

ECG-based Signal Analysis Technologies for Evaluating Acute Coronary Syndrome

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Disclosures

“Speaker Disclosure Summary”

- I or a member of my immediate family **have not** received anything of value related to the technology or topic being presented

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Overview

- Background
 - Acute Coronary Syndrome (ACS)
 - 12-lead electrocardiogram (ECG)
 - Risk stratification for coronary artery disease (CAD)
 - Signal analysis ECG technology
- Key Questions
- Methods
- Results
- Summary
- Questions and Discussion

Acute Coronary Syndrome (ACS)

- “Working diagnosis” for patients presenting with symptoms suggestive of acute ischemic heart disease
- ACS diagnosis typically replaced by more specific diagnosis as additional data becomes available
- Resting, 12-lead electrocardiogram (ECG) is universally the first-line test in patients with ACS

ECG in the Evaluation of ACS

- 3 possible ECG test results in the setting of ACS evaluation*:
 - ST-elevation MI (STEMI)
 - ST-depression or dynamic T-wave inversion (unstable angina or NSTEMI)
 - Normal or nondiagnostic changes in ST segment or T wave

* Acute Coronary Syndromes: 2010 AHA Guidelines for CPR and Emergency Cardiovascular Care

Limitations of Standard ECG

- Resting ECG has low sensitivity for diagnosing ischemia/infarct, with a corresponding high false negative rate
- Misclassification of patients with acute ischemia/infarct is associated with poor clinical outcomes

ECG-based Signal Analysis Devices

- Represent an emerging technology that processes and/or interprets electrical signals generated by the heart differently from the standard, 12-lead ECG
- Examples:
 - Mathematical analysis of ECG signals
 - High frequency QRS sampling
 - Body surface mapping
 - Vectorcardiography

Risk Classification for Coronary Artery Disease

- **High** (includes patients with STEMI and STEMI-equivalent)
- **Intermediate** (includes symptomatic patients with signs/symptoms suggestive of ischemic heart disease)
- **Low** (includes asymptomatic patients, and symptomatic patients with low likelihood of clinically significant CAD)

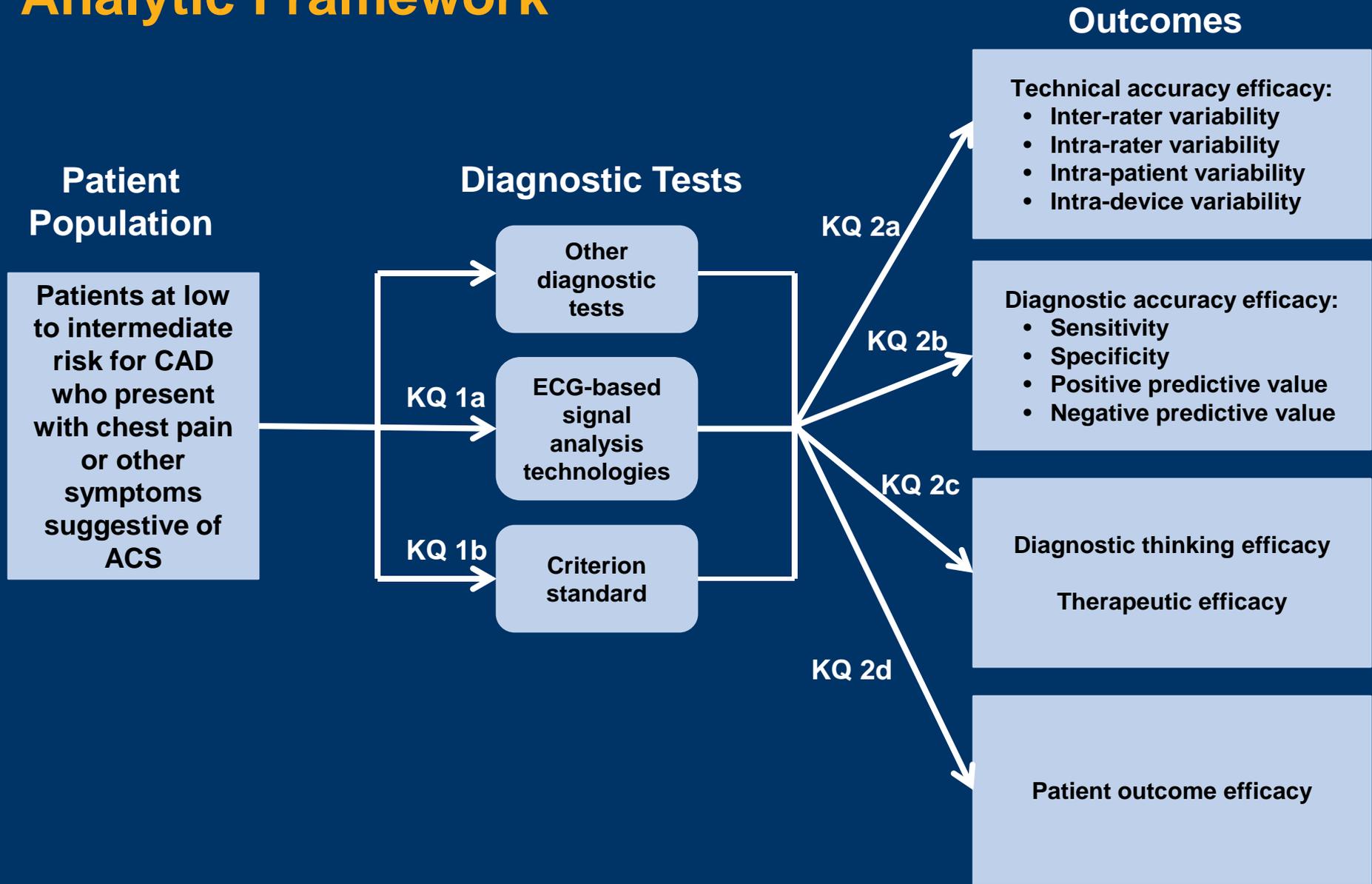
Key Questions

- 1a. What devices and methods for ECG-based signal analysis are used, or are 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 FDA status of these devices?
- 1b. 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?

Key Questions (continued)

- 2. For ECG-based signal analysis devices:
 - 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 decision-making?
 - d) What is the evidence that ECG-based signal analysis technologies impact patient outcomes?

Analytic Framework



Methods

- KQ1a: Gray literature search for eligible devices
 - Google.com, FDA website, freepatentsonline.com, cardiology professional society websites, American Heart Association professional journals website, clinicaltrials.gov, company-sponsored websites
- KQ1b: Expert discussion of criterion standards
- KQ2:
 - Systematic review of identified devices
 - Data synthesis
 - Meta-analysis

Device and Study Eligibility Criteria

- A physical device that obtains and interprets information about the heart's electrical activity in ways that are different from the standard 12-lead ECG
- Device tested in adult patients at low to intermediate risk for CAD who have a clinical presentation consistent with ACS
- Available for purchase in the United States
- Feasible implementation in a typical medical facility
- Study must report relevant outcomes including performance characteristics, effects on diagnostic or treatment decisions, or effects on patient outcomes
- Sample size ≥ 20

RESULTS

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KQ1a: ECG SA Devices

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
CardioSoft®	NASA	Yes	SA (HF-QRS)
HyperQ™ (stress ECG)	Biological Signal Processing	Yes	SA (HF-QRS)
PRIME ECG	Heartscape	Yes	BSM
3DMP/MCG/mfEMT	Premier Heart	Yes	MA
CarDx	Bionetek	No	MA
Cardiologic Explorer	Enverdis	No	VCG
Vascular Explorer	Enverdis	No	VCG

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

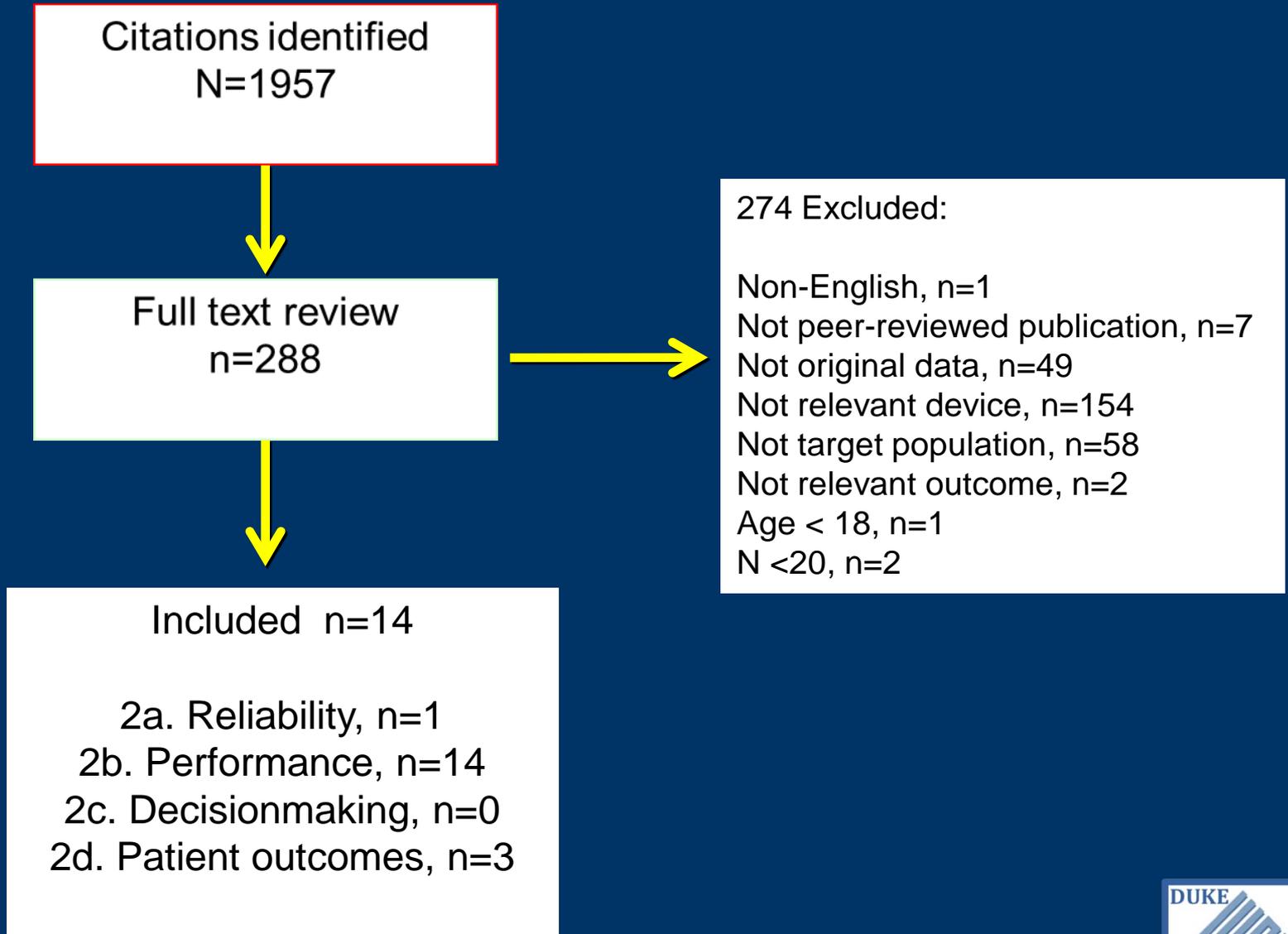
KQ1b: Criterion Standards

- For CAD:

Reference Standard	Advantages	Disadvantages	Acceptability
Coronary angiography	Identifies coronary artery lesions	Invasive, does not provide information about ischemia	Preferred
Stress testing with imaging	Noninvasive	Does not diagnose CAD, can't be performed at time of presentation with acute chest pain	Acceptable
Imaging studies without exercise or pharmacological stress	Always for visualization of heart structure	No direct information about ischemia	Unacceptable
Resting 12-lead ECG	Noninvasive, relatively inexpensive, widely available	Not sufficiently sensitivity of specific for CAD	Unacceptable
Stress testing with ECG	Provides diagnostic and prognostic information, good NPV	Low sensitivity and high rate of misclassification	Unacceptable
Biomarkers (applicable only for identifying myocardial injury)	Widely available and routinely used to evaluate for ischemia or acute infarct	Many clinical conditions associated with elevated biomarkers	Incomplete

- For ACS: No single criterion standard because ACS essentially a “working diagnosis” pending further diagnostic information

Literature Search Flow Diagram



KQ2a: Evidence for inter-rater, intra-rater, intra-patient, and intra-device variability

- Single eligible study. Emergency physicians and body surface mapping (BSM) experts rated 135 PRIME ECG readings as:
 - Normal (negative)
 - Nonspecific (negative)
 - Abnormal (positive)
 - Ischemia (positive)
 - Infarct (positive)
- 52/135 (39% agreement) for negative tests and 63/135 (47% agreement) for positive tests
- Emergency physicians more likely to interpret a study as negative than BSM experts

KQ2b: Diagnostic test performance compared to reference standard

- 11 studies (14 articles)
- 1 good-quality and 10 fair-quality studies
- All observational cohort studies
- Represents 2 eligible devices:
 - LP 3000 System (1 study)
 - PRIME ECG (10 studies)

KQ 2b: LP3000 Device

Characteristic	LP 3000
Reference standard	CAD by coronary angiography
Index Test	
Sensitivity	69% (75/108)
Specificity	89% (16/18)
ECG	
Sensitivity	56% (60/108)
Specificity	89% (16/18)

KQ 2b: PRIME ECG

- 10 studies (1998 – 2010)
- Setting: Emergency departments and cardiology wards.
6 studies conducted by one investigative team that previously developed the device
- MI by biomarkers as reference standard
- Proprietary algorithm evolving over time

KQ 2b: Meta-Analysis

PRIME ECG vs 12-lead ECG

Test Characteristic	PRIME ECG	12-Lead ECG
Sensitivity	68% (95% CI: 35-90)	41% (95% CI: 20-66)
Specificity	91% (95% CI: 84-96)	95% (95% CI: 88-98)
LR+	6.7 (95% CI: 2.8-15.9)	7.5 (95% CI: 2.7-21.1)
LR-	0.31 (95% CI: 0.14-0.69)	0.58 (95% CI: 0.42-0.80)

KQ 2c: Evidence for Impact on Diagnostic Decision-making

- No eligible studies identified

KQ2d: Evidence for Impact on Patient Outcomes

- 2 studies
 - OCCULT MI trial (2009, 2010)
 - *N=1830, including patients with STEMI*
 - *ST-elevation detected by PRIME ECG associated with increased mortality (OR=11)*
 - *ST-elevation detected by standard ECG not associated with increased mortality*
 - Fermann et al. (2009)
 - *Post-discharge events among patients who initially presented with ACS were recorded but not reported in the published study*

Summary of Findings

- 11 studies (14 publications) identified
- No eligible studies included low-risk patients
- 2 devices evaluated in target population
- Meta-analysis suggests that the PRIME ECG may have higher sensitivity for detecting acute MI than the 12-lead ECG (68% vs 41%), but 95% CIs overlap
- Limited evidence that suggests that PRIME ECG may provide early risk stratification information

Applicability of Current Studies

- 6 studies conducted in Ireland, 1 in England, 1 in Greece
- 3 studies conducted in the U.S. and included patients who represent the target population for the purpose of this report
- PRIME ECG algorithm has evolved over time

Future Research Needs

- Studies with appropriate reference standards
- Evaluation of existing ECG-based signal analysis devices other than PRIME ECG among the target population for this report
- Studies that evaluate the impact of new devices on clinical decision-making and long-term patient outcomes
- Evaluation of sub-groups of patients, such as:
 - suspected ischemic heart disease despite nondiagnostic ECG
 - conditions that decrease the standard ECG's utility
 - specific age groups
- Studies that evaluate the utility of new devices in addition to, rather than instead of, a standard ECG
- Studies that compare test characteristics of new devices with ECG among patient populations that include STEMI and STEMI-equivalent

QUESTIONS/DISCUSSION