openheart

The role of cardiac biomarkers for predicting left ventricular dysfunction and cardiovascular mortality in acute exacerbations of COPD

Alice Buchan,[1] Ruth Bennett,[2] Anna Coad,[3] Simon Barnes,[4] Richard Russell,[5] Ari R Manuel[6]

ABSTRACT

The presence of cardiovascular comorbidities is frequently associated with poor outcomes in chronic obstructive pulmonary disease (COPD). No clear role has been defined for cardiac biomarkers in acute exacerbations of COPD (AECOPD). The aim of this systematic review was to examine the prognostic value of brain natriuretic peptide (BNP) and troponins in patients with AECOPD. Two independent authors searched the PubMed and Cochrane Library to collect clinical trials, observational studies and meta-analyses studying the prognostic value of cardiac biomarkers in AECOPD. The reference lists of all the included studies were also reviewed. A total of 14 studies were included in the review, of which 10 measured troponins, 7 measured BNP or NT-proBNP, and 3 measured both. Of the studies that used mortality in AECOPD as an end point, some but not all found that elevated BNP and/or troponins were associated with increased mortality. Of the studies that used left ventricular (LV) dysfunction in AECOPD as an end point, all found a significant association between elevated BNP and troponins in the diagnosis of LV dysfunction. In summary, it appears that there may be a link between an elevated level of BNP or NT-proBNP and increased cardiovascular mortality in AECOPD, although the data currently available are not conclusive. The inconsistencies in biomarkers measured, time points of measurements and the variability in outcome measured preclude more robust analysis.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide, and acute exacerbations of COPD (AECOPD) are the main reason for hospitalisation of patients with COPD. While most exacerbations are due to viral or bacterial infections, up to one-third have an unknown aetiology There is an abundance of literature, which implicates abnormalities of the cardiovascular system as an

For numbered affiliations see end of article.

Correspondence to
Dr Ari R Manuel;
ari.manuel@ouh.nhs.uk

important factor in the prognosis of patients with COPD.[1]

Recent research has suggested that there may be greater overlap between the pathophysiology of the lungs and the heart than was previously appreciated. As both chronic lung disease and cardiac disease are extremely common, there is a large cohort of patients with both conditions. It was recently shown by Andell et al[2] in a previous issue of *Open Heart* that patients with COPD, who constitute 6% of patients diagnosed with myocardial infarction (MI), had a higher mortality and a greater risk of new-onset heart failure. Several biomarkers are currently in routine clinical use for diagnosis, prediction and risk stratification in cardiac disease (table 1) The predictive value of such cardiac biomarkers in AECOPD has not yet been systematically reviewed. Both troponin and brain natriuretic peptide (BNP) are markers of myocardial stress, which can be measured easily and relatively cheaply as a bedside test.

Troponins are widely used as biomarkers to aid the diagnosis of MI and become present in the blood at higher levels when cardiac myocytes are damaged. BNP is currently used as a biomarker in cardiac failure, as it, along with other natriuretic peptides, is released in response to increased atrial pressure. It has long been known that lung pathology can directly lead to cardiac disease, such as in cor pulmonale, in which right-sided heart failure is a result of increased pulmonary arterial pressure; this increase in pressure may be caused by a panoply of diseases, including pulmonary fibrosis and COPD.[3] More specifically, the autoregulation of the pulmonary circulation, such as hypoxic pulmonary vasoconstriction, becomes maladaptive when there is widespread rather than localised hypoxia.[3]

Table 1 An overview of cardiac biomarkers in clinical use

Biomarker	Physiology	Clinical use
cTnT	Released from damaged cardiac myocytes in myocardial infarction	Used in the investigation of suspected myocardial infarction
cTnI	Released from damaged cardiac myocytes in myocardial infarction	Used in the investigation of suspected myocardial infarction
CRP	An acute phase protein released from the liver	Used as a biomarker of inflammation in a variety of clinical contexts
CK-MB	Released from damaged cardiac myocytes in myocardial infarction	Used in the investigation of suspected myocardial infarction
BNP	Released in response to increased atrial pressure	Marker of non-specific cardiac dysfunction, commonly used in the diagnosis of heart failure

BNP, brain natriuretic peptide; CK-MB, creatine kinase MB fraction; CRP, C reactive protein; cTnI, cardiac troponin I; cTnT, cardiac troponin T.

Epidemiological evidence suggests that left ventricular (LV) failure is a common comorbidity in patients with COPD[4] and that outcomes for patients with both LV failure and COPD are worse than those for patients with only COPD. In a long-term study of patients with COPD in Nordic countries, mortality in 36% of patients with COPD was due to cardiovascular causes. In patients with COPD, there is a significant burden of morbidity and mortality related to congestive heart failure, and patients with COPD have been noted to have higher in-hospital mortality.

The aim of this systematic review was to evaluate both BNP and cardiac troponins and their potential prognostic value as markers for LV dysfunction and cardiovascular mortality in patients admitted to hospital with AECOPD.

METHODS
A search of PubMed, MEDLINE and Cochrane Library up to January 2013 was performed without limitations using the search terms 'Cardiac Biomarker COPD', 'Cardiac biomarkers COPD', 'Cardiac biomarkers acute COPD', 'Cardiac biomarker COPD exacerbation', 'Troponin COPD' and 'BNP COPD'. Additional literature was identified through the review of references found in the primary literature search. Identified randomised, placebo-controlled trials, meta-analyses and systematic reviews were reviewed.

A total of 219 titles and abstracts were identified which were then reviewed.

The search criteria is in the online supplementary appendix. The following predetermined criteria were used to determine which studies to evaluate further: written in English, related to AECOPD, use of BNP and/or troponins only, primary literature. On this basis, 35 full texts were obtained and reviewed. Two independent reviewers evaluated the studies against predetermined exclusion criteria. The exclusion criteria were as follows: not including mortality, admission to intensive care unit (ITU), recurrent hospitalisation or diagnosis of LV dysfunction as outcomes. After reviewing the full-text articles to assess relevance, a total of 14 were included (figure 1). The risk of bias was evaluated at the outcome level for all included studies using the QUADAS-2 tool.[5] As the review includes both prognostic and diagnostic studies, we used this tool for all studies for consistency, marking fields relating to the reference standard as N/A where appropriate. Two authors used predefined parameters and a standardised collection method to extract data from the papers. One author conducted the risk of bias analysis (see online supplementary appendix 1).

Outcome variables
The data extracted from the papers were: study type, study aim/objective, study group, inclusion and exclusion criteria, biomarkers measured, and results including HRs, ORs or p values (as reported by each included study) for all outcomes measured in each paper. Risk of bias analysis was conducted for each included biomarker and outcome in each paper, but the risk of publication bias or selective outcome reporting was not assessed.

RESULTS
Summary
Of the 14 papers included, 7 measured BNP or NT-proBNP, and 10 measured troponin, with 3 of those
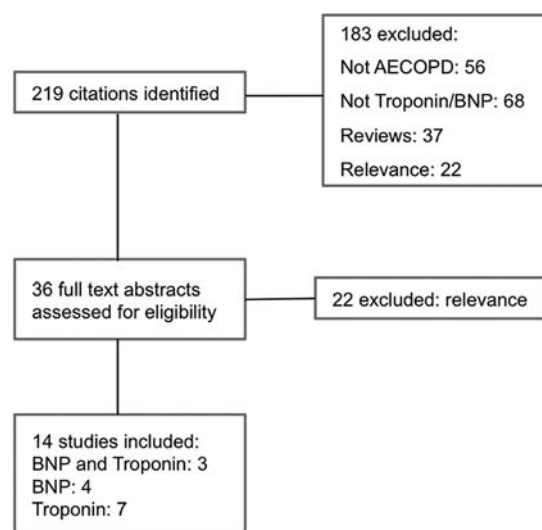

Figure 1 Methods used to select studies included in the review (AECOPD, acute exacerbations of chronic obstructive pulmonary disease; BNP, brain natriuretic peptide).

measuring both biomarkers. These 17 studies measured a variety of different end points, and BNP was measured at several time points.

Brain natriuretic peptide

The seven studies included (tables 2 and 3; further details in online supplementary table S1) ranged in size from 57 to 244 patients. Five of the seven studies included measured mortality; of these, three found a statistically significant association between a raised BNP and NT-proBNP measurement and increased mortality. However, the follow-up period for recording ranged from the length of ITU admission[6] to nearly 2 years.[7] In the two papers that measured mortality at both a short-term and a long-term time point,[6 7] one prospective study[7] found no significant association between BNP and mortality at either short-term or long-term time

points. However, another prospective study found a significant (p<0.001, OR=9.0) association between elevated NT-proBNP and increased mortality at 30 days but not at 1 year (p=0.27). In several of the studies included, a diagnosis of LV failure was included as either a primary or secondary end point. All three of the included papers that looked at this found[8] a significant association between elevated BNP or NT-proBNP and LV failure: (p<0.001) (12) (p=0.005)[9] (p<0.001),[8] respectively. Of the included studies, which measured a natriuretic peptide, five measured NT-proBNP, and the other two measured BNP.

Troponins

Ten of the studies we included measured troponins, of which three also measured BNP (further details in online supplementary table S1). Of these, seven

Table 2 Included studies that measured BNP or NT-proBNP[1 6–11]

Author	Date	Study size	Method	Outcome	OR/HR
Abroug *et al*[8]	2006	n=148	Prospective study	NT-proBNP is a useful tool to rule out association of AECOPD with LVD (p<0.0001)	Left heart involvement in AECOPD was the only variable independently associated with increased secretion of NT-proBNP (OR 74; 95% CI 15 to 375)
Stolz *et al*[7]	2008	n=208	Prospective study	Raised BNP levels on admission are not significantly associated with mortality at any time point. BNP levels are significantly higher in patients requiring ITU care and correlate well with need for ITU care and duration of stay	BNP accurately predicted the need for ICU care (HR 1.13; 95% CI 1.03 to 1.24) per 100 ng/mL increase in BNP. No HRs are available for short-term or long-term mortality
Gariani *et al*[9]	2011	n=57	Retrospective cohort study	LVD associated with AECOPD	BNP value ≥500 (OR 8.5, 95% CI 1.9 to 38.2) of LVD
Chang *et al*[6]	2011	n=244	Prospective cohort study	Elevated NT-proBNP significantly predicts 30-day mortality (p<0.001) but does not predict deaths between 30 days and 1 year (p=0.27)	OR 9.0, 95% CI 3.1 to 26.2, p<0.001
Marcun *et al*[1]	2012	n=127	Prospective observational study	Raised NT-proBNP levels on admission are significantly associated with 6-month mortality	HR 4.20, 95% CI 1.07 to 14.01
Ouanes *et al*[10]	2012	n=120	Prospective study	During ICU stay, NT-proBNP levels are not significantly associated with mortality Admission NT-proBNP levels are significantly higher in patients with LVD (p<0.001)	No OR or HR reported
Høiseth *et al*[11]	2012	n=99, 217 admissions	Prospective cohort study	Raised NT-proBNP is significantly associated with mortality. NT-proBNP grouped into tertiles, and the two higher groups compared with the lowest tertile	HRs for dying were 2.4 (0.95 to 6.0) and 3.2 (1.3 to 8.1) for the middle and top tertiles, respectively, compared with the bottom tertile

AECOPD, acute exacerbations of chronic obstructive pulmonary disease; BNP, brain natriuretic peptide; ICU, intensive care unit; LVD, left ventricular dysfunction.

Table 3 Included studies that measured troponins

Author	Date	Study size	Method	Outcome	OR/HR
Baillard et al[13]	2003	n=71	Prospective cohort study	Elevated cardiac troponin I is a predictor of in-hospital death in patients admitted for AECOPD	ORa 6.52; 95% CI 1.23 to 34.47
Harvey et al[12]	2004	n=188	Retrospective study	Significant association between raised troponin levels and increased length of hospital stay (p<0.001) reported	
Abroug et al[8]	2006	n=148	Prospective study	Useful in excluding AECOPD associated with LVD	A cut-off of 1000 pg/mL was accurate to rule out left heart involvement in AECOPD (sensitivity, 94%; negative predictive value, 94%; negative likelihood ratio, 0.08). A cut-off of 2500 pg/mL had the best operating characteristics to rule in the diagnosis (positive likelihood ratio, 5.16)
Brekke et al[14]	2008	n=396	Prospective cohort study—cross sectional. Used logistic regression to identify factors in AECOPD associated with an increased cTnT	Elevated cTnT is significantly associated with increased all-cause mortality in the observation period (median=1.9 years)	HR 1.61 (1.13 to 2.29)
Fruchter et al[15]	2009	n=182	Retrospective study	Out of hospital mortality. Follow-up from 3–83 months, mean of 35	HR=1.0653, 95% CI 1.0753 to 2.2512
Martins et al[16]	2009	n=173	Retrospective cohort study	In-hospital mortality, 18-month survival	Only p values available. Both peak and baseline cardiac troponin I predict overall 18-month survival (p=0.007 and p=0.012, respectively)
Høiseth et al[17]	2011	n=99	Prospective cohort study	Elevated cTnT during AECOPD is associated with increased mortality over a median follow-up time of 1.9 years	Adjusting for relevant covariables using an extended Cox regression analysis, the HRs (95% CI) for death were 4.5 (1.2 to 16) and 8.9 (2.4 to 32) among patients having hs-cTnT 14.0–39.9 and ≥40 ng/L, respectively, compared with patients with hs-cTnT <14.0 ng/L
Chang et al[6]	2011	n=244	Prospective cohort study	Elevated troponin T predicts 30-day mortality (p<0.001) but does not predict deaths between 30 days and 1-year follow-up (p=0.63)	OR 6.3, 95% CI 2.4 to 16.5, p<0.001
Høiseth et al[11 18]	2012	n=97	Prospective cohort study	survival status	Survival status was significantly associated with hs-cTnT, with a relative value of 1.58 (95% CI 1.11 to 2.23)
Marcun et al[1]	2012	n=127	Prospective observational study	Raised troponin T levels at discharge predict recurrent hospitalisation within the following 6 months	HR=2.89, 95% CI 1.13 to 7.36

AECOPD, acute exacerbations of chronic obstructive pulmonary disease; cTnT, cardiac troponin T; LVD, left ventricular dysfunction; ORa, adjusted OR.

measured mortality, and an association was found with elevated troponins and increased mortality in all these studies. However, these measured mortality at a variety of different time points, ranging from in-hospital death of admitted patients, to deaths of patients discharged from hospital and followed for a mean of 50 months. Other outcomes measured were repeat hospitalisation[1] and length of hospital stay;[12] and these papers found a statistically significant association with increased troponin measurements and repeat hospitalisation (HR=2.89, 95% CI 1.13 to 7.36)[1] and length of stay, respectively (p=0.001).[12]

BNP and troponin

Our search retrieved three papers that examined the predictive value of both BNP and troponins. Two of these three looked at the predictive power of combining the two biomarkers. A prospective cohort study found that while elevations each of NT-proBNP and troponin T measured at admission were associated with a statistically significant increase in 30-day mortality (p<0.001), an elevation of either NT-proBNP or troponin was associated with a 15-fold increased risk of mortality compared with patients with normal levels of both biomarkers.[6] The risk of mortality was 30-fold greater than in patients with normal levels of both biomarkers.[6]

A prospective observational study looked at the association of elevated NT-proBNP and troponin T at admission and discharge with mortality, repeat hospitalisation and a composite outcome of both repeat hospitalisation and death as outcomes.[1] It was found that only recurrent hospitalisations were associated with elevated troponin T and NT-proBNP at discharge (p=0.013). Elevated troponin T and NT-proBNP at admission were not significantly associated with any outcome.

A prospective study also measured NT-proBNP and troponin T in patients admitted to ITU with AECOPD. They found that patients with a plasma NT-proBNP value of less than 1000 pg/mL were unlikely to have LV dysfunction; this cut-off value had a sensitivity of 94% and a negative predictive value of 94%. A value of greater than 2500 pg/mL was used by the authors to rule-in LV dysfunction. They also found that increasing values of troponin T were associated with an increased likelihood of LV dysfunction.[8]

CONCLUSION

In summary, it appears that there may be a link between an elevated level of BNP or NT-proBNP and increased cardiovascular mortality in AECOPD, although the data currently available are not conclusive.

Two of the included studies looked at whether an elevation in BNP or NT-proBNP was associated with LV dysfunction in patients with COPD, and both of these found a significant association. These limited data suggest that BNP or NT-proBNP can be a useful tool in the diagnosis of LV failure concomitant with COPD.

Of the 10 included papers that measured troponins, 7 measured mortality, and in all of these, a significant association was found between elevated levels of troponins and increased mortality. Across the studies, a variety of time points were used, but these were all generally long term (more than 30 days after measurement). In addition, increased levels of troponins were predictors of readmission to hospital after discharge. A recent paper in *Open Heart* has suggested that not only the troponin level but also whether it rises then falls or remains elevated during an acute exacerbation may also have prognostic value.[19]

Three studies measured both BNP/NT-proBNP and a troponin in their study population; this provides us with information about the possible combinatorial value of these biomarkers. Interestingly, Abroug et al[8] found a significant correlation between increased levels of both biomarkers. Chang et al[6] did find that elevations of both biomarkers were associated with greater mortality than elevation of either biomarker alone. At present, this systematic review has identified a gap in terms of information about the combined value of these biomarkers.

Some of the limitations of this review are that the studies did not all define COPD or AECOPD in the same way. The methods used to define COPD include: spirometry; the combined use of ECG, chest X-ray, heart rate, blood pressure, respiratory rate, arterial blood gas results, PaO_2, chest pain and use of accessory muscles; agreement of two physicians on the basis of history and examination.

Another issue is the wide range of biomarkers, time points at which they were measured and end points measured, precluding meta-analysis. Accordingly, future research should aim to address which of the specific biomarkers offer the most value in the setting of AECOPD in terms of influencing clinical decision making and management.

Troponins used as biomarkers can encompass a wide range of molecules, including troponin T, troponin I and cardiac-specific isoforms of troponins. While we did not exclude studies on the basis of which type of troponin they measured, this variety precludes direct comparison of studies or pooling of data.

Given that patients with COPD commonly have cardiovascular comorbidities, the development of biomarkers that can help identify LV dysfunction could guide treatment, improving both prognosis and quality of life. BNP and cardiac troponins are currently in widespread clinical use for patients with cardiac disease, and would be a simple, cheap test to aid COPD investigation and management. They also appear to have a predictive value in terms of prognosis, and could help identify patients with AECOPD who are at greater risks of poor outcomes and allow targeted interventions to improve outcomes.

The results presented above do suggest that NT-proBNP could be a useful biomarker for the diagnosis of LV failure, and also a predictor of mortality, particularly in the short term. However, more research is needed in order to determine the clinical utility of BNP or NT-proBNP as a biomarker in AECOPD.

Author affiliations
[1]Medical School, University of Oxford, Oxford, UK
[2]Medical School, St Hugh's College, University of Oxford, Oxford, UK
[3]Medical School, Queen's College, University of Oxford, Oxford, UK
[4]Department of Respiratory Medicine, Oxford University Hospitals, Oxford, UK
[5]Department of Respiratory Medicine, Lymington Forest Hospital, Southern Health NHS Trust, Hampshire, UK
[6]Oxford Centre for Respiratory Research, Oxford Biomedical Research Centre, Oxford University Hospitals NHS Trust, Oxford, UK

REFERENCES

1. Marcun R, Sustic A, Brguljan PM, et al. Cardiac biomarkers predict outcome after hospitalisation for an acute exacerbation of chronic obstructive pulmonary disease. *Int J Cardiol* 2012;161:156–9.
2. Andell P, Koul S, Martinsson A, et al. Impact of chronic obstructive pulmonary disease on morbidity and mortality after myocardial infarction. *Open Heart* 2014;1:e000002.
3. Shujaat A, Minkin R, Eden E. Pulmonary hypertension and chronic cor pulmonale in COPD. *Int J Chron Obstruct Pulmon Dis* 2007;2:273–82.
4. de Miguel Diez J, Chancafe Morgan J, Jimenez Garcia R. The association between COPD and heart failure risk: a review. *Int J Chron Obstruct Pulmon Dis* 2013;8:305–12.
5. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529–36.
6. Chang CL, Robinson SC, Mills GD, et al. Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD. *Thorax* 2011;66:764–8.
7. Stolz D, Breidthardt T, Christ-Crain M, et al. Use of B-type natriuretic peptide in the risk stratification of acute exacerbations of COPD. *Chest* 2008;133:1088–94.
8. Abroug F, Ouanes-Besbes L, Nciri N, et al. Association of left-heart dysfunction with severe exacerbation of chronic obstructive pulmonary disease: diagnostic performance of cardiac biomarkers. *Am J Respir Crit Care Med* 2006;174:990–6.
9. Gariani K, Delabays A, Perneger TV, et al. Use of brain natriuretic peptide to detect previously unknown left ventricular dysfunction in patients with acute exacerbation of chronic obstructive pulmonary disease. *Swiss Med Wkly* 2011;141:w13298.
10. Ouanes I, Jalloul F, Ayed S, et al. N-terminal proB-type natriuretic peptide levels aid the diagnosis of left ventricular dysfunction in patients with severe acute exacerbations of chronic obstructive pulmonary disease and renal dysfunction. *Respirology* 2012;17:660–6.
11. Høiseth AD, Omland T, et al. NT-proBNP independently predicts long term mortality after acute exacerbation of COPD—a prospective cohort study. *Respir Res* 2012;13:97.
12. Harvey MG, Hancox RJ. Elevation of cardiac troponins in exacerbation of chronic obstructive pulmonary disease. *Emerg Med Australas* 2004;16:212–15.
13. Baillard C, Boussarsar M, Fosse JP, et al. Cardiac troponin I in patients with severe exacerbation of chronic obstructive pulmonary disease. *Intensive Care Med* 2003;29:584–9.
14. Brekke PH, Omland T, Holmedal SH, et al. Troponin T elevation and long-term mortality after chronic obstructive pulmonary disease exacerbation. *Eur Respir J* 2008;31:563–70.
15. Fruchter O, Yigla M. Cardiac troponin-I predicts long-term mortality in chronic obstructive pulmonary disease. *COPD* 2009;6:155–61.
16. Martins CS, Rodrigues MJ, Miranda VP, et al. Prognostic value of cardiac troponin I in patients with COPD acute exacerbation. *Neth J Med* 2009;67:341–9.
17. Høiseth AD, Neukamm A, Karlsson BD, et al. Elevated high-sensitivity cardiac troponin T is associated with increased mortality after acute exacerbation of chronic obstructive pulmonary disease. *Thorax* 2011;66:775–81.
18. Høiseth AD, Omland T, Hagve TA, et al. Determinants of high-sensitivity cardiac troponin T during acute exacerbation of chronic obstructive pulmonary disease: a prospective cohort study. *BMC Pulm Med* 2012;12:22.
19. Høiseth AD, Neukamm A, Hagve TA, et al. The clinical value of serial measurement of high-sensitivity cardiac troponin T in acute exacerbations of chronic obstructive pulmonary disease. *Open Heart* 2014;1:e000001.