

# Improve Management of acute heart failure with ProcAlCiTonin in EUrope: results of the randomized clinical trial IMPACT EU Biomarkers in Cardiology (BIC) 18

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## Aim

To determine whether initiation of antibiotic therapy (ABX) by procalcitonin (PCT) within 8 h of admission in patients presenting to the emergency department with symptoms and signs of acute heart failure (AHF) and elevated natriuretic peptides would improve clinical outcomes.

## Methods and results

The study was a randomized multicentre clinical trial conducted at 16 sites in Europe. Patients were randomized to either a PCT-guided strategy or standard care. Patients with PCT-guided strategy ( $n = 370$ ) had ABX initiated if PCT was  $> 0.2 \mu\text{g/L}$ . Patients with standard care ( $n = 372$ ) had AHF care in accordance with published guidelines without PCT. The primary endpoint was 90-day all-cause mortality. Pre-specified secondary endpoints included 30-day all-cause mortality and readmission and rate of pneumonia. The Data Safety and Review Committee recommended stopping the study for futility when 762 of the planned 792 patients had been enrolled. A total of 742 patients could be analysed. Patients were elderly (median age: 77 years), 38% were women, and had typical signs and symptoms of AHF. All-cause mortality at 90 days was 10.3% in the PCT-guided group vs. 8.2% in standard care ( $P = 0.316$ ). Thirty-day readmission was significantly higher in the PCT-guided group vs. standard care but the difference vanished until day 90. The rate of pneumonia was overall low (7.5%) and not different between groups.

## Conclusions

In patients with AHF, a strategy of PCT-guided initiation of ABX was not more effective than a standard care strategy in improving clinical outcomes.

## Keywords

Acute heart failure • Procalcitonin • Natriuretic peptides • Antibiotic therapy • Mortality

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## Introduction

Acute heart failure (AHF) is a serious condition with high short and long-term mortality.<sup>1</sup>

A specific challenge is to identify infection as a trigger of AHF or as the main reason for presentation, as infections have been reported to accompany AHF events in 6.6–14%<sup>2,3</sup> of all cases. Early and correct detection of infections in the setting of AHF is difficult, as typical symptoms of dyspnoea, fatigue, cough and dysuria may be explained by infections and AHF, making a correct diagnosis challenging. Chest X-ray and C-reactive protein also suffer from low sensitivity in the setting of AHF.

The biomarker procalcitonin (PCT) has emerged as an alternative for C-reactive protein in diagnosing bacterial infection.<sup>4,5</sup> PCT is elevated in common bacterial infections such as pneumonia and urogenital infections, which are very typical infections in AHF. Retrospective analyses from heart failure patient subgroups in studies using PCT for the guidance of antibiotic therapy (ABX),<sup>6</sup> as well as from diagnostic biomarker studies,<sup>7</sup> suggested that PCT may be useful for the decision to initiate or withhold ABX in patients with suspicion of AHF presenting with dyspnoea to the emergency department (ED). In a secondary analysis of the international multicentre Biomarkers in Acute Heart Failure (BACH) study,<sup>8</sup> including 560 patients with the gold standard diagnosis of AHF, patients with negative PCT had worse outcome if treated with antibiotics.<sup>7</sup> The prognostic value of PCT in AHF has been confirmed in several other secondary analyses and observational studies as summarized recently.<sup>9</sup>

In this randomized, international, multicentre, open study<sup>10</sup> we investigated whether initiation of ABX by PCT guidance in patients with suspicion of AHF presenting to the ED would improve clinical outcomes.

## Methods

### Study design

The rationale and study design have been published previously.<sup>10</sup> The study protocol and the statistical analysis plan are provided as supplemental material. The study was approved by the ethics committee of the leading institution (Charité – Universitätsmedizin Berlin; EA4/025/16) and all local institutional review boards. All participants gave written informed consent. An independent Data Safety and Review Committee (DSRC) was appointed by the study sponsor (Thermo Fisher BRAHMS GmbH) and monitored the study by analysing outcome data after each quarter of enrolment. Audits to the study site visits with in depth chart reviews of consented patients were carried out by the principal investigator to ensure protocol adherence. All patients underwent complete independent monitoring (source data verification). The study was registered before enrolment of the first patient (ClinicalTrials.gov, NCT02392689).

### Study participants

Adult patients were eligible for enrolment if they presented to the ED with the leading symptom of dyspnoea, suspected or known heart failure, based on medical history and the presence of structural

heart disease and/or functional cardiac dysfunction, accompanied by an elevated level of a natriuretic peptide [N-terminal pro-B-type natriuretic peptide (NT-proBNP) > 1800 ng/L or B-type natriuretic peptide > 350 ng/L or mid-regional pro-atrial natriuretic peptide (MR-proANP) > 300 pmol/L].

Patients had to give written informed consent within study timelines to allow ABX within 8 h after arrival in the ED, and hospitalization for at least one planned overnight stay in the respective hospital was required.

Key exclusion criteria were trauma-related dyspnoea, diagnosis of severe lung or thyroid cancer, a known terminal disease with life expectancy of < 6 months, e.g. advanced metastatic cancer, end-stage or severely advanced chronic heart failure defined by heart transplantation listing or cardiogenic shock, current use of antibiotics or requirement of immediate ABX before randomization and end-stage renal failure requiring dialysis. The full list of exclusion criteria has been published previously.<sup>10</sup>

### Randomization and group assignment

Patients were randomized by concealed envelopes 1:1 via a centre-stratified, balanced and blocked randomization procedure to either a standard care group or a PCT-guided group with respect to the initiation of an ABX. Given the nature of the study intervention, the group assignment was not blinded.

For patients randomized to the PCT-guided strategy, the attending emergency physicians were instructed to initiate ABX only if the PCT value was > 0.2 µg/L at admission as outlined in detail elsewhere.<sup>10</sup> A second PCT measurement at least 12 h after admission was performed. Again, it was encouraged to start ABX if this second value was > 0.2 µg/L, whereas ABX initiated based on an initial PCT value > 0.2 µg/L should not be stopped if the second value was < 0.2 µg/L. Further adjustments to the ABX for individual patients were at the discretion of the treating physicians. Patients randomized to the standard care group received ABX on the basis of regular clinical decision making, following the respective local standards. Patients in the standard care group had blood samples taken at the same time intervals as the PCT-guided group. PCT levels were determined batch wise for these patients and blinded to the investigators throughout the whole study period.

### Study outcomes

The primary endpoint was 90-day all-cause mortality. The 30-day all-cause mortality rate, 30-day all-cause hospital readmission, and diagnosis of pneumonia during the index hospitalization were assessed as pre-specified secondary endpoints.<sup>10</sup> Additionally, a number of exploratory endpoints were analysed, including 90 day all-cause hospital readmission, which is also reported in this paper.

Additionally, the primary main diagnosis was adjudicated by two independent blinded cardiologists. Adjudication was done separately for each country of inclusion to avoid language-associated mistakes regarding the chart reviews.

### Procalcitonin measurement

Procalcitonin was measured from sample tubes as by standard practice (serum or plasma), either with the B-R-A-H-M-S PCT sensitive KRYPTOR as described in the instruction manual or with the PCT assay available for routine testing at the respective study sites. Other assays than the B-R-A-H-M-S PCT sensitive KRYPTOR had to be approved by

the steering committee to guarantee comparability of the PCT results. The Elecsys B-R-A-H-M-S PCT (Roche) and the ADVIA Centaur® B-R-A-H-M-S PCT (Siemens) were used in addition to the B-R-A-H-M-S PCT sensitive KRYPTOR throughout the study.

Published analytical characteristics of the instruments were: overall coefficients of variations ranged from 3.94% to 1.70% for B-R-A-H-M-S PCT and from 6.57% to 1.90% for B-R-A-H-M-S PCT sensitive KRYPTOR. Limits of detection were 0.014 and 0.040 µg/L for B-R-A-H-M-S PCT and B-R-A-H-M-S PCT sensitive KRYPTOR, respectively. The functional assay sensitivity was 0.045 µg/L for B-R-A-H-M-S PCT and <0.035 µg/L for B-R-A-H-M-S PCT sensitive KRYPTOR. B-R-A-H-M-S PCT and B-R-A-H-M-S PCT sensitive KRYPTOR was linear up to 68.7 µg/L and up to 43 µg/L, respectively.<sup>11</sup> Analytical characteristics of the ADVIA Centaur® B-R-A-H-M-S PCT were similar.<sup>12</sup>

## Gold standard diagnoses

Gold standard diagnoses were assigned country wise by two independent cardiologists, specifically for the diagnoses 'acute heart failure' and 'pneumonia'. Adjudicators were blinded to study arm but not blinded to PCT levels. Agreement for primary diagnosis was 66%, for 34% adjudicators needed to review again and discuss to conclude finally on the diagnosis. In the end, 100% agreement between adjudicators for primary diagnosis was achieved.

## Statistical analysis

Based on a two-sided chi-square test for two independent proportions, 396 subjects per arm would have been sufficient to detect a 7% difference in mortality (11% vs. 18%) at 5% significance level with a power of 80% in a study design with fixed sample size. A two-stage sample-size adaptive design according to Bauer and Kohne<sup>13</sup> was used in this study. The final sample size was planned to be calculated based on the results of the interim analysis after the inclusion of 50% cases for primary analysis (log-rank test and Cox proportional hazards regression for 90-day all-cause mortality). After finalization of the interim analysis whose results were blinded to the investigators, it was decided to maintain the originally planned sample size of 396 patients per study arm. No safety issues were detected.

The intention-to-treat (ITT) analysis as well as the safety population included all randomized patients. For the per-protocol (PP) analysis, all patients without major protocol deviations during study participation were included, who were treated according to the PCT algorithm in the PCT-guided group, and who did not have PCT measurement results within 12 h of presentation to the ED in the standard care group. In a sensitivity analysis, a second PP analysis was conducted expanding the PCT-guided group of the PP population to all PCT-guided patients without major protocol deviations and with PCT measured on day 0. The study sample was described with frequency counts for nominal variables and means with standard deviations or medians with interquartile ranges (IQR) for numerical variables as appropriate to the distributional properties of variables. *P*-values were also computed in order to facilitate a results overview (Wilcoxon rank sum test for numerical variables, chi-square test for binary variables; no correction of *P*-values for multiple testing). Standard uni- and bivariate statistics were applied to check the success of randomization.

The primary study hypotheses were evaluated using log-rank test and Cox proportional hazards regression of 90-day all-cause mortality concerning standard care group and PCT-guided group. As sensitivity analysis and in accordance with the Committee for Medicinal Products

for Human Use (CHMP), 2013 guideline on adjustment for baseline covariates (accessed 3 November 2015), study centres were also included in Cox proportional hazards regression as additional categorical predictors. The significance of additional regression predictors was assessed by likelihood ratio testing comparing the extended model with additional predictor vs. the base model without. For binary endpoints, percentage rates and counts were computed and statistically evaluated by chi-square testing. Note that all reported *P*-values are raw *P*-values, i.e. not corrected for multiple testing. 95% confidence intervals (CIs) were computed according to Clopper and Pearson. A significance level of 5% was used for all two-sided statistical tests (2.5% for one-sided testing).

In order to evaluate the PCT cutoff of 0.2 µg/L pre-specified in the study, we retrospectively varied the PCT cutoff along the range of PCT concentrations observed in the study, defined PCT-negative and PCT-positive patient strata accordingly ('negative' if PCT ≤ cutoff, else 'positive') and computed log-rank tests to compare patient survival within 90-day follow-up time between patient strata. Significant separation between patient strata was expected for adequately chosen PCT cutoffs. The strength of group separation was visualized by plots of selected PCT-cutoff vs. resulting log-rank test *P*-value.

## Safety analyses

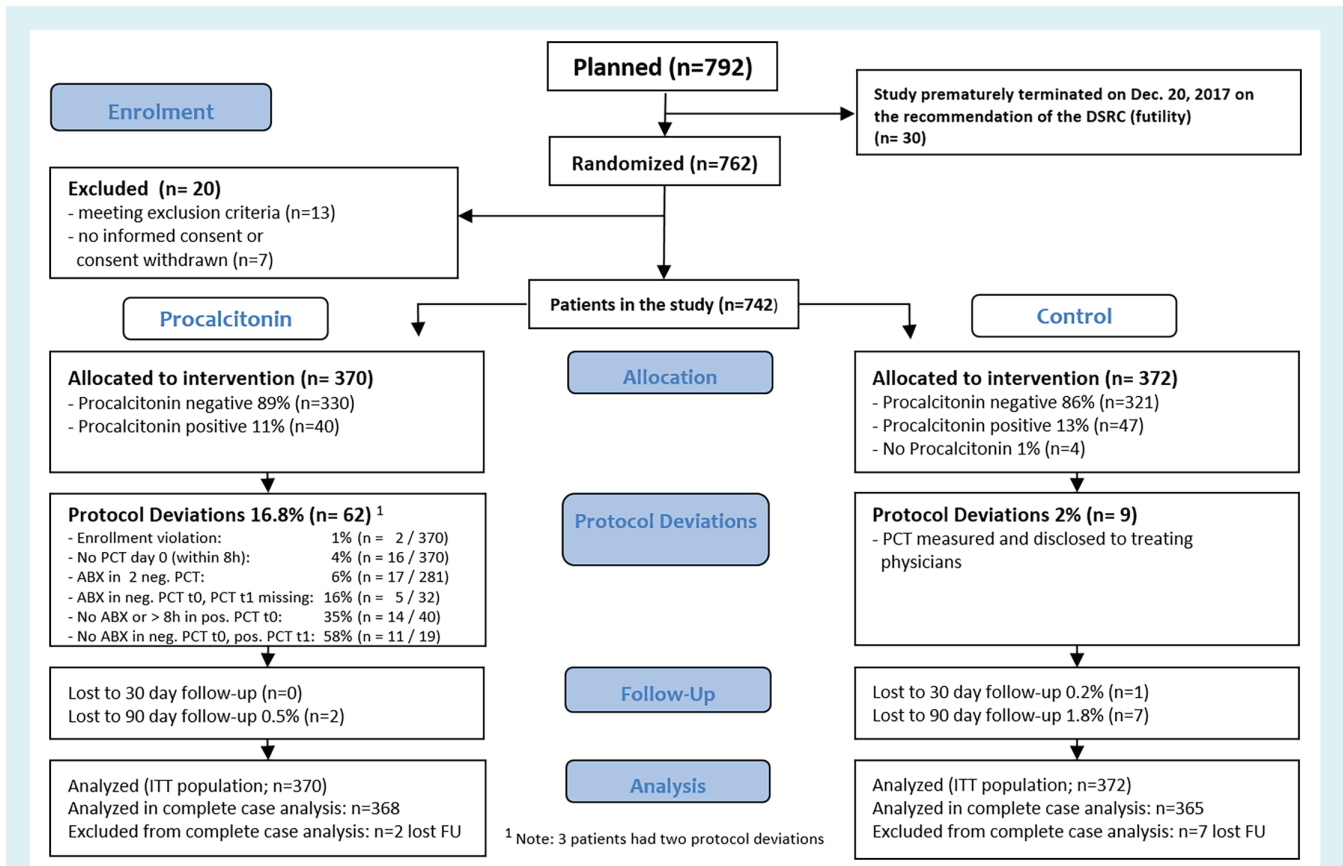
A DSRC was responsible for ongoing, independent review of patient's safety and correct and timely execution of the processes described in the protocol. Furthermore, deviations from the PCT-guided treatment recommendations were monitored by the DSRC, to detect issues related to the proposed treatment schedule. The DSRC conducted their first study safety assessment after 198 patients (25% of the originally planned sample size) had completed the 90-day follow-up. The second meeting of the DSRC was held after 396 patients (50% of the planned sample size) had completed the 90-day follow-up and coincided with the efficacy interim analysis (see above and methods paper<sup>10</sup>). The DSRC decided to have one further meeting after 75% of the patients had completed their 3-month follow-up. After this meeting, the DSRC recommended to stop the study prematurely due to futility. The steering committee convened and discussed the detailed recommendations. The study was stopped on 20 December 2017 after the randomization of 762 patients. This number of patients was only 30 patients short of the planned sample size. The online supplementary Figure S1 shows the recruitment chart of the study.

## Results

### Study patients

A total of 762 patients were enrolled at 16 sites in Germany, Denmark, The Netherlands, and Spain between April 2015 and December 2017 (Figure 1). Patient groups were generally well balanced with respect to baseline characteristics (Table 1).<sup>14</sup> The study enrolled patients with high-risk AHF, as characterized by high natriuretic peptides levels [median NT-proBNP concentration 5350 ng/L (IQR 3200–10 418) or median MR-proANP 504 pmol/L (IQR 397–667)]. The selection of patients was sufficient as 80% of patients had the gold standard main diagnosis of AHF.

The study was terminated prematurely as detailed above in the Methods section (see also Figure 1 and online supplementary Figure S1).



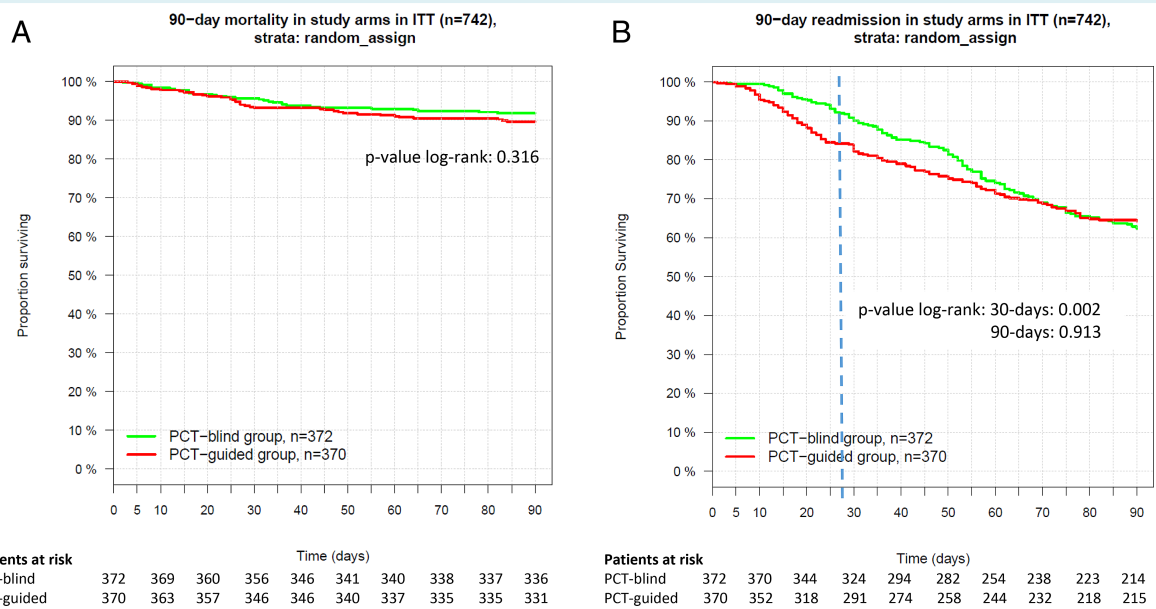
**Figure 1** Consort flow diagram of patient flow of the randomized study. ABX, antibiotic therapy; DSRC, Data Safety and Review Committee; FU-follow-up; ITT, intention-to-treat; PCT, procalcitonin.

**Table 1** Baseline characteristics of study patients

|                                 | All patients (n = 742) | PCT-guided (n = 370) | Standard care (n = 372) | P-value |
|---------------------------------|------------------------|----------------------|-------------------------|---------|
| Age (years)                     | 77 (70–83)             | 77 (70–83)           | 77 (70–83)              | 0.812   |
| Female sex                      | 280 (38%)              | 132 (36%)            | 148 (40%)               | 0.281   |
| BMI (kg/m <sup>2</sup> )        | 27.2 (24.6–31.1)       | 26.6 (23.7–30.8)     | 27.7 (25–31.6)          | 0.006   |
| NT-proBNP (ng/L) <sup>a</sup>   | 5350 (3200–10 418)     | 5523 (3252–10 438)   | 5268 (3145–10 374)      | 0.498   |
| MR-proANP (pmol/L) <sup>a</sup> | 504 (397–667)          | 523 (439–733)        | 459 (378–624)           | 0.133   |
| PCT (µg/L)                      | 0.07 (0.05–0.13)       | 0.08 (0.05–0.13)     | 0.07 (0.05–0.13)        | 0.136   |
| eGFR (mL/min)                   | 63.5 (44.7–78.2)       | 64 (47.7–78)         | 62.9 (43.2–78.8)        | 0.420   |
| eGFR <30 mL/min                 | 80 (11%)               | 33 (9%)              | 47 (13%)                | 0.130   |
| Hypertension                    | 565 (76%)              | 280 (76%)            | 285 (77%)               | 0.831   |
| CAD                             | 347 (47%)              | 174 (47%)            | 173 (47%)               | 0.945   |
| Known CHF                       | 406 (55%)              | 208 (56%)            | 198 (53%)               | 0.457   |
| Diabetes                        | 267 (36%)              | 128 (35%)            | 139 (37%)               | 0.478   |
| CKD                             | 261 (35%)              | 123 (33%)            | 138 (37%)               | 0.307   |

BMI, body mass index; CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (by Chronic Kidney Disease Epidemiology Collaboration formula<sup>14</sup>); MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCT, procalcitonin.

<sup>a</sup>NT-proBNP was measured in 639 patients, MR-proANP was measured in 103 patients, B-type natriuretic peptide was measured in one patient. Concentrations of two different natriuretic peptides were only available for 12 patients (NT-proBNP and MR-proANP).



**Figure 2** Primary (A) and secondary outcomes (B) in the Kaplan–Meier analysis. ITT, intention-to-treat; PCT, procalcitonin.

## Primary outcome

Ninety-day all-cause mortality was considerably lower than expected (8.2% observed vs. 18% expected for standard care, ITT) and there was no significant difference in 90-day all-cause mortality between the randomized groups (PCT-guided: 10.3%, 95% CI 7.4–13.9%; standard care: 8.2%, 95% CI 5.6–11.5%;  $P = 0.316$ , log-rank test; ITT) (Figures 2A and 3). Similar results were obtained for 30-day all-cause mortality (PCT-guided: 6.8%, 95% CI 4.4–9.8%; standard care: 4.3%, 95% CI 2.5–6.9%;  $P = 0.152$ , log-rank test; ITT). The 30-day all-cause hospital readmission rate was significantly lower in the standard care group (PCT-guided: 17.3%, standard care: 9.7%,  $P = 0.002$ , log-rank test), but this difference was not sustained at 90 days ( $P = 0.913$ , log-rank test) (Figure 2B). Also no difference between study arms was observed at 90 days when multiple hospitalizations per patient were considered.

## Treatment details and procalcitonin levels

There were no significant differences in proportions of ABX initiation between groups. The frequency of pneumonia was low (7.5%; PCT-guided: 8.1%, standard care: 7.0%;  $P = 0.661$ ) and the duration of ABX was not different between randomized groups. Also, intensive care unit and total length of stay were not different (Table 2). The most frequent ABX were penicillin (23.2%,  $n = 172$ ), cephalosporins (12.1%;  $n = 90$ ), fluoroquinolones (5.1%;  $n = 38$ ) and macrolides (2.2%;  $n = 16$ ). The choice of antibiotics was not reported in 52.4% ( $n = 389$ ). In the PCT-guided group, the median turnaround time for day 0 PCT measurements (time of day 0 PCT measurement–time of patient presentation) was 4.1 h (IQR 2.7–5.4 h). For those patients of the PCT-guided group that received antibiotic treatment on day 0, the median time between

admission and first-dose therapy was 5.9 h (IQR 4.9–7.5 h). This was not significantly different from the control group (median time between admission and first-dose therapy: 5.5 h, IQR 3.9–7.9 h). All results refer to the ITT patient population. When all within study antibiotic treatments are considered, then time to first antibiotic treatment seems shorter in the PCT-guided group than in the standard care group (median in PCT-guided group: 118 h vs. median in standard care: 180 h, difference almost significant according to Wilcoxon rank sum test:  $P = 0.057$ ).

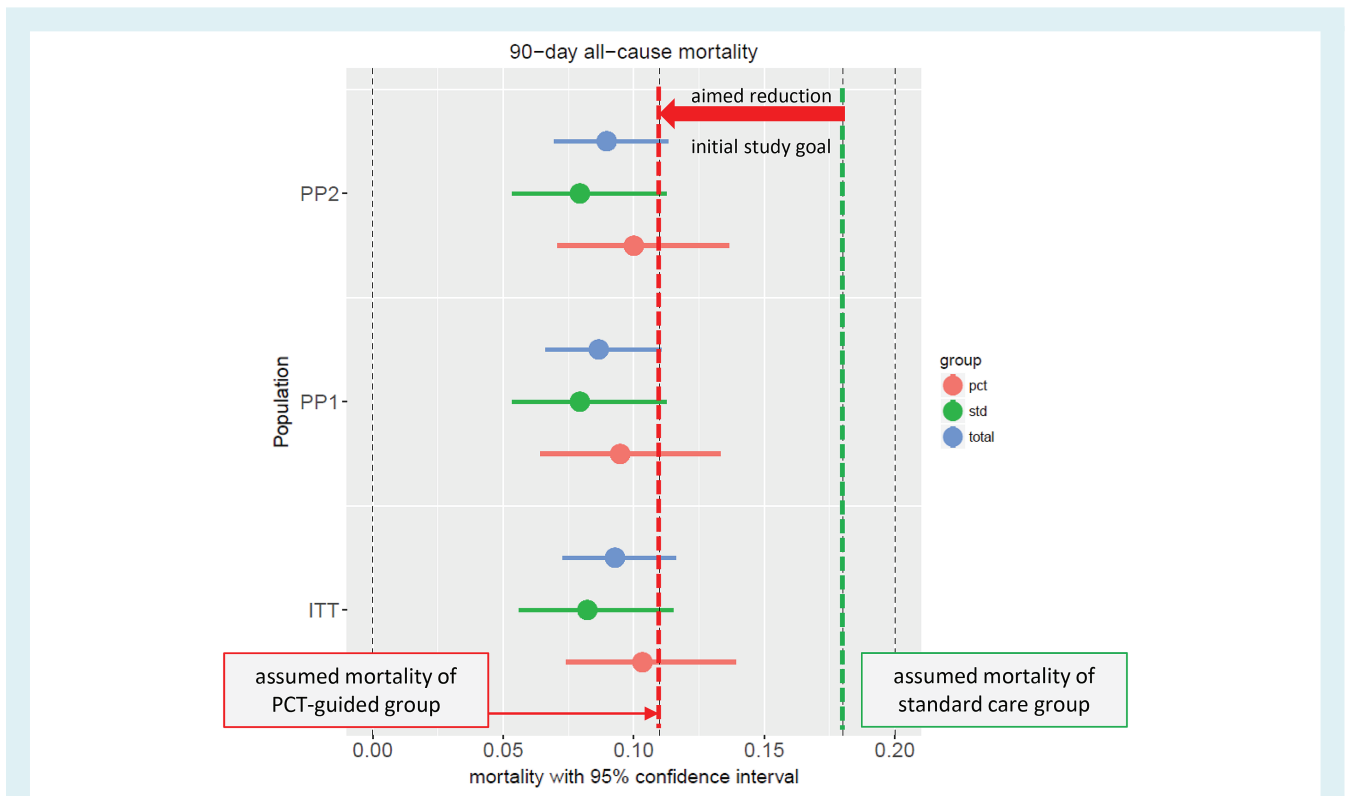
Nine of 372 patients of the ITT standard care population had PCT determined on day 0 within 12 h of presentation. For three of these nine patients, day 0 PCT was above the cutoff 0.2 ng/mL. Two of these three patients with above cutoff PCT received antibiotics on day 0.

## Secondary outcomes

Two pre-specified PP analyses were done: PP1 ( $n = 667$ ) defined the PCT-guided group as adherent with the PCT algorithm and the standard care group having no (early) PCT on day 0. PP2 ( $n = 711$ ) defined the PCT-guided group as PCT measured on day 0 and the standard care group having no (early) PCT on day 0. Figure 3 shows that the PP analyses revealed similar results compared to the ITT analyses with no difference in 90-day mortality between the randomized groups. Figure 3 also highlights the generally low mortality in the study population, which was as low as the assumed mortality of the PCT group.

Online supplementary Figure S2 shows the proportion of surviving patients for the entire study population splitted by day 0 PCT levels at the decision cutoff 0.2 µg/L of the study. Patients with higher PCT levels had a significantly higher mortality ( $P < 0.001$ , log-rank test). Similar statistical significances were obtained for





**Figure 3** Binary endpoints of the intention-to-treat (ITT) and per-protocol (PP) populations. PP1 ( $n = 667$ ) is defined as follows: procalcitonin (PCT)-guided: adherent with PCT algorithm, standard care: no PCT on day 0. PP2 ( $n = 711$ ) is defined as follows: PCT-guided: PCT measured on day 0, standard care: no PCT on day 0. pct, PCT-guided group; std, standard care group.

**Table 2** Antibiotic therapy initiation

|  | All patients ( $n = 742$ ) | PCT-guided ( $n = 370$ ) | Standard care ( $n = 372$ ) | P-value |
|--|----------------------------|--------------------------|-----------------------------|---------|
| ABX initiated  | 117 (16%)                  | 66 (18%)                 | 51 (14%)                    | 0.145   |
| GSD AHF  | 594 (80%)                  | 300 (81%)                | 294 (79%)                   | 0.544   |
| <sup>a</sup>   | 122 (16.4%)                | 61 (16.5%)               | 61 (16.4%)                  | 0.921   |
| PCT > 0.2 µg/L   |                            |                          |                             |         |
| EP 2.1: 30-day all-cause mortality   | 41 (5.5%)                  | 25 (6.8%)                | 16 (4.3%)                   | 0.196   |
| EP 2.2: All-cause hospital readmission within 30 days  | 100 (13.5%)                | 64 (17.3%)               | 36 (9.7%)                   | 0.004   |
| EP 2.3: Pneumonia diagnosis during index hospitalization   | 56 (7.5%)                  | 30 (8.1%)                | 26 (7%)                     | 0.661   |
| EP 3.1: Number of patients on ABX  | 117 (15.8%)                | 66 (17.8%)               | 51 (13.7%)                  | 0.145   |
| EP 3.2: Duration of initial ABX (days)   | 8 (6–11)                   | 8 (6–11.5)               | 8 (7–11)                    | 0.659   |
| EP 3.3: Total hospital length of stay (days)   | 8 (4–14)                   | 7 (4–14)                 | 8 (4–13)                    | 0.863   |
| EP 3.4: ICU length of stay (days)  | 3 (1.5–8)                  | 3 (2–8.3)                | 3 (1–6.5)                   | 0.316   |
| EP 3.5: Need for second-line or additional ABX   | 67 (9.0%)                  | 36 (9.7%)                | 31 (8.3%)                   | 0.592   |
| EP 3.6: In-hospital pulmonary complications other than pneumonia (i.e. lung abscess, empyema, acute respiratory distress syndrome) and other bacterial infections during index hospitalization | 102 (13.7%)                | 48 (13.0%)               | 54 (14.5%)                  | 0.614   |

EP numbers refer to the SAP in the supplemental materials.

ABX, antibiotic therapy; AHF, acute heart failure; EP, endpoint; GSD, gold standard diagnosis; ICU, intensive care unit; PCT, procalcitonin.

<sup>a</sup>At day 0 and/or day 1 (see Methods).

cutoffs around the pre-specified study cutoff [ $P < 0.001$  for all cutoffs between 0.05–0.35  $\mu\text{g/L}$ ; online supplementary Figure S3). The additional inclusion of the factor randomized groups in Cox proportional hazards regression was not statistically justified ( $P = 0.254$ ; likelihood ratio test), neither was the additional inclusion of the interaction between randomized groups and day 0 PCT levels ( $P = 0.219$ ; likelihood ratio test).

## Treatment adherence

Treatment non-adherence was caused by either violation of the PCT algorithm in the PCT-guided group or availability of PCT to the physician in the standard care group. Accordingly, the number of PCT-guided patients was reduced from 370 (ITT) to 308 patients (PP1), which corresponded to 83% adherence in the PCT-guided group. Analogously, the number of standard care patients was reduced from 372 (ITT) to 359 patients (PP1), which corresponded to 97% adherence in the standard care group.

The largest sources of violations were: (i) initiating antibiotics on day 0 in spite of below-threshold day 0 PCT ( $n = 22$ ); (ii) day 0 PCT not available within 8 h ( $n = 16$ ); (iii) not initiating or not early enough initiating antibiotics on day 0 in spite of above-threshold day 0 PCT ( $n = 14$ ); or (iv) not initiating antibiotics on day 1 after below-threshold day 0 PCT and above-threshold day 1 PCT ( $n = 11$ ).

## Centre effect

Patients were enrolled at 16 clinical study centres with considerably varying sample sizes from 169 to 1 ITT patient.

Centre-specific 90-day all-cause mortality estimates showed widely overlapping 95% CIs (online supplementary Figure S4). The inclusion of the covariate clinical study centre in a Cox proportional hazards regression model for 90-day all-cause mortality in addition to the main predictor study arm was not significant according to likelihood ratio testing of hierarchical model comparison ( $P = 0.065$ ).

## Discussion

The randomized IMPACT EU study evaluated if PCT-guided initiation of ABX in patients presenting with AHF would be superior over regular clinical decision making with regard to clinical outcomes. The results show that PCT-guided initiation of ABX confers no clear benefits, and neither the primary endpoint (90-day mortality) nor any of the secondary endpoints hinted towards a benefit of PCT-guided ABX.

The study was terminated due to futility by the DSRC on the basis of the data of 75% of enrolment. As the analysis could only be done after completion of the 3-month follow-up and a slightly increased recruitment rate occurred in the final phase of study recruitment, once terminated, the number of patients included was only 30 patients short of the originally planned number (Figure 1 and online supplementary Figure S1).

In our study, patients were identified in the ED from presentation with typical symptoms and elevated natriuretic peptides. It has

been shown recently in a post-hoc analysis of the diagnostic BACH study<sup>8</sup> that patients with other primary diagnoses than AHF may have also high natriuretic peptide levels and very high mortality<sup>15</sup> as a potential bias for interventions that target heart failure. In our study, gold standard diagnosis of AHF was prevalent in 80% of patients, which shows that patient selection was sufficiently done. Nevertheless, the population studied is somewhat unique as many other cohorts of AHF patients are included only after ED care and have a higher prevalence of pre-existing heart failure.<sup>16</sup> Patients were not characterized with respect to their functional status (New York Heart Association class) and vital signs (blood pressure, respiratory rate, heart rate), which limits the comparability to other dyspnoea studies.

Mortality was much lower than was estimated<sup>10</sup> (Figure 3). In general, contemporary heart failure studies without exemption show lower mortality rates than a decade ago, which must be taken into account in future trial design. The reasons for this may be diverse, but inclusion bias is an obvious explanation. The very ill patients generally are excluded from studies, including IMPACT EU, but mortality is generally the highest in patients with severe co-morbid conditions. Further, recent data have shown that telemedicine in patients with heart failure can reduce mortality<sup>17</sup> and that the mechanism of the effect is most probably the intensified care by specialized nurses and doctors, which leads to the improved outcome in a multi-modal way, e.g. better adherence to treatment, earlier adjustment of medical drugs, and psycho-social coaching.

Furthermore, the PCT cutoff used could have been suboptimal for the intervention. We therefore performed a post-hoc analysis of the PCT cutoffs with respect to the result of a log-rank test for the prediction of mortality. In this analysis we found that PCT cutoffs between 0.10 and 0.50  $\mu\text{g/L}$  had similar performance with the optimum between 0.20 and 0.25  $\mu\text{g/L}$ , lending support for the cutoff used in the study (online supplementary Figure S3).

The most challenging task for treating physicians is the diagnosis of AHF among patients at intermediate pre-test probability because natriuretic peptides improve correct classification.<sup>18</sup> In analogy, PCT was reported to improve diagnosis of severe infection among patients at a medium pre-test probability of pneumonia.<sup>7</sup> The post-hoc analysis of the BACH trial<sup>8</sup> suggested that a combined testing of natriuretic peptides in combination with PCT would avoid unnecessary antibiotic administration in heart failure patients, or conversely unnecessary heart failure treatment in patients with pneumonia. Thus, ideally physicians should have been blinded to both biomarker results in equivocal clinical presentations. Controversially, the IMPACT EU study restricted inclusion to patients at high pre-test probabilities of AHF based on (very) high natriuretic peptide levels exceeding the rule-in cutoff for patients aged  $\geq 75$  years to prospectively find the AHF group, which has been defined retrospectively in the BACH secondary analysis.<sup>7</sup> This pre-selection reduces the risk for inappropriate treatment of heart failure and thus the potential benefits of a combined biomarker strategy. Furthermore, patients with current ABX were excluded from the IMPACT EU study. Thus, the prevalence of severe infection was low, which might also have impacted the low mortality by systematic exclusion of more severe cases. In this cohort with a low

rate of severe infections also the benefits of PCT over other routinely available biomarker including C-reactive protein, leucocytes, and fever might become less important.

Recently, the ProACT study<sup>19</sup> on 1656 patients in 14 US hospitals reported about the usefulness of PCT guidance in suspected lower respiratory tract infection. There was no significant difference in days of ABX or adverse outcomes between the PCT-guided arm and standard care. Among others, it has been hypothesized that the PCT result was almost universally disregarded in patients with pneumonia.<sup>20</sup> This unexpected finding might be attributed to lack of guideline adherence in both directions, i.e. overuse of antibiotics in low PCT tiers and underuse of PCT in high PCT tiers, presumably due to the absence of an antimicrobial stewardship programme.<sup>21</sup> In addition, this trial mostly enrolled low-risk patients with pneumonia with unexpectedly low event rates.<sup>19</sup>

The intervention done in IMPACT EU was the initiation of ABX mainly based on a single PCT level within the first 8 h of admission for AHF. A second measurement was done on the next day (at least 12 h from admission), mostly for safety reasons. The further course of ABX was left to the discretion of the attending physician.<sup>10</sup> The rationale behind this concept was based on retrospective analyses of observational studies.<sup>6,7,10</sup> On the other hand, interventional studies in lower respiratory tract infections with the use of PCT mainly showed that mortality was stable if ABX was shortened and usually daily PCT measurements were done. The latter was also the case in the only study which shows improvement of outcome in intensive care patients where ABX was guided by daily PCT measurements.<sup>22</sup> In a recent commentary, van Oers et al.<sup>23</sup> pointed out that retrospectively assessed single PCT measurement guidance maybe insufficient for prospective use because results are flawed in the post-hoc analyses. PCT has a certain value as a marker of risk stratification (online supplementary Figure S2), but our intervention based on PCT was not effective to lower mortality, calling into question if elevated PCT values are only a marker of worse outcomes, or they directly reflect a disease (infection) that would be easily amenable to treatment. In summary, we think that besides the overall low mortality, the intervention was too weak and further studies should use serial PCT measurements to guide (stop or continue) ABX. Furthermore, it should be considered whether more sick patients were systematically excluded due to their inability to provide written informed consent and thus a cohort with a lower mortality was selected. Future studies could also consider to apply for an exception of informed consent or a delayed patient consent to avoid selection bias.

Finally, 7.5% of patients suffered from pneumonia and ABX initiation was not different between the randomized groups (Table 2). We postulate that within this study in tertiary (expert) centres, the participating clinicians have effectively avoided to randomize patients in whom they suspected pneumonia, excluding them due to the anticipated requirement of immediate ABX. In addition, they might not have trusted the PCT signal and wanted to avoid a study advice which was against their clinical judgement, although overruling was allowed within IMPACT EU. Moreover, also other infections could have been present (urinary tract infections, soft tissue infections) that might have influenced ABX initiation and study enrolment. In any way, the number of patients with suspected bacterial

infections was too low in the end for PCT-guided treatment to show a meaningful difference. PCT-guided treatment did not work in all-comers and future studies should evaluate PCT-guided treatment in AHF patients where antibiotics are considered based on initial clinical judgement.

## Limitations

The study aimed to enrol 396 subjects per arm to detect a 7% difference in mortality (11% vs. 18%). However, the actual event rates were much lower reducing the ability to detect significant differences between randomized groups. Reasons for enrolment of a low-risk cohort are illusive but might involve the triage process, patient mix, the hospital setting, or a more efficacious treatment in experienced academic institutions. PCT was discouraged but *per se* available in most centres also for control patients and therefore could have influenced antibiotic use in some controls. In addition, the lack of more specific inclusion criteria like jugular venous distention, criteria of congestion from chest X-ray or lung ultrasound contribute to heterogeneity of the study population. Furthermore, it should be considered whether more sick patients were systematically excluded due to their inability to provide written informed consent and thus a cohort with a lower mortality was selected. Finally, specific information on other types of bacterial infection than pneumonia was not assessed in detail and information on the type of antibiotics given is incomplete, which limits further explanatory sub-analyses for outcome. Future studies could also consider to apply for an exception of informed consent or a delayed patient consent to avoid selection bias.

## Conclusions

In patients with a high likelihood of AHF, including those with confirmed AHF, a strategy of PCT-guided initiation of ABX was not more effective than a standard care strategy in improving outcomes.

## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Recruitment of patients over time compared to the recruitment plan in the last quarter of the study.

**Figure S2.** Analysis of the prognostic impact of procalcitonin at the study cutoff in a post-randomization cohort of all patients in the study.

**Figure S3.** Dependence of log-rank test *P*-value comparing 90-day all-cause mortality of procalcitonin (PCT)-positive vs. PCT-negative patient strata on PCT cutoff selection with linearly scaled and log-scaled axis.

**Figure S4.** Forest plot of centre- and study arm-specific 90-day all-cause mortality estimates with 95% confidence intervals.

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