REVIEW

Biomarkers in emergency cardiology: cardio-pulmonary resuscitation, acute coronary syndromes, pulmonary thromboembolism, acute aortic syndrome and acute heart failure

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Abstract: Biomarkers have been accepted into daily clinical practice for several decades and are now widely used in the field of emergency cardiology, as a tool for quick diagnosis of some acute critical conditions requiring an early and adequate therapeutic approach. At first, they were frowned upon ("guessing in the blood sample") and then they were used indiscriminately (creating a new so-called disease - "troponinitis" etc). Utilization for diagnosis, risk stratification or treatment strategy purposes requires an appropriate selection of the biomarkers, assuming specific variations in different clinical conditions. The development of these biomarkers have often caused another problem concerning the need for a more cautious interpretation, adapted to the type of patient with single-organ vs multi-organ failure who will require a quantitative multimarker high sensitivity approach: in this case point-of-care assessment is not enough. Reviewing the latest *European Society of Cardiology* (ESC) and *European Resuscitation Council* (ERC) Guidelines on acute cardio-vascular conditions (ESC Guidelines for STEMI–2012, ESC Guidelines for acute pulmonary thromboembolism and Guidelines on the diagnosis and treatment of aortic diseases date from 2014, ESC Guidelines for NSTEMI and cardiac arrest from 2015 and ESC/HFA Guidelines for acute heart failure from 2016) we noticed the considerable proportion achieved by biomarkers as components of decision making in diagnostic, prognostic and therapeutic approaches. Some biomarkers are mentioned in almost all of these Guidelines (natriuretic proteins and cardiac troponins), while copeptin, H-FABP and GFD-15 are more and more frequently referenced in different acute critical conditions and, obviously, a number of particular biomarkers are specific only to certain acute situations (e.g. NSE, S100B in resuscitation, ST2, adrenomedullin and galactin-3 in heart failure). Clearly, it has lately become difficult to contest the role of biomarkers as biological signals that have to be taken into account in daily practice.
Keywords: biomarkers, emergency cardiology, resuscitation, acute coronary syndromes, pulmonary thromboembolism, acute heart failure, acute aortic syndromes

Rezumat: Biomarkerii au fost acceptați în activitatea clinică zilnică de mai multe decenii și sunt acum utilizați pe scară largă în domeniul cardiologiei de urgență, ca instrument de diagnosticare rapidă a unor condiții critice acute care necesită o abordare terapeutică precoce și adecvată. Primiți la început cu circumspecție (un soi de "ghicit în proba de sânge") au fost folosiți ulterior nediscriminatoriu (punând bazele unei pseudo-afecțiuni noi, așa-numită "troponinită" etc). Utilizarea în scop

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diagnostic, de stratificare a riscului sau de stabilire a strategiei terapeutice necesită o selecție adecvată a acestor biomarkeri care prezintă, de altfel, variații specifice în diverse situații clinice. Extinderea utilizării acestor biomarkeri a generat și o serie de dileme referitoare la necesitatea interpretării mai prudente, adaptată tipului de insuficiență unică de organ versus afectarea multi-organ, ceea ce ar impune o abordare cantitativă de înaltă sensibilitate tip multimarker: în aceste cazuri determinările doar *point-of-care* nu sunt suficiente. Trecerea în revistă a ultimelor ghiduri de practică medicală elaborate de către *Societatea Europeană de Cardiologie* (ESC) și *Consiliul European de Resuscitare* (ERC) privind afecțiunile cardiovasculare acute (Ghidul ESC pentru STEMI-2012, Ghidul ESC pentru tromboembolismul pulmonar acut și Ghidul pentru diagnosticul și tratamentul afecțiunilor aortice din 2014, Ghidul ESC pentru NSTEMI și stopul cardiac din 2015 și ghidul ESC/HFA pentru insuficiența cardiacă acută din 2016) permite a se observa ponderea tot mai importantă ocupată de către biomarkeri ca și componente ale procesului de luare a deciziilor în cursul abordărilor diagnostice, prognostice sau terapeutice. Unii biomarkeri sunt menționați în aproape toate aceste ghiduri (proteinele natriuretice și troponinele cardiace), în timp ce copeptina, H-FABP și GFD-15 sunt din ce în ce mai frecvent menționați în variate situații critice acute iar un număr de biomarkeri particulari sunt specifici numai unor anumite situații acute (de exemplu NSE, S100B în resuscitare, ST2, adrenomedulina și galactina-3 în insuficiența cardiacă). Evident, în ultimul timp a devenit dificil de contestat rolul biomarkerilor ca semnale biologice care trebuiesc luate în considerare în practica clinică zilnică.

Cuvinte cheie: biomarkeri, cardiologie de urgență, resuscitare, sindroame coronariene acute, tromobembolism pulmonar, insuficiență cardiacă acută, sindroame aortice acute

INTRODUCTION

Emergency medicine is an officially recognized medical specialty in many countries and is already pivotal in pre-hospital and Emergency Department settings. Chest pain, dyspnea, syncope and cardiac arrest are often reasons for hospitalization in the Cardiology Department or may occur during hospitalization. A significant and delicate part of our daily activity in an ordinary cardiology clinic is dedicated to managing cardiovascular emergencies. Nowadays, biomarkers complement clinical assessment, 12-lead ECG and emergency imaging in the diagnosis, risk stratification and treatment of patients with acute cardiac syndromes[1]. Acute coronary syndromes (ACS), acute heart failure (AHF), acute pulmonary thromboembolism (PTE) and cardiac arrest are diagnoses that cause the most common challenges for any contact points with medical emergencies: pre-hospital, Emergency Department, Intensive Cardiac Care Units or cardiac wards. Of course, numerous cardiovascular biomarkers are now available even in primary care medicine. By adopting easy to use Point-of-Care (POC)-instruments, numerous false-positive ACS, AHF, and PTE diagnoses were avoided, offering more appropriate ruling in/out arguments[2].

Moreover, biomarkers are mainly involved in cardiac arrests, alongside clinical examination, electrophysiology, and imaging, in a multimodal approach[3] within the "fine art of prognostication"[4].

The notion of "biomarker", already introduced in 1980, is considered to be, in the broad sense, "a characteristic that is objectively measured and evaluated as an indication of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"[5] with the aim to improve prevention, prediction, diagnosis, and prognosis of cardiovascular disease and, last but not least, to decrease the related costs.

Interest in using an improved diagnostic test in the emergency department and in the intensive cardiac care unit implies the need to reduce the use of hospital resources and associated costs using three main approaches: by providing arguments for early initiation of a highly effective therapy, thereby reducing the tendency of worsening patient clinical status and the development of complications, by eliminating the need for other, more expensive explorations, or by providing an alternative diagnosis allowing patient treatment in the Emergency Department or as an outpatient[6].

For instance, the use of a 3-in-1 point-of-care testing (POCT) for cardiac troponin T (cTnT), N-terminal pro-brain natriuretic peptide (NT-proBNP) and D-dimer in cardiovascular risk stratification at primary care level for diagnosing acute coronary syndromes (ACS), heart failure (HF) and thromboembolic events (TE) highlights the potential for substantial health-economic savings[7].

In a more strict sense, but adapted to current main research directions using improved automated analytical methodologies, "biomarkers" are those markers which are measured in biological specimens, such as cells or serum (e.g. microparticles, circulating microRNAs, blood transcriptomes, proteomics, metabolomics, lipidomics etc.)[8], pieces of information "written in blood"[9].

A current selection of the most reliable biomarkers requires completion of 9-step criteria for their evaluation: 1. proof of concept, 2. prospective validation, 3. establishing their incremental value, 4. clinical usage, 5. clinical outcomes, 6. cost-effectiveness data, 7. ease of use, 8. methodological consensus and establishment of reference values (or, at least, cut-off values)[10] (Table 1).

Biomarkers are used as a diagnostic tool according to specific rule-in/rule-out protocols that have been validated in clinical studies. On the one hand, the transfer of a potential reproducible, specific and sensitive biomarker from discovery to clinical practice (bench-to-bedside) is not a simple process, mostly filled with pitfalls and limitations, which can be removed through a suite of strategies: improve the assay, combine several markers, check for subpopulations and stratify population[11].

On the other hand, in 2001, at a meeting of the American College of Cardiology, Robert Wilcox (quoted by Marc S. Sabatine)[12] introduced (obvious ironically) new medical terms to which he added explanations:

- "Troponinite (tro'-po-nin-ite)[13] n. a patient with low clinical probability of ischemia who is victimized by reflex responses to inconsequential borderline elevation of the cardiac troponins".
- "Troponinister (tro'-po-nin-is"-ter) n. a staunch (n.n. Wilcox use the term "rabid"), misguided advocate of the importance of troponins".

Far from being seen at present as "icing on the cake", increased biomarker levels must be interpreted only in a clinical context, otherwise, as it was bluntly put by DB Mark, "looking at biomarkers (A/N) in isolation may thus be akin to seeing smoke trailing out of the window of a house without having any notion of what is on fire, where that fire is, or how it can be extinguished"[6].

The progression of all of these biomarkers has often caused considerable difficulties to the critical care physician who deals with multiorgan failure[14]. Some concentrations frequently lead to a more cautious interpretation and subsequent changes in therapeutic decisions rather than to the emergency physician who usually deals with patients presenting with chest pain, breathlessness or other single-organ pathology (Table 2). Depending on whether biomarkers are organ specific vs. unspecific and disease specific vs. unspecific, their incremental clinical value (whether it is diagnostic, prognostic or serves to guide therapy) increases.

Since these are components of patient management more and more frequently mentioned in daily practice, it would be useful to review the place of biomarkers in the current Guidelines on acute cardiac conditions (cardio-pulmonary resuscitation, acute coronary syndromes, pulmonary thromboembolism, and acute heart failure).

Table 1. Biomarkers evaluated for CPR / ACS / PTE/ AHF/AAS

Troponin (cTn)
Copeptin
Natriuretic peptides (NPs - B-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide and midregional pro-A-type natriuretic peptide)
Heart Fatty Acid-Binding Protein (H-FABP)
Serum neuron specific enolase (NSE)
Astroglial protein S100B
Growth Differentiation Factor 15 (GDF-15)
High-sensitivity C-reactive protein
Midregional pro-adrenomedullin
Matrix metalloproteinase-9 (MMP-9)
Ischaemia-modified albumin
Procalcitonine – PCT
Glycogen phosphorylase isoenzyme BB (GPBB)
Unesterified free fatty acids
Myeloperoxidase
Soluble CD40 ligand
Placental growth factor
Pregnancy-associated plasma protein-A (PAPP-A)
Choline
Vascular endothelial growth factor receptor 1 (fms-like tyrosine kinase, Flt-1)
Prothrombin fragment 1 and 2 (f1.2)
Thrombus precursor protein (TpP)
P-selectin
Circulating microRNAs

BIOMARKERS IN EMERGENCY CARDIOLOGY: CARDIAC ARREST AND CARDIO-PULMONARY RESUSCITATION

Biomarkers (cardiac, neurological and inflammatory) represent a growing area of interest in the heterogenous field of cardiac arrest, as they may provide the rescuers with early and valuable information on the severity of organ dysfunction in order for them to make a decision on clinical strategies and prognosticate outcomes[17], even a decision on withdrawal of care, if this is admissible from a legal point of view.

The most commonly used biomarkers to assess the degree of organ damage after cardiac arrest explore[17]:

- the brain status (e.g. a neuronal isoform of the glycolytic enzyme enolase - NSE that is involved in glucose metabolism, an intracellular calcium-binding dimer implicated in neuronal differentiation and proliferation - protein S100B, the Glial

Table 2. Causes of elevated concentrations of cardiac troponin and natriuretic peptides (other than acute coronary syndromes)[15,16]

Causes of elevated concentrations of cardiac troponin	Causes of elevated concentrations of natriuretic peptides
Cardiac • Coronary spasm • Tachy- and bradyarrhythmia • Heart failure (acute or chronic) • Pulmonary embolism • Severe pulmonary hypertension • Myocarditis • Tako-Tsubo cardiomyopathy (stress-induced cardiomyopathy) • Aortic dissection, aortic valve disease, or hypertrophic cardiomyopathy • Hypertensive emergencies • Cardiac contusion • Cardiac procedures (CABG, PCI, ablation, pacing, cardioversion, endomyocardial biopsy) • Infiltrative diseases (e.q. amyloidosis, haemochromatosis, sarcoidosis, scleroderma) • Myocardial drug toxicity and poisoning (e.q. doxorubicin, 5-flourouracil, snake venoms)	**Cardiac** • Heart failure (acute or chronic) • Atrial and ventricular tachyarrhythmias • Pulmonary embolism • Severe pulmonary hypertension • Myocarditis • Left ventricular hypertrophy • Hypertrophic or restrictive cardiomyopathy • Valvular heart disease • Congenital heart disease • Cardiac contusion • Cardioversion, ICD shock • Cardiac surgical procedures involving the heart
Non-cardiac • Acute neurological event (e.g. ischaemic stroke or subarachnoid haemorrhage) • Renal dysfunction • Hypo- and hyperthyroidism • Extreme endurance efforts • Rhabdomyolysis • Critical illness (e.g. shock/ sepsis/ burns if affecting >30% of body surface area)	**Non-cardiac** • Advanced age • Acute neurological event (e.g. ischaemic stroke or subarachnoid haemorrhage) • Renal dysfunction • Liver dysfunction (mainly liver cirrhosis with ascites) • Severe metabolic and hormone abnormalities (e.g. thyrotoxicosis, diabetic ketosis) • Paraneoplastic syndrome • Chronic obstructive pulmonary disease • Anaemia • Critical illness (e.g. shock/ sepsis/ burns if affecting >30% of body surface area)

Fibrillary Acidic Protein – GFAP, a monomeric intermediate-filament component of the astrocytic cytoskeleton, the Brain-Derived Neurotrophic Factor – BDNF, a brain glutamic oxalic transaminase, lactate dehydrogenase and lactate in the cerebrospinal fluid, Neural Cell Adhesion Molecule - N-CAM, also called CD56 and selectins).

- the heart status (cardiac troponin - cTnI, cTnT and brain natriuretic peptide – BNP, creatine kinase – CK).
- the inflammation status that contributes to the development of exaggerate Systemic Inflammatory Response Syndrome - SIRS after cardiac arrest, so-called "sepsis-like syndrome"[18], indirectly reflecting the peripheral circulation status as early as 3 hours after cardiac arrest (C-Reactive Protein - hsCRP, Tumor Necrosis Factor - TNF-α, Interleukin IL-1β, -6, -8, procalcitonine – PCT, soluble Triggering Receptor Expressed on Myeloid cells 1 -sTREAM-1).

Plasma cytochrome c may have been studied in rats as a novel *in vivo* marker of mitochondrial injury after resuscitation from cardiac arrest that relates inversely with survival outcomes[19], but this has not been proven in studies on human subjects[20].

European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care (2015)[21] stated that after cardiopulmonary resuscitation a multimodal approach to prognostication is essential and includes: clinical examination, electrophysiology, biomarkers and imaging.

Cardiac biomarker testing (troponine and CK-MB) should quickly be evaluated in all patients who arrived/ developed a cardiac arrest in the Emergency Department associated with chest pain[22].

Cautionary, in case of cardiopulmonary resuscitation (CPR) two elements must be well-known[23]:

- the delay in release of biomarkers from damaged myocardium makes the certification of acute myocardial infarction diagnosis difficult in the first hours after the onset of symptoms;
- the sensitivity and specificity of the link between biomarkers and the acute coronary artery occlusion as the cause of cardiac arrest are low,

as many other factors can be involved: myocardial injury during resuscitation maneuvers and defibrillation, the duration of resuscitation or of cardiac arrest with diffuse myocardial hypoperfusion, especially if a coronary artery disease is present in the patient's history.

The values of hs-TnT. even if they are elevated in patients with out-of-hospital cardiac arrest ventricular fibrillation or tachycardia, do not improve risk prediction either, as showed by the data from the prospective FINNRESUSCI study[24].

It was believed that percutaneous coronary interventions (PCI), especially if performed early after hospital admission, could influence troponin levels after a cardiac arrest/CPR, but in a small study PCI did not significantly alter serum levels of cardiac markers (cTnI) in patients with AMI compared with those with non-ST elevation CA[25].

The predictive value of NT-pro-BNP/BNP in cardiac arrest/CPR is altered by many factors (myocardial stretching, chronic obstructive pulmonary disease, pulmonary thromboembolism, thyroid disease, sepsis, renal failure), but high BNP levels have been associated to poor outcomes without knowing yet exactly if elevated levels reflect the presence of an significant cardiac overload after global ischemia or just quantify the extent of brain damage[26].

NSE and S-100B are protein biomarkers released following injury to neurons and glial cells, respectively, that are likely to correlate with the extent of anoxic–ischaemic neurological injury and with the severity of neurological outcomes, but hemolysis in blood samples may lead to a potential misclassification prognosis for NSE levels and will not affect S100B values[17,27].

The advantages of the two already mentioned neurological biomarkers compared to both electroencephalography and clinical examination are that they provide quantitative results and they are sedatives effects free. It should be noted, however, that only the combination of these biomarkers with other diagnostic tools (e.g., SSEP, EEG, MRI and clinical examination) could significantly improve their sensitivity and specificity in predicting outcomes after cardiac arrest/CPR and none of these biomarkers can predict a good cerebral post CPR outcome[17]. In addition, it is difficult to find a cut-off value accurate enough to identify patients with a poor outcome with a high degree of certainty and the NSE levels may be significantly reduced during therapeutic hypothermia[28]. Hence, NSE above 28 microg/l at 48 h and a rise in NSE of more than 2 microg/l between 24 and 48 h were markers for a poor outcome after cardiac arrest and induced hypothermia[29].

The combination of brain CT and serum NSE improves the prognostic performance when compared to either alone in predicting poor neurologic outcome in cardiac arrest patients treated with therapeutic hypothermia[30].

Increasing NSE levels are more suitable than its absolute serum levels for the prediction of poor neurologic outcomes[31].

Biomarkers, Somatosensory Evoked Potentials (SSEP) and imaging studies may play a prognostication role in patients with prolonged sedation and/or paralysis, since they are insensitive to drug interference[22].

Only procalcitonin (PCT) as biomarker of inflammation seems to have some correlation with poor outcomes, but, as with other inflammatory markers, sepsis acts as camouflage in the prognostication of patients with hypoxic encephalopathy[32].

Circulating microRNAs (miRNAs), non-protein coding RNA molecules that are evolutionarily conserved and ubiquitously expressed as regulators of gene expression, are released very early after cardiac injury and may be useful predictors of neurological outcomes and survival after cardiac arrest[33].

BIOMARKERS IN EMERGENCY CARDIOLOGY: ACUTE CORONARY SYNDROMES

Along with acute dyspnea and often associated to this, acute chest pain is one of the most common emergency complaints: around 10 million patients per year in Europe and 8 million in the US[34,35]. Therefore, errors can occur: on the one hand, only approximately one-third of patients are diagnosed with an ACS, on the other hand, among patients who are diagnosed with non-cardiac chest pain, 1-4% actually have ACS, making these missed diagnoses a reason for increased mortality[36].

ST elevation myocardial infarction (STEMI)

Nowadays, biomarkers make the distinction between the occurrence of just ischemia or necrosis in acute coronary syndromes, and therefore the current international consensus definition ("universal definition of myocardial infarction") states that the term "acute myocardial infarction" should be used only when there is evidence of myocardial necrosis in a clinical setting where myocardial ischaemia occurred[37].

As set forth by all current guidelines, a combination of criteria is required to meet the diagnosis of acute

myocardial infarction". The detection of rise and/or fall of cardiac biomarker values (preferably any member of the troponin familly: hs+/- T, I,) with at least one value above the 99th percentile of the upper reference limit is essential, associated with at least one of the following[38]:

- symptoms of ischaemia;
- new or presumably new significant ST-T changes or new LBBB;
- development of pathological Q waves in the ECG;
- imaging evidence (usual echocardiographic) of new loss of viable myocardium, or new regional wall motion abnormality;
- identification of an intracoronary thrombus via angiography or autopsy.

Cardiac biomarkers should be measured in all patients who present with chest discomfort consistent with ACS (Level of Evidence: B)[39].

Blood sampling for serum markers is routinely carried out in the acute phase, but one should not wait for the results before initiating reperfusion treatment. Troponin (T or I) is the biomarker of choice, with a proven higher sensitivity and specificity for cardiomyocyte injury than creatine kinase (CK), its MB isoenzyme (CK-MB) and myoglobin[8].

The development of high-sensitivity (hs) assays for troponin I and T has improved the diagnostic sensitivity for acute myocardial infarction, decreased the time to diagnosis (cardiac troponins rise rapidly, usually within 1 h after symptom onset, but remain still elevated for a variable period of time, usually several days) and led to quicker rule-out of myocardial ischaemia[8].

High-sensitivity assays allow overcoming the sensitivity-deficit of the cTn assays available at that time resulting in the "troponin-blind period" and are recommended over less sensitive ones. In a study that revealed correlation between the angiographic culprit lesions and cardiac biomarkers hs-TnT had the highest sensitivity for prediction of lesions requiring emergency PCI and heart-type fatty acid-binding protein (H-FABP) displayed significant correlations with a number of diseased vessels and the presence of a thrombotic lesion[40].

CK-MB shows a more rapid decline after acute myocardial infarction (CKMB is released within 2-4 hours, peaks at 24 hours following pressure overload or ischemia, and returns to normal by 36-72 hours) as compared with cardiac troponin (an increase occurring 2-4 hours after symptoms and remaining elevated for 7-14 days)[41] and may provide added value for the timing of myocardial injury and the detection of early reinfarction[14].

The assessment of copeptin, the C-terminal part of the vasopressin prohormone, may quantify the endogenous stress level in multiple medical conditions (e. g. cardiac ischemia). Copeptin may be used in addition to high-sensitivity cardiac troponin for the early rule-out of MI[42].

Natriuretic peptides rise in response to increased myocardial wall stress[14]. The precursor peptide of BNP stored in granules of ventricular myocytes is cleaved in response to wall stress and myocyte stretch into its physiologically active hormone, B-type natriuretic peptide (BNP) and N-terminal pro-BNP – BNP, both being released simultaneously into the serum as result of increasing hemodynamic stress and cardiac ischemia[43].

However, many studies have established the role of natriuretic peptides in diagnosing, staging, making admission/discharge decisions and identifying patients at risk for adverse clinical events in various acute critical conditions. Normal levels have robust negative predictive value. There are certain limitations in using these biomarkers.

Although studies did not meet sensitivity/specificity criteria for the use of BNP or NT-proBNP in the diagnosis of ACS, they supported the addition of BNP as part of a multimarker approach with TnI, CK-MB and myoglobin to increase the sensitivity of diagnosing AMI from 86% to 100% in chest pain patients presenting to the emergency department without any clinical signs of congestive heart failure[43].

Associated clinical conditions such as advanced age, obesity, tachyarrhythmia, LV hypertrophy, renal dysfunction and some therapeutic resources may influence NPs levels. Even though for acute heart failure some limits are set, there are no definitive cut-off values in patients with signs and symptoms of heart failure following acute myocardial infarction[39].

Heart Fatty Acid-Binding Protein (H-FABPs) are small cytosolic proteins that are important in the transport of long-chain fatty acids in cardiac myocytes. After cardiac ischemia and subsequent cell membrane damage, H-FABP is released into the extracellular space within 1-3 hours, returning to normal within 12-24 h[14,43]. The diagnostic sensitivity of H-FABP for cardiac injury is 93.1%, higher than CK-MB, cTn and myoglobin for the early diagnosis of AMI within first 6 hours of chest pain[44,45].

H-FABP has shown no additional diagnostic value in patients suspected of acute coronary syndrome

presenting to the emergency department when hs-cTnT measurements are also available[46]. The Matrix MetalloProteinase (MMPs) family consists of enzymes involved in extracellular matrix degradation[47]. In the setting of myocardial infarction, coronary mast cells accumulate at the site of an eroded or ruptured plaque as part of an inflammatory response and release proteases that degrade the extracellular matrix via activation of MMPs, particularly MMP-9. MMP-9 is considered a proximal biomarker (shows a close relationship with its target disease) for cardiac remodeling and a distal biomarker (exhibits non-targeted disease modifying outcomes) for inflammation[48].

Higher levels of Growth Differentiation Factor-15 (GDF-15) in patients with ACS are associated with raised risks of all types of major non-CABG-related bleeding, spontaneous MI and stroke, as well as CV disease and total mortality beyond established risk factors, 1 SD increase in ln GDF-15 being associated with increased risk of major bleeding and with a similar increase in risk across different bleeding locations[49].

Non-ST-Segment Elevation ACS (Non-STE-ACS)

Although the names of the two clinical Non-STE-ACS entities include an ECG pattern, at the myocardial level cardiomyocyte necroses express themselves through biomarker release: NSTE-myocardial infarction (NSTEMI) and myocardial ischaemia without cell loss (unstable angina - UA)[50].

Biomarkers (mainly troponin) join clinical assessment and 12-lead ECG (the right and posterior lead can also be helpful) in the diagnosis, risk stratification and treatment of patients with suspected Non-STE-ACS[38].

In the last ACCF/AHA Guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction[51] once it has been established that no biomarker of myocardial necrosis has been released (based on 2 or more samples collected at least 6 h apart, with a reference limit of the 99th percentile of the normal population), the patient with ACS may be considered to have experienced unstable angina (UA), whereas the diagnosis of NSTEMI is established if a biomarker has been released.

The UA Guidelines affirm, with a Level of Evidence B, that, taking into account the uncertainties often present with the exact timing of onset of pain and the sensitivity, precision, and institutional norms of the assay being utilized, as well as the release kinetics of the biomarker being measured, patients with negative cardiac biomarkers within 6 h of the onset of symptoms consistent with ACS should have biomarkers re-measured in the time frame of 8 to 12 h after symptom onset[51].

NSTEMI can already be ruled-out upon presentation, if the hs-cTn concentration is very low. NSTEMI can also be ruled-out by the combination of low baseline levels and the lack of a relevant increase within 1 h / 3 h ("rule-in" and "rule-out' algorithms). 0 h and 1 h/3h refer to the time from the first blood test[50].

"0 h/1 h algorithm" when high-sensitivity cardiac troponin assays are available is based on two concepts[52]:

- hs-cTn is a continuous variable and the probability of acute myocardial infarction increases with increasing hs-cTn values;
- early absolute changes of the levels within 1 h can be used as surrogates for absolute changes over 3 h or 6 h.

Cut-off levels are assay-specific.

Recently, C. Műller highlighted seven clinical rules that may help to ensure best-contemporary clinical use of hs-cTn blood concentrations in the early diagnosis of acute myocardial infarction[39]:

1. First, do not forget the patient! Early diagnosis is based on the careful integration of all information derived from detailed clinical assessment, ECG patterns and the blood concentration of cardiac troponin (cTnT or cTnI).

2. Do not forget the ST-segment elevation! Both hs-cTn 0 h/3 h or 0 h/1 h-algorithms are applied after the initial 12-lead ECG has ruled-out the presence of significant ST-segment elevation, which should trigger emergency myocardial revascularization.

3. Do not forget the pre-test-probability! Do not measure cTn in critically ill patients in the intensive cardiac care unit, unless there is a high pre-test-probability for acute myocardial infarction, because many other causes of cardiomyocyte damage can generate very low-positive predictive values of elevated hs-cTn blood concentrations.

4. Do not forget the staff training! The proper education and training of nurses and juniors doctors avoid difficulties in implementing the hs-cTn assay and/or the hs-cTn 0 h/1 h-algorithm.

5. Keep calm and carry on! hs-cTn assays allow for a shorter time interval to the second cTn measurement after 1, 2, or 3 h reducing time to diagnosis and/or right management, stay and costs in the Emergency Department.

6. Being troponin-positive is not enough! hs-cTn is a quantitative marker of cardiomyocyte injury, the higher its blood concentration, the higher the likelihood for acute myocardial infarction and vice versa. Moreover, very low hs-cTn concentrations at presentation have shown a very high negative predictive value for acute myocardial infarction and were associated with extremely low mortality rates at 30 days.

7. Nothing is 100%! Both the hs-cTn 0 h/3 h- and 0 h/1 h-algorithms allow for a safe and early triage of patients, but do not allow for a 100% diagnosis label. Coronary angiography should be considered in patients for whom there is a high degree of clinical suspicion of N-STE-ACS, while in patients with low to intermediate likelihood for this condition, computed tomography (CT) coronary angiography is a solution to keep in mind.

A useful piece of information is that high-sensitivity cardiac troponin assays also maintain high diagnostic accuracy in patients with renal dysfunction, but "assay-specific" optimal cut-off levels, which are higher in patients with renal dysfunction, should be used[54].

Multiple biomarkers have been associated with mortality in NSTE-ACS: the natriuretic peptides (i.e. B-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide and midregional pro-A-type natriuretic peptide) provide prognostic information on top of cardiac troponin, the high-sensitivity C-reactive protein and novel biomarkers such as midregional pro-adrenomedullin (MPAM), growth differentiation factor 15 and copeptin[55].

However, because these biomarkers have not shown to improve patient management or to increase additionally the short and mid-term prognostic, their routine use cannot be recommended by the Guidelines in the meantime.

Large cohort studies have shown that, even in the range of "normal values", detectable levels of hs- cardiac troponin I identify individuals with cardiac risk for adverse cardiovascular events, even if not diagnosed with acute myocardial infarction, as this may reflect myocite stress[56]. Therefore, hs-cardiac troponins, may lack specificity, but the sensibility is critical important, when used for the diagnosis of acute myocardial infarction. At this point, the most accurate test that can be used for the diagnosis of acute myocardial infarction remains the assessment of cardiac troponins[57]. Current guidelines make recommendations over the use and interpretation for each assay in particular[58]. At the same time, hs-troponins and troponins allow a good negative predictive value, when adequately used (different time frame strategy: 2 test at 1-3 hours vs. 3 tests at 6 hours).

BIOMARKERS IN EMERGENCY CARDIOLOGY: BIOMARKERS IN ACUTE AORTIC SYNDROMES

Aortic dissection also involves an inflammatory response that precludes the dissection, but having a role in the destruction of the median tunic and which is further increased after it occured[59]. Once aortic dissection has occured, there is injury and destruction of the smooth muscle cells which release into the blood flow preoteolysis products and, on the other hand, there are lytic processes of the thrombus in the false lumen[59].

The most important markers used in patients with aortic syndromes are D-dimers. D-dimers (consist of two cross-linked D fragments from fibrinogen) are produced as a consequence of the activation of coagulation when generation followed by degradation of cross-linked fibrin take place[60]. But as there is a close connection between inflammation and coagulation, D-dimers are not just markers of fibrinolysis[60]. Also the values are expected to be increased in the elderly and women[61]. Their levels increase rapidly, up to one hour, adding great utility to fast diagnosis[59,62]. But negative D-Dimers (using the same cut-off value as in pulmonary embolism - 500 ug/l, while having higher negative predictive value for values <100 ug/l) should only rule out an aortic syndrome, in those patients with a low clinical probability; they have no incremental diagnostic value when high risk patients are evaluated[62,63]. Also D-Dimers should not be used in pregnancy, malignancy, infections, post-surgery, trauma (<4 weeks) or liver cirrhosis as they lack specificity[60]. There is data on the prognostic value in patients that have been treated with endovascular aortic repair as high persistent values (more than 20 days) have been associated with increased mortality[59]. However, It should be noticed, that the different assays for the detection of D-Dimers are not well standardized and they should be interpreted with caution, according to clinical practice guidelines[59,60,64].

Several other biomarkers have been investigated for making an early diagnosis, for the monitoring and establishing the prognosis:

- markers of the destruction of smooth muscle cells (smooth muscle myosin) or the the vascular interstitium (calponin, matrix metalloproteinase 8);

- structural proteins of the aorta - soluble fragments of elastin (although its levels increase in less than an hour, the abnormal values are close to the normal interval);
- inflammation markers - C reactive protein (its peak level correlates with a tendency to increased remodelling), tenascin-C;
- circulation beta-TGF[59,65].

BIOMARKERS IN EMERGENCY CARDIOLOGY: PULMONARY THROMBOEMBOLISM (PTE)

Right ventricular pressure overload is associated with increased myocardial stretch, which leads to the release of brain natriuretic peptide (BNP) or N-terminal (NT)-proBNP - markers of right ventricular dysfunction[66]. Markers of right ventricular (RV) dysfunction and the markers of myocardial injury are utilized in the classification of patients with acute PTE based on early mortality risk[66]:

- patients with RV dysfunction (on echocardiography or CT angiography) and elevated cardiac biomarker levels (particularly a positive cTn test) should be classified into an intermediate-high-risk category;
- patients in whom the RV is normal (on echocardiography or CT angiography), and/or have normal cardiac biomarker levels, belong to an intermediate-low-risk group.

In patients at intermediate risk, that is the risk category most difficult to characterize in terms of prognosis, assessment of the right ventricle using echocardiography or CT and of myocardial injury using a laboratory biomarker, should be considered for further risk stratification, finding quoted in the last Guidelines for diagnosis and treatment of PTE in the class of recommendation IIa, level of evidence B[67].

A meta-analysis found that 51% of 1132 unselected patients with acute PTE had elevated BNP or NT-proBNP concentrations on admission, which is associated with a 10% risk of early death and a 23% risk of an adverse clinical outcome[68]. However, in normotensive patients with PTE, the positive predictive value of elevated BNP or NT-proBNP concentrations for early mortality is low[69], and suggesting that higher cut-off values should be considered. In a prospective, multicentre cohort study that included 688 patients, using a stepwise approach based on the simplified Pulmonary Embolism Severity Index (PESI score), NT-proBNP ≥600 pg/mL was identified as the optimal cut-off value for the identification of elevated risk[70].

Elevated plasma troponin concentrations on admission of patients with acute PTE have been reported in connection with PE and were associated with worse prognosis. A meta-analysis covering a total of 1985 patients showed elevated cardiac troponin I or T concentrations in approximately 50% of the patients with acute PTE, results consistent for troponin I or T and for prospective or retrospective studies[71]. Some studies have found that elevated troponin concentrations were associated with high mortality both in unselected patients and in haemodynamically stable patients; however, other systematic reviews and meta-analyses of troponin-based risk stratification of normotensive patients with acute symptomatic PTE have suggested a limited prognostic value of elevated troponins in normotensive patients[72].

In a prospective, multicentre cohort of 526 normotensive patients with acute PTE, troponin T concentrations <14 pg/mL, measured by a high-sensitivity assay, had a negative predictive value of 98% with regard to a complicated clinical course, which was similar to that of the sPESI, combination of cTnI - sPESI being able to identify possible candidates for out-of-hospital treatment[73]. Similarly, the value of NT-proBNP <500 pg/mL as a laboratory biomarker for selecting candidates for home treatment with clinically defined very low-risk PTE revealed that approximately 45% of patients with PTE can be treated in an outpatient setting. None of patients died or suffered recurrence of VTE or major bleeding complications during the three-month follow-up, and there was no increase in patient anxiety scores[74].

In a meta-analysis that has reviewed the role of biomarkers such as B-type natriuretic peptides (BNP and NT-proBNP) and troponins in risk stratification of acute PTE, BNP appeared to have better sensitivity and specificity than NT-proBNP in detecting right ventricular dysfunction. Raised levels of B-type natriuretic peptides at admission identified a subset of patients at higher risk of adverse outcomes and among patients with raised natriuretic peptide levels, increased troponins were found to be an independent prognostic biomarker[75].

Heart-type fatty acid-binding protein (H-FABP), an early marker of myocardial injury, was also found to significantly predict mortality in patients with acute PTE at intermediate risk. It is significantly associated with impaired right ventricular function and shows better

correlation with mortality than troponin I[76]. H-FABP might be a useful biomarker for risk stratification of normotensive patients with acute PTE where circulating H-FABP levels ≥6 ng/mL had a positive predictive value of 28% and a negative predictive value of 99% for an adverse 30-day outcome[77]. A simple score for immediate risk stratification of non-high-risk patients, based on the presence of tachycardia, syncope, and a positive bedside test for H-FABP (a positive result for plasma concentration >7 ng/ml), provided prognostic information similar to that of RV dysfunction on echocardiography[78]. The FAST score prognostic score (H-FABP, Syncope, and Tachycardia; FAST score) where the determination of H-FABP by immunoturbidimetry provides prognostic information superior to that of ELISA, appears more suitable to identify patients with an adverse 30-day outcome compared to the ESC Guidelines model and sPESI[79].

A meta-analysis of studies in patients with acute PTE for the purpose of identifying the prognostic value of elevated D-dimer levels for short-term (within 30 days) and 3-month mortality has shown that elevated D-dimer concentrations were associated with increased short-term mortality in some studies, while levels <1500 ng/mL had a negative predictive value of 99% for excluding three-month all-cause mortality[80]. Searching in 13 databases (n = 1585 patients), the Cochrane Report emphasizes that the negative D-dimer test is valuable in ruling out PTE in patients who present in an emergency setting with a low pre-test probability of PTE determined according to a clinical prediction rule. This test may probably be less useful in older populations (high levels of false-positive results), but no empirical evidence was available to support an increase in the diagnostic threshold of interpretation of D-dimer results for patients over the age of 65[81]. In summary, it is recommended to test D-dimers only in non-high risk suspected pulmonary embolism, when the clinical probability is low or intermediate, with the purpose to exclude the disease in the emergency department and thus reduce the use of unnecessary irradiation imaging; preferably a highly sensitive assay should be used. The use of the different commercial assays should take note that not all are clinically validated by studies[60].

Growth differentiation factor (GDF)-15, a cytokine induced in the heart after ischemia or pressure overload has elevated levels on admission in patients with acute PTE and was strongly and independently related to an increased risk of death or major complications during the first 30 days after diagnosis, prognostic information additive to that of the established biomarkers cTnT and NT-proBNP, and to echocardiographic findings of right ventricular dysfunction[82].

Biomarkers that usually grow in renal injuries were found related to 30-day all-cause mortality in acute PTE: elevated serum creatinine levels, a decreased (calculated) glomerular filtration rate, elevated neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C (N-GAL >75 ng/ml and cystatin C >1900 ng/ml). On the other hand, impaired kidney function was found present in 47% of acute PTE patients[83,84].

Multimarker models integrating information obtained from echocardiography (evidence or exclusion of RV dysfunction) in combination with some laboratory biomarkers (mainly BNP/NT-proBNP, cTnT/hsTnT, GDF-15 or H-FABP) have been reported to improve risk stratification of acute PTE, but require the prospective confirmation of the large studies.

Biochemical markers (for vascular dysfunction, inflammation, myocardial stress, low cardiac output, organ damage) have also been investigated for pulmonary hypertension (PHT), but without any significant clinical value regarding specific diagnosis. The current pulmonary hypertension guidelines only mention natriuretic peptides for their use in the prognostic evaluation at the time of diagnosis and during follow-up (and regarding response to therapy) in PHT patients. BNP values above 300 ng/l and Nt-proBNP values above 1400 ng/l seem to identify a high risk population, when integrated into an algorithm along with other clinical and echocardiographic parametres[85].

BIOMARKERS IN EMERGENCY CARDIOLOGY: ACUTE HEART FAILURE (AHF)

Although the subject of great interest in recent years, the current Guidelines (2016) for diagnosis and treatment of heart failure has few references to the use of biomarkers in acute heart failure: upon presentation to the ED or CCU/ICU, a plasma NPs level (BNP, NT-proBNP or MR-proANP) should be measured in all patients with acute dyspnea and suspected AHF to help in the differentiation of AHF from non-cardiac causes of acute dyspnea[86].

NPs have high sensitivity, and normal levels in patients with suspected AHF make the diagnosis unlikely. Elevated levels, as recommended by ESC/HFA guidelines, in the non-acute setting are BNP >35 pg/ml and/or NT-proBNP >125 pg/mL. In the acute setting, higher values should be used: BNP >100 pg/mL, NT-proBNP

>300 pg/ mL and mid-regional pro A-type natriuretic peptide (MR-proANP) >120 pmol/L[86].

Although there is extensive research on biomarkers in HF (e.g. soluble ST2, galectin 3, copeptin), there is no definite evidence to recommend them for clinical practice[87,88].

One must always bear in mind that elevated levels of NPs do not automatically confirm the diagnosis of AHF, as they may also be associated with a wide variety of cardiac and non-cardiac causes.

On the other hand, low levels of NPs can be detected in some patients with decompensated end-stage HF, flash pulmonary edema or right sided AHF.

Mid-regional proADM (adrenomedullin MR-proADM) is released from a multitude of tissues, and also has potent vasodilatory, hypotensive, and natriuretic effects. A large (1.641 patients presenting to the emergency department with dyspnea), multicenter prospective study demonstrated noninferiority of MR-proANP to BNP for the diagnosis or exclusion of acute HF in patients presenting to the Emergency Department with dyspnea. Moreover, this study found that MR-proADM was superior to BNP or NT-proBNP in identifying dyspneic patients with acute decompensated HF at high risk of 90-day mortality[89].

Detection of ACS as the underlying cause of AHF requires the quantification of cardiac troponins' level; this is particularly relevant, as large studies have shown that when an acute coronary syndrome is the precipitating factor in acute heart failure, the mortality rate is higher[90]. Elevated concentrations of circulating cardiac troponins are frequently detected in patients with AHF, often without obvious myocardial ischaemia or an acute coronary event, or without coronary artery stenoses and are associated with worse outcomes[90,91]. Initial blood pressure and troponin I, can help identify patients with congestive heart failure at low risk for prolonged hospitalization and adverse events since the Emergency Department[92].

Mid-regional proANP (MR-proANP) is released from the atria in response to increased atrial stretch, and has diuretic, natriuretic, and vasodilatory effects[93].

Galectin 3 (Gal-3), a member of the β-galactoside-binding lectin family, is associated with adverse remodeling via activated cardiac fibroblasts and macrophages[94].

The prognostic value of Gal-3 is additive with NPs levels and Gal-3 are independently predictive of recurrent decompensations and death in patients with heart failure[95].

American Heart Association/American College of Cardiology Foundation heart failure Guidelines consider a class IIB indication for the use of a Gal-3 assay for additive risk stratification in patients with established heart failure[96].

A study (4964 patients) found elevations in Gal-3 correlated with an increased risk of heart failure and cardiovascular death in patients after ACS, indicates a potential role for Gal-3 in monitoring patients after ACS[97].

Soluble suppression of tumorigenicity 2 (sST2), a member of the IL-1 receptor family, secreted into the circulation by cardiomyocytes and pulmonary endothelial cells, inhibits IL-33 and, through this, is down-regulating the inflammatory response[98]. High levels of sST2 correlate with disease severity and increased morbidity in patients with ADHF and ACS, providing complementary prognostic information to hs-cTnT and NT-proBNP[99].

ESC/HFA Guidelines 2016 indicates that the assessment of procalcitonin levels may be useful in patients with AHF with suspected coexisting infection, particularly for the differential diagnosis of pneumonia and to guide antibiotic therapy. The results from the BACH trial emphasize that patients with a diagnosis of AHF and an elevated PCT concentration (>0.21 ng/mL) had a worse outcome if not treated with antibiotics, while patients with low PCT values (<0.05 ng/mL) had a better outcome if they did not receive antibiotic therapy[100].

Multiple other biomarkers, including those reflecting inflammation, myocyte oxidative stress, neurohormonal disturbances, matrix remodelling, fibrosis, (most biomarkers integrate information from different disease pathways, e.g. Gal-3 is thought to represent a "link" between inflammation and fibrosis), extracardiac dysfunction, such as acute kidney injury, have been investigated for their diagnostic and prognostic value in AHF and some are developed as "companion biomarkers" to identify patients with the greatest benefit from a therapeutic intervention. Even though none of them has reached the stage of being recommended for routine clinical use, plasma biomarkers, along with imaging and genetic testing, might be used to define HF subtypes responding differently to specific therapeutic interventions[101].

A differential predictive value in HF reduced ejection fraction vs. HF preserved ejection fraction was suggested for some biomarkers, as they assess different pathophysiological pathways[102].

Table 3. Biomarkers in emergency cardiology: proved, potential or expected further clinical value

	proved clinical value	potential clinical value	future value/research
Cardiac arrest and resuscitation	cardiac troponins procalcitonin	neuron-specific enolase S-100B protein	circulating microRNAs
Coronary artery disease	hs troponin I,T	copeptin	Matrix MetalloProteinase (MMPs family: MMP-9)
		Heart-type fatty acid-binding protein (H-FABP)	Growth differentiation factor (GDF-15)
Heart Failure	natriuretic peptides	galectin 3 (Gal-3)	Mid regional proADM (MR-proADM)
		Soluble suppression of tumorigenicity 2 (sST2)	
Pulmonary embolism	cardiac troponins	Heart-type fatty acid-binding protein (H-FABP)	
	natriuretic peptides	Growth differentiation factor (GDF-15)	
Acute aortic syndromes	D-Dimers	C-reactive protein	calponin matrix metalloproteinases soluble fragments of elastin

At this point, biomarkers are being studied not just for their diagnostic value, but also for the prognostic value at admission (with the aim to identify the patients in need of more intensive care), or at discharge (to identify patients at risk for early postdicharge events) (Table 3). But the predictive value of different biomarkers diminishes with time, and multimarker strategy may be more useful[102,103,104].

By extensively stretching the diagnosis palette, into complex and high-risk patients with AHF, for instance, it is possible to use biologically "orthogonal" markers (a multimarker approach) such as NT-proBNP (stress), sST2 (myocardial fibrosis/remodeling), highly sensitive troponin (myocardial injury), MR-proADM (hemodynamic stress), copeptin (salt/water derangement), and renal biomarkers[105].

The "fine tunning" approach, in the use of these biomarkers for diagnosis, risk stratification or treatment strategy purposes requires a good selection of them and a check on their variations in various clinical conditions of emergency cardiology (Figure 1)[106].

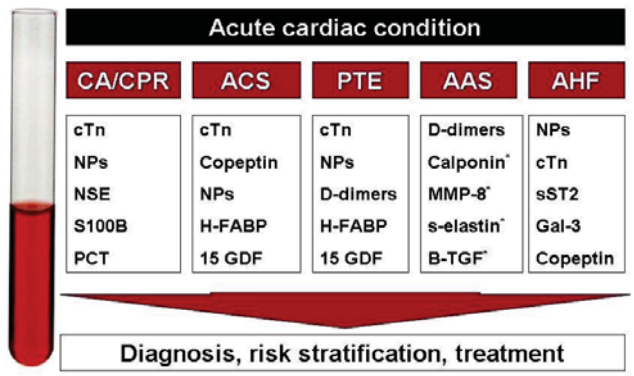

Figure 1. Biomarkers in emergency cardiology: a synopsis from current ESC/ERC Guidelines.
ACS=acute coronary syndrome; AHF=acute heart failure; PT=pulmonary Thromboembolism; CA=cardiac arrest; CPR=cardio-pulmonary resuscitation. cTn=cardiac troponin; NPs=natriuretic peptides; NSE=neuronal enolase; PCT=procalcitonin; H-FABP=heart-type fatty acid-binding protein; 15 GFD=growth differentiation factor; MMP=matrix metalloproteinase; s-elastin=soluble elastin fragments; B-TGF=transforming growth factor beta; sST2=soluble suppresion of tumorigenicity 2; Gal-3=galactin 3.
*biomarkers tested but not yet used into clinical practice.

CONCLUSIONS

Reviewing the latest Guidelines on acute clinical conditions that can be encountered in the field of emergency cardiology we noted the increasing importance achieved by biomarkers as components of diagnostic approache, prognostic stratification and adequate management. However, biomarkers should not be used as an alternative to clinical judgement or to other validated imaging tools. During decision-making process in different clinical settings, judicious use of biomarkers may expedite early diagnosis and may improve early triage and management strategies, but always in conjunction to the well established clinical algorithms. Further research will be needed to validate biomarkers as part of multimarker strategy in different clinical conditions.

Author contributions: All authors contributed to this manuscript.
Supported by: none.
Conflict-of-interest: none declared.

The manuscript represents the conclusions of the Consensus Meeting "Biomarkers in Emergency Department", coordinated by Alexandre Mebazaa and Ovidiu Chioncel, Sinaia, September 2016, and reflects the official position of the Acute Cardiac Care and Heart Failure Working Groups of the Romanian Society of Cardiology.

Acknowledgements: The authors thank Călin Pop for English text revision.

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