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## Perspectives on the Value of Biomarkers in Acute Cardiac Care and Implications for Strategic Management

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**Abstract:** Biomarkers in acute cardiac care are gaining increasing interest given their clinical benefits. This study is a review of the major conditions in acute cardiac care, with a focus on biomarkers for diagnostic and prognostic assessment. Through a PubMed search, 110 relevant articles were selected. The most commonly used cardiac biomarkers (cardiac troponin, natriuretic peptides, and C-reactive protein) are presented first, followed by a description of variable acute cardiac conditions with their relevant biomarkers. In addition to the conventional use of natriuretic peptides, cardiac troponin, and C-reactive protein, other biomarkers are outlined in variable critical conditions that may be related to acute cardiac illness. These include ST2 and chromogranin A in acute dyspnea and acute heart failure, matrix metalloproteinase in acute chest pain, heart-type fatty acid binding protein in acute coronary syndrome, CD40 ligand and interleukin-6 in acute myocardial infarction, blood ammonia and lactate in cardiac arrest, as well as tumor necrosis factor-alpha in atrial fibrillation. Endothelial dysfunction, oxidative stress and inflammation are involved in the physiopathology of most cardiac diseases, whether acute or chronic. In summary, natriuretic peptides, cardiac troponin, C-reactive protein are currently the most relevant biomarkers in acute cardiac care. Point-of-care testing and multi-markers use are essential for prompt diagnostic approach and tailored strategic management.

**Keywords:** biomarker, acute cardiac care, point-of-care, management, assays

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## Introduction

A biomarker (BM) is a biological parameter considered as an indicator of some physiological or pathological process. Generally, a BM reflects the presence of some clinical condition yielding a diagnostic and/or a prognostic value, also allowing disease staging and therapy monitoring in some cases. The ideal BM must be readily available, as well as reproducible with high specificity and sensitivity for a valuable clinical relevance.<sup>1</sup>

Cardiac BMs (CB)s are generally the degradation product of myocardial cells, metabolites, hormones, enzymes, or simple serum markers, such as creatinine. CBs reflect different pathological processes including cardiac injury and necrosis, myocardial stress, inflammation, and plaque destabilization.<sup>2</sup> First described in 1965, creatine kinase (CK) was the first CB used to assess myocardial infarction. CK myocardial band (CK-MB), a more specific indicator, followed in 1972. In 1989, the next major advance in CB development was the introduction of cardiac troponin (cTn).<sup>3</sup> CBs provide insights into variable physiopathological features such as oxidative stress, inflammation, platelet activation, and neurohormonal activity.<sup>4,5</sup> In view of this, assessment via multi-markers assays may help to adjust treatment according to the underlying physiopathological mechanism.<sup>6</sup>

In this study, we sought to review the clinical relevance of different CBs potentially useful in acute cardiac care, not only for diagnostic and prognostic assessment, but also for management objectives. In addition, we outline the principles for the implementation of CB in acute cardiac care, along with a highlight on use of multi-markers assays and point-of-care (POC) testing.

## Study Outline and Method

First, we address the most commonly used and most clinically relevant BMs in acute cardiac care: natriuretic peptides (NPs), CK-MB, cTn, and C-reactive protein (CRP). This was followed by a description and discussion of variable acute cardiac conditions as well as acute conditions that may be related to acute cardiac illness. In each case, there is a focus on correlated BM, whether for diagnostic, prognostic, or therapeutic purpose.

The conditions described include acute dyspnea, acute chest pain, acute coronary syndrome (ACS), acute myocardial infarction, acute decompensated

heart failure, acute circulatory failure, cardiac surgery, coronary revascularization, cardiac arrest, acute atrial fibrillation and hypertensive crisis. A PubMed search was conducted, focusing mainly but not exclusively on the last 10-year-publications, using the keywords “biomarkers; acute cardiac care.” Among the 747 articles, 110 were found relevant and were selected for further discussion.

## Common Cardiac Biomarkers used in Acute Cardiac Care

### Natriuretic peptides

NPs (atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP)) are secreted in the heart in response to cardiac hemodynamic stress mediated by volume and/or pressure overload.<sup>7</sup> In normal conditions, NPs are mainly released from the atrial myocardium. Additionally, BNP results from proBNP metabolism into active BNP and an N-terminal split product, NT-proBNP. In pathological conditions, BNP production is primarily shifted from the atria to the ventricles. However, both NPs have similar biological effects. They both promote diuresis and vasodilatation, antagonize the renin—angiotensin—aldosterone system, and reduce the secretion of arginine-vasopressin.<sup>8</sup> BNP and NT-proBNP are cleared through the kidneys at relatively the same rate, although NT-proBNP values are often higher in renal failure due to its longer half-life. BNP half-life ranges from 13 to 20 minutes while that of NT-proBNP ranges from 25 to 70 minutes.<sup>9</sup> In clinical practice, renal failure confounds interpretation of NP values and accordingly, only marked changes from baseline values are correlated with clinical outcome in this setting.

NPs are predictors of morbidity and mortality in acute heart failure; however, they cannot reliably discriminate systolic from diastolic heart failure. Importantly, BNP is more sensitive than NT-proBNP for diagnosing rapid hemodynamic changes in acute heart failure.<sup>10,11</sup> Moreover, NPs are prognostic markers in acute pulmonary edema and acute coronary syndrome.<sup>12</sup> Using POC testing, NT-proBNP has an excellent practicability in emergency setting. It has lower serum fluctuations than BNP.<sup>13,14</sup>

### C-reactive protein

Initially considered a marker of inflammation, CRP is now considered a BM of several cardiac conditions.<sup>15</sup>



CRP concentrations increase on the basis of genetics and non-Caucasian ethnicity.<sup>16</sup> However, daily serum levels are relatively steady with minimal diurnal variation.<sup>17,18</sup> The development of robust assays such as high-sensitivity CRP (hs-CRP) has allowed for identification of minimal CRP concentration changes. This has led to its increased use as a robust CB of several cardiac conditions and associated comorbidities, like obesity.<sup>19,20</sup>

In view of this, a consensus was issued regarding the predictive ranges for assessment of cardiovascular risk. The low risk group is classified by an hs-CRP level of <1 mg/L, whereas the average and high risk groups have hs-CRP levels of 1–3 mg/L and >3 mg/L, respectively.<sup>21</sup> Of note, the risk of mortality in an unselected intensive care unit patient is usually assessed using clinical-based scores like Acute Physiology and Chronic Health Evaluation II (APACHE II). Interestingly, the addition of NT-proBNP and CRP to APACHE-II score significantly improved the ability to predict mortality in the intensive care unit.<sup>22</sup>

### Creatine kinase

In general, a CB is considered ideal for detection of small myocardial injuries if it has a high cytoplasmic:plasma ratio, a low or undetectable plasma concentration at baseline, and a high cardiac specificity. CK does not fulfill these criteria as it has a moderate cytoplasmic:plasma ratio, a high reference range (up to 200 IU/L), and a low cardiac specificity.<sup>23</sup> CK (and CK-MB) is released within 8–12 hours after onset of myocardial injury, and reaches its peak at 24–36 hours. CK, therefore, has a low clinical relevance for early diagnosis of myocardial damage. It should be noted that a CK-MB:CK ratio >6% is highly predictive of cardiac origin of CK increase.<sup>23,24</sup> CK measurement will probably continue to be used as a marker for myocardial injury and infarct size extent.<sup>25</sup> CK-MB mass is more sensitive than CK-MB activity especially when concentrations are in the low range.

### Cardiac troponins

cTn (I and T) are sensitive CBs of myocardial injury, whatever its origin, and are considered the “gold standard” CBs for the diagnosis of ACS. This is particularly true for the high-sensitivity cTn (hs-cTn), which can measure the 99th percentile of cTn concentration.<sup>26</sup>

hs-cTn has allowed for a recommended upper reference limit to be set up and to determine a “physiological” coefficient of variation of the upper reference limit (usually <10%).<sup>27,28</sup> More importantly, hs-cTn assays detect cTn release at an earlier time point than cTn, which leads to an early diagnosis of ACS.<sup>29</sup> Both cTnT and cTnI are expressed in cardiomyocytes, with minor differences in biochemical characteristics between the two. These minor differences, however, are not clinically relevant.<sup>30</sup> At present cTnT may have an advantage over cTnI given its more standardized availability in core laboratory and POC platforms. The decision to use cTnT or cTnI in a given institution is most likely influenced by the cost and availability of reagents.<sup>31</sup> Physicians should never ignore a cTn increase, even when minimal. Additionally, they must interpret it in view of the clinical context.<sup>32</sup>

### Causes of increased cTn non-related to acute coronary syndrome

With the advent of the hs-cTn assay, even minor damage of the myocardium can be detected. Elevated cTn levels indicate cardiac injury, however do not define the cause of the injury.<sup>33</sup> In view of this, cTn elevations do not necessarily indicate the presence of a thrombotic coronary artery disease, given that a dynamic increase in cTn can occur in many conditions leading to excessive myocardial stress. These conditions include pulmonary embolism, sepsis, acute perimyocarditis, acute heart failure, and excessive persistent tachycardia.<sup>34</sup> Moreover, patients with stable angina and renal failure were found with hs-cTnT values >99th percentile of the upper reference limit in up to 37% of cases.<sup>34</sup> More importantly, hs-cTn elevations, regardless of the cause, are associated with adverse outcome in most clinical conditions and this fact is essential for the prognostic assessment.<sup>35</sup> At present, however, there are no guidelines to implement a specific therapy for patients with elevated cTn without coronary artery disease and the current strategy consists of treating the underlying causes.<sup>36,37</sup>

### Acute Cardiac Conditions

#### Acute dyspnea

BNP and hs-cTn are the cornerstone CBs for assessment of patients presenting with acute dyspnea in the emergency department, not only for diagnostic purpose, but also as indicators of mortality especially



when dyspnea is correlated with acute heart failure and/or ACS.<sup>13,27</sup> ST2, an interleukin-1 receptor family member and a BM of cardiac stretch and inflammation, is a predictor of 1-year-mortality in patients with preserved ejection fraction presenting with acute dyspnea.<sup>38</sup> Dieplinger et al<sup>39</sup> reported that ST2, mid-regional pro-A-type natriuretic peptide (MR-proANP; a marker of cardiac stretch), and chromogranin A (CgA; a marker of neuroendocrine activation) are sensitive predictors of all-cause 1-year-mortality in patients presenting acute dyspnea. Procalcitonin (a BM of inflammation and sepsis), D-dimer, and MR-proANP are essential BMs in the differential diagnosis of acute unexplained shortness of breath. MR-proANP is a very sensitive BM for diagnosing acute heart failure in this setting.<sup>40,41</sup> Finally, mid-regional pro-adrenomedullin (MR-proADM; a marker of neuroendocrine activation), and CgA were found to have additional prognostic value over NP in predicting 1-year-mortality in patients presenting with acute dyspnea.<sup>42-44</sup>

### Acute chest pain

Patients presenting with acute chest pain and a non diagnostic-electrocardiogram must be managed as promptly as possible for establishment of the right diagnosis and initiation of the appropriate therapy. In this setting, CBs play a critical role for diagnosis, risk assessment, and management. Among the multitude of available CBs, hs-cTn is currently the best single diagnostic marker of ACS in patients presenting with acute chest pain.<sup>26,27</sup> Moreover, hs-cTn has a prognostic value in patients presenting with acute chest pain predicting 6-month-event rate (death, myocardial infarction); an hs-cTnT value  $<0.014$   $\mu\text{g/L}$  is associated with low rate while intermediate and high rates are associated with hs-cTnT values of  $0.014$ – $0.04$   $\mu\text{g/L}$  and  $\geq 0.04$   $\mu\text{g/L}$ , respectively.<sup>45</sup> Many studies<sup>46,47</sup> showed that cTnI alone was sufficient for accurate diagnosis of ACS in patients with acute chest pain and non-diagnostic electrocardiogram. Myoglobin and CK-MB did not add any diagnostic benefit. Matrix metalloproteinase (MMP) activity is correlated with atherosclerotic plaque instability. In patients presenting with unexplained chest pain, high levels of MMP-2 and MMP-9 are independently associated with the development of acute myocardial infarction rather than stable angina.<sup>48,49</sup>

### Acute coronary syndrome

#### CB with diagnostic value

Use of POC testing is of utmost importance for prompt diagnostic assessment. Conventional CBs of myocardial injury are CK, CK-MB, and cTn. cTn is the cornerstone CB for diagnosis of ACS, and in particular hs-cTn, which has an increased sensitivity detecting concentrations  $<1$   $\text{ng/L}$ .<sup>26,50</sup> Moreover, hs-cTn assays can detect cTn release at an earlier time point than classical cTn assays, allowing for earlier diagnosis of ACS.<sup>29</sup> Interestingly, patients presenting with chest pain and having fluctuations of cTn  $>15\%$  within 6 hours after admission, even when values are below the institutional upper limit of normal, have a higher odds of ACS.<sup>51</sup> Of note, patients with renal failure require serial measurements to detect significant variation of cTn with clinical relevance given that these patients usually have increased baseline cTn values.<sup>52</sup> Myoglobin, ischemia modified albumin, and heart-type fatty acid-binding protein (h-FABP) allow a very early detection of myocardial injury ( $<4$  hours), nevertheless they lack specificity and at present they have a poor clinical relevance when not coupled with cTn.<sup>53,54</sup> Importantly, MMP-9 is considered as having the earliest diagnostic capability for ACS; nevertheless, it must be coupled with cTn for clinical relevance.<sup>55,56</sup>

#### CB with prognostic value

NT-proBNP and hs-CRP have an incremental prognostic value in risk stratification in ACS when used in combination (cut-off: hs-CRP level  $>3.5$   $\text{mg/L}$ ; NT-proBNP level  $>500$   $\text{pg/mL}$ ), predicting 1-year-cardiac events (myocardial infarction, mortality). Similarly, CRP and leukocytosis used in combination on admission are predictors of triple vessel disease and 30-day-mortality.<sup>57,58</sup> Importantly, CRP values  $>3.0$   $\text{mg/L}$  are found to be independent predictors of leukocytosis and are associated with 3-year adverse outcome (cardiac mortality, myocardial infarction).<sup>59,60</sup> BNP used in combination with placental growth factor and glomerular filtration rate allowed accurate prediction of 1-year-major adverse cardiac events in ACS.<sup>61</sup> cTn is highly useful as both a diagnostic and prognostic marker in ACS, and abnormal values following acute chest pain onset are highly predictive of adverse cardiac events.<sup>26,62</sup> When used in combination with cTn and





pro-BNP, lipoprotein-associated phospholipase A2 (Lp-PLA2), a BM of atherosclerotic process, allowed prediction of 42-day-major adverse cardiac events in ACS, with a synergistic predictive value superior to TIMI risk score.<sup>63,64</sup> MR-proANP and C-terminal portion of pro-vasopressin (copeptin) are associated with increased all-cause mortality at 3 months (cut-off value; 236 pmol/L, 21.6 pmol/L, respectively). Interestingly, the positive predictive value copeptin alone was found superior to that of cTnI.<sup>65,66</sup>

Procalcitonin is gaining increasing interest in ACS and high procalcitonin levels within 48 hours post-ACS are associated with increased early and 1-year mortality.<sup>67,68</sup> Homocysteine, an amino acid of the methionine metabolic cycle, requires folic acid and vitamin B<sub>12</sub> for adequate methylation. When methylation is deficient, L-arginine is converted to asymmetric dimethylarginine thereby increasing oxidative stress, endothelial dysfunction, and atherosclerosis. High levels of homocysteine, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- $\alpha$ ) are found associated with extensive coronary artery disease in ACS and are considered BMs of coronary disease severity.<sup>69,70</sup> Myeloperoxidase (MPO), an inflammatory BM involved in the physiopathology of the atherosclerotic process, is strongly associated with adverse outcome in ACS. Moreover, high MPO concentration is an independent predictor of in-hospital mortality in patients with ST elevation myocardial infarction presenting with cardiogenic shock.<sup>71-73</sup>

h-FABP, a BM of myocardial injury, is recently gaining increasing interest as a predictor of adverse outcome in ACS. Many investigators<sup>74,75</sup> reported that a positive h-FABP test in patients with ACS is an independent predictor of 6-month-adverse events (cardiac death, myocardial infarction). Choline is an emerging BM in ACS, it is related to plaque instability and platelet activation and is highly predictive of myocardial infarction. It allows discrimination of low- from high-risk subgroups in cTn positive patients with ACS, also it helps to differentiate ischemic from non-ischemic causes of troponin elevations.<sup>76,77</sup> Gamma-glutamyl transferase (GGT) is involved in oxidative and inflammatory processes, which play a critical role in the physiopathology of ACS. Ulus et al<sup>78</sup> reported that GGT is an independent predictor of 6-month-major adverse cardiac events in ACS. Additionally, Dogan et al<sup>79</sup> reported that in non ST elevation-ACS,

increased GGT levels are associated with more severe coronary artery disease and higher 12-month cardiac morbidity.

Increased CRP levels are associated with endothelial dysfunction and oxidative; Aspirin and statins reduce serum levels of hs-CRP and their protective effect, both during and post ACS may be partially related to the decrease in CRP.<sup>80,81</sup> Nitric oxide is involved in the regulation of vascular tone and platelet aggregation, a deficiency in nitric oxide is correlated with endothelial dysfunction, increased cardiovascular 7-year-morbidity and mortality post ACS.<sup>82</sup>

### Acute myocardial infarction

Management of acute myocardial infarction and its complications represent decisive challenges in contemporary cardiology. Prevention, early diagnosis, and prompt management are essential to improve outcome and decrease complications.

CBs of myocardial necrosis, such as CK-MB, cTn, myoglobin, and h-FABP, are released from injured cardiomyocytes. However, the diagnostic sensitivity of these CBs during the very earliest stage of myocardial infarction (<2 hours) remains insufficient given that they are released from cardiomyocytes when or after myocardial injury starts. In view of this, a CB derived from a ruptured plaque might be useful for the very early detection of acute myocardial infarction, rather than a BM derived from the injured myocardium. Soluble lectin-like oxidized low-density lipoprotein receptor-1, a BM of endothelial dysfunction and plaque instability, is capable of detecting the very early stages of ST elevation myocardial infarction, earlier than H-FABP, myoglobin, cTn, and CK-MB. However, soluble lectin-like oxidized low-density lipoprotein receptor-1 does not meet current standards for diagnosis of acute myocardial infarction when used alone, hence its use in combination with cTn is recommended.<sup>83,84</sup>

Leukocytosis and IL-6 are found to have higher values in patients with ST elevation myocardial infarction when compared to those with non-ST elevation myocardial infarction. Moreover, among inflammatory BMs, only CD40 ligand was found to be significantly higher in non-ST elevation myocardial infarction and was associated with higher mortality.<sup>85</sup> h-FABP is released after 30 minutes from the cardiomyocytes in response to myocardial injury and, as



a result, it is useful for rapid confirmation or exclusion of acute myocardial infarction particularly when testing is implemented via qualitative POC testing.<sup>86</sup> Furthermore, when combined with the myocardial isoenzyme glycogen phosphorylase isoenzyme-BB (GP-BB), both BMs contribute to early diagnosis of acute myocardial infarction. Nevertheless, these latter BMs do not at present meet the current standards for an efficient diagnosis of acute myocardial infarction when used alone, and their use in combination with cTn is recommended.<sup>87,88</sup>

### Acute decompensated cardio-circulatory failure

Acute heart failure usually comprises one-third de novo heart failure and two-thirds previously documented heart failure with acute decompensation. Identifying heart failure in the emergency department is sometimes challenging. Accordingly, use of CBs, mainly NP, is helpful for diagnostic and prognostic assessment.<sup>7</sup> Acute decompensated heart failure is a critical condition and mortality remains high, especially during the first days of hospitalization. BMs may help to assess the stage of heart failure and the response to therapy. Admission natremia, creatinine, and systolic blood pressure are simple markers that affect short-term prognosis in acute heart failure.<sup>3</sup> Both BNP and NT-proBNP have comparable sensitivity (~90%) and specificity (~70%) in diagnosing heart failure; moreover, the strongest yield of NPs in heart failure is their high negative predictive value.<sup>7</sup> Additionally, BNP is more sensitive to rapid hemodynamic changes in acute heart failure than NT-proBNP.<sup>11</sup> NPs are useful for risk stratification during acute heart failure, and they represent independent predictors of death or hospital readmission.<sup>8,9</sup> The predominant stimulus for release of BNP is end-diastolic wall stress, accordingly NPs may serve as quantitative markers related to the extent of left ventricular dysfunction. Typically, a BNP < 500 is correlated with NYHA I, and a BNP > 500 is associated with more severe functional class, though there is considerable overlap across functional classes. It should be noted that NP cannot distinguish diastolic from systolic heart failure.<sup>10,89</sup>

Cardiac stretch in heart failure is a time dependent process, which may be minimal or missing in acute heart failure. Accordingly, NPs are not necessarily

elevated despite acute hemodynamic compromise in some clinical conditions (eg, pulmonary edema caused by acute mitral regurgitation, and constrictive pericarditis without intrinsic heart disease).<sup>8</sup> Desmoulin et al<sup>90</sup> assessed the value of BMs other than NP in acute heart failure, and reported that a lactate/cholesterol ratio  $\geq 0.4$ , along with APACHE-II score and cardiogenic shock status, is a valuable marker correlated with higher 30-day-mortality. Similarly, Mebazaa et al<sup>91</sup> reported that quiescin Q6 (QSOX1), a protein involved in the formation of disulfide bridges, is a sensitive BM emerging in acute heart failure diagnosis; when combined with BNP, it significantly improves diagnostic accuracy of NPs by increasing sensitivity and specificity. In the MOCA study,<sup>92</sup> the authors reported an incremental value of ST2, MR-proADM, and CRP added to that of clinical variables (eg, age, gender, heart rate, blood pressure, etc.) for 1-year-mortality prediction in acute heart failure.

Nitric oxide is the main endothelial-derived vasodilator crucial for organ perfusion and coronary patency. Acute nitric oxide deficiency may lead to endothelial dysfunction with poor organ perfusion. Nitric oxide availability depends on the balance between a substrate (arginine) and an inhibitor of nitric oxide synthetase (asymmetric dimethylarginine).<sup>93</sup> In patients with circulatory shock, a lack in nitric oxide as manifested by a low arginine:asymmetric dimethylarginine ratio correlates with other markers of circulatory dysfunction (cardiac index, lactate, pH, APACHE II) and is associated with higher in-hospital mortality, whether the origin of circulatory shock was cardiogenic or septic.<sup>93</sup>

Creatinine has been included in many clinical scores (eg, APACHE-II) to assess the prognosis of critically ill patients. Vis et al<sup>94</sup> assessed the value of creatinine clearance measured on admission in patients with cardiogenic shock consecutive to ST elevation myocardial infarction and for whom a percutaneous coronary intervention was performed. Interestingly, the authors found an independent strong association between creatinine clearance on admission and 1-year-mortality, which was significantly higher when creatinine clearance was <67.5 mL/min.<sup>94</sup> Procalcitonin, a BM of severe sepsis and critically ill patients, has significantly higher values in patients with cardiogenic shock following acute myocardial infarction. Of note,



these values are not correlated with CRP, though they reflect a higher degree of inflammatory activation.<sup>95</sup>

### Coronary revascularization and cardiac surgery

Increased cTnI measured before cardiac surgery is considered a strong predictor of in-hospital mortality in patients with non ST-elevation ACS.<sup>96</sup> An increased CRP before and/or after angioplasty is an indicator of unfavorable short- and long-term outcome, whereas abnormal NT-proBNP before angioplasty is associated with unfavorable long-term prognosis. Moreover, abnormal cTnI after angioplasty, when baseline values are normal, is associated with in-hospital complications.<sup>97</sup> Finally, CRP has proven to be the most useful BM for non-invasive screening of acute cellular rejection in the first year post-heart transplantation.<sup>98</sup>

### Cardiac arrest

Survival after an episode of cardiac arrest depends on many factors, mainly the underlying cardiopathy, the cause of cardiac arrest, and the quality and rapidity of management with the potential occurrence of brain anoxia and damage. Shinozaki et al<sup>99</sup> found that blood ammonia and lactate on arrival are independent prognostic factors for out-of-hospital cardiac arrest (cut-off value: 170 µg/dL and 12.0 mmol/L, respectively). It should be noted that when combining both BMs, the positive predictive value is nearly 100%, high enough to be useful in clinical practice. The values of creatinine in aborted cardiac arrest have been assessed and were correlated with Pittsburgh cerebral performance category (CPC) and with serum levels of neuron-specific enolase, a marker of hypoxic brain damage. A decline in serum creatinine (>0.2 mg/dL) in the first 24 hours after cardiac arrest indicates good prognosis whereas a constant or increasing values predict an unfavorable outcome.<sup>100</sup>

### Atrial fibrillation

Atrial fibrillation is a medical condition with multi-factorial physiopathology, including hormonal, valvular, ischemic, inflammatory, oxidative, and endothelial factors. Clinical risk assessment for thromboembolic disease in atrial fibrillation is based on clinical scores CHADS(2) and CHADS(2)-VAsc. Herein, we address mainly paroxysmal and persistent

non-valvular atrial fibrillation as well as atrial fibrillation with normal thyroid function. TNF- $\alpha$  and NT-proBNP are associated with atrial fibrillation with a progressive increase in their levels among the subgroups from paroxysmal to persistent and permanent atrial fibrillation.<sup>7,101</sup> Abnormal NPs, found in patients with atrial fibrillation, reflect hemodynamic dysfunction, whether causative or consecutive to the arrhythmia. An ANP value >220.7 pg/mL was reported as a marker of diastolic dysfunction in this setting.<sup>102</sup> According to a RE-LY substudy,<sup>103</sup> increased cTnI and proBNP in patients with acute (paroxysmal or recurrent persistent) atrial fibrillation are independently correlated with higher odds of stroke and mortality.<sup>104</sup> Finally, Marcus et al<sup>105</sup> reported that CRP and IL-6 were significantly higher in patients during atrial fibrillation episode suggesting an inflammatory process as a trigger of first or recurrent episodes.

### Hypertensive crisis

The physiopathology of hypertension is multi-factorial involving mainly autonomic nervous system and the renin-angiotensin-aldosterone axis. Significant involvement of endothelial dysfunction, systemic inflammation, and oxidative stress in the development of hypertension is already established. Accordingly, BMs of these phenomena such as IL-6, TNF- $\alpha$ , and CRP are found in higher concentrations in patients with hypertension when compared to normotensive people.<sup>106</sup> Besides the special and rare case of pheochromocytoma where vanillylmandelic acid (VMA) is relatively useful for diagnosis, most cases of hypertensive crisis occur on the background of sustained chronic hypertension with paroxysmal peaks related to psychoneuroendocrine mechanism, where psychological stress plays a major role. Walton et al<sup>107</sup> reported that levels of cortisol and norepinephrine metabolites are higher during hypertensive crisis in patients with mood disturbance and anxiety when compared to hypertensive patients with “normal” mood profile.

### Final Remarks and Future Directions

Acute cardiac care comprises life-threatening conditions that require immediate and efficient medical care to improve outcome. Judicious use of CBs is particularly essential for emergency department physicians,



**Table 1.** Biomarkers: physiopathological significance and clinical use in acute cardiac care.

| Biomarker     | Significance                                | Clinical use in Acute cardiac conditions                                |
|---------------|---|---|
| cTn           | Myocardial injury                           | ACS: diagnostic and prognostic<br>heart failure, arrhythmia: prognostic |
| NP            | Myocardial stress                           | Heart failure: diagnostic<br>ACS, arrhythmia: prognostic                |
| CRP           | Inflammatory process                        | ACS: prognostic   |
| CPK           | Myocardial infarction                       | ACS, AHF: prognostic<br>MI: diagnostic                                  |
| Myoglobin     | Myocardial injury                           | Marker of extent in MI<br>Early marker in MI, in combination with cTn   |
| h-FABP        | Inflammatory process                        | Acute dyspnea: prognostic   |
| sST2          | Neuroendocrine activation                   | Acute dyspnea: prognostic   |
| CgA           | Inflammatory process                        | ACS: prognostic   |
| MR-pro ADM    | Atherosclerotic process                     | ACS: prognostic   |
| Procalcitonin | Platelet activation, plaque instability     | ACS: prognostic<br>Predictive of MI                                     |
| Lp-PLA2       | Oxidative stress; inflammation              | ACS: prognostic   |
| Choline       | Plaque instability, endothelial dysfunction | ACS: prognostic<br>STEMI: early diagnosis                               |
| GGT           | Inflammatory process                        | Higher mortality in NSTEMI  |
| sLOX-1        | Endothelial and oxidative stress            | ACS: extensive and severe CAD   |
| CD40 ligand   | Inflammatory process                        | Atrial fibrillation; recurrence   |
| Homocysteine  | Inflammatory process                        | ACS; prognostic<br>ACS; prognostic                                      |
| IL(s)         | Myocardial stretch                          | ACS; diagnostic and prognostic  |
| TNF- $\alpha$ | Plaque instability                          | ACS, STEMI; prognostic  |
| Copeptin, ANP | Inflammation; plaque instability            |   |
| MMP           |   |   |
| MPO           |   |   |

**Abbreviations:** LP-PLA2, Lipoprotein-associated phospholipase A2; sLOX-1, Soluble lectin-like oxidized low-density lipoprotein receptor-1; MI, myocardial infarction; AHF, acute heart failure; CAD, coronary artery disease; STEMI, ST elevation myocardial infarction; NSTEMI, Non-ST elevation myocardial infarction.

cardiac critical care units physicians (cardiologists and fellows), and intensive care physicians. However, at no time should results of the CB tests outweigh clinical findings. Individual assessment with use of both clinical and paraclinical data is criti-

cal for an accurate and prompt diagnosis followed by appropriate management. Thoughtful use of the multi-markers panel may yield insight into physiopathological mechanism of the underlying condition. Therefore, therapy can be targeted accordingly. Future directions should aim to find efficient and evidence-based therapy in acute cardiac conditions such as cytokines modulators, endothelin antagonists, recombinant BNP, vasopressin antagonists, and renin inhibitors. Table 1 summarizes the physiopathological significance of the main BMs along with their clinical relevance.

POC testing, along with the multi-marker approach in acute cardiac care may provide an early and more comprehensive understanding of the physiopathology of many cardiac conditions and associated comorbidities, yielding early diagnosis, accurate risk stratification, and tailored management for a better outcome.<sup>108,109</sup> POC panel tests increase successful home discharge in emergency room and reduces median length of stay. It also reduces unnecessary hospital admission. More particularly in ACS, POC testing yields rapid diagnosis when “time is myocardium.” Therefore this technique may allow for a prompt initiation of therapy.<sup>110</sup>

## Conclusion

The ideal BM for diagnostic application must be readily available, technically feasible, and clinically relevant with high specificity and sensitivity. Fundamental mechanisms such as endothelial dysfunction, oxidative stress, and inflammation are involved in the pathophysiology of most acute cardiovascular conditions including ACS, acute heart failure, and hypertensive crisis. cTn, BNP, and CRP are at present the most clinically relevant CBs in variable acute cardiac conditions. Small increases in cTn concentration even below the upper limit of normal are associated with increased odds of ACS, hs-cTn is able to detect ACS earlier than regular cTn. High CRP levels, regardless of the origin, are associated with adverse outcome in critically ill patients. BNP is more sensitive to rapid hemodynamic changes than pro-BNP, though it cannot differentiate diastolic from systolic dysfunction.

Non-conventional and emerging BMs are helpful on a case-by-case use; however, BMs should not outweigh the clinical setting. The judicious use of





BM whether in core laboratory or as POC testing is critical for enhanced diagnostic outcome. Moreover, a BM guided triage of patients with acute cardiac conditions allows for a more strategic and tailored management. CBs allow diagnostic assessment in most acute cardiac conditions, and they allow for monitoring of disease progression and response to therapy, yielding a prognostic index regarding potential morbidity and/mortality. In view of this, management strategy must address not only the acute cardiac condition, but also the future risk of major adverse events.

### List of Abbreviations and Acronyms

CB: cardiac biomarker; BM: biomarker; CK: creatine kinase; CK-MB: creatine kinase myocardial band; cTn: cardiac troponin; hs-cTn: high-sensitivity cTn; POC: point-of-care; NP: natriuretic peptides; CRP: C-reactive protein; hs-CRP: high-sensitivity CRP; ACS: acute coronary syndrome; BNP: brain natriuretic peptide; ANP: Atrial natriuretic peptide; APACHE-II: Acute Physiology and Chronic Health Evaluation II; MR-proANP: midregional pro-A-type natriuretic peptide; CgA: chromogranin A; MR-proADM: Midregional-proadrenomedullin; MMP: Matrix metalloproteinase; h-FABP: heart-type fatty acid-binding protein; IL-6: interleukin-6; TNF- $\alpha$ : tumor necrosis factor-alpha; MPO: myeloperoxidase; GGT: gamma-glutamyl transferase.

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### Author Contributions

Conceived and designed: AK. Analyzed the data: AK, AG, SS, AI, NM, MK, GG. Wrote the first draft of the manuscript: AK, AG, SS, AI, NM, MK, GG. Contributed to the writing of the manuscript: AK, AG, SS, AI, NM, MK, GG. Agree with manuscript results and conclusions: AK, AG, SS, AI, NM, MK, GG. Jointly developed the structure and arguments for the paper: AK, AG, SS, AI, NM, MK, GG. Made critical revisions and approved final version: AK, AG, SS, AI, NM, MK, GG. All authors reviewed and approved of the final manuscript.

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