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Saudi Heart Association Position Statement on the Use of Biomarkers for the Management of Heart Failure and Acute Coronary Syndrome

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Abstract

Background: **The burden of acute coronary syndrome (ACS) and heart failure (HF) remains high in Saudi Arabia. Biomarkers can greatly improve the management and outcomes of these conditions, but no official guidance is available on their use in Saudi Arabia.**

Consensus panel: **An expert panel of cardiologists, interventional cardiologists and cardiac surgeon reviewed available evidence and formulated recommendations relevant to clinical practice in Saudi Arabia.**

Consensus findings: **high-sensitivity cardiac troponins play a major role in the diagnosis of ACS and the exclusion of myocardial infarction in patients with HF. Natriuretic Peptides are recommended to determine the likelihood of a diagnosis of HF in a chronic setting and rapidly exclude HF in an acute setting. High-sensitivity cardiac troponins and NT-proBNP have good prognostic ability in ACS and HF. These biomarkers could also facilitate discharge planning and reduce unnecessary hospital admissions and resource wastage. The use of biomarkers should not be excessive and should abide by appropriateness criteria. High-sensitivity assays and NT-proBNP measurements are preferred.**

Conclusion: **By outlining expert recommendations on the best practices in the use of biomarkers, the panel hopes to contribute towards a recognized updated guidance for all healthcare providers in Saudi Arabia on the evidence-based management of HF and ACS.**

Keywords: Acute coronary syndrome, Heart failure, Biomarkers, Saudi Arabia, Management

1. Introduction

Despite the availability of advanced guidelines for the management of both heart failure (HF) and acute coronary syndrome (ACS), these conditions continue to carry a significant burden in terms of morbidity and mortality in the Kingdom of Saudi Arabia (KSA). National awareness campaigns, primary prevention programs and appropriate policy changes are urgently needed to promote adherence and curb the rise in the prevalence and mortality of heart disease [1,2]. In fact, the prevalence of unhealthy lifestyles and cardiovascular disease (CVD)

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risk factors (diabetes, dyslipidemia, hypertension, obesity, smoking) continues to be alarmingly high in the general adult Saudi populations [3]. These exacerbating factors are clearly reflected in patients with acute or chronic HF [4,5], as well as those with ACS [6,7]. Age of HF and ACS onset is relatively low in the KSA compared to western countries. 44.7% of patients with acute HF were found to have a history of chronic HF [4], while mean age of ACS patients was 58 years old [7]. Evidence from the HEARTS registry shows that chronic HF patients not only present at younger ages, but also exhibit relatively high mortality and re-hospitalization rates [4,5]. The SPACE registry revealed delayed initiation of thrombolytic therapy or primary percutaneous coronary intervention [7]. Moreover, around 28% of patients with acute HF have concomitant ACS and subsequently have worse hospital prognosis [8]. Timely recognition and management of both HF and ACS is therefore crucial.

The cardiac troponin complex is composed of three distinct proteins, of which cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are expressed almost exclusively in cardiac muscle. cTnT and cTnI are released by the heart following myocyte damage and can be detected in the blood, which prompted their use as reliable and specific markers of myocardial injury. Of atrial natriuretic peptides (ANPs), B-type natriuretic peptide (BNP) is initially synthesized as proBNP, which is then cleaved into the active peptide hormone (BNP) and the inactive N-terminal fragment (NT-proBNP). These biomarkers are also secreted in response to cardiac hemodynamic stress, and are consequently used in the primary prevention of heart disease. The main objective of this position statement is to assist cardiologists, internal medicine specialists and emergency department personnel in the KSA to better diagnose and treat HF and ACS through sharing the key opinion leaders' best practices on the use of biomarkers. This project can be a step forward towards a recognized updated guidance for all healthcare providers in the KSA on the evidence-based management of HF and ACS.

2. Methods

In a meeting held virtually in January 2022, 8 experts representing the Saudi Heart Association (SHA) reviewed current evidence and guidelines regarding the use of biomarkers for the management of HF and ACS. Expert opinion was gathered on each topic and synthesized into position statements formulated specifically to reflect Saudi healthcare needs, resources and practice.

Abbreviations

ACS	Acute coronary syndrome
ANP	Atrial natriuretic peptides
BNP	B-type natriuretic peptide
COVID-19	Coronavirus disease 2019
cTn	Cardiac troponins
CVD	Cardiovascular disease
ECG	Electrocardiogram
GDF-15	Growth Differentiation Factor 15
HF	Heart failure
h-FABP	Heart-type fatty acid binding protein
Hs-CRP	High sensitivity C reactive protein
Hs-cTn	High-sensitivity cTn (Hs-cTn)
KSA	Kingdom of Saudi Arabia
MR-proADM	Mid-regional proadrenomedullin
MR-proANP	Mid-regional pro-atrial natriuretic peptide
NT-proBNP	N-terminal fragment B-type natriuretic peptide
PCI	Percutaneous coronary intervention
SHA	Saudi Heart Association

3. Results - consensus statements

3.1. Acute coronary syndrome (ACS)

a) Diagnosis of ACS

Position statement: Diagnosis

Diagnosis and initial short-term risk stratification should be founded on a combination of clinical history, physical findings (symptoms, vital signs, others), electrocardiogram (ECG), and laboratory results (i.e. high-sensitivity cardiac troponin).

The measurement of cardiac troponins is recommended with high-sensitivity assays. Measurement should be done as soon as possible at admission and time to obtaining test results should not exceed 60 minutes since blood sampling.

Obtaining a second blood sample is recommended within 2 hours of admission, although it is also reasonable to obtain a second sample within 1 or 3 hours of admission.

If the first two consecutive samples are inconclusive or if the clinical situation is uncertain, cardiac troponins should be measured for the third time to determine whether the diagnosis of ACS is unlikely.

While cardiac troponin can be detected in healthy individuals, the rise and fall or cardiac troponin levels allow the differentiation between acute cardiomyocyte damage, such as myocardial infarction, and chronic damage [9]. high-sensitivity cTn (Hs-

cTn) levels are quantitative markers of cardiomyocyte damage; the likelihood of myocardial infarctions increases along with elevation of hs-cTn levels [9]. The highest positive predictive value is observed with elevations of hs-cTn exceeding 5-fold the upper reference limit [9]. When compared to standard cardiac troponin assays, hs-cTn assays were shown to be more cost effective and have higher negative predictive value for acute myocardial infarction, as well as ensure earlier and higher detection of acute myocardial infarction and both type 1 and type 2 myocardial infarction [9–13]. Moreover, the diagnostic accuracy of hs-cTn assays is not compromised in patients with renal dysfunction and myocardial injury can be ruled out at assay-specific thresholds [14]. Rigorous quality specifications are set forth by international guidelines for immunoassays to be considered 'high-sensitivity", leading to a notable increase in the analytical performance of immunoassay methods [15]. For example, the IFCC Task Force on Clinical Applications of Cardiac Bio-Markers (Academy of AACC and Task Force of IFCC) suggested in 2017 that cTn assays are "guideline acceptable" if they can measure the 99th URL value with a % CV of $\leq$10, "clinically useable" if the % CV is > 10 to $\leq$20, and "not clinically acceptable" if the % CV is > 20 (for detailed information, see Ref. [16]). To note while both cTnT and cTnI carry high diagnostic and prognostic value [17], cutoff points are assay-specific for cTnT and cTnI owing to their distinct biological properties and the differences in the commercial immunoassays used for their detection. These differences should be carefully considered when interpreting results to ensure accurate interpretation of cTnT and cTnI levels (Table 1).

Hs-cTn (either T or I) should be measured immediately upon admission, with repeat testing recommended within 2 hours (±1 hour). Results should be obtained within 60 minutes of blood draw. Diagnosis should be based on available clinical information (history, signs, symptoms, electrocardiogram (ECG), laboratory results) in addition to the use of hs-cTn [9,18].

Cardiac troponins should not be measured in all patients presenting to the emergency room with chest pain. Elevated troponin levels are observed in cardiac pathologies other than ACS (i.e. Tachyarrhythmias, heart failure, hypertensive emergencies, critical illness, myocarditis) as well as non-cardiac conditions (i.e. renal impairment in the elderly, acute neurologic event) and should be carefully considered as differential diagnoses. Studies show that about half of troponins ordered in the emergency room were not appropriate [19,20]. Emergency personnel and cardiologists have different perceptions of clinically appropriate use of cTn testing, with broader appropriateness perceived by emergency personnel [21]. In order to avoid overuse of cTn measurement, testing should only be undertaken when appropriate (*see appropriateness criteria*).

Position statement: cTn measurement appropriateness criteria

- Patients who present with consistent chest pain/discomfort without relief for at least 30 minutes
- Patients who present with acute shortness of breath, collapse of unknown origin
- Patients with diabetes who present with history of weakness, shortness of breath collapse with or without chest pain/discomfort
- Unclear ECG (for confirmation of myocardial infarction)
- Arrythmias
- Patients with ischemic ECG changes
- New or presumed new left bundle branch block (LBBB) on ECG

* cTn testing is not required for patients diagnosed with ST-elevation myocardial infarction and who are treated promptly (unless requested by cardiologist).

* Patients with no CAD risk factors and cTnT < 14 ng/L or equivalent assay-specific cTnI levels (see Table 1) do not require repeat testing.

Table 1. Assay specific cut-off levels for cTnT and cTnI.

Assay	Cutoff level (ng/L)		
	Very low	*Low*	*High*
hs-cTn T (Elecsys; Roche)	<5	<14	≥52
hs-cTn I (Architect; Abbott)	<4	<6	≥64
hs-cTn I (Centaur; Siemens)	<3	<8	≥120
hs-cTn I (Access; Beckman Coulter)	<4	<5	≥50
hs-cTn I (Clarity; Singulex)	<1	TBD	≥30
hs-cTn I (Vitros; Clinical Diagnostics)	<1	TBD	≥40
hs-cTn I (Pathfast; LSI Medience)	<3	TBD	≥90
hs-cTn I (TriageTrue; Quidel)	<4	TBD	≥60

b) Prognosis

Position statement: Prognosis

cTn levels are useful for prognosis.

High-sensitivity cTn is favored as a biomarker in cases of acute chest pain upon presentation due to its more

rapid detection/exclusion of myocardial injury and higher diagnostic accuracy.

BNP or NT-proBNP plasma concentration measurement should also be considered.

Other biomarkers (MR-proANP, hs-CRP, MR-proADM, GDF-15, copeptin, and h-FABP) are not currently recommended for prognosis or risk assessment.

While there is currently not enough evidence to support the use of biomarkers such as mid-regional pro-atrial natriuretic peptide (MR-proANP), high sensitivity C reactive protein (hs-CRP), Mid-regional proadrenomedullin (MR-proADM), Growth Differentiation Factor 15 (GDF-15), copeptin, and heart-type fatty acid binding protein (h-FABP) for prognosis in ACS, cTn is an important prognostic factor in this setting. Elevated troponins in the general population were found to be most strongly correlated with fatal cardiovascular disease, including coronary heart disease and stroke [22]. Patients with chest pain and no myocardial infarction commonly exhibit cTn levels higher than the 99th percentile [23]. A higher risk of death and adverse cardiovascular outcomes is associated with detectable cTn among patients with chest pain and no myocardial infarction or unstable troponin levels [24]. There is also evidence to support the preoperative predictive value of BNP and NT-proBNP in the context of adverse outcomes after cardiac surgery [25]. NT-proBNP was also shown to have good predictive value for 30-day mortality in patients with non-ST-elevation ACS [26]. BNP or NT-proBNP as well as troponin can also enhance the performance of cardiac risk indexes in predicting major adverse cardiac events [25].

Postoperative changes in hs-cTnT concentrations have been shown to be useful for detecting the risk of perioperative myocardial infarction, major adverse events or mortality. Post-percutaneous coronary intervention (PCI) peak cTn levels was associated with a 7% increase in mortality after 1 year [27]. Similarly, peak post-procedural cTn was correlated with 3-year mortality after early PCI in non-ST-elevation myocardial infarction patients [28] and independently associated with clinical outcomes and cardiac function 3 months after PCI for ST-elevation myocardial infarction [29]. Post-PCI cTn levels are therefore Pre-PCI cTn levels could also be important to understand the variations of this biomarker post-PCI and their prognostic value [30]. Elevations of troponin levels within the first day of CABG were also predictive of intermediate and long-term mortality [31]. In fact, peak hs-TnT level >400 ng/L within 24 hours post-CABG is associated with major adverse cardiac or cerebrovascular event, 30-day mortality, myocardial infarction and intensive care unit stay longer than 2 days [32,33].

Elevated troponin levels are also one of the hallmarks of viral myocarditis [34], and are detected in most patients with viral illnesses associated with myocardial injury, such as coronavirus disease 2019 (COVID-19) [35]. Patients who had severe infections, who were admitted to the intensive care unit or who have died from COVID-19 had significantly higher levels of cTn [36].

c) Resource use

Position statement: health outcomes

Cardiac troponins can be used for the early exclusion of myocardial infarction, which could subsequently reduce hospital admissions for serial cardiac biomarker testing and unnecessary use of resources.

The implementation of hs-cTn testing can lead to improved detection of ACS and unstable angina [37]. The introduction of hs-cTn ensures a better rule-out process in the emergency department, thereby reducing the need for stress testing and decreasing time to discharge without increasing the use/inappropriate use of coronary angiography [38]. The use of high sensitivity cTn testing has positive organizational value seeing as it leads to reduced cost, improved referral to the appropriate department and reduced hospital length of stay in patients with suspected ACS [39].

3.2. Heart failure (HF)

a) Detection of high-risk patients and prevention of HF

Position statement: Prevention of HF

For patients at high risk of cardiac injury (e.g. diabetic patients, patients receiving chemotherapy), screening with biomarkers (NT-proBNP and high sensitivity cTn) can be helpful to prevent the development of HF.

NT-proBNP was strongly associated with first onset HF and can improve the prediction of strokes and coronary heart disease in the absence of

baseline cardiovascular disease [40]. High sensitivity cTn was also shown to play a role in risk stratification for new onset HF as well as the prediction of HF [41]. These biomarkers are also useful in special populations, with both NPs and troponin showing benefit for the early detection of cardiac dysfunction in cancer patients at risk of cardiotoxicity [42,43]. Troponin is more sensitive than BNP for the detection of subclinical cardiotoxicity in the context of chemotherapy and elevated cTn levels are actually an indicator to initiate therapy with angiotensin-converting enzyme inhibitors [42–44]. NT-proBNP levels can also predict cardiovascular outcomes, HF, and HF-related hospitalization in patients with type 2 diabetes mellitus [45]. Both BNP and NT-proBNP were also demonstrated as strong predictors of cardiovascular morbidity and mortality in diabetic patients with recent ACS [46]. The PONTIAC I trial results were indicative that the primary prevention of cardiac events among diabetic patients can safely incorporate NT-proBNP for patient selection for therapy up-titration [47]. It is therefore the experts' opinion that biomarker-based screening should be incorporated into standard practice to assist in efforts for the primary prevention of HF. NT-proBNP and high-sensitivity cTn are the preferred biomarkers. Screening should be conducted annually in the absence of an alarming change in clinical status. Patients receiving chemotherapy should be monitored every 3 months until the end of treatment, after which the screening frequency can be decreased to once yearly. It is important to note that while the measurement of NT-proBNP and BNP levels can be achieved through different techniques and commercially available assays, the results obtained are not interchangeable. The differences in diagnostic cutoff levels emphasizes the importance of monitoring all HF patients using the same assay (BNP or NT-proBNP) [48]. While the pathophysiological and clinical characteristics of NPs and cTn are different, they remain complementary and their measurement offers valuable insights into cardiac dysfunction and/or cardiomyocytes damage. As previously mentioned, increased levels of NPs reflect alterations in cardiac function and cardiac stress, and increases in hs-cTn (I and T) indicate myocardial injury [49]. Combined measurement of NP and cTn can therefore be useful for the evaluation of cardiovascular risk in patients with cardiac disease, as well as the general population [50,51].

b) Diagnosis of chronic and acute HF

Chronic HF

Position statement: Diagnosis of chronic HF

Measurement of NPs is recommended to determine the likelihood of a diagnosis of HF.

HF can be ruled out (further testing not necessary) at a plasma concentration of B-type natriuretic peptide (BNP) <35 pg/mL, or N-terminal pro-B-type natriuretic peptide (NT-proBNP) <125 pg/mL.

NP should be evaluated as an essential test before echocardiography to avoid delay in diagnosis and reduce unnecessary echocardiographs. An NT-proBNP cut-off of 125 pg/mL exhibits high sensitivity and negative predictive value for HF diagnosis [52]. A diagnosis of HF can be effectively ruled out when NT-proBNP levels are below the threshold [53]. Some evidence suggests that the diagnostic accuracy of BNP and NT-proBNP is similar [54], while others report higher specificity and sensitivity with NT-proBNP [55,56]. MR-proANP has diagnostic value in chronic HF similar to NT-proBNP [57]. However, it is not available in the KSA and will therefore not be considered in this position statement. Available evidence shows that evaluation of NPs is essential for the prevention of misdiagnosis or diagnosis delays. Ensuring the availability of NT-proBNP in primary care leads to improvement of care and reduces healthcare costs through the reduction of resource wastage.

Acute HF

Position statement: diagnosis of acute HF

In the acute setting, measurement of NPs and serum troponin is recommended to rapidly exclude the diagnosis of acute HF and reduce resource wastage.

Acute HF can be ruled out (further testing not necessary) at a plasma concentration of B-type natriuretic peptide (BNP) <100 pg/mL, or N-terminal pro-B-type natriuretic peptide (NT-proBNP) <300 pg/mL.

If the diagnosis of acute HF is likely (B-type natriuretic peptide (BNP) ≥100 pg/mL, or N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥300 pg/mL), proceed to other diagnostic modalities to confirm the diagnosis.

In the context of suspected acute HF, plasma NPs (BNP or NT-proBNP) should be measured upon presentation to help rule out the diagnosis. BNP or NT-proBNP levels below the cut-offs (<100 pg/mL for BNP, <300 pg/mL for NT-proBNP) greatly reduce the likelihood of diagnosing acute HF [58,59]. While NPs allow emergency personnel to strongly exclude acute HF and avoid unnecessary testing, their positive predictive value falls short of their negative predictive value. Moreover, other non-cardiac conditions (i.e. cancer, concomitant atrial fibrillation and/or reduced renal function) can lead to elevated NP levels [59–61]. Patients presenting with BNP >100 pg/mL or NT-proBNP >300 pg/mL should therefore be subjected to further diagnostic tests, such as ECG, echocardiography and chest X-ray. This approach would not only help confirm/exclude the diagnosis of acute HF, but would also reduce healthcare cost by preventing the need for imaging all patients suspected of acute HF [62].

c) Prognostication in heart failure

Position statement: Prognostication in HF

Baseline NP biomarkers and/or cardiac troponin could be measured to establish prognosis in both acute HF (upon hospital admission) and chronic HF (at presentation).

In addition to ruling out the diagnosis of HF, elevated serum NPs can shed valuable insights into patient prognosis. Elevated NT-proBNP levels at admission are independently and positively associated with cardiovascular mortality and all-cause mortality in patients with acute decompensated heart failure [63]. BNP and NT-proBNP have similar prognostic value in chronic HF on the level of mortality (all-cause, cardiovascular, HF mortality) [64] and HF-related hospitalization [65]. Serum troponin T levels can also serve for the early prediction of short-term outcomes such as 28-day mortality in acute HF [66]. In the context of chronic HF, hs-cTnT strongly predicts mortality (all-cause and cardiovascular), in addition to cardiovascular-related hospitalization [67,68].

d) Discharge planning

Position statement: Discharge planning in HF

NP measurements pre-discharge should be considered for discharge planning and patient follow-up.

Serum NPs can also be predictive of outcomes after hospitalization and could therefore inform discharge planning. Changes in NT-proBNP levels from admission to discharge as well as absolute value of NT-proBNP at discharge carry prognostic value and can predict adverse events [69]. Discharge risk models including NT-proBNP are strongly predictive of all-cause mortality, cardiovascular events, as well as 30-days readmission or death [69–71].

e) Outpatient prognostication

Position statement: Outpatient prognostication

NT-proBNP measurements (NT-proBNP threshold 1000 pg/mL) might be useful for outpatient prognostication, taking into consideration biological variability of NP levels (e.g. gender, age, BMI, renal function, comorbidities, medication).

NT-proBNP 1000 pg/mL was validated as a threshold of risk of subsequent cardiovascular events [72,73]. Patients with baseline NT-proBNP >1000 pg/mL who achieve NT-proBNP levels below this threshold have approximately 60% less risk of HF hospitalization and cardiovascular death [74]. Reduction of NT-proBNP levels is associated with greater cardiac remodeling, improved clinical outcomes and better quality of life [73,75,76]. That being said, it is important to take into consideration the biological variation of NP levels according to age, gender, body mass index, cardiac and non-cardiac conditions, and renal function [77]. It is also crucial to account for the effect of therapy on NP levels. Specifically, caution should be exercised in the interpretation of elevated BNP values in patients receiving angiotensin receptor-neprilysin inhibitors (ARNis), in which case NT-proBNP measurement might be preferable [78]. In this regard, clinicians should therefore be aware of the seemingly contradictory clinical variations of NPs and their implications to clinical practice. The levels of the active peptide hormone BNP depend on the *in vivo* enzymatic cleavage of the proBNP precursor by plasma proteases, which have different mechanisms of action on the inactive peptide NT-proBNP. Studies have made it evident that ARNIs can selectively inhibit natriuretic peptide degradation, causing an increase in the circulating levels of BNP, a substrate of neprilysin, while concomitantly reducing the levels of NT-proBNP (which is not a substrate of neprilysin). As such, decreases in NT-proBNP levels in the first days of treatment with ARNI can be interpreted as an indication of favourable

myocardial and vascular outcomes with treatment, and increases in BNP levels reflect the inhibiting effects of the drug or clinical deterioration due to failure of treatment [79].

f) Treatment

Position statement: Treatment

The choice and up-titration of therapy is not dependent on NPs and treatment should be planned regardless of NP levels.

NT-proBNP guide therapy was not associated with improvement in HF outcomes among high-risk HF patients with reduced ejection fraction in the GUIDE-IT trial when compared to usual care [80], nor among chronic HF patients in general [81,82]. This is in contrast with an earlier trial where the use of NT-proBNP to guide the treatment of HF patients with left ventricular systolic dysfunction led to improved outcomes and quality of life [73]. Regardless, the routine measurement of BNP or NT-proBNP cannot be recommended to guide therapy choice or titration. For guidance on patient management, refer to the latest SHA HF guidelines.

4. Conclusion

The burden of ACS and HF continues to be significant in Saudi Arabia. The appropriate use of biomarkers can not only improve the diagnosis and prognostication of these conditions, but also reduce unnecessary hospitalizations and resource wastage. Recommendations on the use of biomarkers in ACS, acute HF and chronic HF are outlined in this position statement. Healthcare providers are highly encouraged to strive for appropriate integration of biomarkers in clinical practice and subsequently improve the diagnosis and prognosis of patients with ACS and HF.

Author contribution

Conception and design of Study; W. A. Literature review; WA, AAT, FA, KAG, MA, MA, SK, WA. Acquisition of data; WA, AAT, FA, KAG, MA, MA, SK, WA. Drafting of manuscript; AAT, FA, KAG, MA, MA, SK, WA. Revising and editing the manuscript critically for important intellectual contents; AAT, FA, KAG, MA, MA, SK, WA. Supervision of the research; WA, AAT, FA, KAG, MA, MA, SK, WA. Research coordination and management; WA.

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Conflict of interest

None declared.

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