The influence of heart failure co-morbidity on high-sensitivity troponin T levels in COPD exacerbation in a prospective cohort study: data from the Akershus cardiac examination (ACE) 2 study

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Abstract

Context: Troponin (hs-TnT) levels predict mortality after acute exacerbation of COPD (AECOPD). Whether this is independent of heart failure (HF) is not established.

Material and methods: Prospectively included AECOPD patients adjudicated for acute HF categorized into three groups: (A) AECOPD, but acute HF the primary cause for hospitalization; (B) AECOPD the primary cause, but co-existing myocardial dysfunction and (C) AECOPD without myocardial dysfunction.

Results: About 103 AECOPD patients; 18% A, 27% B and 54% C. Hs-TnT level differed between the groups: (ng/l, median) A: 41, B: 25 and C: 15, \( p = 0.03 \) for A versus B and \( p = 0.005 \) for B versus C. During a median 826 days, 47% died. In Cox analysis, hs-TnT levels remained associated with mortality (hazard ratio per 10 ng/l 1.3, \( p < 0.0001 \)).

Conclusion: hs-TnT levels are influenced by myocardial dysfunction/HF in AECOPD, but provide independent prognostic information. The prognostic merit of hs-TnT cannot be attributed to HF alone.

Keywords

COPD, epidemiology, heart failure, troponin

Introduction

Dyspnoea is a principal symptom in heart failure (HF) and chronic obstructive pulmonary disease (COPD). Both conditions are common and may have acute deteriorations with worsening of dyspnoea. These deteriorations are referred to as acute HF and acute exacerbation of COPD (AECOPD), respectively. Among patients with COPD, the prevalence of HF is \( \sim 20\% \) (Hawkins et al., 2009; Mascarenhas et al., 2010). Thus, decompensated HF may represent the primary clinical problem in a substantial group of patients presenting with AECOPD. The prevalence of COPD among patients with HF is even higher. Having HF and COPD in combination is associated with a worse prognosis compared with having only HF or COPD (Hawkins et al., 2009; Sidney et al., 2005; Sin & Man, 2005). In spite of this knowledge, heart disease is under-diagnosed and under-treated among patients with COPD (Breke et al., 2008b).

In patients with COPD, elevated concentrations of cardiac troponin T (TnT) are commonly seen both in the stable phase and during exacerbations, particularly when using a high-sensitivity (hs) assay (Chang et al., 2011; Hoiseth et al., 2011; Neukamm et al., 2013; Soyseth et al., 2013). Still, the mechanism behind troponin release during AECOPD remains unresolved. Cor pulmonale, type 1 or 2 myocardial infarction (MI), myocardial remodelling, stress cardiomyopathy and HF are possible mechanisms. Although closely associated with coronary artery disease in patients with acute coronary syndrome (ACS), hs-TnT levels seem to be more closely associated with myocardial remodelling (tissue rearrangements leading to change in shape or size of the ventricles; Knoll et al., 2011) and HF outside of the classical chest pain setting (de Lemos et al., 2010; Neeland et al., 2013; Rosjo et al., 2011b,2012). We have found elevated hs-TnT levels in COPD patients to be influenced by age, history of hypertension and electrocardiographic evidence of prior MI (Hoiseth et al., 2012), variables that over time are associated with progressive myocardial remodelling and HF. Although other variables, including renal function, also influence hs-TnT levels in COPD patients, our previous results support a link between elevated hs-TnT levels and HF also in patients with COPD. Potentially, having a biomarker representing a signal of myocardial dysfunction and HF could prove important for later studies of tailored HF therapy in a subgroup of AECOPD patients. The strategy of targeting co-morbidity is also
recommended in the GOLD guidelines on COPD management. Accordingly, to promote our understanding of elevated hs-TnT levels in COPD, in the present study, we wanted to: (1) explore the association between hs-TnT and HF in patients with severe AECOPD and (2) to assess the prognostic merit of hs-TnT in AECOPD after adjustment for HF and other established risk factors.

Methods

Study population
This study is a sub-group analysis of the Akershus Cardiac Examination (ACE) 2 Study that in total included 314 consecutive patients with dyspnoea admitted to Akershus University Hospital, a Norwegian teaching hospital with a catchment area of ~460 000 inhabitants. Due to logistics, we only included patients Monday–Thursday 8.00 a.m.–2 p.m. starting June 2009 and ending November 2010. With exclusion criteria confined to disseminated malignant disease and inability to cooperate, we prospectively included unselected patients admitted through the Emergency Department (ED) with acute dyspnoea as their primary complaint. We approached the patients within 24 h to obtain consent and relevant clinical and biochemical data, and we had chest radiograph and ECG recorded. The attending physician’s findings on examination, assessment of diagnosis, their certainty of this diagnosis (on a scale from 0% to 100%) and their estimated probability (0–100%) of HF as the principal diagnosis were recorded in a designated form. The physicians in the ED were all junior staff in the Department of Internal Medicine within their first years of residency. More experienced physicians were on call, but not normally present in the ED. Detailed information regarding previous medical history and medication was obtained directly from the patients and checked against medical records by dedicated study personnel on day 1. Results on pulmonary testing and blood gas analyses were obtained from the medical records. We recorded survival status from electronic hospital records, which are synchronized with Statistics Norway, with follow-up ending 1 November 2012.

The ACE 2 Study was conducted according to the Declaration of Helsinki and was approved by the ‘Regional Ethics Committee South East’ (#6.2008.2832). All the patients provided written informed consent before study commencement.

Adjudication of diagnosis
A median of 464 (interquartile range [IQR] 304–705) days after inclusion, using all the available data in the electronic medical records, including that from later admissions (but blinded for the study-specific cardiac biomarkers) an end-point committee of two senior physicians determined whether the patients fulfilled the criteria for an AECOPD, as defined by GOLD: ‘[…] a worsening of the patient’s symptoms [dyspnoea, cough and/or sputum production] that is beyond day-to-day variation and that leads to a change in medication’ (2015). The end-point committee also classified each patient’s final diagnosis into one of three groups: (A) medical history, symptoms and signs of AECOPD, but with acute HF as the underlying cause for the deterioration, (B) co-existing myocardial dysfunction (i.e. reduced ejection fraction and diastolic dysfunction), but AECOPD rather than HF the primary cause for hospitalization and (C) AECOPD without prior or current HF or myocardial dysfunction. HF and myocardial dysfunction were diagnosed according to the recent European Society of Cardiology (ESC) guidelines requiring symptoms and clinical signs of HF, and objective evidence of systolic or diastolic myocardial dysfunction (McMurray et al., 2012). Presence of symptoms and signs were collected from the forms completed by the attending physicians’ on admission. Signs of congestion on chest radiograph were noted. Evidence of myocardial dysfunction was sought in ECGs and echocardiography reports by evaluating LVEF, mitral E/A, E deceleration time, E/e′, left atrial size and the severity of valvular stenosis and regurgitations.

The two members of the adjudication committee worked independently and provided the same diagnosis in 298 of the 314 patients (95%) included in the total study population with disagreements resolved by consensus, which is higher than other studies reporting the results of the adjudication committee (Januzzi et al., 2005; McCullough et al., 2002).

Laboratory analyses and cardiac biomarker measurements

Blood samples for study biomarker measurements were obtained from the patients within 24 h of hospitalization (baseline) and after 24 h by dedicated study personnel. Blood samples were immediately put on ice, processed in a uniform way throughout the study and stored at −80 °C before analyses. We used serum samples to measure TnT levels by a hs assay (Elecsys TnT hs stat, Roche Diagnostics, Penzberg, Germany). The hs-TnT has a range of detection from 3 to 10 000 ng/l, the 10% coefficient of variation is 13 ng/l and the 99th percentile in healthy individuals is 14 ng/l. The analytical characteristics of hs-TnT analysis in our laboratory have previously been reported (Rosjo et al., 2012). In the analyses, hs-TnT concentrations below the range of detection were assigned a value of 3.0 ng/l. A significant hs-TnT rise/fall was defined as a change from baseline to day 1 (ΔTnT) of ≥20% when baseline hs-TnT was ≥14 ng/l and ΔTnT ≥50% when baseline hs-TnT was <14 ng/l (Group et al., 2007; Thygesen et al., 2012). N-terminal pro-BNP (NT-proBNP) levels were measured by the proBNP II assay (Roche Diagnostics), and creatinine clearance was estimated by the Cockcroft–Gault formula.

Statistical analyses

Fractions are reported as numbers with percent, continuous variables as mean with SD or as median with IQR, and estimates with 95% confidence intervals (CI). We compared baseline data between the three diagnosis groups using chi-squared, Kruskal–Wallis’, Student’s t test or Fisher’s exact test. We examined the data for univariable associations with log-transformed hs-TnT concentrations using age-adjusted linear regression. Crude hazard ratios for mortality were analyzed using age-adjusted Cox regression analysis and the following variables were analyzed both as continuous variables and dichotomized at pre-specified limits: FEV1 at 11, heart rate at 100 bpm, pH at 7.35, PaCO2 at 6.7 kPa, PaO2 at 8.0 kPa and creatinine clearance at 60 ml/min.

Determinants of hs-TnT concentration were assessed using an ordinary least square linear regression model with
the natural logarithm of the hs-TnT concentration as the dependent variable. We developed two models; with and without the end-point committee diagnosis. Medication, NT-proBNP concentration and medical history were highly correlated, thus these variables were not included in the same multivariable model. This was also the case for physician-assessed HF probability and end-point committee diagnosis. The variables that were associated with hs-TnT with a $p$ value $<0.20$ in the age-adjusted analyses were included in the initial multivariable linear regression model. This was manually backwards reduced, removing one by one the variables that showed a $p$ value $>0.05$. The variables that had been removed were finally individually re-entered. If this lead to a $p$ value $<0.05$, they were kept in the model. Association between hs-TnT levels and mortality was explored by Cox regression analysis. All the variables that were associated with mortality with a $p$ value $<0.20$ in the age-adjusted Cox analysis were included in a multi-variable Cox model using the same strategy as for the linear regression analyses. In this model, we kept the end-point committee diagnosis in the model regardless of $p$ value.

Table 1. Baseline data stratified by diagnosis group.

| Variable                        | Group A (HF + AECOPD) ($n=19$) | Group B (AECOPD + LV dysfunction) ($n=28$) | Group C (AECOPD) ($n=56$) | $p$ value |
|---------------------------------|----------------------------------|---------------------------------------------|---------------------------|-----------|
| Age (years)                     | 79.6 (5.9)                       | 71.4 (8.0)                                  | 68.4 (9.6)                | $<0.0001$ |
| Female                          | 10 (53%)                         | 11 (39%)                                    | 38 (68%)                 | 0.040     |
| FEV$_1$ (l)$^a$                 | 0.96 (0.42)                      | 1.10 (0.45)                                 | 0.90 (0.42)              | 0.169     |
| FEV$_1$ (% of predicted)$^b$    | 44 (16)                          | 40 (20)                                     | 36 (17)                  | 0.182     |
| FEV$_1$/FVC$^c$                 | 50 (13)                          | 53 (16)                                     | 43 (14)                  | 0.015     |
| FEV$_1$ $<1$ l$^d$              | 34 (68%)                         | 12 (48%)                                    | 9 (50%)                  | 0.171     |
| NYHA class on admission         |                                  |                                             |                          | 0.202     |
| II                              | 1                                | 1                                           | 9                        |           |
| III                             | 7                                | 13                                          | 14                       |           |
| IV                              | 11                               | 14                                          | 33                       |           |
| BMI (kg/m$^2$)                  | 26 (5.8)                         | 27 (7.0)                                    | 23 (5.3)                 | 0.015     |
| Duration of dyspnoea (days)     | 4.8 (1.7)                        | 4.4 (1.8)                                   | 4.0 (1.5)                | 0.037     |
| History of                      |                                  |                                             |                          |           |
| Heart failure                   | 9 (47%)                          | 9 (32%)                                     | 0                        | $<0.0001$ |
| Diabetes mellitus               | 4 (21%)                          | 5 (18%)                                     | 4 (7.1%)                 | 0.147     |
| Atrial fibrillation             | 7 (37%)                          | 7 (25%)                                     | 7 (13%)                  | 0.058     |
| $\beta$-blocker                 | 10 (53%)                         | 16 (57%)                                    | 15 (27%)                 | 0.012     |
| Medication on admission         |                                  |                                             |                          |           |
| ACEi/ARB                        | 6 (32%)                          | 28 (54%)                                    | 12 (21%)                 | 0.12      |
| Statin                          | 9 (47%)                          | 13 (46%)                                    | 14 (25%)                 | 0.069     |
| ASA                             | 13 (68%)                         | 10 (43%)                                    | 18 (32%)                 | 0.021     |
| Warfarin                        | 3 (16%)                          | 9 (32%)                                     | 7 (13%)                  | 0.086     |
| Loop diuretic                   | 9 (47%)                          | 16 (57%)                                    | 12 (21%)                 | 0.003     |
| Nitrate                         | 2 (11%)                          | 6 (21%)                                     | 2 (3.6%)                 | 0.019     |
| LAMA                            | 1 (5.3%)                         | 7 (25%)                                     | 14 (25%)                 | 0.153     |
| Insulin                         | 2 (11%)                          | 2 (7.1%)                                    | 1 (1.8%)                 | 0.149     |
| Findings on admission           |                                  |                                             |                          |           |
| Heart rate (bpm)                | 95 (16)                          | 92 (18)                                     | 99 (18)                  | 0.114     |
| Prehospital SaO$_2$             | 85.2 (9.0)                       | 83.5 (12.2)                                 | 85.3 (8.8)               | 0.959     |
| Heart rate $\geq$100 beats/min | 28 (50%)                         | 8 (29%)                                     | 8 (42%)                  | 0.173     |
| Cardiac murmur                  | 7 (37%)                          | 0                                           | 2 (3.6%)                 | $<0.0001$ |
| Creatinine clearance (ml/min)   | 58 (23)                          | 76 (28)                                     | 80 (24)                  | 0.003     |
| hs-TnT on admission (ng/l)      | 41.2 (19.2–74.2)                 | 24.8 (13.1–36.8)                            | 15.2 (7.5–24.6)          | $<0.0001$ |
| hs-TnT on day 1 (ng/l)          | 32.1 (24.9–59.9)                 | 18.9 (12.4–27.1)                            | 14.8 (6.4–30.5)          | 0.003     |
| hs-TnT rise/fall (ng/l)         | 10.4 (16)                        | 5.2 (6.6)                                   | 4.4 (6.1)                | 0.624     |
| hs-TnT significant rise/fall    | 7 (37%)                          | 12 (43%)                                    | 24 (43%)                 | 0.891     |
| NT-proBNP (pg/ml)               | 2380 (621–17 087)                | 1012 (340–2268)                             | 298 (145–578)            | $<0.0001$ |
| Physician’s assessment of diagnosis |                                  |                                             |                          |           |
| Acute heart failure             | 2 (11%)                          | 2 (7.1%)                                    | 4 (7.1%)                 | 0.885     |
| AECOPD                          | 13 (68%)                         | 20 (71%)                                    | 51 (91%)                 | 0.024     |
| Other                           | 0                                | 1 (3.6%)                                    | 2 (2.6%)                 | 0.999     |
| Pneumonia                       | 4 (21%)                          | 6 (21%)                                     | 6 (11%)                  | 0.337     |
| ED physicians’ certainty (%)    | 74 (15)                          | 81 (11)                                     | 77 (18)                  | 0.358     |
| ED physician probability of HF (%) | 36 (21)                      | 23 (16)                                     | 17 (12)                  | 0.0003    |
| Mortality                       | 13 (68%)                         | 10 (37%)                                    | 25 (45%)                 | 0.095     |
| Mortality rate per 100 patient-years | 47.5 (27.6–81.8)            | 19.1 (10.3–35.5)                            | 20.8 (14.1–30.8)         | 0.027     |

The table contains variables that varied between the diagnosis groups at a level of $p<0.20$ along with a few selected variables. Data reported as numbers with percent of column total, mean with SD or median with interquartile range. $p$ value for difference between any two groups.

$^a$All values are post-bronchodilation in the stable phase.

BMI, body mass index; ACEi/ARB, angiotensin converting enzyme inhibitor or angiotensin receptor blocker; ASA, acetylic salicylic acid; LAMA, long-acting Muscarinic antagonist; bpm, beats per minute; ICS, inhaled corticosteroids; BP, blood pressure; ED, emergency department.
A/B and B/C, respectively. p = 0.030 between groups A/B and A/C21 50%) left ventricular ejection fraction was 9 versus 10 patients, respectively. The baseline data, stratified by diagnosis group, are reported in Table 1.

Patients with AECOPD and HF were elderly, had more substantial history of HF and used more cardiac medications, while pulmonary and blood gas status were similar. Table 1 also demonstrates that the ED physicians recognized AECOPD in the majority of cases (93% identified as AECOPD or pneumonia), but often failed to recognize HF in the COPD patients hospitalized due to HF (11% correctly identified). A table containing all the investigated variables is presented in Supplementary Table 1. Among patients with a history of HF, 61% used an ACE inhibitor/Angiotensin blocker, 83% used beta-blocker and 72% a loop diuretic. Among patients with a history of CAD, 71% used ASA, 20% a blood pressure; pulmonary attenuation on admission and others, the mechanism behind TnT release during hospitalization for AECOPD and survival during follow-up

The patients were followed for a median of 826 (363–1015) days. In total, 48 patients (47%) died. There was significantly higher mortality among COPD patients with HF as the main cause for hospitalization (group A): mortality rate 47.5 per 100 patient-years versus 19.1 and 20.0 in groups B and C, respectively. Adjusting for age in Cox regression analysis, there was a statistically non-significant trend towards improved survival in groups B and C (hazard ratios 0.51, p = 0.13 and 0.56, p = 0.16). Supplementary Table 2 shows the age-adjusted hazard ratios for all-cause mortality during long-term follow-up for all the investigated variables. Age, BMI, lung function, the use of insulin, tachycardia on admission, creatinine clearance, hs-TnT and NT-proBNP levels, and physician assessment of HF probability were all associated with mortality with p values <0.05. In multivariable Cox regression analysis, we found age, history of HF, decreasing pH, increasing hs-TnT levels and the use of an aldosterone antagonist or insulin to be independently associated with all-cause mortality, while higher systolic blood pressure; pulmonary attenuation on admission and higher BMI were associated with a favourable outcome (Table 3).

Replacing hs-TnT concentrations below the range of detection with values <3 ng/l made no changes to any of the estimates presented. Of note, the majority of patients did not demonstrate a significant change in hs-TnT levels from baseline to day 1, and we found no difference for hs-TnT dynamics between the diagnosis groups (Table 1). Furthermore, the change in hs-TnT levels did not differ between survivors and non-survivors: 42% with significant change among non-survivors versus 43% with significant change among survivors, p = 0.925.

Discussion

The principal results and the novel findings of this study are that hs-TnT concentrations during AECOPD are strongly influenced by the presence of myocardial dysfunction and left-sided HF, but that hs-TnT levels still provide independent information to established risk indices and diagnosis group regarding long-term mortality.

Various groups and a recent meta-analysis have shown that TnT elevation during AECOPD is associated with increased mortality (Pavasini et al., 2015), while in a recent paper, not all-cause mortality but cardiac death and non-fatal MI were predicted by TnT (Campo et al., 2015). As pointed out by us and others, the mechanism behind TnT release during AECOPD may be complex and is currently not established.

For all the examined variables, the age-adjusted associations with hs-TnT are shown in Supplementary Table 2. We found significant associations between hs-TnT and the following variables: age, gender, history of hypertension and atrial fibrillation, the use of loop diuretics, ASA and oral corticosteroids, pre-admission SaO2, renal function, NT-proBNP levels, physician-assessed probability of HF and the end-point committee diagnosis. The final multivariate models are presented in Table 2.

### hs-TnT levels on hospitalization for AECOPD and survival during follow-up

The medians of hs-TnT concentrations in AECOPD patients with heart failure (group A), left ventricular dysfunction (group B) and without ventricular dysfunction (group C) were: 2380 (621–17 087), B: 1012 (340–2268) and C: 298 (145–578), respectively. There were also highly significant differences in NT-proBNP concentrations (pg/ml); A: 2380 (621–17 087), B: 1012 (340–2268) and C: 298 (145–578), p values 0.049 and 0.0008 for the differences between groups A/B and B/C, respectively.

### Determinants of admission hs-TnT levels

The median hs-TnT concentration in the total cohort of AECOPD patients was 19.2 (11.0–33.9) ng/l. The three groups showed marked differences in hs-TnT concentrations (ng/l, Figure 1); A: 41 (19–74), B: 25 (13–37) and C: 15 (7.5–25), p = 0.030 between groups A/B and p = 0.005 between groups B/C. There were also highly significant differences in NT-proBNP concentrations (pg/ml); A: 2380 (621–17 087), B: 1012 (340–2268) and C: 298 (145–578), p values 0.049 and 0.0008 for the differences between groups A/B and B/C, respectively.

### Results

#### Study population

Of the 314 patients in the ACE 2 cohort, 103 patients (33%) satisfied the criteria for AECOPD and were included in this sub-study. Their mean age was 71.3 (9.5) years and 59 (57%) were female. Spirometry was available in 93 patients with mean FEV1 0.96 (0.43) l, mean FEV1% of predicted 39 (17) and mean FEV1/FVC 0.47 (0.15). The end-point committee classified 19 patients (18%) in group A, 28 patients (27%) in group B and 56 patients (54%) in group C. In group A, the distribution of HF with reduced (<50%) and preserved (≥50%) left ventricular ejection fraction was 9 versus 10 patients, respectively. The baseline data, stratified by diagnosis group, are reported in Table 1.

### Figure 1. hs-TnT concentrations in AECOPD patients with heart failure (group A), left ventricular dysfunction (group B) and without ventricular dysfunction (group C), p value <0.05 for all differences.

### Discussion
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Table 3. Cox regression model for long-term mortality after admission for acute exacerbation of COPD. Models 1 and 2 are without and with inclusion of medication, respectively.

| Variable                  | Model 1                        | Model 2                        |
|---------------------------|--------------------------------|--------------------------------|
| Age (per 5 years)         | 1.16 (0.96–1.38)               | 1.25 (1.02–1.51)               |
| BMI (per kg/m²)           | 0.92 (0.87–0.98)               | 0.90 (0.85–0.96)               |
| History of heart failure  | 3.83 (1.53–9.57)               | 3.55 (1.39–9.03)               |
| Systolic BP (per mmHg)    | 0.98 (0.97–0.99)               | 0.98 (0.97–0.99)               |
| Pulmonary attenuation     | 0.21 (0.06–0.72)               | 0.20 (0.06–0.72)               |
| pH (per 0.05)             | 0.60 (0.44–0.82)               | 0.63 (0.45–0.86)               |
| hs-TnT (per 10 ng/l)      | 1.29 (1.15–1.45) <0.0001       | 1.31 (1.16–1.48) <0.0001       |
| Insulin use               |                                | 5.20 (1.46–18.4)               |
| Aldosterone antagonist use|                                | 3.06 (1.18–7.97)               |

The models are additionally adjusted for end-point committee diagnosis A–C, it was weakly and clearly non-significantly associated with mortality in the final model.

HR, hazard ratio; CI, confidence interval; BMI body mass index; BP, blood pressure.

(Hoiseth et al., 2012; Soyseth et al., 2013; Stone et al., 2013; White & Stewart, 2012). Type 2 MI caused by hypoxia has been suggested, but we and others have previously failed to find associations between arterial oxygen content and troponin concentrations. When investigating pre-admission SaO₂, we found a 2% decrease in hs-TnT per percentage-point increase in SaO₂ in age-adjusted analysis. However, this association was attenuated and no longer significant in multivariable analysis. In contrast, we found hs-TnT levels to increase in proportion to the influence by HF, and several variables known to be associated with myocardial remodelling influenced hs-TnT levels in linear regression analyses. Thus, our results support the association between high hs-TnT levels and HF in patients with AECOPD. These results are in line with previous results exploring determinants of TnT concentration in three different cohorts of AECOPD patients (Brekke et al., 2009; Hoiseth et al., 2012; Soyseth et al., 2013). In two of the three cohorts, signs of prior MI in the ECG were associated with higher TnT concentrations, thus alluding to a situation of myocardial remodelling in these patients. An association between TnT and arterial hypertension was also reported in another cohort of AECOPD patients (Hoiseth et al., 2012), and hypertension is a key factor in the development of myocardial remodelling. Pertinent to this, LV hypertrophy, assessed by both echocardiography and magnetic resonance imaging (de Lemos et al., 2010; Neeland et al., 2013), has previously been found closely associated with hs-TnT levels outside of the chest pain setting. Recent data also support hs-TnT levels as primarily associated with LV mass in aortic stenosis (Rosjo et al., 2011a), and also provide additional support for hs-TnT as a marker of myocardial fibrosis in non-chest pain patients (Chin et al., 2014). The association to myocardial remodelling is also supported by elevated hs troponin levels predominantly being associated with HF development, and not recurrent MIs, in community-based prospective cohorts (de Lemos et al., 2010; Omland et al., 2009, 2013).

In previous COPD cohorts exploring determinants of TnT concentration, increasing heart rate and decreasing renal function also influenced hs-TnT levels. Although increasing heart rate could be a result of HF, pathophysiology besides HF clearly also influence hs-TnT levels in patients with AECOPD. Accordingly, HF alone, as assessed by the end-point committee, did not fully explain the association between hs-TnT elevations and mortality in our study. Based on our data and the literature, pathophysiology besides LV dysfunction that could explain increased mortality in AECOPD patients with elevated hs-TnT levels are renal failure and
coronary artery disease, although we did not find changes in hs-TnT levels to influence prognosis in our patients.

We found that close to half of the patients fulfilling AECOPD criteria either suffered from acute HF (18%) or had concomitant LV dysfunction (27%). This prevalence is substantial, but of similar magnitude as data reported by Abroug (Abroug et al., 2006), and LV dysfunction is a major problem in elderly patients with COPD. In our study, 47% and 32% of the patients with overt HF and LV dysfunction, respectively, had a known history of HF. The corresponding fractions of patients with either HF or CAD known at inclusion were 69% and 53%. Many of these were under-treated for their cardiac conditions. Additionally the physicians working in the ED failed to recognize the majority of COPD patients with acute HF. This shows that in patients with known COPD, particularly presenting with symptoms of an exacerbation, diagnosing HF remains a significant challenge. It may be surprising to find that knowledge of HF did not improve survival. On the contrary, we found poorer survival among patients with prior HF in the multivariable Cox model. We believe this reflects more severe disease in this subgroup of AECOPD patients, and subsequently, less effect by standard therapy on outcome. This also resonances with a markedly worse outcome in patients being treated with aldosterone antagonists in our study. The finding that decreasing BMI is associated with increased mortality is in accordance with the literature (Brekke et al., 2008a; Landbo et al., 1999; Vestbo et al., 2006).

Limitations
Cardiac imaging was not performed per protocol. Although all the patients diagnosed with HF had echocardiographic data available, we do not have such data from all the patients in this sub-study. Selective cardiac imaging is expected to underdiagnose HF and myocardial dysfunction rather than increase the prevalence of HF, thus attenuating rather than exaggerating the association between HF and hs-TnT levels in our cohort. Furthermore, the reported NT-proBNP concentrations in our study, which were not available to the endpoint committee, are in accordance with previous reported guidelines for NT-proBNP considering NT-proBNP concentrations >2000 pg/ml as indicative of HF (‘rule in’), NT-proBNP concentrations <400 pg/ml as indicative of non-HF related dyspnoea (‘rule out’), and patients with dyspnoea and NT-proBNP 400–2000 pg/ml as possible HF patients (Dickstein et al., 2008). We also lack data on epicardial coronary artery status and additional studies that characterize the coronary arteries of AECOPD patients will supplement our work. We did not include data on the cause of death as death certificate diagnoses have been found unreliable for the purpose of differentiating between cardiac and pulmonary causes of death in patients with AECOPD (Jensen et al., 2006). We also used clinical data for pulmonary testing and made the AECOPD diagnosis based on chart reviews. Ten patients were included despite incomplete spirometry data. These patients had either spirometry performed, but not reported to us, by their primary care physician and/or spirometry without bronchodilation.

Conclusions
hs-TnT levels are strongly influenced by the presence of myocardial dysfunction and HF in patients with AECOPD. However, hs-TnT levels on admission for AECOPD still provide information regarding all-cause mortality during follow-up, also after adjustment for standard risk factors in COPD. Hence, the prognostic information by elevated hs-TnT levels in patients with AECOPD cannot be attributed to myocardial remodelling and HF alone. We demonstrate a high prevalence of HF in patients presenting with AECOPD, and show that diagnosing HF in these patients may represent an important challenge to clinicians.

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Declaration of interest
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Supplementary materials available on line
Supplementary Tables S1 and S2