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

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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 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

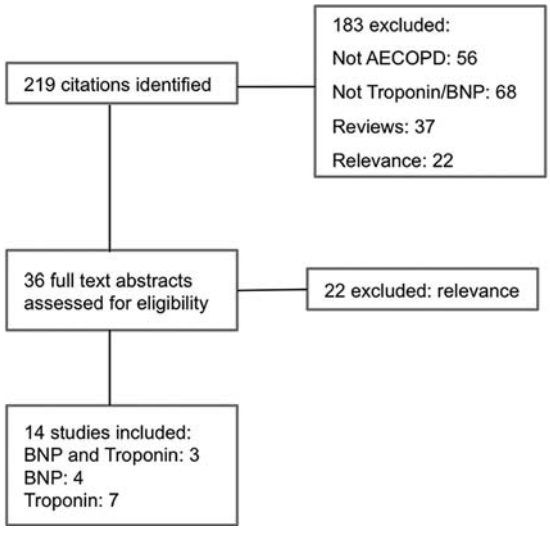

Figure 1 Methods used to select studies included in the review (AECOPD, acute exacerbations of chronic obstructive pulmonary disease; BNP, brain natriuretic peptide).

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.

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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.

Appendix I – Outcome-level risk of bias analysis for all included studies

Study	**Biomarker**	**Outcome**	**Overall Domain 1**	**Overall Domain 2**	**Overall Domain 3**	**Overall domain 4**
Marcun R *et al.* 2012 [3]	NT-proBNP	6 month Mortality	low risk	unclear	n/a	low risk
Marcun R *et al.* 2012 [3]	NT-proBNP	Hospitalisation	low risk	unclear	n/a	low risk
Marcun R *et al.* 2012 [3]	Troponin T	6 month Mortality	low risk	unclear	n/a	low risk
Marcun R *et al.* 2012 [3]	Troponin T	Hospitalisation	low risk	unclear	n/a	low risk
Chang *et al.* 2011 [10]	NT-proBNP	30-day mortality	low risk	low risk	n/a	low risk
Chang *et al.* 2011 [10]	Troponin T	30-day mortality	low risk	low risk	n/a	low risk
Chang *et al.* 2011 [10]	NT-proBNP	30-day to 1 year mortality	low risk	low risk	n/a	low risk
Chang *et al.* 2011 [10]	Troponin T	30-day to 1 year mortality	low risk	low risk	n/a	low risk
Stolz *et al.* 2008 [13]	BNP	2 year mortality	low risk	high risk	n/a	low risk
Stolz *et al.* 2008 [11]	BNP	intensive care admission	low risk	high risk	n/a	low risk
Stolz *et al.* 2008 [11]	BNP	in-hospital mortality	low risk	high risk	n/a	low risk

Høiseth *et al.* 2012 [15]	NT-proBNP	long-term mortality	low risk	high risk	n/a	low risk
Ouanes *et al.* 2012 [12]	NT-proBNP	LV dysfunction diagnosis	low risk	low risk	low risk	low risk
Gariani *et al.* 2011 [13]	BNP	diagnosis of LVD	medium risk	medium risk	low risk	low
Abroug *et al.* 2006 [14]	NT-proBNP	diagnosis of LVD (or exclusion)	low risk	medium risk	low risk	low risk
Abroug *et al.* 2006 [14]	Troponin T	diagnosis of LVD (or exclusion)	low risk	low risk	low risk	low risk
Baillard *et al.* 2002 [17]	Troponin I	in-hospital mortality	low risk	low risk	n/a	low risk
Brekke *et al.* 2009 [18]	cTnT	mortality	low risk	low risk	n/a	low risk
Fruchter *et al* 2009 [19]	Troponin I	mortality following discharge from hospital	low risk	low risk	n/a	low risk
Høiseth *et al.* 2012 [21]	cardiac Troponin T	mortality until end of study (mean follow-up 1.9 years)	low risk	low risk	n/a	low risk

Høiseth *et al.* 2012 [22]	cardiac Troponin T	survival	low risk	high risk	n/a	low risk
Martins *et al.* 2009 [20]	cardiac Troponin I	18-month survival	low risk	low risk	n/a	low risk
Harvey *et al.* 2004 [16]	"serum troponin" - looked at both TnI and TnT	increased length of hospital stay	low risk	low risk	low risk	low risk

Name	Year	Biomarker(s) measmeasured	Study group	inclusion criteria	Exclusion criteria	Mean age	Endpoints included	Total duration of follow-up	Number of patients	Total deaths in study	Assay used	Threshold for elevation.

BAILLARD	2003	cardiac troponin I, assayed in blood samples obtained on admission and 24 hours later	71 consecutive patients at Two intensive care units at two french university hospitals	patients admitted with severe exacerbation of COPD	Patients with evidence of pulmonary embolism (PE) or Q-wave myocardial infarction were not included. Exclusion of PE was based on clinical signs and symptoms, laboratory tests (blood gas analysis and D-Dimer tests) at admission. When the diagnosis of PE was suspected, it was ruled out or confirmed by high probability lung scan and Doppler echography examination of the lower limbs, followed by spiral computed tomography scan when doubts remained. The diagnosis of COPD was made according to American Thoracic Society criteria. Severe exacerbation was defined as an acute increase in dyspnoea requiring ICU admission and likely to require ventilatory support.	71	in-hospital mortality	in-hospital mortality	n=71	18	(Stratus II immunoassay analyser, Dade In- ternational)	Levels above 0.5 ng/ml were considered positive.

ABROUG	2006	NT-proBNP	All consecutive patients admitted to the medical ICU between October 2001 and March 2005 for severe AECOPD were considered for inclusion	consecutive patients hospitalised in ICU for the first time for an AECOPD and requiring non-invasive or conventional mechanical ventilation. AECOPD defined as increased in cough and dyspnea nad as a change in sputum abundance and purulence. Severity of AECOPD was defined	patients with an obvious cause of exacerbation (pneumonia or oneumothorax on CXR or PE diagnosed on CT). Patients experiencing cardiac arrest before ICU admission and patients with persistent haemodynamic instability requiring inotropic or vasoactive support. Patients with acute renal failure (calculated creatinine clearance <15ml/min) or who were nonechogenic on echocardiographic evaluation.	median 68	LV dysfunction	In hospital - at diagnosis	n=148	?	NT-proBNP and cardiac troponin T were determined by quantita- tive electrochemiluminescence assay (Elecsys proBNP and Elecsys Troponin; Roche Diagnostics, Indianapolis, IN) on an Elecsys 2010 analyzer (Roche Diagnostics)	A cutoff of 1,000 pg/ml was accurate to rule out left-heart involvement in AECOPD (sensitiv- ity, 94%; negative predictive value, 94%; negative likelihood ratio, 0.08). A cutoff of 2,500 pg/ml had the best operating characteristics to rule in the diagnosis (positive likelihood ratio, 5.16).

BREKKE	2008	Troponin T	patients discharged after treatment for COPD exacerbation from Akershus hospital between 2000-2003. Followed up until 2005.	cases identified using the hospital's patient database. Patients 40 yrs or older who were admitted between January1 2000 and December 31 2003 and were discharged with a primary diagnosis of COPD exacerbation with ICD codes J44.0, J44.1 or COPD as an underlying diagnosis combined with pneumonia as the main diagnosis were included.	patients with a previous diagnosis of sarcoidosis, interstitial lung disease or neuromuscular disease were excluded.	70.9	Mortality following hospital discharge	median 1.9 years		312	Elecsys® Troponin T STAT (Roche Diagnostics GmbH)	cTnT >/=0.04 mug.L(-1)
STOLZ	2008	B-type Natriuretic Peptide (BNP)	208 consecutive patients presenting to the ED of University Hospital Basel with AECOPD from November 2003 to March 2005	COPD as diagnosed by two physicians based on clinical history, physical examination and spirometric criteria as determined by the GOLD guidelines	patients with cystic fibrosis, active pulmonary TB or infiltrates on chest radiographs on presentation. Severely immunocompromised patients also excluded	70	need for intensive care, short-term mortality, long-term mortality	2 years		46	fluorescence immunoassay (Biosite Diagnostics; La Jolla, CA).	none used

BREKKE	2009	Cardiac Troponin T	patients admitted with COPD exacerbation in 2000-03 were identified. 441 had measurement of cTnT performed. Levels of cTnT > or = 0.04 microg/l were considered elevated. Clinical and historical data were retrieved from patient records, hospital and laboratory databases. Odds ratios for cTnT elevation were calculated using logistic regression.	exacerbation of COPD on 2000-2003 who had cardiac troponin T measured	patients with a previous diagnosis of sarcoidosis, interstitial lung disease or neuromuscular disease were excluded	72.2					Elecsys Troponin T STAT	Levels of cTnT ≥ 0.04 µg/l were considered elevated.

FRUCHTER	2009	troponin I	The records of 182 patients with acute exacerbation in whom troponin I levels were sampled during their hospitalization were reviewed retrospectively. Receiver operator curve was used to determine the cut-off level for troponin I that discriminated survivors and non-survivors, and predictors for all-cause mortality were tested in a multivariate analysis.	"Patients were included if the following criterion was met: diagnosis of COPD according to the criteria set by The Global Initiative for Chronic Obstructive Lung Disease (GOLD) (21). AECOPD was defined by the presence of an increase in at least two of three symptoms—dyspnea, cough, and sputum purulence - severe enough to warrant hospital admission without concomitant evidence of pneumonia. " and cTnI measured (this left to discretion of ED physician	"patients with chronic renal failure, defined as calculated serum creatinine level of more than 1.5 mg% (normal <1.1 mg%) for 3 months or more, were excluded. Patients with other conditions known to af- fect troponin levels (9) such as sepsis, pulmonary embolism, myocarditis, cardiomyopathy, and chest contusion were also excluded. "	71.2	Mortality following hospital discharge	3-83 months, median 35		66	cTnI assay used by the hospital labora- tory was AxSYM troponin-I ADV	0.03 ng / L (determined using ROC)

MARTINS	2009	troponinI	analysis of admissions for acute exacerbation of COPD with cardiac tropninI being obtained within the first 48hours of admission. 173 patients of which 05 male and 68 female.previous medical condidtions didnt vary according to sex tough women were more prone to usign beta blockers and diuretics and men to o2 therapy. patients with cardiac troponinI greater than 99th percentile were significantly older.	"Cases were identified by consulting the electronic records for all admissions to the hospital during the year 2007, with primary discharge coding diagnosis of COPD exacerbation. "	exclusion criteria included: marked renal failure (eGFR <15ml/min), persistent haemodynamic instability requiring inotropic or vasoactive support, pulmonary embolus, MI and cardiac arrest prior to admission(diagnoses made by attending physician)	median 77 years	in-hospital death, 18-month survival (for patients with a valid contact number)	18 months		5.9% in-hospital mortality, 21.1% post-discharge	chemiluminescence's microparticle immunoassay, using the ARCHITECT STAT system	0.012 ng/ml.

CHANG	2011	NTproBNP	unselected patients admitted to hospital with physician diagnosed COPD without evidence of acute cardiac disease over 1 year.	admitted to hospital with physician diagnosed COPD	no evidence of acute cardiac disease	71.7	all-cause mortality at 30 days and 1 year	1 year		42	quantitative electrochemiluminescence assay (Elecsys proBNP and Troponin; Roche Diagnostics Corporation, IN, USA)	NT-proBNP >220pmol/L and troponin T > 0.03μg/L are considered abnormal
GARIANI	2011	BNP	Retrospective medical records analysis of all patients hospitalised between January 2003 and May 2009 with the final diagnosis of acute exacerbation of COPD, and who had undergone BNP dosage at admission followed by an echocardiography	hospitalised between January 2003 and May 2009 with a final diagnosis of acute exacerbation of COPD who had undergone BNP analysis at admission followed by and ECHO. Over 18yrs old	patients with a known history of heart failure	75	LV dysfunction	n/a		?	not stated	500 pg/ml (also looked at below 110 pm/ml to rule out LV dysfunction.

Høiseth	2011	Troponin T	Patients were included from 3 January 2005 to 30 November 2006 and followed until 31 December 2008 or death. All patients admitted with assumed AECOPD were eligible for preliminary inclusion in the emergency room, prior to the emergency physicians' knowledge of any blood tests. The research fellow contacted the patient on the ward within a day to retrieve written informed consent and medical history.	The diagnosis of copd, as defined by the British Thoracic Society in 2004,24 was later verified by two study doctors by independent review of the hospital records, blinded for the result of the troponin analysis. In case of disagreement, the diagnosis was settled by consensus. Mortality data were gathered from the National Population Registr	Exclusion criteria were: age <50 years, metastatic cancer and ECOG (Eastern Cooperative Oncology Group) performance status grade ?2, neuromuscular disease with respiratory failure and non-cooperability.	71.5	mortality up until end of study	1.9 years (median)		57	(cobas e 411 immunoanalyser, Roche Diagnostics, Mannheim, Germany)	> 14 ng/l, with a third tertile at 40 ng/l

Høiseth (BMC pulm med)	2012	hs-cTNT	All patients admitted with AECOPD during 23 months between 2003 and 2006. 97 patients included. Mean age at inclusion was 71.5 years and 47% were female.	All patients admitted with AECOPD during 23 months between 2003 and 2006 were eligible	PE	71.5	n/a	n/a	n=97		hs-cTnT (cobas e 411 immunoanalyser, Roche diagnostics)	14 ng/L
Høiseth (Respir red)	2012	NT-proBNP				71.5	Mortality following hospital discharge	1.9 years (median)	n=99, 217 admissions	57	(Roche Diagnostics, Mannheim, Germany)	NT-proBNP tertile limits were 264.4 and 909 pg/m
MARCUN	2012	NT-proBNP	patients admitted for an acute exacerbation of COPD	– age over 35 years old with AECOPD stage II-IV, with residence within the geographical area linked to the study hospital in Slovenia. Able to communicate by telephone.	diagnosis of cognitive impairment, unstable of terminal disease other than COPD, death during hospitalisation.	70	Mortality following hospital discharge, re-hospitalisation	6 months		17	Elecys 2010 (Roche Diagnostics) using Electrochemiluminescence immunoassay (ECLIA)	n age and gender adjusted 95-percentile values for NTproBNP (ng/L) and a single value of 0.012 ng/L for TnT.

OUANES	2012	NT-proBNP	all patients consecutively admitted with severe AECOPD	diagnosis of COPD was based on clinical history and assessment of respiratory function, when available. AECOPD defined according to GOLD guidelines. Severe AECOPD were defined according to clinical findings of respiratory fatigue.	Patients with an obvious cause for AECOPD (pneumonia, pneumothorax and PE) and patients who had cardiac arrests were excluded.	67	LV dysfunction	none		n/a	NT-proBNP levels were determined by quantitative electrochemiluminescence assay (Elecsys proBNP; Roche Diagnostics, Indianapolis, IN, USA) on an Elecsys 2010 analyzer (Roche Diagnostics	The threshold NT-proBNP value with the highest diagnostic accuracy was greater in the setting of renal dysfunction (2000 pg/mL; sensitivity 71%, specificity 82%, compared with 1000 pg/mL in patients with normal renal function; sensitivity 94%, specificity 82%

SOYSETH	2013	Troponin T	consecutive admissions to participating units(a teaching hospital and a pulmonary rehabilitation clinic) for the years 2010-2011 meeting opbjective, standardised criteria for AECOPD and stable COPD. Index group – patients hospitalised for AECOPD at Akershus University hospital Feb2010 – Dec2011. Referrences recruited at lung rehabilitation hospital.	– all the patients had COPD confirmed by spirometry in their stable state within the last five years. All patients between 40 and 79 years old with cumulative tobacco consumption of 10 pack years or more. Current and former smokers included.								