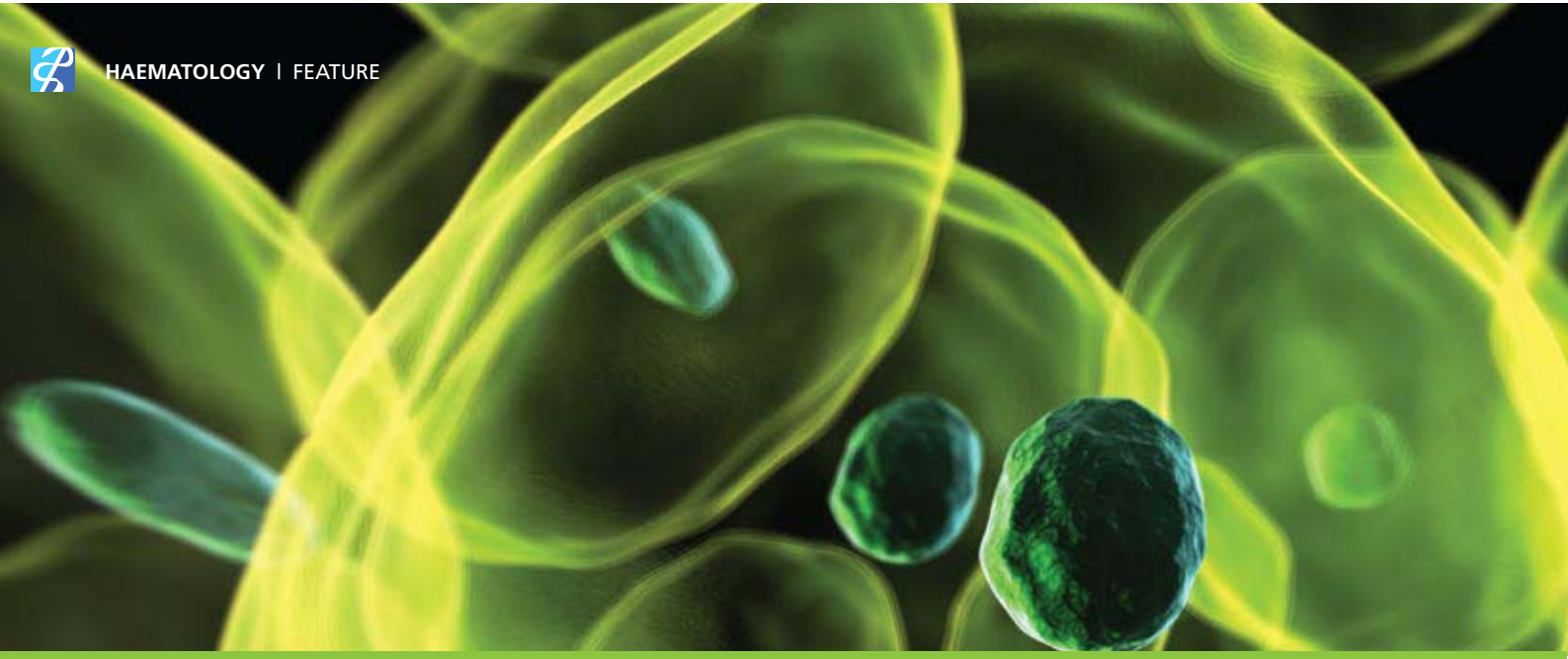

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Improved risk stratification in Acute Coronary Syndrome using a multimarker approach

Following a myocardial infarction, risk stratification and a valid prognosis are essential requirements for an optimised, individualised treatment strategy in rehabilitation and outpatient care by the family physician.

IN COMPARISON with single marker tests, simultaneous determination of selected biomarkers, especially of combined markers for myocardial cell damage (troponins), inflammation (hsCRP) and neurohumoral activation (NT-proBNP/BNP), yielded better-quality data and more reliable prognostic information as shown in recent studies (e.g. [1]). The innovative migration technology in conjunction with immuno-chemiluminescence detection proved to be particularly useful for the application of a multimarker approach. This novel method allows, within a few minutes, the simultaneous determination of relevant cardiovascular biomarkers in a single sample of whole blood and can be easily applied in a doctor's practice, intensive or emergency care unit.

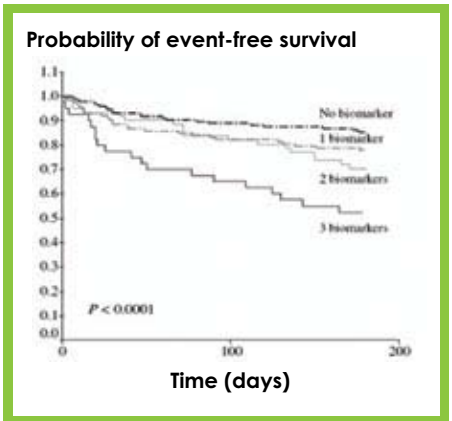

Figure 1. Histology of a resected intracranial germinoma revealing an infiltrate composed of CD20+ B cells and antibody producing CD138+ plasma cells (inset).

Current guidelines [2] state that biochemical markers, in addition to ECG, play a key role in the diagnosis and risk stratification of acute coronary syndrome (ACS) and, in particular, of non-ST-elevation-ACS (NSTE-ACS). This view is based on the findings of recent large clinical studies that were conducted to assess the diagnostic value of various cardiac markers. Biomarkers that reflect pathophysiological aspects of ACS, such as myocardial cell damage, activation of the haemostatic system, and neurohumoral activation, proved to be clinically meaningful parameters.

Myocardial cell damage induces the release of various proteins, e.g. myoglobin, CK/CK-MB or cardiac troponins. The specificity and sensitivity of troponin I and T is very high, which makes them ideal markers for the diagnosis of ACS and myocardial infarction according to a consensus document from the Joint European Society of Cardiology/American College of Cardiology Committee [3]. In patients with myocardial infarction, elevated troponin concentrations are observed 3 to 4 hours after the onset of chest pain. Myoglobin gives a first signal about 2 h earlier, but with lower cardiac specificity. The combination of myoglobin, CK-MB and troponin represents a suitable set of markers for the diagnosis and follow-up of acute myocardial infarction. An important aspect of the troponins is their prognostic power with regard to the short-term risk for myocardial infarction and death. They contribute substantially to the risk stratification of ACS [4].

Besides myocardial cell damage, the inflammatory process associated with acute myocardial infraction is another important prognostic factor. The C-reactive protein (CRP) is the most extensively studied inflammatory marker with respect to prognosis. The determination of CRP using highly sensitive assays, i.e. the determination of so-called high-sensitive CRP (hsCRP), provides a valid prognosis for long-term risk (> 6 months) in patients with ACS. The clinical relevance of hsCRP is underlined by the presence of inflammation in vulnerable plaques, which adds to the cardiovascular risk [5].

The neurohumoral activation of the heart leads to the release of the natriuretic peptides N-terminal pro-type B natriuretic peptide (NT-proBNP) and type B natriuretic peptide (BNP). Both proteins are sensitive and specific markers for left-ventricular dysfunction and are used for the diagnosis and management of heart failure. For the application by the general practitioner, the high negative predictive value is of importance because it facilitates the

» Besides myocardial cell damage, the inflammatory process associated with acute myocardial infraction is another important prognostic factor «

Figure 2. PATHFAST

exclusion of heart failure in the case of non-specific symptoms such as dyspnoea [6]. In this way, time-consuming and expensive diagnostic procedures can often be avoided. One of the main advantages of the natriuretic peptides is their high prognostic value, which even exceeds that of haemodynamic parameters like left-ventricular ejection fraction (LVEF) or maximum oxygen uptake. This holds true for chronic heart failure and also applies to coronary heart disease [7]. Thus, ACS patients with increased NT-proBNP- or BNP-values carry a 3- to 5-times higher mortality risk [8]. Moreover, in patients admitted to the emergency ward, the NT-proBNP/BNP marker allows the differentiation between cardiac and non-cardiac causes of chest pain symptoms and acute dyspnoea [9]. In this situation, it is advisable to determine also D-Dimers in order to exclude pulmonary embolism [10]. In problematic cases, the determination of the markers troponin, NT-proBNP/BNP and D-Dimer provides a diagnostic orientation already at an early stage and obviates the need for subsequent diagnostic procedures. When making a prognosis, it is also important to consider that renal impairment causes an additional increase in NT-proBNP/BNP values. Renal impairment is known to be an independent risk factor for long-term mortality in patients with ACS [11].

Based on these findings, it is obvious to suggest the simultaneous determination of several selected markers for risk stratification of ACS. In fact, it could be demonstrated that the combination of markers for myocardial cell damage (troponin I/T), inflammation (hsCRP), and neurohumoral activation (NT-proBNP/BNP) promotes a highly reliable identification of ACS patients with a high risk for subsequent cardiovascular complications. Since each marker (troponin I/T, hsCRP, and NT-proBNP/BNP) on its own is an independent predictor for death, myocardial infarction, and ACS, the simultaneous determination of the combined markers using a multimarker approach considerably increases the diagnostic sensitivity and specificity as compared to analysing these markers individually [1]. In summary, the cardiovascular risk increases with the number of elevated markers, with the cardiovascular risk being highest when all three markers are elevated (Figure 1) [12].

The findings described above were further substantiated by clinical studies so that the multimarker approach was finally incorporated in the current guidelines for diagnosis and treatment of NSTE-ACS [2]. Since diagnosis and risk stratification of acute myocardial infarction and NSTE-ACS should be performed in a timely manner and as fast as possible, the guidelines explicitly point out that point-of-care (POC) test systems must be used to determine cardiac markers at bedside if the central laboratory generally cannot provide the test results within 60 minutes at most. It is, however, required that for POC test systems only those methods be used which provide quantitative test results, as opposed to conventional qualitative or semi-quantitative quick tests. This requirement is met by the innovative migration technology of the PATHFAST system (Figure 2) [13] in conjunction with immunochemiluminescence detection. Extensive comparative studies show that this system, as a POC-test, provides results that compare well with modern laboratory analytical systems with respect to precision and validity [14]. Using this novel technology, a choice of up to 6 biomarkers can be determined simultaneously from a single whole blood sample - the test results are available already after 17 minutes of processing time. ■

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