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Opinion Paper

Considerations for early acute myocardial infarction rule-out for emergency department chest pain patients: the case of copeptin

Giuseppe Lippi[1,*], Mario Plebani[2], Salvatore Di Somma[3], Valter Monzani[4], Marco Tubaro[5], Massimo Volpe[6], Paolo Moscatelli[7], Arialdo Vernocchi[8], Mario Cavazza[9], Marcello Galvani[10], Piero Cappelletti[11], Giancarlo Marenzi[12], Simona Ferraro[13], Alberto Lombardi[14] and Andrea Peracino[14]

[1] U.O. Diagnostica Ematochimica, Dipartimento di Patologia e Medicina di Laboratorio, Azienda Ospedaliera di Parma, Parma, Italy
[2] Dipartimento Medicina di Laboratorio, Azienda Ospedaliera-Università di Padova, Padua, Italy
[3] Medicina d'Urgenza e Pronto Soccorso, Ospedale Sant'Andrea, Rome, Italy
[4] U.O. Medicina d'Urgenza e Pronto Soccorso, Ospedale Maggiore Policlinico Milano, Milan, Italy
[5] ICCU, Cardiovascular Department San Filippo Neri Hospital, Rome, Italy
[6] Dipartimento di Medicina Clinica e Molecolare, Facolta' di Medicina e Chirurgia, Universita' di Roma Sapienza, Rome, Italy e IRCCS Neuromed, Pozzilli, Italy
[7] U.O. Medicina d'Urgenza e Pronto Soccorso, Azienda Ospedaliera Universitaria San Martino, Genoa, Italy
[8] Servizio di Medicina di Laboratorio, IRCCS Multimedica, Milan, Italy
[9] U.O. Medicina d'Urgenza e Pronto Soccorso, Policlinico Sant'Orsola Malpighi, Bologna, Italy
[10] U.O. Cardiologia, Ospedale G.B. Morgagni-L. Pierantoni, Forli', Italy
[11] Laboratorio di Patologia Clinica, Azienda Ospedaliera "Santa Maria degli Angeli", Pordenone, Italy
[12] Unità Operativa di Cure Intensive Cardiologiche, Centro Cardiologico Monzino, Milan, Italy
[13] Ospedale Maggiore della Carità, SCDO Cardiologia 2, Novara, Italy
[14] Fondazione Giovanni Lorenzini Medical Science Foundation, Milan, Italy, and Houston, TX, USA

*Corresponding author: Giuseppe Lippi, Direttore U.O. Diagnostica Ematochimica, Dipartimento di Patologia e Medicina di Laboratorio, A.O. Universitaria di Parma, Italy
Phone: +39 0521 703050, Fax: +39 0521 703197,
E-mail: glippi@ao.pr.it
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Abstract

The evaluation of patients admitted at the emergency department (ED) for chest pain is challenging and involves many different clinical specialists including emergency physicians, laboratory professionals and cardiologists. The preferable approach to deal with this issue is to develop joint protocols that will assist the clinical decision-making to quickly and accurately rule-out patients with non life-threatening conditions that can be considered for early and safe discharge or further outpatient follow-up, rule-in patients with acute coronary syndrome and raise the degree of alert of the emergency physicians on non-cardiac life-threatening emergencies. The introduction of novel biomarkers alongside the well-established troponins might support this process and also provide prognostic information about acute short-term or chronic long-term risk and severity. Among the various biomarkers, copeptin measurement holds appealing perspectives. The utility of combining troponin with copeptin might be cost-effective due to the high negative predictive value of the latter biomarker in the rule-out of an acute coronary syndrome. Moreover, in the presence of a remarkably increased concentration (e.g., more than 10 times the upper limit of the reference range), to reveal the presence of acute life-threatening conditions that may not necessarily be identified with the use of troponin alone. The aim of this article is to review current evidence about the clinical significance of copeptin testing in the ED as well as its appropriate placing within diagnostic protocols.

Keywords: acute myocardial infarction; biomarkers; chest pain; copeptin; troponin.

Chest pain in the emergency department: the central role of the patient and the clinical questions

Chest pain is a general symptom associated with a broad spectrum of cardiac as well as non-cardiac diseases. It characterizes patients in benign conditions of pulmonary, gastrointestinal, musculoskeletal, and psychogenic origins, who often do not require hospital admission, as well as those needing urgent triage and treatment (1). In Italy, approximately 1 million patients each year present to the emergency department (ED) with chest pain symptoms. Forty five percent of these have acute coronary syndromes (ACS), whereas nearly

17.6% have a final diagnosis of acute myocardial infarction (AMI) (2, 3).

The remarkable advances in understanding the pathophysiology of ACS and AMI that has achieved over the last 20 years have led to the validation of new diagnostic techniques, development of specific chest pain units (CPU), introduction of evidence-based protocols, integration of novel biomarkers or improved assays, and validation of risk scores to assist clinicians to better stratify the patients with suspected ACS (4–8).

The problem of chest pain management is not marginal, since at least one third of all chest pain patients are hospitalized for an average of about 4 days without a final discharge diagnosis related to cardiac disease, whereas nearly 2%–8% are inadvertently discharged despite having an ACS (9–11). In a large study from the US including 10,689 chest pain patients, the number of missed diagnosis in the ED was estimated to be relatively low, i.e., 2.1% for AMI and 2.3% for unstable angina, respectively, although these patients had high mortality (7).

Thus, the management of these patients poses a major challenge for the ED, to quickly and correctly identify all ACS and contextually avert unnecessary invasive procedures and inappropriate use of hospital and healthcare resources. The inadvertent discharge of ACS patients is associated with a short-term mortality of 2%–4% and a two-fold increase in risk-adjusted mortality as compared with hospitalized patients (12).

Despite a slight change of mortality rates in recent years, AMI still represents the leading cause of death in industrialized countries (13), while its prevalence is also sharply increasing in third-world countries. An effective management of chest pain patients requires two distinct approaches, both meeting the immediate need for ruling out of AMI and the longer term need for ACS risk stratification. ACS represents a pathophysiological continuum, ranging from a transitory decrease of myocardial perfusion (i.e., ischemia) at rest, to infarction of myocardial tissue and irreversible injury (i.e., necrosis). The importance of focusing on ruling out ACS, and not only AMI, reflects the need to identify patients with unstable angina (UA) to prevent the morbidity and the mortality associated with untreated cardiac ischemia (14–17).

Currently, the main goal of an effective step-wise workup for chest pain is to provide early discrimination of patients with life-threatening conditions, requiring urgent triage and care (e.g., AMI, pulmonary embolism and aortic dissection), from those carrying more benign entities not requiring admission, or that could be safely discharged for further testing (18). The aim of the diagnostic strategy is to focus on the differentiation between high- and low-risk patients, with the primary endpoint to correctly identify patients that can be considered for an early discharge (i.e., 'rule-out strategy'). To this purpose, a minimal set of effective diagnostic tests with a high negative predictive value (NPV) for ACS should be performed and interpreted together, according to defined protocols and validated diagnostic algorithms (19).

Scoring systems are often used for stratifying risk, but they present several limitations. They are generally derived from selected populations enrolled in clinical trials and often exclude patients in the highest and lowest risk categories (20). Therefore, in clinical practice, some variables (i.e., ECG findings, biomarkers of necrosis, renal dysfunction, older age, evidence of hemodynamic instability) common to different scoring systems seem to be more effective to identify patients at lower risk and allow consideration for management in the CPU or outpatient setting in current clinical practice (21).

It is important to achieve an effective clinical decision regarding the diagnosis and treatment. This is not a trivial task since the percentage of repeated visits to the CPU by patients with negative evaluations can be as high as 21% (22, 23). These patients often require attention to possible psychological issues, but also a more careful reassessment, to rule-out potential cardiac causes of symptoms and to plan other diagnostic investigations. The availability of a broad spectrum of second level diagnostic tools should be optimized, due to the considerable prevalence of chest pain patients with unconventional risk profiles requiring additional tests upon presentation, in order to improve the diagnostic accuracy (in terms of NPV) of the conventional first level tools (24, 25).

Myocardial perfusion imaging should be assessed in patients with diabetes mellitus and previous history of coronary artery disease (CAD) as well as increased risk for ACS because the diagnostic performance of conventional tests may be limited by these co-morbidities at presentation (26, 27). In particular, female patients may exhibit a higher rate of false-positive tests, often due to labile ST-segment changes, baseline ECG alterations and breast artifact. AMI can also be easily misdiagnosed since patients may initially present with atypical symptoms, such as shortness of breath, abdominal pain, symptoms of congestive heart failure and a young age, all factors suggestive for a lower risk for ACS (28). Thus, in certain clinical settings exercise treadmill test (ETT), along with myocardial imaging or stress echocardiography are specifically recommended (29–32). Although young patients are generally considered at lower risk for ACS under normal conditions, the presence of co-morbidities, metabolic syndrome, and the use of cocaine and other drugs may shift these patients from a lower to a higher risk category (16). Within the diagnostic approach, CT angiography is increasingly being used in the assessment of chest pain, although this frequently varies according to local practice and availability.

A cost-effective diagnostic pathway to meet the needs of the different stakeholders

Many stakeholders (33, 34) are involved in the appropriate diagnostic pathway and care of patients that present to the ED with chest pain. Healthcare facilities and hospitals should consider both a cost-effective diagnostic pathway and contextually offer services that consider the patient's best interest. This assessment needs ideally to maximize the benefit for the national healthcare system, the local hospital as well as the patient health (35–38).

Several national and international guidelines have been released to meet this goal, which offer standardized diagnostic approaches in order to ensure fast and effective triage, avoid unnecessary expenditures, patient complications and

hospital/ED overcrowding. However, these are often underused due to differences in local clinical practice and cost restrictions (2, 3, 39).

The laboratory is one of the primary stakeholders in the integration of new biomarkers or improved assays, since it can help evaluate test effectiveness, as well as offer considerations on test appropriateness (40, 41). Other key stakeholders in the evaluation of new biomarkers for patients with chest pain include the ED (usually the main point of patient presentation), cardiology departments, and hospital administration.

In particular, the hospital administration needs to face the economic aspects related to introduction of new diagnostic and therapeutic tools, including the proposed context of use, the potential clinical benefits and the cost effectiveness (42–45).

Chest pain assessment is a critical point for organizational, economical and clinical perspectives. The 'economic' role of novel or traditional biomarkers and their cost effectiveness should be evaluated in the local scenario, thus considering the number of subjects presenting to the ED, the available diagnostic tools and the efficiency of the continuity of care between the hospital and the country health organization.

The role of biomarkers

Biomarkers do play a key role in the diagnosis and risk assessment of patients referring for chest pain. The detection of blood troponin levels, by highly sensitive assays, is a basic diagnostic aid for either identifying low-risk patients who can be discharged early and safely, or high-risk patients who must be treated timely and more aggressively (46). Current recommendations for the triage and management of chest pain patients advise that all patients suspected for ACS must be tested with serial troponin T (TnT) or troponin I (TnI) measurements (47). The improved analytic sensitivity of the highly sensitive troponin assays (hsTns) has increased the detection of myocardial injury, limiting the potential usefulness of additional biomarkers of necrosis (48). However, the increased diagnostic sensitivity for myocardial necrosis has also complicated the triage and management of chest pain patients (49). In fact, the introduction of these more sensitive assays has considerably increased the number of positive tests on admission as compared with the previous and less sensitive assays. Therefore, the biochemical indication of myocardial injury provided by hsTns has even increased the need to definitely ascertain the presence of ischemia (50, 51). This concept has also been clearly highlighted in the recent Universal Definition of Myocardial Infarction document, which has been revised after the introduction of these assays (52). Currently, there is a general consensus that this improved analytical sensitivity enables the detection of myocardial injury due to a broad spectrum of pathologies (both cardiac and extra cardiac), which may be sustained by mechanisms other than myocardial ischemic, as well as myocyte physiologic remodeling (53–57).

Although one single troponin value exceeding the conventional diagnostic threshold for AMI might reflect a serious and probably irreversible myocardial injury, the definite diagnosis of AMI on the basis of a single measurement is impossible, since it cannot allow unequivocal discrimination of ischemic from non-ischemic causes in the challenging context of ACS or AMI (54). Current guidelines recommend the interpretation of a rise or fall of serial hsTn measurements, to help discriminate acute injury from chronic causes, thereby addressing ischemia as the leading mechanism for myocardial injury (48). However, there is still poor consensus about the required degree (i.e., percentage) of variation during serial measurements, nor on the timing of sampling when using hsTn assays. Although some assays can discriminate an acute event with an increment of 20%–30%, recent studies also emphasize that higher deltas are needed to account for the biological variability of these biomarkers (47, 58). As such, it is difficult to state a general rule since the Reference Change Value (RCV) must be calculated according to the analytical variability of the assay and to the biological variability of the relative troponin isoform (48, 59–61).

Biomarkers, such as troponin, were originally introduced to help understand the underlying etiologies of signs and symptoms characterizing patients presenting with chest pain. They help to standardize definitions and gain a new joined perspective. The development of more sensitive assays and technologies also add a higher degree of complexity in the clinical decision-making (50). In this framework, the efficiency of hsTn testing is strongly threatened by the high prevalence of patients with co-morbidities or conditions affecting troponin release and thus diminishing the diagnostic performances (i.e., specificity) of the marker for specifically ruling out an AMI (50).

Despite recommendations, guidelines, and the recent advances on establishing the RCVs, there are still several unsolved issues, concerning both the pathophysiological and analytical characteristics of this marker (53, 62, 63). Therefore, the use of additional biomarkers reflecting the ischemic etiology of the event might be advisable to improve AMI rule-out and to lower the still considerable number of improper CPU admissions. Several biomarkers have been proposed over the past several decades, both alone and in combination with troponins, to aid the rule-in and rule out of AMI (51, 64, 65). Although several reports show additive effect of natriuretic peptides plus troponin on the prognostic value for risk stratification in patients with acute coronary syndromes (66), no data are available with these biomarkers to improve the ability of physicians to make a fast diagnosis of ACS in chest pain patients. Currently, copeptin is gaining much interest, since preliminary evidence seems to attest the potential to increase the diagnostic value of troponin and therefore to enhance the early rule-out of AMI.

The role of copeptin

Copeptin is a 39 amino acid peptide produced stoichiometrically with arginine vasopressin peptide (AVP) from the precursor pre-provasopressin. It is thought to be produced primarily by the magnocellular neurons of the hypothalamus

and released from the posterior pituitary in response to hemodynamic and osmotic stimuli [reviewed in (67–70)]. As such, it closely mirrors the production of AVP, which is in turn one of the key hormones for maintaining fluid balance, vascular tone and cardiovascular homeostasis. Interestingly, de novo synthesis of vasopressin in the heart, as well as release of the hormone into cardiac effluents has been shown in a model of pressure overloaded rat hearts, with vasopressin concentrations sufficient to cause local and systemic effects (71).

Vasopressin acts on three main receptors, where it mediates antidiuretic effects, strong arteriolar vasoconstriction and ACTH secretion during stress response. The rapid release of AVP and copeptin reflects endogenous stress levels and the individual response (72, 73). Early and relevant increases of both markers in the bloodstream may be triggered by the onset of acute and life-threatening conditions, such as AMI and stroke, causing a homeostatic imbalance (74, 75). Biomarkers, such as copeptin or AVP, which find their ideal place upstream to necrosis biomarkers, have hence been proposed to improve the early diagnosis of AMI, by anticipating the typical delayed release of cardiac troponins (i.e., 3–4 h after an AMI) and contributing an independent pathophysiologic response to endogenous stress. An increase of AVP is also reported to have a role in the pathogenesis of both heart failure and AMI remodeling. A net copeptin increase after AMI has been described in patients with ECG signs of cardiac injury (76, 77). Under filling of the left ventricle consequent to AMI, results in baroreceptor stimulation, or even the direct damage to the cardiac baroreceptors. These have both been proposed as the most likely causes of vasopressin/copeptin secretion from the posterior pituitary.

Although vasopressin has provided important information on the pathophysiological mechanisms underlying several endocrine disorders, its diagnostic usefulness has been seriously challenged by a variety of technical and analytical issues (67, 68, 78). Vasopressin has a high biological instability (even stored at –20°C), which is also worsened by a very short in vivo half-life, platelet binding, and additional cumbersome pre-analytical preparation. Moreover, the small protein size challenges detection by sandwich immunoassays and therefore requires the use of less sensitive competitive immunoassays. Conversely, copeptin is reported to be extremely stable, which would make its measurement much more robust in clinical practice. Detection does not require any extraction step or complex preanalytical procedures (e.g., the addition of protease inhibitors). The current assay requires minimal plasma/serum volumes (i.e., approx. 50 μL) and the overall time for completing the analysis is between 20 min and 30 min (as compared with 12–24 h for AVP), which makes it suitable for the application in urgent (stat) clinical settings (78). Considering the potential application of copeptin, it seems important to emphasize some characteristics of this molecule that may strengthen its high diagnostic accuracy as compared with other biomarkers.

In healthy volunteers the median copeptin levels are <5 pmol/L (95% CI 1–2 pmol/L) and albeit higher values are detected in males than females, only a slight difference (i.e., approx. 1 pmol/L), has been reported (78, 79). Moreover, at variance with troponin and other 'diagnostic' biomarkers, the plasma levels of copeptin are not significantly influenced by age (78). Copeptin levels are usually decreased in patients with diabetes insipidus, hyponatremia and other conditions associated with reduced AVP concentration (80).

Interestingly, a gradient of copeptin levels has been observed in relation with different degrees of stress. Changes in plasma osmolarity or water deprivation cause only moderate increases (up to approx. 20 pmol/L), whereas median levels from 20 pmol/L to 45 pmol/L, may be associated with advanced and acute heart failure. A significant increase, typically >100 pmol/L, occurs in acute life-threatening conditions, such as severe sepsis, septic shock, hemorrhagic shock, ischemic stroke and AMI (67). Copeptin was also reported to have superior diagnostic performance over cortisol for discriminating different degrees of stress, and it was hence proposed as a reliable prognostic marker in patients with acute illness (73).

Copeptin levels reflect disease and can discriminate patients in life-threatening conditions from patients with more favorable outcomes. In the emergency setting, this biomarker can aid in the management of chest pain patients, since its measurement simultaneously with troponin, meets both the immediate need for AMI rule-out and possibly the longer term requirement of ACS risk stratification. Although the combination of negative copeptin and troponin markers (together with the clinical features) can efficiently rule-out an acute cardiac event, a single elevation of copeptin levels above a threshold of 100–150 pmol/L can also alert ED physicians to the onset of an acute condition, requiring an immediate differential diagnosis and urgent treatment. In this perspective, copeptin levels are likely to improve the information provided by risk scoring algorithms in current use. Accordingly, the introduction of copeptin in the chest pain pathway may help in the overall process, by guiding early intervention, optimizing the management of individual patients, and finally enhancing the appropriate allocation of healthcare resources.

There are however several important drawbacks of copeptin in the context of AMI exclusion. Copeptin provides little clinical information when measured alone, due to its nonspecific elevation in many pathophysiological conditions. For this reason it should be assessed along with other more specific biomarkers, such as cardiac troponins. The concentration of copeptin increases almost immediately after onset of chest pain, then rapidly decreases over the first 6–12 h, so that its measurement appears more significant in patients that present at the ED with chest pain onset within 6–8 h. Finally, patients with unstable angina do not always display increased levels of copeptin, which makes this marker more useful for ruling out AMI, but not necessarily ACS (79, 81).

Copeptin is sometimes but not always elevated in ACS, so it should be used only in consideration of clinical judgment for the rule-out of AMI, primarily NSTEMI (81). The biomarker provides a physiologic pathway other than myocyte necrosis, which enables a redundant safety pathway to rule-out AMI and other life-threatening conditions (81).

Basically, evidence for a role of vasopressin in AMI was recognized in the mid-1970s (82, 83). Since copeptin mirrors

AVP changes in the bloodstream, it was not surprising to detect an immediate increase of copeptin levels after the onset of AMI. The release of the marker is characterized by an almost instantaneous increase at the onset of symptoms. Levels then appear to decrease in the next 2–5 days, often stabilizing at concentrations significantly higher than in healthy controls (84). Moreover, the highest copeptin levels are prognostic for death and re-hospitalization for heart failure. In particular, patients with a concentration within the highest quartile showed an increase of short-term event rate (>40%) during a 60 day follow-up.

These results stimulated further studies (Table 1) to evaluate whether copeptin assessment, in combination with troponin, might improve the AMI rule-out in patients presenting with chest pain to the ED (81).

In one study consisting of 487 patients presenting with chest pain to the ED and with an AMI prevalence of 17%, higher copeptin levels were detected at ED presentation, showing an immediate increase in the first 4 h after the onset of chest pain symptoms, when troponin levels measured with a traditional assay were often still undetectable or non-diagnostic. During the following hours, copeptin levels declined while troponin levels simultaneously increased. The evidence of distinct kinetics suggested that each marker might provide a different and thereby additive diagnostic value to the other, thus increasing the diagnostic performances of the overall two-biomarker strategy to rule-out AMI, particularly in the early diagnostic window. The discriminating capability vs. AMI of the first single troponin level recorded at the ED presentation was significantly improved by adding copeptin detection, since the combination of TnT and copeptin at presentation resulted in an area under the curve (AUC) of 0.97, which was significantly higher than the AUC of 0.86 obtained from TnT alone. However, since biomarker testing must be contextualized in a defined diagnostic pathway, the authors proposed to integrate the information on the clinical history and patient risk together with an algorithm based on these biomarkers. The algorithm considered the negative result of both markers, respectively dichotomized according to specific threshold levels (<14 pmol/L for copeptin and <0.01 μg/L for Roche TnT assay). According to this strategy, a negative result of both troponin and copeptin at presentation achieved a remarkable NPV >99% for ruling-out AMI.

A second multicenter trial, enrolling 1386 patients with a prevalence of suspected ACS and AMI of 21%, assessed the added diagnostic value of copeptin to conventional TnI in the early diagnosis of AMI (79). When considering a first sampling at ED admission, the addition of copeptin to TnI measurement significantly improved the c-statistic from 0.85 to 0.94. This result was obtained in the overall population, whereas in a subset of patients presenting within 3 h after the onset of chest pain the combination of the two biomarkers remarkably increased the c-statistic from 0.77 to 0.91. In a subset of patients, the study also compared the combined use of copeptin and TnI measured by a highly sensitive assay (Siemens Advia). In this subset, TnI displayed an AUC of 0.96, whereas the combination of both biomarkers slightly improved the AUC, up to 0.97. Nevertheless, the combination of both markers (considering a TnI threshold at the 99th percentile of 0.04 ng/mL and a copeptin threshold at the 97.5th percentile of 13 pmol/L) significantly improved the NPV value for AMI from 95% to 98.3%. When referring to the rule out of ACS, the NPV changed from 81.6% for TnI alone to 84.4% for the combination of both markers. In this case it is also noteworthy that the use of different thresholds for copeptin (respectively at the 95th, 97.5th and 99th percentiles) did not modify significantly the NPV.

More recently, Karakas et al. measured both hsTnT and copeptin in 366 consecutive patients that presented to the ED within 24 h after the onset of chest pain of suspected cardiac origin lasting at least 5 min and with a negative initial conventional TnT test (i.e., <0.03 μg/L) (87). Although the statistical analysis of the data revealed that copeptin concentration was not independently predictive of ACS and did not improve the diagnostic value of the single hs-cTnT measurement, there are some further aspects in this study that should be highlighted. First, the number of patients with a definitive diagnosis of AMI was very low (8 out of 366, i.e., 2%), whereas unstable angina could only be diagnosed in 27 patients (i.e., 7%). It is rather understandable that the diagnostic performance of copeptin in the setting of AMI diagnosis should however be redefined on a much larger population of diseased patients before drawing definitive conclusions. The timing of testing was also questionable, inasmuch as the biology of copeptin (i.e., early raise after neuroendocrinological stress) would make it a more suitable biomarker for the early diagnosis of AMI, rather than in the following hours. Accordingly, it was also reported that copeptin concentrations on admission were remarkably higher in the group of patients presenting 0–4 h from the onset of the symptoms. Finally, in patients with raised copeptin concentrations, a significantly increased rate of regional left-ventricular dysfunction was observed, thereby confirming the important prognostic information and risk stratification significance of this promising biomarker.

The net clinical benefit of introducing copeptin in the ED to improve the diagnostic accuracy of AMI rule-out (with both conventional or hsTn assays) is still under evaluation. The integration of copeptin in the diagnostic algorithm reported by Reichlin may potentially be a cost-effective strategy, since serial sampling of troponin and continuous ECG monitoring would no longer be useful in patients testing negative for both biomarkers (i.e., nearly two thirds of patients in this case series) (81). On the contrary, serial measurement and prolonged monitoring may be limited to patients positive either for troponin or copeptin, who represent nearly one third of the entire enrolled population. This strategy may accelerate the rule-out of AMI, and globally result in a cost saving by reducing the number of patients requiring a second (and even a third) troponin sampling in the ED (95). This is noteworthy, considering that the introduction of hsTn assays has further worsened the issue of inappropriate and redundant requests of this biomarker, posing a relevant burden on the laboratory budget (96). In several cases the indiscriminate measurement (and often the

Table 1 Articles on copeptin.

Authors	No. patients	Main conclusion
Articles on combined determination of troponin and copeptin		
Lotze et al. (85)	142 consecutive patients with suspected AMI	Single determination of copeptin and hsTN ruled out AMI in 45/142 (31.7%) patients with NPV of 100%
Giannitsis et al. (86)	503 patients with suspected ACS with chest pain <12 h	hsTnT+copeptin yielded diagnostic sensitivity of 97.7%, NPV of 99.03%, diagnostic specificity of 55.9% and PPV of 34.4%
Karakas et al. (87)	377 patients with ACS (NSTEMI+UA) with negative conventional troponin T that presented within 24 h of chest pain Used hsTNT, copeptin and CT imaging	Copeptin concentration >7.38 had a NPV and 94% for ACS and sensitivity of 51%. Combination of copeptin and hsTNT had a lower diagnostic accuracy than hsTNT alone
Meune et al. (88)	58 consecutive patients with acute and non-acute coronary syndrome Measured hsTNT and copeptin	Combination of copeptin and hsTNT identified 26 patients with ACS with a negative predictive value of 82.6%
Keller et al. (79)	1386 patients with suspected AMI. Measured TnT, myoglobin, CKMB and copeptin at admission, 3 h and 6 h	Copeptin+troponin revealed highest diagnostic power with AUC of 0.91, 0.92 and 0.93 in patients with <6 h, <12 h and overall population. Combination of copeptin and TnT was superior to all single marker determinations or other marker combinations
Reichlin et al. (81)	487 consecutive patients with suspected AMI	Combination of copeptin and troponin T at initial presentation ruled out AMI with a sensitivity of 98.8% and NPV of 99.7%
Gu et al. (89)	145 patients undergoing PCI with STEMI	Copeptin levels were already elevated on admission and were higher with a shorter time from symptom onset to reperfusion and lower systolic blood pressure. Copeptin levels peaked immediately after symptom onset at a maximum of 249 pmol/L and normalized within 10 h. In contrast, CK-MB, cTnT, and hs-cTnT peaked after 14 h from symptom onset at a maximum of 275 U/L, 5.75 μg/L, and 4.16 μg/L, respectively, and decreased more gradually
Other copeptin articles related to risk stratification and short-term mortality		
Nickel et al. (90)	438 patients with non-specific complaints (BANC study)	Copeptin and Prx4 were significantly higher in non-survivors than in survivors (28 patients died) and predictive of 30 day mortality
Peacock et al. (91)	1641 patients that presented to the ED with dyspnea (multicenter BACH trial)	MRproADM or copeptin alone and or in combination provided superior short-term mortality prediction (14 day) compared to natriuretic peptides and troponin
Narayan et al. (92)	754 NSTEMI patients	Copeptin improved accuracy of risk classification when used in combination with GRACE score (determined by net reclassification improvement) where NTproBNP did not. Copeptin is elevated after NSTEMI and higher levels are associated with worse outcomes
Potocki et al. (93)	287 patients with dyspnea	When adjusted for common cardiovascular risk factors and NT-proBNP, copeptin was the strongest independent predictor for short-term mortality in all patients [HR 3.88 (1.94–7.77); p<0.001] and especially in patients with acute decompensated heart failure (ADHF) [HR 5.99 (2.55–14.07); p<0.0001]
Maisel et al. (94)	557 acute heart failure patients from BACH total patient group 1641	Significantly increased 90 day mortality, readmissions and ED visits in patients with elevated copeptin, especially in those with hyponatremia. Copeptin was highly prognostic for 90 day adverse events in acute HF patients, adding prognostic value to clinical predictors, serum sodium and natriuretic peptides

serial monitoring) of troponin tests to all chest pain patients, likewise as a screening marker and without a specific suspicion of ACS, has remarkably increased the costs of the overall diagnostic management (97). A misleading interpretation of guidelines has also contributed to worsen this aspect (i.e., in some institutions the third sampling is still drawn routinely in all patients, even though it adds no vital information regarding patient treatment, and increases the extension of the admission period and costs) (98).

Taken together, the available data suggest that a biomarker strategy integrating copeptin might potentially reduce inappropriate troponin request and testing at least in patients with low/moderate pretest probability (99) and in those with early presentation at the ED (i.e., <4 h from the onset of the symptoms), thereby lowering the incremental cost due to the introduction of hsTn testing. It is also noteworthy that the introduction of copeptin in combination with troponin can improve the risk assessment of chest pain patients. Several studies have reported that copeptin levels above well-defined thresholds are associated with acute life-threatening condition (67, 68, 72–75, 90, 91, 100). This evidence might be used as a (rule-in) warning to ED physicians regarding patients who need urgent triage and a more aggressive treatment. In fact, according to the significant increase of copeptin in the individuals displaying a marked stress reaction, the emergency setting seems to be the ideal environment to fully exploit the information carried by the measurement of this marker and assess the risk for an acute life-threatening condition (85, 86, 88, 92, 93).

The role of copeptin in the assessment of the life risk in subjects admitted to the ED, lies beyond the early diagnosis of AMI. Elevated copeptin concentrations have been associated with increased 90-day mortality, heart failure (HF) readmissions, and HF related ED visits in patients with elevated copeptin, especially in those with hyponatremia. Copeptin was highly prognostic for 90-day adverse events in patients with acute HF, adding prognostic value to clinical predictors, serum sodium, and natriuretic peptides. When combined, sodium and copeptin provided incremental prognostic value to clinical predictors of mortality and NT-proBNP (94).

Chest pain assessment is a critical point that affects a life-threatening patient condition, but with a considerable impact on hospital costs. The ‘economic’ role of novel or traditional biomarkers (or combinations) are moving beyond the traditional approach based on the evaluation of the predictive value of the new combination of tests in large populations. The cost-effectiveness should be assessed locally, taking into consideration the local prevalence of subjects with chest pain admitted to the ED, the diagnostic strategies within the ED, the turnaround time, as well as the organization of the Coronary Unit in the healthcare network. In a recently published randomized controlled trial which compared rapid diagnosis based on point of care (in ED) to conventional diagnosis, the point-of-care biomarker strategy reduced the length of stay, but did not reduce overall costs (45), thereby highlighting the importance of evaluating the introduction of new diagnostic tools in consideration of benefits and costs from all involved stakeholders.

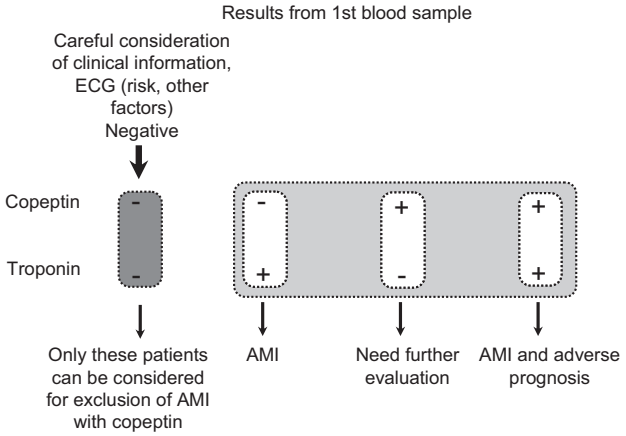

Figure 1 Possible early acute myocardial infarction rule-out for emergency department chest pain patients using a combination of troponin and copeptin. Copeptin must always be considered together with troponin.
Only patients with suspected AMI and early chest pain onset (<6–8 h) should be evaluated.

Conclusions

The evaluation of chest pain patients is critical and involves several different clinical specialties including the ED, Laboratory and Cardiology departments. Each has its own competency in contributing to the development of protocols that will help (among other goals) to quickly and correctly (a) rule-out patients with benign non life-threatening (non-cardiac conditions) that can be considered for discharge or further outpatient follow-up; (b) rule-in patients with ACS (unstable angina, NSTEMI, STEMI); and (c) alert the ED about non-cardiac life-threatening emergencies. The use of biomarkers can undoubtedly assist this process, as well as add prognostic information regarding acute short-term or chronic long-term risk and severity.

The recent introduction of highly sensitive troponins has improved the overall ability to identify higher-risk chest patients, but at the expense of decreasing the specificity of this marker for acute myocardial infarction. The utility of combining additional biomarkers to troponin, such as copeptin, may provide additional value by its high NPV to aid in the clinical exclusion (rule-out) of AMI; or in the case of a dramatically increased concentration (>10× the upper limit of the reference range), to reveal the presence of acute life-threatening conditions that may not necessarily be identified with the use of a single biomarker, such as troponin (Figure 1).

Although guidelines are helpful in creating a certain ‘standardization’ of care, they are frequently developed by using highly selected patient inclusion criteria and often drafted in the context of a mono-discipline point-of-view. Integration of different specialties involved in acute patients’ care might yield a better integration of the different criteria, such as clinical considerations, test performance, and diagnostic accuracy.

Novel biomarkers and other diagnostic tools need to be validated by different stakeholders before incorporation into

routine clinical protocols. The correct application of these new tests should offer an overall patient benefit and a net contribution to improve hospital organization and limit overall healthcare expenditures. Moreover, the net economic impact should be considered on the basis of overall costs vs. benefits balance.

Conflict of interest statement

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