surface maps to 12-lead electrocardiogram for diagnosis of acute myocardial infarction. Am J Cardiol. 2008;102(3):257-65. PMID: 18638583.

Owens C, McClelland A, Walsh S, et al. Prehospital 80-LAD mapping: does it add significantly to the diagnosis of acute coronary syndromes? J Electrocardiol. 2004;37 Suppl:223-32. PMID: 15534846.

Owens C, Navarro C, McClelland A, et al. Improved detection of acute myocardial infarction using a diagnostic algorithm based on calculated epicardial potentials. Int J Cardiol. 2006;111(2):292-301. PMID: 16368156.

Appendix E: Excluded Studies

All studies listed below were reviewed in their full-text version and excluded. Following each reference, in italics, is the reason for exclusion. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Abboud S. High-frequency electrocardiogram analysis of the entire QRS in the diagnosis and assessment of coronary artery disease. Prog Cardiovasc Dis. 1993;35(5):311-28. *Exclude - Does not present original data*

Abboud S, Belhassen B, Miller HI, et al. High frequency electrocardiography using an advanced method of signal averaging for non-invasive detection of coronary artery disease in patients with normal conventional electrocardiogram. J Electrocardiol. 1986;19(4):371-80. *Exclude - Does not include a relevant device*

Abboud S, Berenfeld O, Sadeh D. Simulation of high-resolution QRS complex using a ventricular model with a fractal conduction system. Effects of ischemia on high-frequency QRS potentials. Circ Res. 1991;68(6):1751-60. *Exclude - Does not present original data*

Abboud S, Cohen RJ, Selwyn A, et al. Detection of transient myocardial ischemia by computer analysis of standard and signal-averaged high-frequency electrocardiograms in patients undergoing percutaneous transluminal coronary angioplasty. Circulation. 1987;76(3):585-96. *Exclude - Does not include a relevant device*

Abboud S, Zlochiver S. High-frequency QRS electrocardiogram for diagnosing and monitoring ischemic heart disease. J Electrocardiol. 2006;39(1):82-6. *Exclude - Does not present original data*

Abildskov JA, Green LS, Lux RL. The present status of body surface potential mapping. J Am Coll Cardiol. 1983;2(2):394-6. *Exclude - Does not present original data*

Ackaoui A, Nadeau R, Sestier F, et al. Myocardial infarction diagnosis with body surface potential mapping, electrocardiography, vectorcardiography and thallium-201 scintigraphy: a correlative study with left ventriculography. Clin Invest Med. 1985;8(1):68-77. *Exclude - Does not address target population, or address diagnosing CAD, ischemia, or ACS*

Adam D, Gilat S. Classification of pathologies by reduced sequential potential maps. Med Biol Eng Comput. 1992;30(1):26-31. *Exclude - Does not present data specific to patients 18 yrs of age or older*

Afsar FA, Arif M, Yang J. Detection of ST segment deviation episodes in ECG using KLT with an ensemble neural classifier. Physiol Meas. 2008;29(7):747-60. *Exclude - Does not include a relevant device*

Agarwal M, Mehta PK, Bairey Merz CN. Nonacute coronary syndrome anginal chest pain. Med Clin North Am. 2010;94(2):201-16. *Exclude - Does not present original data*

Agetsuma H, Suzuki A, Hirai M, et al. Evaluation of QRST isointegral maps in detecting posterior myocardial infarction with and without conduction disturbance. Clin Cardiol. 1995;18(2):73-9. *Exclude - Does not include a relevant device*

Ammar KA, Kors JA, Yawn BP, et al. Defining unrecognized myocardial infarction: a call for standardized electrocardiographic diagnostic criteria. Am Heart J. 2004;148(2):277-84. *Exclude - Does not present original data*

Andersen K, Eriksson P, Dellborg M. Non-invasive risk stratification within 48 h of hospital admission in patients with unstable coronary disease. Eur Heart J. 1997;18(5):780-8. *Exclude - Does not include a relevant device*

Andersen MP, Terkelsen CJ, Struijk JJ. The ST Compass: spatial visualization of ST-segment deviations and estimation of the ST injury vector. J Electrocardiol. 2009;42(2):181-9. *Exclude - Does not include a relevant device*

Anonymous. ST-segment distortion in manual report mode of electrocardiographs. Health Devices. 1995;24(8-9):362-3. *Exclude - Not a full peer-reviewed publication*

Astrom M, Garcia J, Laguna P, et al. Detection of body position changes using the surface electrocardiogram. Med Biol Eng Comput. 2003;41(2):164-71. *Exclude - Does not include a relevant device*

Aufderheide TP, Rowlandson I, Lawrence SW, et al. Test of the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) for prehospital use. Ann Emerg Med. 1996;27(2):193-8. *Exclude - Does not include a relevant device*

Bacharova L, Mateasik A, Carnicky J, et al. The Dipolar ElectroCARdioTOpographic (DECARTO)-like method for graphic presentation of location and extent of area at risk estimated from ST-segment deviations in patients with acute myocardial infarction. J Electrocardiol. 2009;42(2):172-80. *Exclude - Does not include a relevant device*

Bahr RD. Body Surface Mapping. Potential Role in a Chest Pain Critical Care Pathway: Commentary. Crit Pathw Cardiol. 2003;2(1):52-53. *Exclude - Does not present original data*

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Bell AJ, Briggs CM, Nichols P, et al. Relationship of ST-segment elevation to eventual QRS loss in acute anterior wall myocardial infarction. J Electrocardiol. 1993;26(3):177-85. *Exclude - Does not address target population, or address diagnosing CAD, ischemia, or ACS*

Bell AJ, Loughhead MG, Walker SJ, et al. Prognostic significance of ST potentials determined by body surface mapping in inferior wall acute myocardial infarction. Am J Cardiol. 1989;64(5):319-23. *Exclude - Does not address target population, or address diagnosing CAD, ischemia, or ACS*

Bell AJ, Walker SJ, Kilpatrick D. Natural history of ST-segment potential distribution determined by body surface mapping in patients with acute inferior infarction. J Electrocardiol. 1989;22(4):333-41. *Exclude - Does not address target population, or address diagnosing CAD, ischemia, or ACS*

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Bigger JT, Jr., Hoover CA, Steinman RC, et al. Autonomic nervous system activity during myocardial ischemia in man estimated by power spectral analysis of heart period variability. The Multicenter Study of Silent Myocardial Ischemia Investigators. Am J Cardiol. 1990;66(4):497-8. *Exclude - Does not include a relevant device*

Bigi MAB, Aslani A. SAECG in exercise test for prediction of diabetic coronary artery disease. Central European Journal of Medicine. 2010;5(3):298-302. *Exclude - Does not address target population, or address diagnosing CAD, ischemia, or ACS*

Birnbaum Y, Wagner GS. The initial electrocardiographic pattern in acute myocardial infarction: correlation with infarct size. J Electrocardiol. 1999;32 Suppl:122-8. *Exclude - Does not include a relevant device*

Bjerle P, Niklasson U. Comparison between three different stand-alone ECG interpretation systems. J Electrocardiol. 1988;21 Suppl:S163-8. *Exclude - Does not include a relevant device*

Block P, Eeckhout E, Convents K, et al. Analysis of the cumulative RMS amplitude curve of the signal-averaged ECG in the subacute stage of myocardial infarction. J Electrocardiol. 1992;24 Suppl:195-6. *Exclude - Does not address target population, or address diagnosing CAD, ischemia, or ACS*

Bojovic B, Hadzievski L, Vukcevic VD, et al. Visual 3Dx: algorithms for quantitative 3-dimensional analysis of ECG signals. Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine & Biology Society. IEEE Eng Med Biol Mag.2009:6751-4. *Exclude - Does not include a relevant device*

Bond RR, Finlay DD, Nugent CD, et al. XML-BSPM: an XML format for storing Body Surface Potential Map recordings. BMC Med Inform Decis Mak. 2010;10:28. *Exclude - Does not include a relevant device*

Borbola J, Denes P. Short- and long-term reproducibility of the signal-averaged electrocardiogram in coronary artery disease. Am J Cardiol. 1988;61(13):1123-4. *Exclude - Does not include a relevant device*

Boudik F, Stojan M, Anger Z, et al. Evaluation of body surface potential mapping changes after successful percutaneous transluminal coronary angioplasty. Can J Cardiol. 1996;12(8):745-9. *Exclude - Does not address target population, or address diagnosing CAD, ischemia, or ACS*

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Burattini L, Zareba W. Time-domain analysis of beat-to-beat variability of repolarization morphology in patients with ischemic cardiomyopathy. J Electrocardiol. 1999;32 Suppl:166-72. *Exclude - Not a full peer-reviewed publication*

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Electrocardiol. 1998;31(1):9-15. *Exclude - Does not include a relevant device*

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Dori G, Denekamp Y, Fishman S, et al. Non-invasive computerised detection of acute coronary occlusion. Med Biol Eng Comput. 2004;42(3):294-302. *Exclude - Does not include a relevant device*

Douglas PK, Batdorf NJ, Evans RT, et al. Temporal and postural variation of 12-lead high-frequency QRS electrocardiographic signals in asymptomatic individuals. J Electrocardiol. 2006;39(3):259-65. *Exclude - Does not include a relevant device*

Dranca L, Goni A, Illarramendi A. Real-time detection of transient cardiac ischemic episodes from ECG signals. Physiol Meas. 2009;30(9):983-98. *Exclude - Does not include a relevant device*

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Drew BJ, Schindler DM, Zegre JK, et al. Estimated body surface potential maps in emergency department patients with unrecognized transient myocardial ischemia. J Electrocardiol. 2007;40(6 Suppl):S15-20. *Exclude - Does not include a relevant device*

Drew BJ, Wung SF, Adams MG, et al. Bedside diagnosis of myocardial ischemia with ST-segment monitoring technology: measurement issues for real-time clinical decision making and trial designs. J Electrocardiol. 1998;30 Suppl:157-65. *Exclude - Does not include a relevant device*

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Exarchos TP, Papaloukas C, Fotiadis DI, et al. An association rule mining-based methodology for automated detection of ischemic ECG beats. IEEE Trans Biomed Eng. 2006;53(8):1531-40. *Exclude - Does not include a relevant device*

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Fenici R, Brisinda D, Meloni AM. Effects of filtering on computer-aided analysis for detection of chronic ischemic heart disease with unshielded rest magnetocardiographic mapping. Neurol Clin Neurophysiol. 2004;2004:7. *Exclude - Does not include a relevant device*

Fenici R, Brisinda D, Meloni AM. Clinical application of magnetocardiography. Expert Rev Mol Diagn. 2005;5(3):291-313. *Exclude - Does not present original data*

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