ORIGINAL RESEARCH ARTICLE

Early identification of acute heart failure at the time of presentation: do natriuretic peptides make the difference?

Martin Möckel[1,2]* 🆔, Stephan von Haehling[3], Jörn O. Vollert[4], Jan C. Wiemer[4], Stefan D. Anker[3,5], Alan Maisel[6] on behalf of the BACH study group[†]

[1]Division of Emergency and Acute Medicine, Charité-Universitätsmedizin Berlin, Berlin, Germany; [2]Department of Cardiology, Charité-Universitätsmedizin Berlin, Berlin, Germany; [3]Department of Cardiology and Pneumology, University Medical Center Göttingen, Göttingen, Germany; [4]BRAHMS, Thermo Fisher Scientific, Hennigsdorf, Germany; [5]Division of Cardiology and Metabolism, Department of Cardiology (Campus Virchow-Klinikum), Berlin-Brandenburg Center for Regenerative Therapies (BCRT) and German Centre for Cardiovascular Research (DZHK), Berlin, Germany; [6]University of California, San Diego and Veterans Affairs Medical Center, San Diego, CA, USA

Abstract

Background   The early identification of patients with acute heart failure (AHF) is challenging as many other diseases lead to a clinical presentation with dyspnea.
Aim   The aim of the study was to evaluate the impact of natriuretic peptides at common HF study cut-offs on the diagnosis of patients with dyspnea at admission.
Methods and results   For this post hoc analysis, we analysed n = 726 European Union (EU) patients from the prospective BACH (Biomarkers in Acute Heart Failure) study. Cut-offs were 350 ng/L (BNP), 300 pmol/L [pro-atrial natriuretic peptide (proANP)], and 1800 ng/L (NT-proBNP). These cut-offs had equivalent 90 days' mortality in the EU cohort of BACH. We analysed the effect of selection using these cut-offs on the prevalence of the gold standard diagnoses made in the BACH study and the respective mortality. The prevalence of AHF is increased from 47.5 to 75.6% (NT-proBNP criteria) up to 79.7% (BNP criteria). With the use of the proANP criteria, 90 days' mortality of patients with AHF rose from 14 to 17% (P = 0.029). In the group with no-AHF diagnoses, mortality rose from 10 to 25% ($P < 0.001$).
Conclusions   The prevalence of patients with the gold standard diagnoses of AHF among those presenting with dyspnea to the emergency department is significantly increased by the use of natriuretic peptides with common cut-offs used in prospective HF studies. Nevertheless, in the selected groups, patients with no AHF diagnosis have the highest mortality, and therefore, the addition of a natriuretic peptide alone is insufficient to start specific therapies.

Introduction

Natriuretic peptides (NPs) are recommended in the initial workup of patients with suspected heart failure (HF).[1] In the acute phase, B-type NP (BNP), N-terminal proBNP (NT-proBNP), or mid-regional pro-atrial NP (MR-proANP) have equal diagnostic value.[2] Besides their diagnostic capabilities, NPs are strong prognostic markers predictive of short-term and long-term cardiovascular events independent of the underlying main diagnosis. On the basis

of their diagnostic and prognostic power, it has been tested whether NPs can be used also for therapeutic guidance of therapy, but results of different studies were rather mixed. Most recently, the randomized GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure) study investigated whether an NT-proBNP-guided therapy can improve outcomes. The study was prematurely stopped owing to futility and could not show any benefit of NT-proBNP as compared with usual care.[3]

The perspective of emergency medicine is the assessment of patients in the first few hours of presentation.[4] Several opinion papers have been published in recent years with expert recommendations about the early assessment of patients with suspected HF.[5,6] In a literature overview, Pang *et al*. highlight the fact that most published data on acute HF (AHF) stem from databases that included patients only after the acute phase, mostly starting on the day after admission, when patients had already arrived in specialized hospital units.[5] Even though a huge number of papers have been published on NPs in the acute setting, there is still a lack of evidence with regard to their usefulness in improving outcomes if applied at the door of the emergency department (ED). Carpenter *et al*. reviewed the literature from this emergency medicine perspective and came to the conclusion that 'clinicians, patients, and policymakers cannot be confident that knowledge of BNP or NT-proBNP levels will improve outcomes or reduce costs when evaluating ED patients with dyspnea'.[7]

The prospective, international BACH (Biomarkers in Acute Heart Failure) diagnostic biomarker study in patients admitted with dyspnea forms the largest available database about NPs in the acute setting.[2] Patients were characterized in detail, and gold standard diagnoses were made. We aimed to analyse NP values with respect to diagnoses in order to evaluate whether a certain level of NPs together with dyspnea correctly identifies the diagnosis of AHF as the predominant need for treatment and how the prevalence and mortality of other, non-AHF diagnoses is influenced.

Methods

Study population

The present study is a post hoc analysis of the BACH study.[2] We focused our analysis on the European cohort as the US cohort had a lower mortality and the New Zealand patient

group was very small.[8] This had no influence on the primary comparison of different NPs but may have influenced our outcome analysis.

In brief, the BACH study was a prospective international study in Europe, the USA, and New Zealand including 15 centres and *n* = 1641 patients. To be eligible, adult patients had to report dyspnea as their leading complaint. Patients were excluded if they had an acute ST-segment elevation myocardial infarction, or had renal failure, defined as chronic dialysis therapy. Gold standard diagnoses were established by independent cardiologists. If none of the pre-specified diagnoses (*Table 1*) were made, the patient fell into the category 'other'. The diagnosis of AHF was adjudicated in *n* = 568 (34.6%) of cases. The receiver operating characteristics analysis for the diagnosis of AHF revealed non-inferiority of MR-proANP vs. NT-proBNP [area under the curve (AUC) = 0.9] and BNP (AUC = 0.91).

Hypothesis

For this post hoc analysis, we analysed *n* = 726 European Union (EU) patients and applied certain cut-offs that are used in the randomized RELAX-AHF (Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure)[9] and IMPACT-EU (Improve Management of Heart Failure With Procalcitonin) studies.[10] The primary aim was to describe how pre-selection by NP cut-offs influences the prevalence of certain diagnoses groups and their respective mortality. Cut-offs were 350 ng/L (BNP), 300 pmol/L (proANP), and 1800 ng/L (NT-proBNP).[10,11] These cut-offs had also equivalent 90 days' mortality in the EU cohort of BACH.[10]
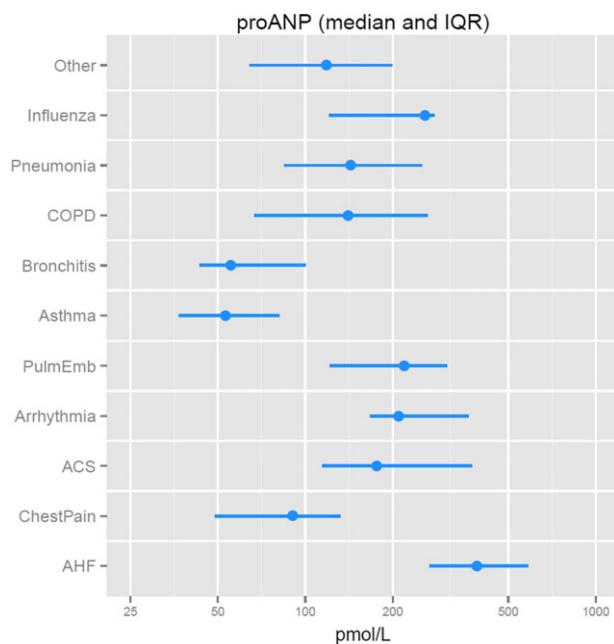
Statistics

Binary variables are reported as numbers and percentages for the entire BACH EU patient population as well as for the two complementary patient subgroups 'AHF' and 'Other

Table 1 Prevalence of acute heart failure and the other gold standard diagnoses by selection with natriuretic peptides

Diagnoses	All EU patients (*n* = 726) (%)	BNP > 350 (*n* = 316) (%)	MR-proANP > 300 (*n* = 298) (%)	NT-proBNP > 1800 (*n* = 356) (%)
AHF	47.5	79.7	79.5	75.6
Chest pain	2.3	0.3	0.3	0.3
ACS	2.9	3.2	2.0	2.8
Arrhythmia	3.0	1.6	2.7	1.4
Pulmonary embolism	2.8	1.3	2.0	2.2
Asthma	2.2	0.3	0.3	0
Bronchitis	2.3	0.3	0	0.3
COPD	11.2	5.7	4.7	6.7
Pneumonia	7.0	3.8	3.0	4.8
Influenza	0.8	0	0.3	0.6
Other diagnoses	17.8	3.8	5.0	5.3

ACS, acute coronary syndrome; AHF, acute heart failure; COPD, chronic obstructive pulmonary disease.
Units: ng/L (BNP), pmol/L (proANP), and ng/L (NT-proBNP).

Figure 1 ProANP levels by gold standard diagnoses in the analysed co-hort. ACS, acute coronary syndrome; AHF, acute heart failure; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; proANP, pro-atrial natriuretic peptide.

diagnoses'. Differences between the latter patient groups are described by P-values according to Pearson's χ^2 test. Numeric variables are reported by median values and interquartile

ranges for the entire BACH EU patient population as well as for the two complementary patient subgroups 'AHF' and 'Other diagnoses'. Differences between the latter patient groups are described by P-values according to Wilcoxon rank-sum test.

The distributions of MR-proANP concentrations (*Figure 1*) are visualized by gold standard diagnoses by plotting median values (circles) and interquartile ranges (horizontal lines). A log-scaled horizontal axis is used to illustrate well the distribution of concentration within the entire concentration range.

Confidence intervals of mortalities were determined according to the standard method introduced by Clopper and Pearson.

Group comparisons concerning 90 days' mortality of BACH EU patients were conducted by Pearson's χ^2 test on the basis of corresponding 2 × 2 frequency tables. The following associations were tested:

(1) 90 days' mortality (yes/no) vs. gold standard diagnoses (AHF, no-AHF) without MR-proANP filtering,
(2) 90 days' mortality (yes/no) vs. gold standard diagnoses (AHF, no-AHF) with MR-proANP filtering (MR-proANP > 300 pmol/L),
(3) for EU-AHF patients, 90 days' mortality (yes/no) vs. MR-proANP concentration ($\leq$300 pmol/L, >300 pmol/L), and
(4) for EU-no-AHF patients, 90 days' mortality (yes/no) vs. MR-proANP concentration ($\leq$300 pmol/L, >300 pmol/L).

Table 2 Characteristics of patients

Variable	EU cohort (n = 726)	All patients		Patients with MR-proANP > 300 pmol/L	
		AHF (n = 345)	Non-AHF diagnoses (n = 381)	AHF (n = 237)	Non-AHF diagnoses (n = 61)
Age (years)	73 (62–81)	77 (67–83)	68 (57–78)***	77 (69–83)	78(70–83)
Female	46.1%	42.3%	49.6%	40.5%	49.2%
Presentation symptoms and findings					
Dyspnea at rest	45.5%	45.5%	45.4%	48.1%	52.5%
Orthopnoea	46.6%	59.4%	35.4%***	60.8%	41.0%*
Dyspnea at night	36.0%	46.4%	26.5%***	48.9%	52.5%**
Rales	44.4%	59.7%	30.4%***	63.7%	37.7%***
Wheezing	23.6%	22.6%	24.4%	23.6%	16.4%
Oedema	40.9%	55.1%	28.1%***	59.9%	49.2%
Heart rate	88 (75–105)	86 (73–105)	89 (76–105)	86 (72–108)	100 (80–113)
Systolic BP	140 (125–160)	139 (121–160)	140 (127–160)	135 (117–157)	135 (113–157)
Respiratory rate	20 (17–25)	20 (16–25)	20(18–25)	20 (16–24)	23(18–29)
History					
CAD	36.0%	50.1%	23.1%***	51.1%	42.6%
Prior MI	22.7%	33.3%	13.1%***	33.8%	27.6%
Chronic heart failure	36.9%	57.4%	18.4%***	61.2%	44.3%*
Asthma/COPD	61.0%	70.7%	52.2%***	26.6%	42.6%**
HLP	32.4%	38.3%	27.0%**	38.8%	26.2%
Hypertension	68.3%	73.6%	63.5%**	71.3%	78.7%
Diabetes	26.7%	36.2%	18.1%***	34.6%	18.0%*
Stroke	11.2%	13.9%	8.7%*	14.8%	8.2%

AHF, acute heart failure; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HLP, hyperlipid-aemia; MI, myocardial infarction; MR-proANP, mid-regional pro-atrial natriuretic peptide.
Variables are given as proportions except age, heart rate, and systolic blood pressure (median, 25%/75% centiles).
***P < 0.001; **P < 0.01; *P < 0.05.

Table 3 Outcome of patients' diagnosis and natriuretic peptide defined subgroups after 7, 30, and 90 days

Biomarker for patient selection	Endpoint	No. of patients		Mortality %					
		Subgroup after selection by NP	AHF (%)	AHF			No-AHF		
				Est	95% CI.lo	95% CI.hi	Est	95% CI.lo	95% CI.hi
None	90 days' mortality	726	47.5	14	10	18	10	7	14
BNP		316	79.7	17	12	22	25	15	37
MR-proANP		298	79.5	17	12	22	25	14	37
NT-proBNP		356	75.5	16	12	21	23	15	33
None	30 days' mortality	726	47.5	8	6	12	6	4	9
BNP		316	79.7	10	6	14	16	8	27
MR-proANP		298	79.5	10	7	15	13	6	24
NT-proBNP		356	75.5	10	6	14	15	8	24
None	7 days' mortality	726	47.5	3	2	6	2	1	4
BNP		316	79.7	3	1	6	8	3	17
MR-proANP		298	79.5	3	1	7	5	1	14
NT-proBNP		356	75.5	3	1	6	6	2	13

AHF, acute heart failure; NP, natriuretic peptide; CI.lo, confidence interval low; CI.hi, confidence interval high.
Cut-offs were 350 ng/L (BNP), 300 pmol/L (MR-proANP), and 1800 ng/L (NT-proBNP).

Results

The characteristics of patients are displayed in *Table 2*. There were significant differences between patients with AHF, who were significantly older than those with non-AHF diagnoses. Once filtered by elevated proANP, the differences were much less; specifically, the age was no longer statistically different. The prevalence of asthma/chronic obstructive pulmonary disease (COPD) was higher among those with AHF in the entire group, but vice versa in the group with elevated MR-proANP.

Table 1 shows the prevalence of the gold standard diagnoses in the total cohort and subgroups defined by the cut-offs used in the IMPACT-EU study.

The prevalence of AHF is increased from 47.5 to 75.6% (NT-proBNP criteria) up to 79.7% (BNP criteria) (*Table 3*).

Figure 1 shows MR-proANP levels by gold standard diagnoses.

The mortality of AHF is higher than that in all no-AHF patients. Once selected by NP criteria, the mortality increases in the subgroup, but although the prevalence of AHF increases, the mortality of the no-AHF group increases more owing to the selection by high NPs. The short term mortality is comparably low and is highest mortality occurred between 30 and 90 days. *Figure 2* shows the change of mortality in patients with a gold standard diagnosis of AHF or no-AHF in the entire dyspnea population and the selected group by elevated NP.

We observe that filtering to patients with MR-proANP > 300 pmol/L increases 90 days' mortality significantly for AHF patients and even highly significantly for no-AHF patients. Mortality differences between AHF and no-AHF patients were not statistically significant, neither before nor after filtering with proANP.

The driving diagnoses for 90 days' mortality (frequency in per cent) in the non-AHF group after the selection with MR-proANP were COPD (35.7%), acute coronary syndrome (ACS;

Figure 2 Comparison of the entire population with dyspnea and the selected group by MR-proANP > 300 pmol/L with respect to the 90 days' mortality by the gold standard diagnoses of AHF or no-AHF. AHF, acute heart failure; proANP, mid-regional pro-atrial natriuretic peptide.
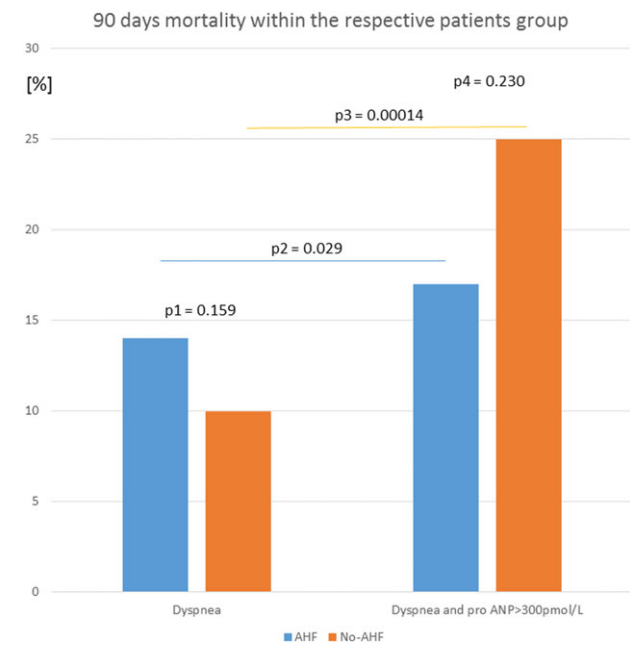
33.3%), other (33.3%), and pneumonia (22.2%). All details of mortality by diagnoses are listed in *Table S1*.
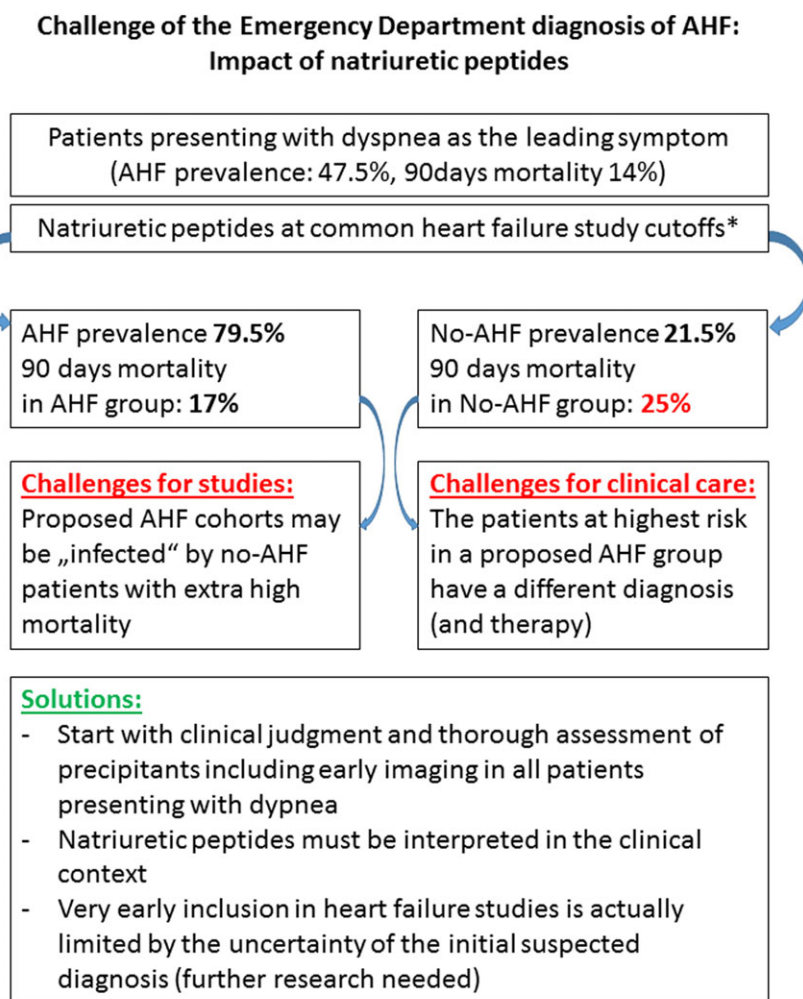
Discussion

The present analysis of patients presenting to the ED with dyspnea shows that (i) NPs are effective in selecting those with AHF as main diagnosis and (ii) high-risk patients with other diagnosis are also identified.

The use of NPs in the ED for diagnostic purposes has been studied extensively with concordant results.[2,12–14] Nevertheless, no studies were able to provide strong evidence that this has a beneficial impact on outcome. In addition, interventional studies using nesiritide[15] or serelaxin[16] in the very early phase of presentation failed to show survival benefits. While one explanation is the lack of effective therapeutic concepts, another point could be the difficulty to identify a certain patient population who benefits from a specific intervention in the very early phase of the presentation. Most recently, a sub-analysis from ASCEND-AF showed that patients who presented during off hours profit more than do others from nesiritide.[17]

In our study, we could show that NPs have a very strong prognostic impact, which is not only related to the diagnosis of AHF. Specifically, patients with ACS and COPD/pneumonia had the highest mortality when MR-proANP was >300 pmol/L. Therefore, clinicians need to be aware that the prognostically most important disease in a certain patient with dyspnea and high NP is not AHF. The actual heart failure guidelines of the European Society of Cardiology (ESC) have already anticipated this partly with the CHAMP-concept which helps to identify an acute etiology (acute Coronary syndrome, Hypertension emergency, Arrhythmia, acute Mechanical cause, Pulmonary embolism),[1] and an expert paper about AHF in the ED focused on the so-called precipitants,[5] which are sometimes the cause of a syndrome with dyspnea and high NPs that need primarily therapy of the underlying disease. Therefore, the future view on the syndrome of AHF should involve always the underlying disease, and therefore, a wording like 'AHF on the basis of pulmonary infection' or 'AHF on the basis of acute coronary syndrome' seem to be appropriate.

Figure 3 Central illustration of the main findings of the study. AHF, acute heart failure.

Challenge of the Emergency Department diagnosis of AHF: Impact of natriuretic peptides

Patients presenting with dyspnea as the leading symptom (AHF prevalence: 47.5%, 90days mortality 14%)

Natriuretic peptides at common heart failure study cutoffs*

AHF prevalence **79.5%**
90 days mortality
in AHF group: **17%**

No-AHF prevalence **21.5%**
90 days mortality
in No-AHF group: **25%**

Challenges for studies:
Proposed AHF cohorts may be „infected" by no-AHF patients with extra high mortality

Challenges for clinical care:
The patients at highest risk in a proposed AHF group have a different diagnosis (and therapy)

Solutions:
- Start with clinical judgment and thorough assessment of precipitants including early imaging in all patients presenting with dypnea
- Natriuretic peptides must be interpreted in the clinical context
- Very early inclusion in heart failure studies is actually limited by the uncertainty of the initial suspected diagnosis (further research needed)

*numbers given for proANP > 300pmol/L; similar results for BNP > 350ng/mL and NT-proBNP > 1800ng/L

Implications for clinical practice

Taking the actual results into consideration, clinicians need to anticipate that NPs used in the ED have diagnostic and prognostic implications and select a patient population with AHF as the primary diagnosis and a heterogeneous group of patients with high risk and mortality. In our data, the specific driving diagnoses for mortality were ACS, COPD, and pneumonia. These findings are in line with the guidelines and the 'CHAMP'-concept.[1] *Figure 3* summarizes the challenge in patients presenting with acute dyspnea and possible solutions. The proposal is, to imply strictly a thorough clinical assessment first and add imaging whenever appropriate. This is in line with the recommendations of the ESC expert group.[18]

Implications for research

In the light of the failure of studies that used NPs as one main inclusion criteria,[16] there is need for further studies that identify AHF subgroups who may profit from specific interventions regarding HF therapy. This means also to identify specific therapeutic options like non-invasive ventilation (NIV), which allow immediate reversal of hypoxia and therefore gain time for a more thorough diagnostic workup. NIV is, from the clinical viewpoint, a major breakthrough in acute dyspnea and hypoxia in the ED but has limited evidence from prospective clinical studies.[19] Future interventional studies in AHF should therefore take into account the uncertainty of the exact diagnosis in the very acute phase and propose a more detailed workup to identify a more individualized patient population.

Conclusions

The prevalence of patients with the gold standard diagnoses of AHF among those presenting with dyspnea to the ED is significantly increased by the use of NPs with common cut-offs used in prospective HF studies. Nevertheless, in the selected groups, patients with no AHF diagnosis have the highest mortality, and therefore, the addition of an NP alone is insufficient to start specific therapies.

Conflict of interest

M.M. received consulting and speaker's honoraria and research support from Roche Diagnostics, Bayer, and BRAHMS. S.v.H. has received consulting honoraria from Roche and BRAHMS. J.O.V. is medical director and J.C.W. is biostatistician at BRAHMS. S.A. reports personal fees from BRAHMS for his work in the BACH steering committee and consultancy and received personal fees from Bayer, Boehringer Ingelheim, Vifor Int., Servier, and Novartis for committee work outside the submitted work. A.M. reports personal fees from BRAHMS for his work in the BACH steering committee.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1. 90 days mortality of patients with AHF and the different non-AHF diagnoses.

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