Mini-review

Novel biomarkers in diagnosing cardiac ischemia in the emergency department: A systematic review☆

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ABSTRACT

Background: Novel biomarkers of myocardial ischemia and inflammatory processes have the potential to improve diagnostic accuracy of acute coronary syndrome (ACS) within a shorter time interval after symptom onset.
Objective: The objective was to review the recent literature and evaluate the evidence for use of novel biomarkers in diagnosing ACS in patients presenting with chest pain or symptoms suggestive of cardiac ischemia to the emergency department or chest pain unit.
Methods: A literature search was performed in MEDLINE, EMBASE, Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED for studies from 2004 to 2010. We used the inclusion criteria: (1) human subjects, (2) peer-reviewed articles, (3) enrolled patients with ACS, acute myocardial infarction or undifferentiated signs and symptoms suggestive of ACS, and (4) English language or translated manuscripts. Two reviewers conducted a hierarchical selection and assessment using a scale developed by the International Liaison Committee on Resuscitation.
Results: Out of a total 3194 citations, 58 articles evaluating 37 novel biomarkers were included for final review. Forty-one studies did not support the use of their respective biomarkers. Seventeen studies supported the use of 5 biomarkers, particularly when combined with cardiac-specific troponin: heart fatty acid-binding protein, ischemia-modified albumin, B-type natriuretic peptide, copeptin, and matrix metalloproteinase-9.
Conclusion: In patients presenting to the emergency department with chest pain or symptoms suggestive of cardiac ischemia, there is inadequate evidence to suggest the routine testing of novel biomarkers in isolation. However, several novel biomarkers have the potential to improve the sensitivity of diagnosing ACS when combined with cardiac-specific troponin.

1. Introduction

Chest pain is a common presentation to the emergency department and accounts for approximately 5–10% of all visits.[1] Most of these patients have relatively unremarkable electrocardiograms. The identification and diagnosis of acute coronary syndrome (ACS), including acute myocardial infarction (AMI), in these patients pose significant challenges. Rates of missed ACS among patients who present to the emergency department remain inappropriately high,

ranging from 2 to 5%.[2,3] Recent efforts have focused on improving the accuracy of identifying patients with ACS who are at high risk of having an adverse event within the short term after assessment.

The importance of cardiac biomarker testing has been widely accepted and is suggested as part of the initial evaluation of patients presenting with chest pain or other symptoms suggestive of cardiac ischemia.[4] In a recent expert consensus document from a joint international task force, the revised universal definition of myocardial infarction includes a rise in cardiac biomarkers above the 99th percentile as a primary criterion.[5] Biomarkers are useful in the evaluation of chest pain patients when they are highly sensitive to safely "rule out" cardiac ischemia or when they are highly specific to capture patients with ACS who otherwise have non-diagnostic tests (e.g. ECG). Appropriate patient selection and an exclusionary algorithm are often used in emergency departments and chest pain units. However, these patients often require 6–12 h of observation

or longer depending on the time of symptom onset, the cardiac biomarker assay used, and other diagnostic techniques used in the protocol.

Common biomarkers such as cardiac-specific troponins (TnI or TnT), are markers of myocardial necrosis and are currently recommended in the evaluation of chest pain patients.[4,5] However, myocardial ischemia and inflammation precede necrosis. Markers of myocardial ischemia and inflammation have the potential to differentiate chest pain patients in shorter time intervals than cardiac-specific troponin, which may lead to earlier treatment or discharge. There has been growing interest in the study of *novel* biomarkers over recent years.

This systematic review was used in part during the evaluation process for the 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations.[6–9] The aim of this study was to update and expand the evaluation of the recent evidence of using novel biomarkers in the diagnosis of ACS in patients presenting to the emergency department or chest pain unit.

2. Objective

The objective of this study was to review the recent literature and evaluate the evidence for the effectiveness of novel biomarkers in diagnosing ACS in patients presenting with chest pain or symptoms suggestive of cardiac ischemia to the emergency department or chest pain unit.

3. Methods

3.1. Search strategy

We undertook a systematic review of the literature. The search was performed in the following databases: MEDLINE, EMBASE, Cochrane Database Systematic Reviews, American College of Physicians Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Controlled Trials Register, Cochrane Methodology Register, Health Technology Assessment, and National Health Service Economic Evaluation Database for studies from January 1, 2004 to December 31, 2010. Using search strategies designed by an information specialist to be maximally inclusive and tailored specifically for each database, we used the following key words: Clinical enzyme tests, isoenzymes, troponin, creatine kinase (CK), myoglobin, myocardial ischemia, emergency, prehospital, and inhospital as well as the names of multiple other markers that were considered *novel* from narrative reviews.[10,11] We used troponin, CK, CK-MB and myoglobin in the search in order to capture studies that evaluated multimarker testing in combination with these *common* biomarkers. The search was then limited to diagnostic sensitivity and specificity limits. Detailed search criteria are outlined in Appendix A. A hand search of the bibliographies of selected articles was also performed for additional studies.

3.2. Study selection

Two reviewers (S.L. and H.Y.) performed an independent selection of studies, blinded to author and journal. Citations were reviewed for inclusion in a hierarchical fashion by title, abstract and then full article. Disagreements between authors on inclusion were resolved by consensus. Studies were included if they met the following criteria: (1) human subjects, (2) peer-reviewed articles, (3) enrolled patients with ACS, AMI or undifferentiated signs and symptoms suggestive of ACS, and (4) English language or translated manuscripts. We excluded (1) expert opinion reviews, (2) studies evaluating biomarkers exclusively for prognostication, (3)

> **Box 1: Definitions of levels of evidence (LOE) for diagnostic studies defined by the ILCOR evaluation process.**
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> - **LOE 1:** Validating cohort studies (or meta-analyses of validating cohort studies), or validation of Clinical Decision Rule (CDR).
> - **LOE 2:** Exploratory cohort study (or meta-analyses of follow up studies), or derivation of CDR, or a CDR validated on a split-sample only.
> - **LOE 3:** Diagnostic case control study.
> - **LOE 4:** Study of diagnostic yield (no reference standard).
> - **LOE 5:** Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models etc.).
>
> *Adapted from: Morley PT, Atkins DL, Billi JE, et al.*[8,9]

studies evaluating only common biomarkers such as cardiac-specific troponin, CK, CKMB or myoglobin in isolation, and (4) narrative reviews, commentaries, editorials and abstract-only publications.

3.3. Evaluation of included studies

The level of evidence for each article was graded from 1 (highest level) to 5 (lowest level) based on the evaluation process defined by the C2010 International Liaison Committee on Resuscitation (ILCOR) listed in Box 1.[6,7] Finally, each study was classified as supporting the respective biomarker in the diagnosis of ACS if the biomarker showed a sensitivity >95%, which was previously used in the 2005 ILCOR evaluation of biomarkers,[12,13] or a specificity >92% combined with a sensitivity >90%. Otherwise, those studies not meeting either of these criteria were classified as opposing evidence. These criteria for classification were discussed and agreed upon by expert members of the ILCOR ACS Task Force.[14] Interim results of the evaluation process were presented in both written and oral formats to the ILCOR ACS Subcommittee for discussion, input and approval.[8,9]

4. Results

The initial electronic database search identified a total of 3194 citations. After duplicates were removed, the remaining titles were screened by 2 independent investigators (S.L. and H.Y.) for relevance. This yielded 429 citations, of which these abstracts were reviewed. At this stage, 190 remained and their corresponding full texts were retrieved. After reviewing full text articles, a total of 58 studies evaluating 37 unique novel markers in diagnosing ACS in patients presenting with chest pain or symptoms suggestive of cardiac ischemia were included for final review (Table 1).

The included studies were heterogeneous in their diagnostic endpoints. There were some studies that used ACS as an endpoint, which includes AMI as well as unstable angina, while others used only AMI. In addition, there was heterogeneity in the reference standards used to define their respective diagnostic endpoints (e.g. final diagnosis by a cardiologist, emergency department discharge diagnosis or positive troponin assay). Of the included studies, there were 49 studies that evaluated central lab assays and the remaining 9 studies evaluated bedside point-of-care (POC) testing.[15–23]

Of the 58 articles, 41 studies (LOE 2–4) provided evidence opposing the use of their respective markers in the diagnosis of ACS. The other 17 studies (LOE 2–4) were classified as supportive. These 17 studies reported on the diagnostic accuracy of 5 different novel markers for ACS. These biomarkers included