Can copeptin emerge from the growing shadow of the troponins?

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This editorial refers to ‘Early discharge using single cardiac troponin and copeptin testing in patients with suspected acute coronary syndrome (ACS): a randomized, controlled clinical process study,’†, by M. Möckel et al., on page 369.

Evaluation of suspected acute coronary syndrome (ACS) accounts for a staggering 10 million emergency department visits per year in Europe and > 8 million in the USA. Many patients that undergo evaluation for suspected ACS unfortunately spend countless hours waiting for the results of diagnostic evaluation to determine their fate: discharge, continued observation, or admission, with the possibility of supplementary testing to explore their presentation further. While patients anxiously and eagerly await their results, the harried emergency department physician continues to triage more patients with similar complaints and various acuities; in this context, both patients and physicians alike watch the emergency department fill and often overflow. Clearly, how suspected ACS is evaluated needs serious reconsideration.

Historically, the means by which physicians have evaluated patients with suspected acute myocardial infarction (MI) or unstable angina pectoris (UAP) evolved rapidly over the later decades of the last century, particularly with the development of adjunctive diagnostic biomarker testing to augment clinical evaluation. In particular, with the emergence of cardiac troponin (Tn) testing in the 1990s, clinicians had more accurate tools to identify and exclude acute MI. However, until recently, methods for Tn measurement remained reasonably insensitive and were only diagnostic after a period of time had passed since onset of cardiac injury (the ‘troponin blind’ interval); furthermore, by definition, UAP is associated with a Tn in the normal range, leaving this diagnosis to be based on clinical judgement and electrocardiography (ECG). These issues often rendered physicians unable to make rapid decisions about triaging patients with chest pain in an accurate and cost-effective manner.

Recently, considerable effort has been made to improve the biomarker-based evaluation and management of patients with suspected ACS, the most significant of which being the development of highly sensitive (hs)Tn methods, which are now available in many countries. The hsTns have truly changed the practice of medicine, and mostly for the better. Their use has been shown to increase clinician ability to recognize myocardial necrosis in a much more rapid fashion than when using conventional Tn assays (reducing the ‘troponin blind’ interval dramatically).® and—compared with conventional Tn—the hsTn methods substantially increase the recognition of acute MI in patients previously thought to have UAP.® Importantly, recent studies have examined the use of hsTn testing to evaluate those with ACS more rapidly, suggesting that acute MI may be excluded as quickly as 2–3 h.6 Indeed, thanks to the increasing radiance of the data supporting hsTnT and hsTnI for chest pain evaluation, the shadow of these assays may potentially eclipse other diagnostic biomarkers that might be used to evaluate patients with chest discomfort.

Some of the other biomarkers that have been examined to supplement evaluation for suspected ACS are listed in Table 1, and include various assays reflecting a broad array of processes, including cardiac ischaemia, platelet activation, inflammation, and plaque rupture. Many will probably never be used clinically; however, one promising biomarker that has received substantial recent interest for evaluation of suspected ACS is C-terminal provasopressin, or copeptin.

Copeptin was first discovered in 1972 from the posterior pituitary of pigs. Along with arginine vasopressin (AVP), it originates from the precursor pre-provasopressin. Unlike AVP, copeptin is stable and easily measured; given the stoichiometric relationship between the two peptides, copeptin can serve as a surrogate for AVP.®® Copeptin has been studied in multiple conditions and has implications for diagnosis and prognosis both within the cardiovascular realm and beyond, as shown in Figure 1. In the setting of MI, copeptin is probably released in conjunction with cortisol and adrenocorticotropic hormone secondary to the body’s individual stress response. It is also hypothesized that copeptin secretion by the posterior pituitary

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occurs in response to baroreceptor stimulation either from hyponension or from direct injury to baroreceptors.\textsuperscript{8,10} Importantly, despite being influenced by the presence and severity of myocardial ischaemia/infarction, copeptin is non-specific for MI or ACS, thus limiting its use alone for diagnostic evaluation of chest pain; its use in conjunction with Tn has been of particular interest and has subsequently been examined in this regard;\textsuperscript{11} however, uncertainty about the role of copeptin remains.

In this context, Möckel and colleagues report their findings from an important prospective randomized trial focused on the use of copeptin in a very low risk population of patients presenting to the emergency department with suspected ACS.\textsuperscript{12} In the trial, patients with an initially negative Tn, normal ECG, and GRACE score <140 (mean = 80) were randomized to one of two arms: one group was treated per ‘standard of care’ with usual Tn testing, while the other group was evaluated with both copeptin and Tn. In the setting of a copeptin value < 10 pmol/L, together with a negative Tn value, the managing physician could decide to discharge the patient or over-rule the copeptin/Tn result to evaluate the patient further.

The results of the study indicate that the combination of copeptin plus Tn allowed for considerably larger numbers of patients to be discharged from the emergency department (67.6% vs. 12.0%), associated with substantial reduction in length of stay (4 h vs. 7 h). Unfortunately, there was no economic analysis performed in this trial, but it is easy to envisage substantial cost-effectiveness associated with use of copeptin in this study.

Möckel and colleagues should be commended, as their study represents the first randomized controlled trial examining copeptin and Tn, an extremely important endeavour that is necessary to bridge the gap towards changing practice, which has been heading in a ‘troponin-centric’ manner over recent years. Indeed, the strategy by Möckel and colleagues is a novel and radical departure from current position statements from the Joint Task Force for the Universal Definition of Myocardial Infarction, which recommended serial biomarker measurements with a rise and/or fall of cardiac biomarker concentrations (preferably Tn, with one value above the 99th percentile upper reference limit).\textsuperscript{13} On the surface, the results of Möckel et al. appear to suggest that copeptin may have a role next to Tn; however, three important factors raised by this study warrant further consideration.

First and foremost, one must consider the Tn assays utilized in the study. The methods used at the multiple centres were a mix of both conventional and hsTn assays, a major caveat for the reader. The use of copeptin has been reported particularly to improve sensitivity for acute MI when used with a conventional (and thus less precise and sensitive) Tn assay.\textsuperscript{10,14} However, the additive benefit of copeptin when combined with hsTn assays has thus far revealed mixed results.\textsuperscript{15–17}

Secondly, one should consider how the Tn assays were used in the present study: clinicians interpreted the Tn result using thresholds optimized to diagnose acute MI, rather than to exclude it rapidly. This is not without ramification: in biomarker testing, the optimal threshold to exclude a diagnosis is that which maximizes the negative predictive value, a value frequently quite different from the cut-off with best positive predictive value. Using hsTnT, for example, the optimal threshold for rapidly excluding ACS is likely to be its limit of detection of 5 ng/L, while the 99th percentile cut-off of 14 ng/L is considered the diagnostic threshold; waiting for a rise across the 99th percentile by definition leads to delayed decision-making. In contrast, more rapid triage based on a value < 5 ng/L might provide ‘copeptin-like’ accuracy from hsTnT: a recent, large observational study of utilizing hsTnT at a threshold of 5 ng/L demonstrated a first-draw negative predictive value of 99.8% for MI.\textsuperscript{18} Thus, while the study by Möckel and colleagues is an advance, a study comparing copeptin and hsTn vs. hsTn alone, using an hsTn at a value that maximizes a rapid negative predictive value for MI or ACS, would be the next important study to undertake.

Finally, this study underscores the importance of utilizing biomarkers in conjunction with sound clinical judgement, as 12 of the 14 patients with a copeptin <10 pmol/L in the unblinded arm who experienced the primary endpoint were reassuringly ‘over-ruled’ and not discharged by the treating emergency department physician. The medical community relies extensively on biomarkers for diagnosis, prognosis, and management of patients with cardiovascular diseases (particularly in ACS and heart failure), but, as demonstrated in this study, it is imperative to maintain the balance between the science and the art of medicine. The study investigators are to be congratulated in running an excellent study that balances new technology with excellent clinical judgement. Given the low risk of the patients included in this study and very low rates of ACS, it remains unclear if the benefits of copeptin testing on speed of triage would have been as useful in a higher risk patient population with greater medical complexity, a circumstance where clinician uncertainty is higher and the risk, by definition, is greater.

In summary, this seminal randomized study in low risk chest pain patients suggests the combination of copeptin with Tn (in conjunction with clinical intuition) may be useful to exclude MI safely in a more timely manner than the Tn methods used in the study alone. Randomized controlled clinical strategy trials of biomarker testing

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Table 1 | Novel biomarkers evaluated for acute coronary syndrome

<table>
<thead>
<tr>
<th>Biomarker</th>
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<tbody>
<tr>
<td>Copeptin</td>
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<tr>
<td>Natriuretic peptides</td>
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<tr>
<td>Heart fatty acid-binding protein (H-FABP)</td>
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<tr>
<td>Glycogen phosphorylase isoenzyme BB (GPBB)</td>
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<tr>
<td>Unesterified free fatty acids</td>
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<tr>
<td>Myeloperoxidase</td>
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<tr>
<td>Soluble CD40 ligand</td>
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<tr>
<td>Placental growth factor</td>
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<tr>
<td>C-reactive protein</td>
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<tr>
<td>Matrix metalloproteinase-9 (MMP-9)</td>
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<tr>
<td>Pregnancy-associated plasma protein-A (PAPP-A)</td>
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<tr>
<td>Choline</td>
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<tr>
<td>Vascular endothelial growth factor receptor 1</td>
</tr>
<tr>
<td>(fms-like tyrosine kinase, Flt-1)</td>
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<tr>
<td>Ischaemia-modified albumin</td>
</tr>
<tr>
<td>Prothrombin fragment 1 and 2 (f1.2)</td>
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<tr>
<td>Thrombus precursor protein (TpP)</td>
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<tr>
<td>P-selectin</td>
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<td>Circulating microRNAs</td>
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Copeptin as a diagnostic and prognostic biomarker

Emerging roles:
- Identify patients who may benefit from use of AVP receptor antagonists
- Prognostic evaluation of diabetes mellitus, abdominal obesity and metabolic syndrome
- Prediction of microalbuminuria onset
- Diagnostic evaluation in valvular heart disease (e.g. aortic stenosis)
- Prognostic evaluation in acute pancreatitis

Figure 1 Copeptin possesses diagnostic and prognostic properties in multiple organ systems. AVP, arginine vasopressin; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; VAP, ventilator-associated pneumonia.

are difficult to execute, but the fine trial by Möckel and colleagues clearly demonstrates the feasibility of such badly needed studies. As the number of new biomarkers continues to expand, the need for stringently designed and executed trials focused on comparative effectiveness of various biomarkers is critical. Further meticulous and robust studies such as the trial by Möckel and colleagues will be needed to determine whether copeptin will continue increasingly to shine, or whether it will be eclipsed by the ever growing shadow of the hsTn assays.

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References


