Biomarkers: past, present, and future

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Summary

In recent decades biomarkers have become accepted tools in clinical practice [1]. Although there is no widely accepted definition of what constitutes a biomarker, for the context of this review we consider a biomarker to be a protein or other macromolecule that is associated with a biological process or regulatory mechanism. Hence measurement of this biomarker in blood, for example, might provide quantitative information that could be clinically helpful regarding this biological process or regulatory mechanism.

In this paper we review recent advances with the use of biomarkers in three major clinical areas: diagnosis of myocardial infarction, diagnosis and management of heart failure, and diagnosis and management of inflammatory conditions in general and systemic infections in particular. Although these may look like unrelated medical challenges, recent clinical research in these areas by our groups and others has opened up opportunities and challenges that seem fundamental for biomarkers in general.

Key words: biomarkers; diagnosis; prognosis; myocardial infarction; heart failure; pneumonia

Myocardial infarction

Myocardial infarction is the cause of death in more persons worldwide than any other disease [1, 2]. With effective treatment within our grasp, accurate and rapid diagnosis is of major medical and economic importance. With the development of sensitive assays depicting either cardiac troponin I or cardiac troponin T, the only current biomarkers thought to be unique to the heart, the diagnosis of myocardial infarction has been veritably revolutionised [2–5]. In a patient presenting with chest pain, a rise in cardiac troponin has become a sine qua non for the clinical diagnosis of myocardial infarction. Cardiac troponins are our current gold standard for the detection of myocardial necrosis. The more sensitive the cardiac troponin assay used, the smaller the number of dying myocardial cells necessary for this signal to be detected. This has enabled us to detect high risk acute coronary syndrome patients with only minor myocardial damage [4]. Unfortunately, current cardiac troponin assays have one major limitation in common with their predecessor (CK-MB): it takes 3–4 hours after symptom onset until cardiac troponin becomes detectable. Ongoing large clinical multicentre studies, including the Advantage Predictors of Acute Coronary Syndromes Evaluation (APACE), are assessing whether novel very high sensitivity cardiac troponin assays with or without other biomarkers reflecting different pathophysiological processes such as, for example, myeloperoxidase (reflecting plaque instability and inflammation) will significantly shorten the “troponin-blind” period. Obviously, this would constitute a major medical and economic improvement in clinical practice.

However, the development of high sensitivity cardiac troponin assays poses at least three dilemmas: first, we are unsure whether the label “myocardial infarction” is appropriate for patients with acute coronary syndromes and tiny elevations of cardiac troponin. As these patients still seem to be at increased risk of death as compared to patients without detectable cardiac troponin levels, the current ESC/AHA/ACC guidelines encourage us to do so [1–5]. Second, myocardial damage is not restricted to myocardial infarction but may also accompany other medical conditions such as septic shock, pulmonary embolism, end-stage kidney disease or acute heart failure. As we currently lack a biomarker that reliably detects plaque rupture or coronary thrombosis, we are left with our basic clinical tools, including patient history, to differentiate myocardial infarction from other causes of myocardial damage. Third, once a diagnostic test is declared “gold standard”, it becomes practically impossible to rule out definitely false positive test results. This is currently the case of cardiac troponin. We are very much of the opinion that the heart is invariably the exclusive source of cardiac troponin elevations, regardless of the specific patient condition. However, as both the ECG and imaging techniques have far lower sensitivity for myocardial necrosis than cardiac troponin, scientific proof cannot be provided.
Heart failure

Accurate biomarkers of heart failure are highly desirable tools for physicians with which either to improve their ability to make an early and accurate diagnosis or to follow positive or negative changes as a result of therapeutic intervention. The ability of physicians to make earlier diagnoses is valuable because therapeutic interventions are available that can make a significant impact on patient quality of life and cost of care [6–12]. Annual costs of heart failure in Europe and the United States are estimated at $130 billion, 70% of which is attributable to hospitalisation. Half of heart failure patients are readmitted within 6 months and 10% are readmitted twice for heart failure [8, 9]. Fewer readmissions by guided therapy methods could have a significant impact on these costs associated with this prevalent disease. Two accurate markers of heart failure have been validated in large observational and randomised controlled clinical studies [6–19]: B-type natriuretic peptide (BNP) and the amino terminal fragment of proBNP (NTproBNP). Like other hormones, BNP is processed from allegedly inactive precursor molecules. Inactive proBNP is cleaved into biologically active BNP and the inactive NTproBNP fragment. BNP is a regulatory peptide with biological effects which counterbalance the pathophysiological effects underlying heart failure. BNP and NTproBNP have both been shown to be highly specific and quantitative markers for heart failure [6–19]. BNP and NT-proBNP are extremely useful in diagnosis, risk stratification, and management of patients presenting with acute dyspnoea to the emergency department [6–14]. In addition, BNP and NT-proBNP, as quantitative markers of heart failure summarising the extent of systolic and diastolic left ventricular dysfunction, valvular dysfunction and right ventricular dysfunction [11], provide valuable information for risk stratification in patients with acute and chronic heart failure [15–19]. Although still intensively debated, BNP and NT-proBNP measurements also seem capable of improving the long-term management of patients with HF [16, 17]. Detailed recommendations on how best to apply these biomarkers have recently been provided in this journal [11]. Appropriate cut-off values have been defined in large observational studies, and evidence from large randomised controlled studies confirms both medical and economic benefit from their use. Whereas troponin has become the most sensitive test to detect myocardial necrosis, BNP and NT-proBNP are increasingly recognised as the most sensitive test to detect cardiac stress and heart failure. Their use has enabled us to detect heart failure in additional patients in classical settings (dyspnoea patients) and in additional clinical settings. BNP or NT-proBNP should therefore be included in protocols defining the gold-standard diagnosis regarding heart failure in current and future studies. Elevated levels of BNP and NT-proBNP are, for example, commonly encountered in critically ill patients with septic shock [20]. Most of these have septic myocardial depression, a condition associated with impaired outcome and classified as high-output heart failure in current guidelines on acute heart failure [21]. Treatment of heart failure in this setting is obviously very different from that in other types of heart failure. Further studies are now needed to evaluate whether increased detection and diagnosis of heart failure may translate into improvements in patient management. The use of BNP and NT-proBNP shares one important challenge comparable to that of cardiac troponins: having become the most sensitive test to detect a disorder (heart failure), other current clinically available methods, including cardiac imaging, suffer major limitation in the clarification of unexpected and potential “false positive” elevations of BNP and NT-proBNP.

Systemic inflammation and infections

The observation regarding heart failure in patients with septic shock can to some extent be generalised and constitutes one of the most intriguing findings in this area: biomarkers reflecting and quantifying cardiac stress and cardiovascular homeostasis are powerful predictors of death in patients presenting with common systemic infections such as community-acquired pneumonia [22–26]. This indicates that cardiovascular stress ultimately determines prognosis in many primarily non-cardiac conditions.

One should distinguish between the detection of an inflammatory reaction to any stimulus, since clinical signs can be very elusive, and the use of biomarkers to differentiate the type of inflammatory stimulus (e.g., viral vs. bacterial). In most institutions C-reactive protein is the biomarker of choice to detect an infection and to establish the diagnosis.

Rapid and accurate diagnosis remains the major clinical challenge and to a vast extent an unmet need in patients with an inflammatory state and suspected septic systemic infections. In view of the ambiguities of signs and symptoms of severe infection, biomarkers provide a more reliable tool in estimating the probability of the presence of a relevant bacterial infection, its severity and treatment response [27–32]. Procalcitonin and, less evidence-based, C-reactive protein, are the established biomarkers in
this setting. Cut-off ranges of both biomarkers must be chosen in the specific clinical context and they should be used as a complementary tool to reinforce the clinical diagnostic workup. As shown in the figure, the most appropriate cut-off value for procalcitonin depends on the clinical setting. Biomarkers cannot determine the causative organisms and associated patterns of antibiotic susceptibility.

If used in the proper setting, serial measurements of diagnostic biomarkers may provide an opportunity to adapt the treatment early in the course of patients with severe infections, either to intensify treatment when their levels stay high, or to avoid unnecessarily prolonged courses of antibiotics, when their levels rapidly decrease, and thereby improve the allocation of health care resources [33–35].

Different microbes may induce a distinct response in various organs, resulting in a variable repertoire of circulating biomarkers and mediators. Any infection is obviously far too complex to be reduced to a single diagnostic cut-off of any biomarker. However, the likelihood of a bacterial aetiology for an inflammatory state increases gradually with increasing serum levels of, for example, procalcitonin. Nevertheless, critically ill patients and patients after major surgery may present with very high levels of procalcitonin and no signs of infection [36]. As in patients with heart failure, the dynamics of biomarker levels have prognostic implications in systemic infections, since persistently elevated or increasing levels can be associated with an adverse outcome. Conversely, decreasing biomarker levels suggest a favourable outcome. If this is borne in mind, biomarkers can be used as valuable and helpful tools.

The definition of a gold-standard diagnosis in observational studies including patients with suspected systemic infection remains an unresolved dilemma. The causative organism of fever cannot be detected in 60–80% of patients with suspected bloodstream infection [37, 38]. Differentiating true infection from contamination after growth of common skin commensals in blood cultures, or respiratory commensals in sputum of patients with chronic obstructive pulmonary disease, poses a diagnostic headache.

Ultimately, the potential for improved clinical decision-making is the most important performance measure for a biomarker. Hence randomised intervention studies should be conducted in which the therapy is guided by a biomarker and in which the primary measure of efficacy is outcome. Given the unresolved dilemma of defining a gold-standard diagnosis in observational studies, we have decided to embark on randomised controlled studies to evaluate the clinical usefulness of procalcitonin [29–31]. Procalcitonin is a precursor peptide from the hormone calcitonin. Using a sensitive and rapid procalcitonin assay, we conceived and validated a procalcitonin-guided diagnosis and antibiotic stewardship using cut-off ranges in the continuum of lower respiratory tract infections (LRTI). Subsequent data from three randomised controlled trials suggest that the use of procalcitonin improves the diagnosis and clinical management of patients with acute respiratory tract infections, including community-acquired infections.

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**Figure 1**

Diagnostic algorithm incorporating procalcitonin levels in patients with suspected respiratory tract infection.

- **Caveats**
  - patient with respiratory tract infection
  - withhold AB therapy
  - start AB therapy
- **Clinical setting?**
  - clinical
- **Clinical diagnosis?**
  - clinical findings
  - radiological
  - microbiology
- **Goldstandard?**
  - clinical suspicion of relevant bacterial infection
  - severity of disease
- **Assay Sensitivity?**
  - procalcitonin
  - 0.1–0.25
  - 0.25–0.5
  - <0.1
  - >0.5
- **Mortality Risk?**
  - other diagnosis?
  - localised infection
  - complicated course?
  - adverse outcome?
  - follow up PCT measurements
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...diagnose, risk-stratify, and manage patients. Markers will significantly improve our ability to individual patient, and interpreted appropriately, biomarkers are indeed useful in conjunction with all other clinical information available to the individual patient, and interpreted appropriately, biomarkers are...widely available. When used in conjunction with all other routine clinical and laboratory variables available, including serial measurements of C-reactive protein. The success of this procalcitonin algorithm was measured by clinical outcomes, assuming that if the patient recovered without antibiotics then there was no serious bacterial illness. This circumvented the problem of the non-existent diagnostic "gold standard" based on traditional criteria. Specifically, in the ProRESP study, procalcitonin guidance reduced antibiotic prescription in 243 patients with LRTI by almost 50% [29]. In the ProCAP study, procalcitonin-guided antibiotic duration was shortened by 65% from 12.9 to 5.8 days with a similar outcome in patients with all severities of community-acquired pneumonia [30]. In the ProCOLD-study we demonstrated long-term safety with a similar readmission rate over 6 months in over 200 acute exacerbations of chronic obstructive lung disease, with markedly reduced, procalcitonin-guided antibiotic use of 40% as compared to 72% in the control group [31]. The additional value of these novel biomarkers in the careful clinical assessment of LRTI is currently addressed in the large multi-centre “ProHOSP”-trial (http://www.controlled-trials.com/ISRCTN95122877).

A high degree of clinical suspicion must remain when empyema is considered. We have evidence from those patients who developed empyema in our intervention studies [29–31] that empyema as a localised complication of pneumonia is typically associated with fever, variably elevated C-reactive protein, but relatively low procalcitonin levels. Caution is also required in settings where infection with coagulase negative staphylococci or some intracellular bacteria (ie, Mycoplasma pneumoniae) are suspected [27–32]. These are often associated with low procalcitonin concentrations and may be overlooked using standard assays with a functional assay-sensitivity of >0.1 ug/L. Using an ultrasensitive assay, procalcitonin was found to be the best discriminator of contamination versus infection with coagulase negative S. aureus and of infectious arthritis respectively [39, 40]. Also, we think it is important to stress that no biomarker is sensitive enough to definitely rule out bacterial infection. Thus current data is insufficient to withhold antibiotic therapy in a critically ill patient with suspected sepsis on the basis of a single measurement of any biomarker. Follow-up measurements are required in these patients during immediately instituted antibiotic and early goal-directed therapy. If, however, follow-up levels of procalcitonin remain low, the likelihood of a clinically relevant infectious cause being present becomes marginal and early termination of antibiotic therapy and an alternative diagnosis should be considered.

Outlook

Various factors make it highly probable that the use of biomarkers will further increase in clinical practice. In many areas, biomarkers are far better validated than, for example, imaging techniques. Biomarkers are relatively inexpensive, are not associated with harm or risk to the patient, such as, for example, radiation exposure, and are widely available. When used in conjunction with all other clinical information available to the individual patient, and interpreted appropriately, biomarkers will significantly improve our ability to diagnose, risk-stratify, and manage patients.

References


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