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Update: Acute Coronary Syndromes (III)

Complementary, Alternative, and Putative Nontroponin Biomarkers of Acute Coronary Syndrome: New Resources for Future Risk Assessment Calculators

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ABSTRACT

Biomarkers, other than cardiac troponin, with potential sensitivity and selectivity that provide diagnostic and prognostic insights into the tissue–specific injury processes underlying acute coronary syndrome and their possible use in risk stratification algorithms are discussed. Such biomarkers may be useful as complementary or alternative to cardiac troponin (I or T) assays in early diagnosis of acute coronary syndrome, as well as for monitoring acute coronary syndrome progression and prognosis assessment. The information included in this article is based on a critical analysis of selected published biomedical literature accessible through the United States National Library of Medicine's MEDLINE-PubMed and Scopus search engines. The majority of articles cited in this review and perspective, except for a few historical publications as background, were published between January 2000 and December 2013.

Biomarcadores no troponínicos, complementarios, alternativos y presuntos, para el síndrome coronario agudo: nuevos recursos para los futuros instrumentos de cálculo del riesgo

Palabras clave:
Inflamación
Activación plaquetaria
Micro-ARN
Estratificación del riesgo en el síndrome coronario agudo

RESUMEN

En este artículo se revisan los biomarcadores no troponínicos con posibles sensibilidad y selectividad, que aportan una perspectiva diagnóstica en el síndrome coronario agudo, y su posible uso en los algoritmos de estratificación del riesgo. Dichos biomarcadores pueden ser útiles como análisis complementarios o alternativos a los de troponina cardiaca (I o T) en el diagnóstico precoz del síndrome coronario agudo, así como para monitorizar su progresión y evaluar el pronóstico. La información presentada en este artículo se basa en un análisis crítico de una selección de la literatura biomédica disponible a través de los motores de búsqueda Scopus y MEDLINE-PubMed de la *National Library of Medicine* de Estados Unidos. La mayor parte de los artículos citados en este trabajo de revisión y perspectiva, excepto unas pocas publicaciones históricas de referencia, se publicó entre enero de 2000 y diciembre de 2013.

Abbreviations

ACS: acute coronary syndrome
BNP: brain natriuretic peptide
CK-MB: creatine kinase–MB fraction
CRP: C-reactive protein
hs-cTn: high-sensitivity cardiac troponin
miRNAs: micro RNAs
MVs: microvesicles

INTRODUCTION

This literature review presents a critically selected set of publications from our comprehensive search of the published biomedical literature archived by the United States National Library of Medicine Library (MEDLINE-PubMed) and alternatively retrieved using the *Scopus* search engine. For this article, we selected original nonclinical and clinical research, and a representative sample of historical and recent reviews, that identify established and putative nontroponin biochemical markers (aka biomarkers) of acute coronary syndrome (ACS). This review identifies blood sample biomarkers in current use as complementary or alternative to high-sensitivity cardiac troponin (hs-cTn) assays and emerging tissue and ischemic process-related biomarkers proposed for use in ACS risk stratification. Clearly, risk stratification of patients screened for possible ACS is performed most effectively by combining patient history and available medical data with electrocardiographic evaluation and serial

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analysis of blood for relevant biomarkers; typically hs-cTn, myoglobin, and creatine kinase–MB fraction (CK-MB) assay results. This review includes both early-phase and late-phase nontroponin biomarkers purported to identify—with varying degrees of sensitivity and specificity to reliably detect underlying biological events and processes– ischemic injury to myocardial cells, endothelial cells, plaque formation and eruption, platelet aggregation and other blood cell reporters associated with clot formation, and coronary or myocardial inflammation.

To set the stage, we compiled the frequency of original articles and reviews reporting on biomarkers and ACS (Figure 1) or on risk stratification and ACS (Figure 2), including original articles published for nontroponin biomarkers from January 2000 to December 2013 using the United States National Library of Medicine search engine, PubMed.[1] While the number of original research publications reporting biomarkers for ACS appears to have reached an apex in 2011, publications related to risk stratification for ACS appear have steadily increased over the entire 14-year period, except for a small decline from 2009 to 2012. In a similar manner, the number of original research articles addressing ACS risk stratification with biomarkers other than troponin leveled out in 2009 at around 40 articles annually, with a slight increase in the number of original articles projected for 2013. The publication trends illustrated in Figures 1 and 2 were similar when we performed a literature search over the same time period with the same search terms, using the Scopus[2] search engine. To assure that we had captured guidelines and consensus opinions and practices with ACS biomarkers, we also searched The Cochrane Library database.[3]

The term ACS is used to describe myriad situations where the heart's coronary arterial blood supply is suddenly interrupted or blocked, typically as the terminal event of a progressive vascular disease process in one or more of the major branches of the coronary arterial circulation. ACS encompasses both classes of myocardial ischemia/infarction as assessed by electrocardiography —ST-segment elevation myocardial infarction and non—ST-segment elevation myocardial infarction— as well as unstable angina pectoris and coronary disease associated with various metabolic disorders (eg, diabetes mellitus).

The 2011 European Society of Cardiology Task Force defines ACS as "a life-threatening manifestation of [progressive] atherosclerosis [. . .] usually precipitated by acute thrombosis induced by a ruptured or eroded atherosclerotic coronary plaque, with or without concomitant vasoconstriction, causing a sudden and critical reduction in [coronary/myocardial] blood flow." The European Society of Cardiology, the American College of Cardiology Foundation, and the American Heart Association guidelines for ACS biomarkers place serial hs-cTn assays as the number one indicator, with CK mass, CK-MB isoenzyme, and myoglobin assays as secondary biomarkers.[4,5] Clearly, early onset biomarkers that potentially identify cellular and tissue pathology events that underlie the progressive nature of ACS are receiving the most attention at present, as new diagnostic and prognostic screening tools and technologies are increasingly refined.

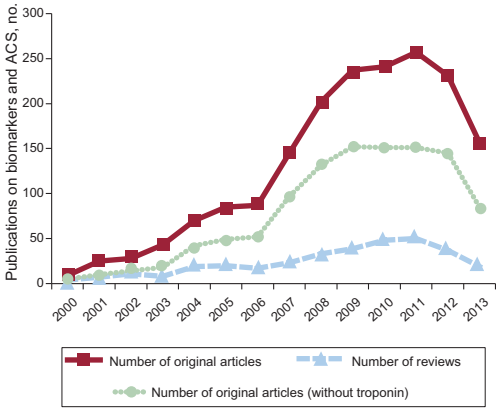

Figure 1. PubMed search results, 2000 to 2013 (2013 actual through October 31; estimated for 12 months), for the combined search terms "biomarker" and "acute coronary syndrome". Total number of published original articles (solid line, squares), total articles without troponin as one of the biomarkers (dotted line, circles), and total number of review articles (dashed line, triangles). ACS: acute coronary syndrome.

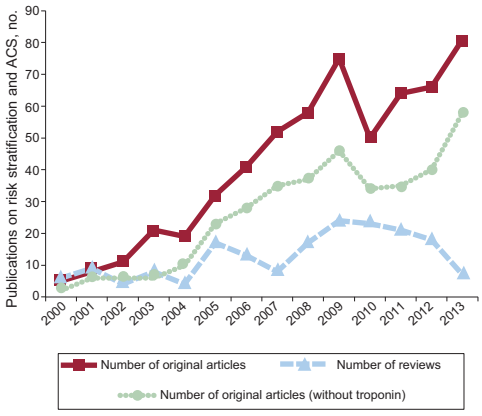

Figure 2. PubMed search results, 2000-2013 (2013 actual through October 31; estimated for 12 months), for the search terms "risk stratification" and "acute coronary syndrome". Total number of published original articles (solid line, squares), total articles without troponin as one of the biomarkers (dotted line, circles), and total number of review articles (dashed line, triangles). ACS: acute coronary syndrome.

Whenever coronary blood flow supply providing nutrients and oxygen to myocardium falls below the required threshold to meet myocardial metabolic demand, a condition of relative myocardial ischemia presents and is associated with a switch from aerobic to anaerobic metabolism.[6] When coronary flow reduction is sufficiently significant and sustained, myocardial tissue injury occurs. Due to physical forces during the cardiac cycle, the endocardial region of the ventricular wall is most susceptible to ischemia during such acute or progressive reductions in coronary perfusion pressure distal to points of stenosis or occlusion.

At the cellular level, regional myocardial ischemic injury leads to heart muscle cell membrane disruption and leakage of cell contents that may be detectable and useful as important biomarkers of ACS. A number of additional tissue type disruptions occur during ACS that involve pre-existing atherosclerotic plaques, endothelial cells, vascular smooth muscle cells, and blood elements including platelets, neutrophils and white blood cells.

CK was perhaps one of the earliest identified biochemical (intracellular enzyme) markers released into the blood following transient and sustained coronary artery occlusion.[7–9] The myocardial isoenzyme CK-MB is perhaps the earliest reliable "gold standard" biomarker for assessment of ACS. In addition to CK-MB, assays for myoglobin and the cardiac contractile protein troponins (cTnI and cTnT) released from injured cardiac muscle cells are used in combination to diagnose or confirm ACS. Today hs-cTn assays are relied upon as the most relevant, sensitive, and specific overall reference biomarker for early and late-stage ACS and myocardial ischemic injury assessment in patients presenting at the emergency department after symptom onset.[10] Clearly, the advent of hs-cTn assays, early-detection capability ACS has elevated the hs-cTn (I or T) as a biomarker of preference over earlier candidates, including myoglobin and copeptin.[11]