Time to move from prognostication to diagnosis and treatment of heart disease in acute exacerbation of COPD

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The link between copeptin, troponin and mortality indicates a strong need for examining cardiac mechanisms in AECOPD http://ow.ly/iehc30cxZB0

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In this edition of the journal, Laribi *et al.* [1] report the incremental value of biomarkers relative to the CURB-65 score for predicting 30-day mortality in acute exacerbations of chronic obstructive pulmonary disease (COPD). The derivation cohort of 356 elderly patients combined four single centre studies of consecutive emergency department attendees, 12% being subsequently admitted to the intensive care unit (ICU). Cardiovascular comorbidity was common (41% hypertension, 20% heart failure). The primary end-point of 30-day mortality occurred in 27 patients (7.6%), congruent with existing literature reporting variable rates of 4.6–12% short-term mortality [2, 3]. The authors focus on the performance of myocardial injury markers, recognising that cardiac disease is a common cause of death in patients with COPD [4].

CURB-65 was selected as comparator to biomarkers, a six-point score derived to predict 30-day mortality in patients hospitalised for community-acquired pneumonia of whom 35% had chronic lung disease (sensitivity of 75% and specificity of 74.7% in predicting 30-day mortality with a score $\geqslant$3) [5]. The points allocation (confusion, urea, respiratory rate, blood pressure and age) creates a general picture of sepsis impact. CURB-65 provides a simple, generalisable tool, which enables "point of care" risk stratification in a relatively homogeneous population with an established diagnosis (pneumonia). This tool is currently used to assess illness severity along with clinical judgment, and helps physicians in planning appropriate treatment (*e.g.* admission to ICU) [6]. The score is recognised to perform less well in unselected acute exacerbations of COPD (area under curve (AUC) for inpatient and 30-day mortality 0.72 and 0.73, respectively) [7], a finding replicated in the present study (AUC 0.67).

Five different biomarkers were evaluated, namely C-reactive protein (CRP), procalcitonin (PCT), high-sensitivity cardiac troponin I or T (hs-cTnI or hs-cTnT), B-type natriuretic peptide (BNP) and copeptin. The biomarkers reflect different pathogenic mechanisms (inflammation, infection, cardiac overload, and cardiac injury), aligning with the many precipitants of COPD "exacerbation", which include heart failure, acute coronary syndromes (ACS) and arrhythmia [8]. Troponin and BNP were independently correlated with mortality, as observed in previous studies and systematic reviews [9, 10]. Copeptin also exhibited a similar association, while CRP and PCT did not predict survival.

Troponin is ubiquitous to contemporary acute medical practice, the cardio-specific isoforms I and T being highly indicative of myocardial damage when assessed with sensitive assays [11]. However, the causes of

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troponin elevation are equally ubiquitous, encompassing nearly every acute medical conditions depending on severity and the physiological stress imposed on the heart. The central issue is differentiating type I (a primary coronary event) from type II (secondary ischaemia related to increased demand or impaired supply) myocardial infarction [12]. To do so requires assessment of symptoms, ECG changes, coronary perfusion and anatomy. Raised troponin alone cannot (and should not) be used to differentiate between coronary or non-coronary causes of myocardial injury [12]. Diagnosing ACS in turn enables risk stratification using validated tools, and evidence based application of early *versus* delayed invasive management strategies [13, 14].

Copeptin is the C-terminal component of antidiuretic (vasopressin) prohormone, a key hormone of the hypothalamic-pituitary-adrenal axis, involved in the endocrine stress response and maintaining blood pressure. Copeptin may quantify endogenous stress level in multiple medical conditions including myocardial infarction and heart failure [15, 16]. As the level of endogenous stress is invariably high at the onset of myocardial infarction, copeptin may have added value even over high-sensitivity cardiac troponin in the early rule out of myocardial infarction [17, 18]. The role of copeptin in acute exacerbation of COPD (another stress state) is less clearly defined [19], particularly in relation to other markers of myocardial injury, like troponin.

Finally, the natriuretic peptide BNP is related to ventricular wall stretch due to increased end-diastolic pressure, and its clinical application has been studied mostly in the setting of heart failure. In this setting, the diseased heart is unable to maintain normal cardiac output and intracardiac pressures, resulting in systemic volume imbalance and fluid overload, eventually with redistribution to the lungs and/or peripheral accumulation. The secretion of natriuretic peptides is one of the numerous compensatory mechanisms, as these peptides reduce cardiac preload, sympathetic tone, and activation of the renin–angiotensin–aldosterone system. Since the secretion is directly proportional to ventricular volume and pressure load, BNP is regarded as a marker of elevated cardiac pressure and/or volume overload. However, blood levels of natriuretic peptides are affected by a variety of physiological factors, *e.g.* age and body mass index, and may be raised in conditions other than heart failure (*e.g.* myocarditis, amyloidosis, pulmonary embolism, kidney disease) [20]. Consequently, this marker performs relatively well in excluding heart failure when negative, while elevated BNP levels have only a limited value in establishing the diagnosis, especially in patients with concomitant COPD [21].

All five biomarkers have been the subject of numerous prognostic studies, systematic reviews or meta-analyses in acute COPD exacerbation [9, 10, 21]. Biomarkers are invariably associated with adverse outcomes, the strength of association influenced by population, comorbidities, inclusion/exclusion criteria, follow-up period, outcome studied, and adjustment methods. In the current and most previous studies, the lack of blinded endpoint adjudication using standardised criteria represents a major limitation in correlating biomarkers with cardiac specific outcomes and mortality [19, 22, 23]. In the present study, all biomarkers displayed similar AUCs for predicting 30-day mortality to the CURB-65 score. After confirming the association between biomarkers and short-term mortality, the authors examine net reclassification relative to CURB-65. This strategy has a sound rationale: to characterise the heterogeneity of acute COPD exacerbations including cardiovascular causes using objective measures, which are complementary to the simple clinical variables of CURB-65. All three biomarkers significantly improved the total net reclassification index, with the highest value obtained by combining copeptin and troponin (Hs-cTnI alone 0.378, 95% CI −0.005–0.761; BNP 0.572, 95% CI 0.167–0.976; copeptin alone 0.616, 95% CI 0.213–1.02; Hs-cTnI with copeptin 0.653, 95% CI 0.241–1.064).

Our interpretation of these results should be cautious. The application of reclassification statistics is the subject of much debate, particularly in the realm of biomarkers [24]. All the indices of reclassification were remarkably similar for BNP, copeptin alone and Hs-cTnI with copeptin. The slightly greater value of the latter does not appear from the confidence intervals to be statistically different to BNP or copeptin alone, and may simply reflect the play of chance. It is equally uncertain whether this does indeed represent myocardial injury, given the strength of copeptin alone in reclassification, and its physiological role in the overall stress response. Possibly copeptin, either alone or in combination, is acting as a general marker of acute COPD exacerbation severity, potentially reflecting the cause, consequences or both.

The question of cause *versus* consequence in many way parallels the earlier subject of diagnosis *versus* prognostication. Acute exacerbation of COPD, defined as episodes of acute worsening of respiratory symptoms that result in additional therapy [8], is characterised by heterogeneity. Many different events may trigger, worsen, or simply be associated with an acute exacerbation, especially when it is severe enough to warrant hospital admission [25]. A major limitation of the present study is the lack of objective cardiac investigations, and the authors are appropriately cautious in their interpretation. A previous Scottish study documented chest pain and serial ECG changes, consistent with the diagnosis of myocardial infarction, in one in every 12 patients hospitalised for acute exacerbation of COPD [26]. Detailed, serial

cardiac investigations including ECG and echocardiography are essential to establish a causative relationship between stress biomarkers and clinically relevant myocardial injury. We must also consider the mechanism of cardiovascular death from this putative injury; are patients dying of recurrent ACS, ventricular arrhythmia or pump failure within 30 days? Or is this overwhelming sepsis, respiratory failure, undiagnosed pulmonary emboli or other conditions associated with biomarker elevation? Blinded, standardised end-point adjudication is central to answering these questions. Prognostic models begin at the end of the patient journey, yet are most effective when guiding therapy targeted to a diagnosis at the start of that journey.

Despite these limitations the results are striking. This is the largest study to date examining copeptin in acute exacerbation of COPD, and the first to combine with troponin in this population. For example, copeptin has been previously evaluated in 167 patients hospitalised for acute COPD exacerbation, along with CRP and procalcitonin; all biomarkers were raised during the acute phase, but only copeptin was significantly related to poorer outcomes [19]. Further, recently, a multicentre study has developed a novel, simplified, prognostic tool for COPD, independent of lung function, and copeptin was included among the independent predictors of long-term mortality [23]. Interestingly, a French study including 277 patients hospitalised for acute exacerbation of COPD reported opposite results, as copeptin levels were not independently related to 30-day outcomes, including death; however, in the same cohort, copeptin was independently associated with 7-day death/need for ICU [22]. Thus, the debate on the utility of copeptin in acute exacerbation of COPD is actual and ongoing. In this study, the combination between copeptin and troponin conferred an especially high risk of mortality (20%), three-fold greater than in patients with elevated hs-cTnI alone (5.7%). The findings are certainly suggestive that non-pulmonary mechanisms may impact short-term prognosis of patients hospitalised with acute COPD exacerbation, and that future research should strive to identify and classify these (likely cardiac) mechanisms.

A final observation from cardiology is also relevant, namely the contrasting utility of heart failure and ACS risk stratification scores. Acute heart failure has many similarities to acute COPD exacerbation: a heterogeneous syndrome with numerous and diverse precipitants, prognostic models of limited accuracy and uptake in routine clinical practice [27, 28]. Contrast this with risk scores for ACS, such as TIMI and GRACE. Similar to acute COPD exacerbation and heart failure, there is considerable variability in patient outcomes across the ACS spectrum, and clinical judgment may not always be adequate. The GRACE score was devised from a large, multinational registry, and combines markers of myocardial damage (*e.g.* Killip class, ST-segment deviation, cardiac biomarkers) with more general risk measures, such as age and creatinine level [29]. Over 20 validation studies have demonstrated good discriminatory performance across a broad spectrum of ACS. Most importantly, patients with high risk scores benefit more from early intervention than patients with lower scores [13]. Thus international guidelines are unanimous in recommended risk stratification for all patients with ACS, to guide initial evaluation, site of care, therapy including antithrombotic agents, and timing of coronary angiography [14].

The present study elegantly highlights the strengths and weaknesses of biomarker based approaches to disease management. There is undoubtedly additional information gained, which may improve our understanding of disease phenotypes and standardise research practice. These results also underscore the importance of cardiac assessment, and offer direction in refining the role of troponin and copeptin. As the authors conclude, future trials should assess biomarkers guided management. A multi-biomarker approach could compare usual care *versus* protocolised investigations, risk stratification and treatment pathways: echocardiography for elevated BNP; ACS risk scores, serial ECG, and possibly stress tests for all elevated troponin-copeptin. High-risk patients would receive invasive angiography, and most importantly all patients receive guideline directed cardiovascular therapy. If such a strategy proved effective, *e.g.* through increased diagnosis of cardiac disease, implementation of protective therapies such as antiplatelet [30], and ultimately better outcome, it would provide an innovative approach to the management of acute COPD exacerbation. The question is whether there is sufficient evidence from observational and biomarker studies to design and conduct these intervention studies: the work by Laribi *et al.* [1] is certainly an important step along the road.

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