Multimarkers approach in chest pain management in Emergency department: a focus on the prognostic role of sST2 and suPAR

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Abstract

Chest pain is one of the most prevalent causes of Emergency Department (ED) admission and could be a presenting symptom of Acute Coronary Syndrome (ACS). The aim of this review was to provide an overview of the research about troponin and its limitations and new biomarkers used in patients with cardiovascular diseases, with a special focus on soluble Suppression of Tumorigenicity 2 (sST2) and Soluble Urokinase Plasminogen Activator Receptor (suPAR). In January 2024, a PubMed and Reviews in Cardiovascular Medicine (RCM) search was carried out to identify all relevant papers in the past five years. 80 articles were included in the final review. ssT2 and suPAR are involved in both acute and chronic cardiovascular disease and can predict the risk of adverse events. sST2 and suPAR are promising biomarkers that, in combination with troponin, could help in the management of patients with chest pain in the ED. Further studies are needed to validate their role in management of ACS in this specific setting.

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Introduction

Chest pain is one of the most frequent symptoms of admission to the Emergency Department (ED). It represents a continuous defiance in emergency departments, which requires an accurate assessment in order to identify serious conditions that are potentially deadly and predict associated risks. Cardiovascular Disease (CVD) can present with different manifestations, of which chest pain represents the most frequent symptom. Although sometimes it is not related to acute syndromes that require immediate treatment, other times it indicates acute situations such as Acute Coronary Syndrome (ACS) which can endanger the patient's life. CVD is a major disease globally and the leading cause of death and disability worldwide.[1] CVD is typically diagnosed based on history, clinical examination, risk factors, ECG tracing, and laboratory criteria. Chest pain is a symptom of ACS, but also of other cardiothoracic situations as well as manifestations of non cardiothoracic syndromes. The risks of misdiagnosis are high. In spite of recent efforts to develop a model that could help in estimating the cardiovascular risk in patients presenting to the emergency room with chest pain, we are still unable to rely on trustworthy instruments to estimate the risk of acute coronary syndromes in all patients.[2] According to the Centers for Disease Control and Prevention, about 130 million patients visit the ED in the United States per year, and of these the 31% admitted to the ED with initially normal vital signs show deterioration in the first 24 hours.[3] Despite the attempt to build standardized models for the correct management of patients with chest pain in the short and long term, there are no ideal criteria for determining the cardiovascular risk of patients who present with chest pain at the ED. Because of this, it is crucial to identify markers that help ED physicians diagnose and treat these conditions accurately for both immediate diagnosis and accurate long- and short-term risk assessment, as well as for guiding patients to the appropriate follow-up. Thanks to its high specificity and sensitivity, troponin, a reference biomarker for myocardial damage, is nearly always employed to diagnose Acute Myocardial Infarction (AMI) since it represents the main biomarker in the management of patient with chest pain in ED, which can be measured in its two isoforms TnI and TnT. Since the plasma levels of these two molecules can rise in a variety of illnesses, including heart failure, chronic kidney disease, sepsis, and many others, dos-

ing these molecules frequently results in false positive results. Furthermore, cardiac troponin levels in the peripheral blood can be detected for days following myocardial cell death, which typically occurs 2-4 hours after the ischemia event.[2] However, the limitations of troponin entail the search for novel diagnostic biomarkers of ACS that could complement troponin. Therefore, in recent years, a number of emerging biomarkers have been proposed to facilitate the risk stratification of patients with CVD. These include sST2, suPAR, miRNA, galectin-3, GDF-15 and others.

For this reason, the aim of this review is to evaluate, on the basis of the most recent literature, which biomarkers are currently most helpful in the diagnosis of patients with chest pain and to predict cardiovascular risk, with a special focus on sST2 and SUPAR, beyond the widely used troponin, with the further aim of improving patient management within the ED. Indeed, emergency department overcrowding is a huge problem which entails increased mortality rates, costs and prolonged length of stays, decreased treatment quality and decreased safety of acute care. The ability to reliably predict future cardiac event incidence in patients is essential for their effective care and for the more appropriate allocation of limited healthcare resources.[4] By allowing more safe discharges in a short time, the patient flow could be improved and overcrowding avoided. In a clinical setting where diagnostic accuracy is crucial, the search for additional and complementary biomarkers to troponin reflects the growing need to improve the sensitivity and specificity of diagnoses.[5,6]

cTN

Cardiac troponin is one of the main biomarkers used in the assessment of cardiac damage. Its complex consists of the subunits troponin I (TnI), troponin T (TnT), and troponin C (TnC). During the cardiac cycle, this protein complex plays the main role in regulating Ca2+-dependent muscle contraction. These three subunits serve different functions: TnI regulates the interaction between actin and myosin, thus enabling the relaxation of the heart. TnT is involved in tropomyosin binding, promoting a controlled interaction between actin and myosin. TnC, the calcium-sensitive subunit, initiates muscle contraction, activating the complex.[7-9] This complex meticulously controls the heart muscle's cycles of contraction and relaxation under normal circumstances. Troponin is typically found in extremely low amounts; it is released into the bloodstream when cardiac muscle cells experience injury and its concentration in the blood rises with increasing injury. Since TnT and TnI subunit assays are the most cardiac-specific and offer equivalent diagnostic accuracy, they are frequently tested in the context of myocardial damage.[10] Because of their increased analytical precision, high-sensitivity troponin (hs-cTn) tests have made it possible to develop decision-making algorithms that are more accurate. The recent guideline issued by the European Society of Cardiology reiterates the preeminent role of cardiac troponins. The Fourth Universal Definition of MI in fact provided that a rise or fall of troponin I or T, when at least one hs-cTn value is above the 99th percentile of a normal population establishes the diagnosis of acute myocardial infarction.[11,12] This statement has been emphasized by recommendations issued by numerous scientific societies and several published articles.[13] Because of troponins' excellent diagnostic accuracy, individuals with chest pain can be quickly diagnosed with acute cardiac injury, facilitating safer and quicker "rule-in" and "rule-out" procedures. However, despite the broad support and evidence in favor of cardiac troponins, several studies highlight a persistent lack of confidence on the part of some physicians, who continue to use a combination of sometimes obsolete biomarkers. This discrepancy underscores the importance of carefully considering the clinical context and the different subcategories of cardiac injury when adopting valid multi-marker approaches for the diagnosis, prognosis and management of cardiac conditions. Four clinical factors, in addition to the presence or absence of MI, can influence hs-cTn values in a patient presenting with a suspected ACS, according to the 2023 ESC Guidelines for the Management of Acute Coronary Syndromes. These variables are: age, renal dysfunction, time from chest pain onset and sex.[14] It is important to note that, despite the significant innovation represented, high-sensitivity troponin presents some limitations in the evaluation of suspected ACS. As non-cardiac disease can cause increased troponin levels, troponin results need to be interpreted within a clinical decision protocol.[8] In some cases, troponin baseline value is chronically elevated and remains stable over time, as in Heart Failure (HF), a condition in which troponin has been shown to be an important prognostic factor. Elevated cardiac troponins (TnT and TnI) mainly reflect the progressive death of cardiomyocytes and the exosomal release of cytosolic troponin and are associated with an increased rate of hospitalization and death.[11] In contrast, a rising or falling troponin pattern can be attributable to a variety of underlying conditions other than ACS (e.g., valvular heart diseases, pulmonary embolism, sepsis, atrial fibrillation).[8,10,12] Furthermore, due to a decreased renal clearance of troponin and a myocardial damage associated with CKD, increased hsTn concentrations may be found in individuals with severe chronic kidney disease, even in the absence of ACS.[15] More crucial to proving the ACS hypothesis is the different increase and fall of hsTn. Regarding sex, significant variations in baseline results of extremely sensitive cardiac troponin may be explained by anatomical differences in the heart between men and women; nevertheless, sex-specific thresholds for ACS diagnosis are debatable.[16,17] Therefore, biotin, a water-soluble vitamin, could interfere with cardiac troponin assays. An elevated biotin concentration would in fact be responsible for falsely low hsTn results. For that reason, a safety communication to ward against this possible interference has recently been released by the Food and Drug Administration (FDA).[18] This potential phenomenon is of increasing interest due to high-dose biotin supplements taken for multiple sclerosis, dietary multivitamin preparations, and cosmetics. High-dose biotin could also be used by patients with metabolic disorders.[12,19,20] hs-cTn may be susceptible to interfere from heterophile antibodies,8-20 hemolysis, biological variation of cardiac troponin T, cardiac troponin autoantibodies, rheumatoid factor, lipemia, and hyperbilirubinemia.[12] Lastly, elevated values could be found in some patients with skeletal muscle disease.[8] In conclusion, multiple biomarkers in addition to cardiac troponin should be used to gain a more comprehensive and differentiated perspective of cardiac conditions due to the aforementioned restrictions. This method enables the evaluation of specific aspects of cardiac function, inflammatory responses and other factors that may contribute to diagnosis and prognosis. The combination of biomarkers improves the sensitivity and specificity of assessment, especially in complex situations, allowing for more precise and individualized management of cardiac conditions.

sST2

Suppression of tumorigenesis-2 (ST2), originally described in 1989,[21] is a member of interleukin (IL)-1 family receptors that

exists in two forms: a membrane-bound receptor (ST2L) and a soluble one (sST2). The natural ligand of ST2 is IL-33, a member of the IL-1 family, that has been involved in the pathogenesis of several diseases.[22] The IL-33/ST2L signaling inhibits Th1 cytokine production and leads to transcriptional activation of inflammatory genes, thereby increasing Th2 cytokine production that inhibits adverse cardiac remodeling and fibrosis, significantly reducing atherosclerosis progression.[23,24] Therefore, the interaction of IL-33 and ST2L may represent a cardioprotective factor. Conversely, sST2 is known to bind IL-33 thus playing a role of a decoy receptor and attenuates positive cardiac effects of IL-33/ST2L pathway.[22-28] ST2L and sST2 in the circulatory system are mainly found in the endothelial cells and secreted by fibroblasts and cardiomyocytes in response to mechanical stretching.[22] Cytokines from damaged tissues seem to induce the production of sST2 by the neighboring cells.[29]

ST2 has gained interest as a relevant tool in many fields. It was originally thought to be primarily involved in inflammatory diseases and allergies, including asthma, rheumatoid arthritis and inflammatory bowel disease.[21]

Currently its role as a relevant biomarker for patients with various cardiovascular diseases is recognized.

An increasing number of recent studies have advocated an important prognostic value of sST2, in both chronic and acute heart failure since it is less influenced by age, renal function than traditional biomarkers (NT-proBNP and hs-TnT).[30] sST2 in fact meets some interesting criteria of clinically useful biomarkers. First of all, it's accurate and provides information to guide risk stratification; secondly it has a reasonable cost.[28]

A prospective cohort study by Wang *et al*. enrolled 331 patients with acute HF stratifying them according to sST2 levels. The study revealed that higher sST2 concentrations are strongly correlated with adverse outcomes.[31,32]

A systematic review and meta-analysis by Ip *et al.* demonstrated that elevated levels of sST2 are a predictor of severe chronic HF and tend to be associated with a higher risk of mortality in chronic HF and stable CAD.[29] A prospective study by Rezar *et al.* also suggests measuring serum sST2 levels 24 h after admission for prognostication after cardiopulmonary resuscitation.[33] Furthermore, in the STADE-HF study, an ancillary study of a randomized trial: NCT02963272, sST2 showed to be better associated with the risk of hospitalization when compared to suPAR, which, in contrast, resulted associated with long term mortality.[34] It was also revealed that sST2-guided therapy does not decrease readmissions. This study was aimed to evaluate a sST2-guided treatment in patients hospitalized for acute HF. Unlikely, the approach proposed failed.[35]

The American Heart Association/American College of Cardiology (AHA/ACC) Guidelines for HF Management included as a risk stratification marker (class II level of evidence B) the measurement of sST2 levels in patients with ADHF. A cut-off value of sST2 $\geq$ 35 ng/mL is proposed as a predictor for worse prognosis in patients with HF.[36] In the latest edition of the same guidelines, dated 2022, however, this recommendation is not reported.[28]

Concerning ACS, the role of sST2 in less clear. It seems to be involved in the progression of atherosclerosis. Several studies have proposed that the IL-33/ST2L interaction in the coronary arterial wall may prevent cardiomyocyte apoptosis, reduce myocardial fibrosis and myocardial maladaptive hypertrophy thus limiting plaque inflammation and evolution.[21,26,29] Therefore, elevated sST2 levels would promote inflammation and result in plaque progression preventing the circulating IL-33 from binding to ST2L. A recent review proposes sST2 assisted flowcharts as an innovative useful tool to manage very common clinical scenarios of the ED: Acute HF, type 1, and type 2 AMI.[22]

The predictive value of sST2 and IL-33 in patients with ACS has been investigated recently. A significant increase in sST2 and IL-33 was found in patients with AMI compared with healthy controls.[25] A recent cross-sectional study found that sST2 levels did not correlate with infarct location in a statistically significant way.

On the contrary, it was advocated that serum sST2 levels correlated with baseline infarct volume and endocardial extent of infarction.[37]

A recent study by Zhang *et al.* also proposed that sST2 could be a useful tool in the detection of atherosclerotic plaques vulnerability[38] and this correlation was further investigated by *Luo et al.* who proposed a correlation between serum sST2 levels and the necrotic core in coronary lesions.[39] Furthermore, Van den Berg *et al.* showed that post-ACS patients with persistently elevated sST2 concentrations are at higher risk of recurrent ACS or cardiac death during one year of follow-up.[40] In agreement with these findings, a recent meta-analysis and a prospective observational study investigated the association between sST2 and long-term prognosis of patients with CVD showing that elevated baseline sST2 concentrations were associated with higher risk of major adverse cardiovascular events (MACE).[41,42] Chen *et al.* hypothesized that in a cohort of patients admitted to hospital with various forms of CVD higher sST2 level correlated with the risk of future hospital admission due to MACE within 1 year.[43]

suPAR

The soluble urokinase plasminogen activator receptor (suPAR) is a soluble form of the urokinase plasminogen activator receptor (uPAR), bound to the cell membrane across a glycosylphosphatidylinositol anchor, and released from the proteolytic cleavage of uPAR.[44] This protein is anchored to the membranes of different types of cells, like endothelial and smooth cells, and it is involved in different pathophysiological pathways, like plasminogen activation, fibrinolysis, angiogenesis, and inflammatory response, contributing to leukocyte migration.[45,46] SuPAR is mainly localized in immunity cells; therefore, plasma levels of this protein correlate to immunological activation.[3] A correlation between increased suPAR values and molecules involved in the inflammatory response like TNFα, IL-6, and CRP is known.[45] SuPAR can be measured in different biological fluids, like plasma, urine, and cerebrospinal fluid;[47] generally, it is assessed in plasma using the enzyme-linked immunosorbent test (ELISA).[44]

Commonly, values <3 ng/mL are considered normal, values > 6 ng/mL are indicative of abnormalities, and intermediate values (3-6 ng/mL) need to be contextualized.[45] Literature reports variations in suPAR values in relation to socio-biological factors. For example, differences based on sex and age are known; in their study, *Rasmussen et al.* showed that men and women ≥74 years present approximately the same suPAR levels, while in younger women suPAR levels are higher; however, in males suPAR appears to rise more with increasing age than in women.[45] Furthermore, habits like drinking or smoking appear to be related to increased suPAR values.[48] About that, Wohlwend *et al.* demonstrated higher suPAR plasma levels in smokers, an inverse proportionality between suPAR and HDL serum values, and the relationship between suPAR and endothelial dysfunction.[49] Due to its involvement in various pathophysiological pathways and its examination

in various situations for its diagnostic and prognostic role, suPAR has generated a great deal of fascination in recent years. It has been studied, for instance, in cases of septic shock, acute pancreatitis, cardiovascular and pulmonary disease, and SARS-CoV-2 infection.[47] A few numbers of studies show a relationship between suPAR and proinflammatory cytokines, including TNF-α, IL-1β, and IL-66,[50] which may be connected to the susceptibility of the atherosclerotic plaque to rupture.[47] Indeed, various cell types that express uPAR on their cell membranes have been discovered in the atherosclerotic arteries, including macrophages and endothelial cells. Proinflammatory cytokines and proteolytic enzymes are generated throughout time, increasing the quantity of suPAR and encouraging uPAR cleavage.[4] Hindi *et al.* showed increased circulation levels of suPAR in suPARTg animals with larger atherosclerotic plaques in a study based on transgenic mice (suPARTg). Several studies have examined the connection between cardiovascular disease and suPAR levels in recent years, considering the protein's function in endothelial damage and inflammatory response.[50] In one of their meta-analyses, Pruc *et al.* underline how suPAR seems to be involved in the pathogenesis of ACS. Indeed, in the 5 studies that they have examined, including 3417 patients (1148 with ACS and 2269 in the control group), they demonstrated a statistically significant relationship between ACS and suPAR levels.[47] Literature shows many studies which suggest that prognostic data may be obtained from suPAR for patients with suspected AMI, considering the prognostic value in the short and long term. In their study, Sörensen *et al.* evaluated suPAR in a population of 1314 patients presenting to the emergency department for chest pain and suspected AMI. To evaluate the one-year mortality, these patients have been followed for 12 months. suPAR levels were slightly higher in the patients who were diagnosed with AMI than in the non-AMI patients; however, in this study, the difference did not reach statistical significance. Follow-up of 1 year documented 39 deaths among non-AMI patients and 29 among AMI patients; in this case, suPAR was revealed to be an independent risk factor for all-cause mortality.[51] A recently published meta-analysis by Rehan *et al.* investigated the impact of suPAR in the setting of the emergency department, valuing different outcomes such as 30-day mortality, 90-day mortality, 30-day readmission, discharge within 24 hours and length of hospital stay. In particular, they showed that there is a higher risk of death within 30 and 90 days when suPAR concentrations are elevated. Indeed, they observed a significant association with 30-day readmissions and a lengthening hospital stay.[3] Several studies demonstrated that suPAR is elevated in patients with cardiovascular disease and acute myocardial infarction. In one of their studies, Chenevier-Gobeaux *et al.* considered the early prognostic value of suPAR in patients presenting to the ED with chest pain suggestive of ACS, compared to that of usual cardiac biomarkers. Their results showed that suPAR concentrations at the admission were higher in chest pain patients with a 30-day event in comparison to patients without, and a suPAR value at admission above 3.3 ng/mL was independently associated with a 30-day event. Therefore, suPAR demonstrated to be a strong predictor of mortality and of readmission. They also showed an association of HEART score (a ESC tool wich calculate the 10-year risk of fatal and non-fatal cardiovascular disease events, based on 5 points: history, ECG, age, risk factors, troponin) and biomarkers at admission; particularly, low suPAR, low NT-proBNP and a low HEART score had a high negative predictive value to exclude a 30-day event.[52] In their study based on 1747 acute medical patients, Santeri *et al.* proposed possible cutoffs of suPAR to predict low, medium and high risk of 30- and 90-day follow-up. Of these patients, almost half had a suPAR level below 4 ng/mL, and the 30- and 90-day risk of mortality were below 1%, while patients with suPAR above 6 ng/mL had a high 90-day mortality of 20%. In consideration of these data, they suggest that a cut-off below 4 ng/mL seems useful as a potential discharge biomarker, and may be part of a decision to discharge the patient.[53] In their review of 39 studies, Vellisaris *et al.* summarizes the published literature about suPAR values in patients with cardiac diseases. They considered patients with acute coronary syndromes and congestive heart failure, and demonstrated that suPAR elevation may be an independent predictor of mortality in these conditions, representing a promising prognostic and diagnostic indicator for improved accuracy in patient risk stratification.[54] In their study (STADE-HF study), Huet *et al.* showed high suPAR serum levels in case of HF, evaluating its use as a prognosis biomarker in global mortality and risk of readmission after acute HF. They measured suPAR level at patient admission in 47 patients from the control group; moreover, they measured sST2 in 50 patients belonging to the sST2 group. They proved that suPAR levels were independently associated with mortality at 1 month and 1 year for patients with acute HF, but without significant prediction of the hospitalization risk and it was a stronger predictor for mortality than other biomarkers (sST2, NT-proBNP or CRP).[34] Bengaard *et al.* described an overall risk of readmission and mortality significantly increased for patients with higher suPAR,[55] while Al-Badri *et al.* showed that high suPAR and hsTnI levels were independently associated with a higher risk of all□cause death and MACE.[56] Moreover, hs-CRP, NT-proBNP, and suPAR showed different associations with cardiovascular death among apparently healthy younger and older men and women.[57] Hodges *et al.* also demonstrated that suPAR is an independent predictor of death/myocardial infarction in patients with suspected or known coronary artery disease, but they showed that it is not associated with the presence or severity of coronary artery disease, probably because a high suPAR is reflecting end organ damage regardless the degree of atherosclerosis.[58] In a their interesting study, Vellisaris *et al.* are agree that suPAR may be a promising addition to the established biomarkers for the initial assessment of patients in the ED, management and risk stratification, but additional studies are necessary to evaluate the usefulness of suPAR guided management algorithms.[48] These results are in line with the recent literature and suggest that suPAR appears to be more effective than diagnostic biomarkers, and it can predict the occurrence of cardiovascular disease and tends to positively correlate with its severity.[47] For this reason, suPAR may be useful in the assessment of the emergency department's risk stratification and in improving its management.[59] However, further evidence is needed.

Other biomarkers

In the past few years, numerous inflammatory mediators have been studied as potential biomarkers of cardiovascular and ischemic heart disorders in addition to the molecules previously described. In particular, these are mediators implicated in the inflammatory response and in the process of formation and complication of atherosclerotic plaques which, as is known, are often implicated in cardiovascular disease. Indeed, a plaque complication is actually the primary cause of AMI in most patients. Likewise, inflammatory processes in the core of a complex atheromatous plaque dictate its rupture and consequent ACS. While sST2 and suPAR, beyond troponin, seem to be the emerging biomarkers for ACS risk, involved in patient outcome prediction too, other biomarkers that are still under investigation appear to be signifi-

cant in the prediction of cardiovascular events such as interleukin, miRs and GDF-15. Some examples are briefly shown below.

Copeptin

Copeptin, first described in 1972 by Holwerda, is a 39-aminoacid glycopeptide derived from the C-terminal segment of Arginine Vasopressin (AVP) precursor. AVP has a role in fluid imbalance and in vascular tone regulation, thus contributing to cardiovascular system homeostasis. Copeptin is released into the bloodstream, in equivalent amounts to AVP, so measuring copeptin appears to be a clinically valuable approach for assessing plasma amount of vasopressin. Unlike AVP, copeptin's physiologic role is not yet clear. At present, copeptin was proven to show the same response as AVP to hypotension or hemodynamic stress.[60-64]

In recent years, Copeptin has gained growing interest as part of a Dual Marker Strategy (DMS) in combination with Cardiac Troponin (cTn) in promptly ruling out Acute Myocardial Infarction (AMI) in patients presenting with symptoms suggestive of ACS.[63] Several studies, among which the most important is the Copeptin Helps in the Early Detection of Patients with Acute Myocardial Infarction (CHOPIN) trial, a multicenter international cohort study, support that copeptin and hs-cTnT in combination has the potential to allow a faster ruling of AMI when compared to the hs-cTnT-only-based algorithms and enables a useful reclassification of profile risk of patients.[65-68] In fact, it has been shown that copeptin rises to peak values within 30 min after the onset of chest pain in patients with acute MI, thus covering the period where hsTn levels are still undetectable and gradually decreases within 12–36 hours in early presenters.[66,69-72] Therefore, the DMS has been seen to early detect acute myocardial injury and also obviates the need for serial sampling. In contrast, it provides no further information that standard troponin in late presenters.[68,69-71] Furthermore, In the Accelerated Rule-Out of AMI using copeptin and high sensitivity troponin (AROMI) trial, that enrolled 4351 patients with chest pain, it was found that an accelerated DMS that integrates prehospital copeptin and first in-hospital hs-cTnT can safely reduce patients' length of stay in ED.[73]

In addition, the 2023 ESC Guidelines on patients without persistent ST-segment elevation states a possible value of copeptin as additional biomarker to high-sensitivity cTn, since copeptin may quantify the endogenous stress level that characterize MI even if its incremental value beyond cTn is referred as limited.[14]

Moreover, copeptin plays a role as a prognostic biomarker, being associated with the 1-year mortality and adverse outcomes not only in ACS but also in non-ACS conditions. [64-67]

However, recent studies, suggest that serum levels of copeptin are upregulated under various conditions (e.g. heart failure, metabolic syndrome, hypertension, acute kidney injury, pulmonary embolism, sepsis, acute pancreatitis,ischemic stroke) and that they are linked to the severity of these clinical situation.[62-64,66,67-70]

Interleukins

The Interleukin (IL) family includes numerous molecules implicated in various biochemical pathways and in the majority of inflammatory processes. In recent years, many of these have been studied for their role in CVD. Of these, the IL-17 family better correlates with the development of ACS; it has been demonstrated that both IL-17A and IL-17E plasma levels are increased in such patients. Furthermore, their increase correlates with the severity of the condition. Moreover, inflammatory cytokines such as IL-1β and IL-6 have adverse impacts on the structure and function of the heart. According to some studies, a correlation between sST2 and IL-1β has been identified in patients with HF: patients with heart failure who had low sST2 and low IL-1β, in particular, had a much decreased risk of dying from cardiovascular disease as compared to patients with high sST2 and high IL-1β.[2,62]

Adhesion molecules (ICAM-1 and VCAM-1)

Adhesion molecules called VCAM-1 and ICAM-1 also appear to participate in the inflammatory process and, in particular, shown a role in drawing leukocytes to the endothelium during inflammation and sustaining the inflammatory response. These leads to the creation of atheromatous plaques, which raises the risk of CVD and ACS.[2]

miRs

miRs are small, non-coding RNAs, which are involved in the regulation of gene expression, modulating protein synthesis. Different miRs could be involved in atherosclerosis and CVD, such as miR-146a, miR-26a, miR-499, miR-133b and miR-21. Of these, miR-146a seems to be more involved in development of coronary heart disease. Xue *et al.* studied patients with acute myocardial infarction observing how miR-146a represents an optimal diagnostic biomarker of cardiovascular disease.[74]

However, while some miRs correlate positively with cardiovascular risk, others correlate negatively, being downregulated in presence of myocardial damage.[2]

In recent years, several studies have addressed these molecules as possible biomarkers of cardiac damage and prediction of cardiovascular risk; however, further evidence is needed.

GDF-15

Growth differentiation factor 15 (GDF-15) is a biomarker belonging to the TGF-β cytokine, especially expressed in myocardium and endothelial cells, implicated in the inflammatory response and oxidative damage, considered as the triggers that can up regulate its expression.[75] It has been mainly studied in the context of acute and chronic heart failure. However, it is currently being studied primarily for its role in chronic heart failure. Based on current evidence, high levels of GDF-15 are associated with a poor prognosis for patients with acute heart failure. The elevated serum level of GDF-15 was the most prognostic biomarker in comparison to NT-proBNP, hs-CRP, and hs-TnT and an independent predictor of long-term mortality in advanced HF.[62,76] Recent studies propose an association between elevated GDF-15 levels and different clinical conditions (e.g., ineffective erythropoiesis inflammation, acute injury, cancer, and chronic kidney disease, ischemic stroke). Concerning ACS, it has been established that GDF-15 levels rise in just a few hours after MI.[64] However, in consideration of its important functions, a role in acute care must be further evaluated; for these reasons focused studies are necessary.

MR-proADM

Mid regional pro adrenomedullin (MR-proADM) is the precursor of adrenomedullin, a protein expressed in different tissues and cells and involved in several pathways and biological mechanisms, such as natriuresis or vasodilatation. In recent years, it has been demonstrated that MR-proADM plays an important role in the course of cardiovascular disease, in relation to its multiple functions.

A significant review by *Berezin AE* and *Berezin AA*, showed that circulating levels of MR-proADM were increased in patients with acute HF and STEMI, and also allowed to estimate adverse outcomes, including death. Additionally, serum levels of MR-

proADM >0.70 nmol/L were proposed to be the rule-in criteria of AMI. In the same review, the results of the DANAMI-3 (The Danish Study of Optimal Acute Treatment of Patients with ST-segment-elevation myocardial infarction) study have shown that elevated levels of MR-proADM were strong predictor of shortand long-term mortality and hospital admission for HF after AMI. Mostly, MR-proADM was able to predict major adverse cardiac events in patients suspecting AMI regardless of HF.[62] MR-proADM also emerged as the best predictor of 1-year death after the diagnosis of acute HF in some recent studies.[76]

Galectin-3

Galectin-3 is a β-galactoside-binding protein expressed in myocardial cells and released from activated macrophages, and it is implicated in myocardial remodeling.[63] It had been investigated as a biomarker of inflammation with a promising predictive value for heart failure and cardiovascular events. Galectin-3, like GDF-15, has also been more investigated in heart failure. Different studies showed that serum galectin-3 values were significantly higher in patients with acute HF. In a prospective study on chronic HF and coronary heart disease, increased galectin-3 levels in patients with HF were an independent predictor of all-cause mortality and rehospitalization within a 12-month follow-up period.[77] Elevated levels of galectin-3 were also found in patients with adverse cardiac remodeling, but comparison of sST2 and galectin-3 has revealed the superiority of sST2 in long-term risk stratification.[62,76] Patients who experienced early MACE had significantly higher galectin-3 and MR-proANP levels assessed on admission; however, a high concentration of galectin-3 observed on admission may also identify patients at high risk of late MACE.[78]

H-FABP

Heart-type Fatty Acid Binding Protein (H-FABP) is a low molecular weight protein that is expressed in cardiomyocytes and released when myocardial damage has occurred. This is the reason why it could be considered as an early predictor of ischemic heart damage. Its concentration increases before that of Troponin in ACS and is not affected by renal function. These features suggest H-FABP could be a useful tool in clinical practice.[75] Furthermore, H-FABP and sST-2 are the most promising markers with better accuracy in differential diagnosis between Takotsubo syndrome and acute coronary syndrome, which are clinically indistinguishable. In their study, *Topf et al.* show how H-FABP is significantly higher in ACS patients compared to TTS patients; whereas sST-2 was significantly elevated in TTS patients.[75,79]

Renelase

Renalase is a new class of flavin adenine dinucleotide-containing Monoamine Oxidases (MAOs). They are Involved in numerous cardiovascular diseases, such as HF, Coronary Artery Disease (CAD), hypertension, diabetes mellitus. Stojanovic *et al.* confirmed that elevated plasma renalase concentration in chronic HF patients.[80] Renalase may be a valuable prognostic factor for ischemia during exercise stress tests in chronic HF patients. Renalase, in line with sST2, galectin-3, and GDF-15, clearly demonstrated non-inferiority for ischemia prediction compared to BNP. In the HF, renalase discriminatory potential was similar to that of sST2, but better compared to those of galectin-3 and GDF-15.[80]

Discussion

ACS remains the leading cause of death in the world and carries the risk of the development of Major Adverse Cardiovascular Events (MACE). According to standard clinical care, sequential troponin measurement (0-1h) accompanied by ECG tracing represents the goal standard of diagnosis. Despite several attempts to build standardized models for the correct management of patients presenting with chest pain and no diriment ECG findings and troponin measurement, there are no ideal criteria for determining the likelihood of a cardiovascular etiology and the diagnostic pathway. Because of this, numerous biomarkers have gained growing interest with the purpose of helping ED physicians to diagnose and treat these conditions in a proper way also allowing faster discharge.

This review has the aim to summarize the published literature in the last five years referring to the contemporary use of some promising biomarkers. The strengths and limitations of conventional biomarkers as cTn have also been evaluated. A PubMed and Reviews in Cardiovascular Medicine search was conducted from January 2019 to January 2024 aiming to identify all interesting publications. The search terms were: suPAR (or soluble urokinase plasminogen activator receptor), sST2 (or soluble suppression of tumorigenesis), acute coronary syndrome, cardiac troponin. A total of 80 articles were included in the final review. At first this review focuses on cardiac troponin (cTn) that, to date, is the main biomarker used in the assessment of cardiac damage, being released into the bloodstream when cardiac muscle is injured. For its elevated accuracy, numerous scientific societies indicate determination of serum cTn as the choice criteria for the diagnosis of acute cardiac ischemia and to facilitate safer and quicker patients "rule-in" and "rule-out". However, cTn values must be contextualized with the clinics and electrocardiographic findings. In fact, non-cardiac etiologies of myocardial damage can cause increased troponin levels.[8,10,12,14]

sST2 and suPAR (the two main biomarkers on which we focused) have been investigated for their diagnostic role and for their ability to predict short and long-term mortality. Recently, those tools have also been considered in the context of chronic cardiovascular pathologies.

sST2 is the soluble form of ST2, a member of interleukin-1 family receptors. Cytokines from damaged tissues, such as myocardium, seem to induce the production of sST2, contributing to the persistence of the inflammatory process. [21,22,25-28] Recently, several studies have advocated an important prognostic value of sST2; indeed, its values do not depend on factors such as age or renal function than standard biomarkers.[30] Different studies showed a correlation between its levels and chronic cardiovascular diseases associated with higher risk of MACE.[29,41]

In the ED setting, the role of sST2 in ACS is still unclear. Certainly, it seems to be involved in the progression of atherosclerosis and its complications, thus often representing the ACS trigger.[20,25,28] Some studies showed a significant increase of sST2 and IL-33 in patients with AMI when compared to healthy controls.[22] sST2 levels were also evaluated as a prognostic factor after cardiopulmonary resuscitation.[33] In addition, other studies highlighted that patients with persistently elevated sST2 concentrations post-ACS have a higher risk of recurrence or death during one year after the event.[40] Other studies analyzed are listed in Supplementary Table 1.

Therefore, suPAR is another biomarker on which authors have shown great interest in recent years. It is the soluble form of the urokinase plasminogen activator receptor (uPAR), bound to differ-

ent cell membranes and it is involved in several pathophysiological pathways.[4,50,51] Commonly, values < 3 ng/mL are considered normal, but literature reports variations in suPAR threshold in relation to socio-biological factors.[44,48,50] Some studies showed a relationship between suPAR plasma levels and endothelial dysfunction, explaining its relationship with cardiovascular risk factors, since it correlates with the release of proinflammatory cytokines, which may be linked to the susceptibility of the atherosclerotic plaque.[4,45,49,50]

A statistically significant relationship between ACS and suPAR levels is demonstrated in different studies.[47,58]

In researches performed in the emergency setting, suPAR levels correlated positively with suspected AMI and assessed one-year mortality, resulting higher in patients who were diagnosed with AMI than in the non-AMI patients. It correlates also with post-discharge mortality.[3,51] For these reasons, suPAR may be a promising addition to the consolidated biomarkers for the management of patients in the ED and for their risk stratification. However, further evidence is needed.

Furthermore, other molecules which have attracted greater interest in the field of cardiovascular disease have been taken into account and their possible use in clinical practice is summarized below.

For instance, Copeptin has gained attention as part of a dual marker approach, in combination with cardiac troponin (cTn), in promptly ruling out Acute Myocardial Infarction (AMI) when patients present with chest pain.[63] Indeed, copeptin rises to peak values within 30 min after the onset of chest pain in patients with acute MI, unlike troponin whose levels may still be undetectable in the early hours; for this reason copeptin could allow a timely diagnosis even before the troponin rise.[66,69-72]Also the latest 2023 ESC Guidelines indicate a possible value of copeptin as an additional biomarker to high-sensitivity cTn in patients without persistent ST-segment elevation states.[14]

Moreover, copeptin appears to be associated with 1-year mortality and adverse cardiovascular outcomes.[64-67]

In addition, IL- family molecules seem to be involved in the inflammatory mechanism underlying the complication of atherosclerotic plaque; in fact molecules such as IL-17 and inflammatory cytokines like IL-1β and IL-6 correlate with the development of CAD.[2,62] Adhesion molecules like VCAM-1 and ICAM-1 also have a role in drawing leukocytes to the endothelium during inflammation and sustaining the inflammatory response; for this reason they have shown a role in the atheromatous plaques creation and complication which raises the risk of CVD and ACS.[2] miRs, such as miR-146a, miR-26a, miR-499, miR-133b and miR-21, could be involved in atherosclerosis and CVD. Of these, miR-146a seems to be more implicated in development of CHD.[2,72] GDF-15 has been largely studied in the context of acute and chronic heart failure. Based on the current evidence, high levels of GDF-15 are associated with a poor prognosis.[62] Likewise MR-proADM plays an important role in the course of cardiovascular disease. An increased value has been found in both chronic and acute cardiovascular disease too. An interesting study has shown that elevated levels of MR-proADM were a strong predictor of short and long-term mortality and hospital admission for HF after AMI.[62,76] Galectin-3, a protein expressed in myocardial cells and released from activated macrophages, had been investigated as a biomarker of inflammation with a promising predictive value for heart failure and cardiovascular events. Increased galectin-3 levels in patients with HF were an independent predictor of all-cause mortality and rehospitalization within a 12-month follow-up period.[63,77,78] Elevated levels of galectin-3 were also found in patients with adverse cardiac remodeling, but sST2 seems to be superior in long-term risk stratification in HF.[62] A high concentration of galectin-3 observed on admission may also identify patients at high risk of late MACE.[78]

H-FABP is a protein expressed in cardiomyocytes and released when myocardial damage has occurred, which seems to be decisive in the differential diagnoses of some conditions.[79] Finally, Renalase, a new class of MAOs, are involved in numerous cardiovascular diseases, such as HF, CAD, hypertension, diabetes mellitus. Elevated plasma Renalase concentration had been found in chronic HF patients.[80]

In summary, several recent studies have addressed these molecules as possible biomarkers of cardiac damage and predictors of cardiovascular risk; however, larger further investigations are needed to better understand the correlation between these molecule levels and ACS risk, to allow prompt diagnosis and facilitate patients' management in the ED.

Conclusions

Biomarkers play a key role in risk stratification, diagnosis and prognosis assessment of patients with suspected ACS; indeed, some circulating biomarkers may reflect pathophysiological pathways involved in ACS. sST2 and suPAR are promising biomarkers that, given the limitations of troponin, could help in the management of patients with chest pain in the ED. Further studies are needed to validate their role in management of ACS in this specific setting. Therefore, further evaluation to establish the diagnostic and prognostic value of these biomarkers is warranted. Additional future research should also compare the accuracy of these tools with the traditional approved biomarkers in the ED and to evaluate their introduction in clinical practice.

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Online Supplementary Materials

Table 1. Brief summary of all studies performed on sST2 in relation to CVD.

Table 2. Brief summary of all studies performed on suPAR in relation to CVD.