A PERSPECTIVE OF CARDIOVASCULAR EVENTS PREDICTION STRATEGIES

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Abstract. The incidence of cardiovascular events at elderly patients is very high. Therefore, it is necessary to detect the presence and severity of an acute heart condition as soon as possible. Prognostic evaluation is based on choosing the right risk markers, who must accomplish certain clinical features. Recent research has shown new emerging biomarkers, capable of providing significant information, which could be added to increase prediction ability. Thus, diagnostic and therapeutic strategies are highly needed. The latest studies have focused on finding a multimarker strategy which combines utility of several cardiac markers, employing different pathophysiological aspects. Present review aims to discuss new cardiac biomarkers and strategies that could facilitate not only risk stratification of short and long term adverse cardiovascular events appearance, but also a more accurate and proper diagnosis, prognostic and treatment.
Key words: cardiovascular diseases, biomarkers, multimarker strategy

STRESUL GLICOXIDATIV ÎN ÎMBĂTRÂNIRE ŞI PATOLOGIE

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Rezumat. La pacienţii vârstnici incidenţa evenimentelor cardiovasculare este foarte mare. Prin urmare este necesar să se detecteze cât mai curând posibil prezenţa şi severitatea unei afecţiuni cardiace acute. Analiza prognostică se bazează pe alegerea markerilor de risc adecvaţi, care trebuie să îndeplinească anumite caracteristici clinice. Cercetări recente au relevat noi biomarkeri capabili să asigure informaţii semnificative şi care ar putea fi adăugaţi pentru a spori capacitatea de predicţie. Astfel, sunt foarte necesare strategiile de diagnostic şi tratament. Ultimele studii s-au concentrat pe găsirea unei strategii multimarker, care să combine utilitatea mai multor markeri cardiaci, folosind diferite aspecte patofiziologice. Prezentul review urmăreşte să discute noi biomarkeri cardiaci şi strategii care ar putea facilita nu numai stratificarea riscului apariţiei evenimentelor cardiovasculare adverse pe termen scurt şi lung, ci şi un diagnostic, prognostic şi tratament mai precis şi adecvat.
Cuvinte cheie: boli cardiovasculare, biomarkeri, strategie multimarker

INTRODUCTION

Cardiac biomarkers are molecules linked with heart function and their detection could predict the presence and/or severity of cardiovascular diseases (CVD). The sooner they are detected an appropriate treatment can be initiated [1]. As we aged, the incidence of CVD is very high, so cardiac markers must accomplished certain clinical characteristics in order to be independent predictors. In screening and cardiovascular disease management there is an increasing interest in the use of new biomarkers [2].

To be good predictors, the new biomarkers must show a significant association with CVD events and bring new information into risk stratification when added to risk prediction models. Thus, new markers are

required, alone and/or in combination with other markers, to be used as prognostic indicators for future CVD events and in monitoring of treatments [1, 2].

POTENTIAL NEW BIOMARKERS - CLINICAL RELEVANCE

•Chitinase-3-like protein 1 (YKL-40), is a secreted glycoprotein by macrophages, chondrocytes, and some types of cancer cells. YKL-40 is regarded as an acute phase protein but in contrast to C-reactive protein (CRP), mainly produced by hepatocytes in response to high IL-6, YKL-40 is produced by macrophages and neutrophils in tissues with inflammation and by differentiated macrophages and activated neutrophils [3].

Studies suggest that serum YKL-40: could be a new biomarker of acute and chronic inflammation in patients with stable coronary artery disease; can reflect the overall burden of coronary atherosclerosis or may identify a high-risk phenotype of atherosclerosis; may be a useful marker for myocardial ischaemia, remodelling and probably prognostic.

Serum YKL-40, CRP, and natriuretic peptide-NT-proBNP were measured in 4265 patients with stable coronary artery disease included in the CLARICOR trial [4], and death was registered in a 6-years follow-up period. Study concluded that serum YKL-40 is a predictor of long-term mortality in patients with stable coronary artery disease, independent of common risk factors.

•Recently, copeptin, a 39 amino acid glycopeptide comprising the C-terminal portion of vasopressin, has been shown to be a stable and sensitive vasopressin-releasing marker analogous to insulin peptide C. Measurement of copeptin has proven useful in various diseases, including the diagnosis of insipid diabetes and monitoring of CVD [5]. Because it is not specific for a particular disease, it could be used as an adjunct to more specific biomarkers, increasing the accuracy of the diagnosis.

-Normal values in healthy volunteers range from 1.70-11.25 pmol/l.

-In advanced and acute heart failure, it varies between 20 and 45 pmol/l.

-In septic shock, haemorrhagic shock, ischemic stroke and acute myocardial infarction, increase to over 100 pmol/l.

-In insipid diabetes, hyponatremia and other conditions associated with decreased vasopressin, it decreases.

•Modified ischemia albumin (IMA) is a marker formed after the destruction of the N-terminal part of albumin under ischemic conditions. The IMA test should be interpreted in association with other tests for cardiac function such as troponin, myoglobin and EKG. IMA increases in 6h and remains elevated for 12 hours. IMA is useful in differentiating angina pectoris from myocardial ischaemia: if IMA is within normal limits and troponin and myoglobin are within normal limits and there are no changes in electrocardiogram, then chest pain is not due to heart attack [6]. The IMA test is important in the first few hours, so if the chest pain occurred a few hours ago, then the test is not useful because the IMA may have returned to normal levels.

•Placental growth factor (PLGF) is a multitasking cytokine capable of stimulating angiogenesis by direct or indirect mechanisms. Recently, an increasing number of clinical evidence suggests that PLGF alone or in combination with other biomarkers is a strong predictor of survival or cardiovascular events [7] in patients with stable and unstable coronary disease (PLGF alone and BNP alone have similar diagnostic precision for prediction of cardiovascular events, and the combined use of PLGF and BNP would have a higher diagnostic accuracy than each biomarker taken separately). However, some studies have not demonstrated that PLGF is independently associated with survival in patients with chronic heart failure or suspected acute myocardial infarction [7].

•Sphingolipids have recently been discovered to be not only plasma membrane components but also bioactive mediators that can induce different biological responses. Of these lipids, sphingomyelin (SM) and sphingosine-1-phosphate (Sph-1-P) are proposed to be involved in the pathogenesis of atherosclerosis and could become biomarkers useful for atherosclerotic disorders [8]. However, the measurement of Sph-1-P and SM levels has not been introduced into clinical practice because of the difficulty of accurate, rapid and convenient measurement of these sphingolipids. But it is true that the level of sphingolipids can accurately predict acute coronary syndrome and undoubtedly can act as future biomarkers to confirm atherosclerotic disorders as well as neurological disorders [8].

•Homocysteine is a factor involved in promoting thrombosis and inflammation, as well as vascular damage [9].

Numerous studies have shown that hyperhomocysteinemia is associated with:

- Increased cardiovascular disease - independent risk factor for both women and men;
- Increased venous thrombosis

A meta-analysis of 27 epidemiological studies indicated that a 5 μmol/l increase in homocysteinemia is associated with a risk of coronary disease similar to that induced by a 0.5 mmol/l increase in cholesterol [10]. Theories have been developed to justify the pathogenic role of homocysteine such as favouring platelet aggregation, development of endothelial lesions, alteration of fibrin affinity of lipids and lipoproteins, alterations in smooth muscle cell proliferation and increased production of reactive oxygen species, leading to increased stress oxidative. Normal levels should be less than 10 μmol/l.

•The A-plasma protein (PAPP-A) is a homodimer that is not covalently bound to the major eosinophilic basic protein who has proteolytic activity and is considered to play an important role in cardiovascular disease [11]. Recently, PAPP-A has been found to be a useful biomarker for cardiovascular dysfunction, inflammation and malnutrition in patients with chronic renal disease undergoing hemodialysis. High levels of PAPP-A are found in patients with unstable plaques, aggravated unstable angina and acute myocardial infarction. Very high plasma stability has given it clinical potential but currently there is no clinically standardized method of determination. Levels above 1.74 mIU/l are considered abnormal.

•Phospholipase A2 (Lp-PLA2) is an enzyme produced by inflammatory cells and is associated with atherogenic proteins. Nearly 80% is linked to LDL and 20% to HDL and VDRL. Lp-PLA2 is an inflammatory biomarker secreted by the atherosclerotic plaque and blood levels would predict the most recent cardiovascular events in patients with ischemic heart disease or heart failure. This association seems to be independent of traditional risk factors [12]. Lp-PLA2 is believed to play a dual role in atherosclerosis, with both proaterogenic and anti-inflammatory properties. It has also been demonstrated that levels of LpPLA2 are reduced by statins, suggesting that it could be a target for therapies, besides being a cardiovascular risk biomarker.

•Fatty acid binding protein (FABP) is a small cytosolic protein responsible for the transport and storage of fatty acids in the cell. Recently, H-FABP has been shown to be useful as an early marker of myocardial infarction and early detection of minor myocardial events such as unstable angina [13]. It is also a potential marker for cerebral lesions and stroke with high specificity and predictive positive value. Tomographic analysis has demonstrated the association between high levels of H-FABP and infarction, and preliminary studies have shown that FABP isoenzymes are more sensitive markers in brain injuries than currently used markers-S100 and NSE-neuronal specific enolase.

•ST2 is a member of the interleukin-1 receptor family, being released from myocytes under mechanical stress. Soluble concentrations of ST2 are associated with adverse cardiac events [14]. In addition to its potential as a biomarker for adverse cardiovascular events, ST2 is believed to play a causal role in chronic cardiovascular disease such as atherosclerosis and heart failure. Furthermore, the combination of NT-proBNP, ST2 and transthoracic echocardiography can be useful as a strong predictor of mortality in patients with dyspnea and for triage and risk stratification [15].

•Growth differentiation factor 15 (GDF-15) is a stress-sensitive cytokine that could be used as a biomarker of cardiac and vascular dysfunction. Elevated levels of GDF-15 have been found in patients at increased risk of cardiovascular disease, from stable coronary artery disease to acute coronary syndrome and heart failure. The association between GDF-15 and cardiovascular disease is independent of stable risk factors and biomarkers, including NT-proBNP and troponin. Prognostic information provided by GDF-15 in cardiovascular disease may be useful in identifying patients with acute coronary syndrome without ST segment elevation who benefit from an invasive strategy or monitoring response to treatment in heart failure [16].

•Recent studies provide important information on the clinical relevance of CD40L in patients with acute coronary syndrome [17]. If the troponin reflects the ability and tendency of the coronary thrombus to embolize with micronecrosis, then CD40L appears to reflect the prothrombotic inflammatory activity of the plaque with recurrent and platelet activation. Its increase indicates an increase in cardiac risk at 6 months following follow-up. Furthermore, in patients without myocardial necrosis, CD40L appears to identify a high risk subgroup, suggesting that its measurement could have additional benefits when combined with current myocardial infarction analyses [17]. As CD40L is elevated also in those with inflammatory diseases the question arises about the specificity of this marker.

•miRNA is involved in all biological processes, from cell differentiation to cell death and apoptosis [18]. Many types of miRNA can be detected in the blood, with remarkable stability, each with a specific pattern of expression. miRNA that regulates the cardiovascular system can be divided into 4 groups:

1. miRNA that regulates endothelial function and angiogenesis: miR126, miR17-92 cluster, miR130a, miR221, miR21
2. miR208a specific miRNA miRNA
3. miRNA for myocytes and striated muscles: miR1, miR133a, miR499
4. miRNA for smooth muscle: miR1443, miR145

miRNA is very promising, being a very specific marker and with high accuracy for heart failure [18]. Tian Jian et al. [19] conclude that studies strongly implicate certain miRNAs such as miR499 as useful biomarkers of a given heart disease.

MULTIMARKER APPROACH - PROGNOSTIC ABILITY

All of the above markers (and many others who have not been included in this review due to the large amount of references) could be capable of providing significant prognostic information [1, 2]. Of late years, studies are focused on a strategy that combines utility of all these cardiac markers. Because these are very different, each of them reflecting various pathological ways, a multimarker strategy needs to be considered [20-24]. Using this multimarker strategy, clinicians could stratificate the risk of long/short term adverse cardiovascular events appearance.

James et al. [20] showed in a substudy of GUSTO trial that a combination of NT-proBNP, troponin T and creatinine clearance, leads to a better risk stratification, than each of them separately.

Also, Sabatine et al. [21] in OPUS-TIMI 16 and TACTICS-TIMI 18, found too than simultaneously measurement of CRP, BNP and troponin brings important prognostic information.

Zhang et al. [22] examined the inflammatory plasma cytokines: CD40, cathepsin S, chemokine ligand 16, interleukin-10, PLGF, GDF-15, matrix metallopeptidase-9, 1 and CRP in 964 patients with mild to moderate lesions and evaluated their association with the risk of cardiovascular events occurring in a follow-up of 3 years. It was concluded that CD40L, cathepsin S, PLGF and GDF-15 were useful biomarkers for predicting cardiovascular disease.

Similarly, Schnabel et al. [23] investigated 12 biomarkers linked to inflammation, lipid metabolism, renal/cardiovascular function and remodelling: CRP, GDF-15, neopterin, apolipoprotein AI, B100, cystatin C, serum creatinine, copeptin, proadrenomedullin (MR-proADM), MR-proANP (mid-region-pro-natrial natriuretic peptide) and Nt-proBNP. The study concluded that Nt-proBNP, GDF-15, MR-proANP, cystatin C and MR-proADM are the strongest predictors of cardiovascular outcomes in patients with stable angina.

Conflicts of interest

The authors declare no conflicts of interest.

The Food and Drug Administration approved in 2010 a multimarker strategy for cardiac ischemia combining EKG, troponin I and IMA with a 95% sensitivity for acute coronary syndromes [24].

Therefore, these studies have shown that multimarker approach is much more useful to predict the evolution of cardiovascular disease than individual marker approach.

CONCLUSIONS

- The role of cardiac markers in diagnosis, risk stratification and treatment of patients with cardiovascular disease is central according to the new diagnostic and treatment guidelines;
- Further investigations will clarify which of these potential markers have clinical value;
- Longitudinal studies are required to confirm whether discriminatory markers maintain long-term prognostic ability;
- The multimarker strategy can help stratify the risk of adverse cardiovascular events occurring both in the short and long term.

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