Neurohormones as Predictors of Outcome in an Elderly Heart Failure Population Naïve of Neurohormonal Blockers Results from the CIBIS III Neurohormonal Substudy

Friedrich M. Fruhwald*[,1], Astrid Fahrleitner-Pammer[2], Barbara Obermayer-Pietsch[2], Michael A. Goulder[3], Henry Krum[4], Dirk J. van Veldhuisen[5], Louis van de Ven[6], Patricia Verkenne[6], Burkert Pieske[1], Wilfried Meyer[6] and Ronnie Willenheimer[7]

[1]*Department of Cardiology, Medical University Graz, Austria*

[2]*Department of Endocrinology and Nuclearmedicine, Medical University Graz, Austria*

[3]*Worldwide Clinical Trials, Nottingham, UK*

[4]*Departments of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia*

[5]*Thoraxcenter, Department of Cardiology, University Hospital Groningen, The Netherlands*

[6]*Merck Serono, Darmstadt, Germany*

[7]*Dept of Clinical Sciences Cardiology, Lund University and Heart Health Group, Malmoe, Sweden*

Abstract: *Objectives*: Although neurohormones have a well-established prognostic value in patients with chronic heart failure (CHF), little is known about this in CHF patients untreated with angiotensin-converting enzyme (ACE)-inhibitors, angiotensin-receptor blockers (ARBs) and beta-blockers.

Methods: Baseline N-terminal pro atrial natriuretic peptide (NT-pro-ANP), N-terminal pro B-type natriuretic peptide (NT-pro-BNP), big endothelin (big-ET) and arginine-vasopressin (AVP) were tested for prognostic importance to predict the primary endpoint (death or hospitalisation) in 109 patients participating in the third Cardiac Insufficiency BIsoprolol Study(CIBIS III). Minimum follow-up time was 12 months (6 months monotherapy followed by 6 months combinationtherapy).

Results: On average, patients had moderate elevation of all neurohormones tested. In univariate analysis, both below-median NT-pro-BNP (HR 0.37, 95% confidence interval [CI] 0.17-0.81, p=0.013) and below-median big-ET (HR 0.39, 95% CI 0.18-0.86, p=0.02) predicted decreased risk of all-cause death or hospitalisation, compared with above-median values. NT-pro-BNP lost its predictive power in multivariate analysis, while big-ET above median as well as body mass index (BMI) below median and presence of ischemic heart disease were predictive of increased risk of death or hospitalisation. Using Cox stepwise regression analysis, only BMI (p=0.011) and big-ET (p=0.003) remained significant predictors of death or hospitalisation.

Conclusion: In a cohort of elderly CHF patients naïve of ACE-inhibitors, ARBs and beta-blockers, the best predictors of all-cause death or hospitalisation were a low BMI and elevated levels of big-endothelin.

Keywords: Bisoprolol, enalapril, chronic heart failure, elderly patients, neurohormones.

1. INTRODUCTION

Treatment of chronic heart failure (CHF) is based on the concept of neurohumoral blockade of both the renin-angiotensin-system (RAS) and the sympatho-adrenergic system (SAS). Guidelines recommend starting treatment with an angiotensin-converting-enzyme inhibitor (ACE-inhibitor) or an angiotensin receptor blocker (ARB) and later adding a beta-blocker [1]. However, the results of the third Cardiac Insufficiency BIsoprolol Study (CIBIS III) suggest that it is reasonable to start with the beta-blocker bisoprolol in elderly patients naïve of RAS-blockers [2].

Neurohormones, such as natriuretic peptides are among the best-investigated predictors of prognosis in patients with both acute and chronic heart failure [3-5]. However, the majority of the randomised controlled trials from which these data emerged requested pre-treatment with ACE-inhibitors. Little is known about the prognostic value of neurohormones in CHF patients untreated with ACE-inhibitors, ARBs and beta-blockers.

We investigated neurohumoral parameters in the CIBIS III trial to elucidate the context of neurohormones and prognosis in elderly patients untreated with neurohormonal blockers.

*Address correspondence to this author at the Department of Cardiology, University Clinic of Internal Medicine, Auenbruggerplatz 15, A-8036 Graz, Austria; Tel: +43/316/385-2544; Fax: +43/316/385-3733;
E-mail: friedrich.fruhwald@meduni-graz.at

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2. PATIENTS AND METHODS

2.1. The CIBIS III Investigation

CIBIS III was a multinational study with a prospective, randomized, open-label blinded endpoint evaluation (PROBE) design, including patients with mild to moderate CHF (New York Heart Association [NYHA] class II or III), at least 65 years old. Patients had to be naïve for treatment with ACE-inhibitors, ARBs and beta-blockers within 3 months before entering the study. Patients were randomized to start treatment with either bisoprolol or enalapril for around six months as monotherapy followed by at least six months of combined therapy [6]. The major results of CIBIS III have been published [2]. In brief, 1010 patients were randomized and uptitrated towards a target dose of bisoprolol (target 10mg/day) or enalapril (target 20mg/day). The intention-to-treat analysis showed non-inferiority of bisoprolol as first-line drug, compared with enalapril, in terms of the primary endpoint of all-cause death or hospitalisation.

The neurohumoral substudy of CIBIS III included 109 patients (60 randomised to bisoprolol-first and 49 randomised to enalapril-first) recruited in centres willing to participate and able to store the samples at -70°C. At baseline, at the end of the monotherapy phase and at study end, samples of 7.0 ml of blood were drawn into chilled tubes containing EDTA-plasma. Vials were immediately put into ice-cold water and centrifuged at -4°C at 4000 rpm for at least 10 minutes. Supernatant plasma was aliquoted and stored in labelled vials at -70°C until the end of the CIBIS III study. Finally, vials were transported on dry ice using a courier-service to the neurohumoral core-laboratory (Medical University Graz). After a check on delivery (frozen status, accurate labelling) they were kept frozen at -70°C until analysis after completion of the CIBIS III study.

N-terminal pro B-type natriuretic peptide (NT-pro-BNP) was measured using a commercially available electrochemiluminescence immunoassay (ECLIA) based on a polyclonal antibody-based sandwich chemiluminescence assay (Roche Diagnostics, Germany). Normal values in a healthy population are <125 pg/ml with a lowest detection limit of <5 pg/ml.

N-terminal pro-atrial natriuretic peptide (NT-pro-ANP) was measured using a commercially available enzyme linked immuno assay (ELISA, Biomedica Austria). Normal values in a healthy population are <1.45 nmol/l with a lowest detection limit of 0.05 nmol/l.

Big-endothelin (big-ET) was measured using a commercially available ELISA (Biomedica Austria). Normal values in a healthy population are <0.20 fmol/ml with a lowest detection limit of 0.020 fmol/ml.

Table 1. Baseline Characteristics of the CIBIS III Patients Participating in the Neurohumoral Analysis

Variable	Entire Patient Population (n= 109)	Bisoprolol-First Group (n= 60)	Enalapril-First Group (n= 49)
Median age, years (IQR)	73 (68-78)	73 (68-77)	73 (68-78)
Male, n (%)	77 (71)	42 (70)	35 (71)
Median Heart Rate, bpm (IQR)	76 (70-88)	78 (71.5-88.0)	75 (70-86)
Median Systolic Blood Pressure, mm Hg (IQR)	135 (120-145)	140 (125-146)	130 (120-140)
Median Diastolic Blood Pressure, mm Hg (IQR)	80 (75-88)	80 (76.5-89)	80 (72-87)
Median LV-ejection fraction (IQR)	29 (25-32)	30 (26.0-33.5)	25 (23-30)
NYHA class II, n (%)	55 (50)	28 (47)	27 (55)
NYHA class III, n (%)	54 (50)	32 (53)	22 (45)
Median BMI, kg/m^2, (IQR)	25.8 (23.4-28.4)	26.2 (23.6-28.4)	25.7 (23.0-28.6)
Median Creatinine clearance ml/min, (IQR)	57.3 (43.6-74.1)	57.8 (44.2-73.7)	54.6 (43.4-74.4)
Median Serum sodium, mmol/l (IQR)	141 (138-142)	141 (138-142)	141 (138-142)
Cause of heart failure			
Ischemic heart disease, n (%)	55 (50)	29 (48)	26 (53)
Hypertension, n (%)	37 (34)	22 (37)	15 (31)
Valvular disease, n (%)	4 (4)	3 (5)	1 (2)
Primary dilated cardiomyopathy, n (%)	16 (15)	10 (17)	6 (12)
Other, n (%)	20 (18)	11 (18)	9 (18)
Median NT-pro-BNP, pg/ml (IQR)	1592 (570-3596)	1170 (554-3596)	1664 (656-3585)
Median NT-pro-ANP, nmol/l (IQR)	5.3 (2.13-8.65)	5.3 (1.75-7.24)	6.1 (3.20-8.80)
Median big-ET, fmol/ml (IQR)	0.52 (0.36-0.77)	0.56 (0.37-0.77)	0.48 (0.32-0.76)
Median AVP, pg/ml (IQR)	3.10 (1.70-5.40)	3.20 (1.50-5.30)	3.00 (1.80-5.45)

Abbreviations: IQR = Inter-Quartile Range; LV = left ventricular; BMI = body mass index; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; NT-pro-ANP = N-terminal pro-atrial natriuretic peptide; big-ET=big endothelin; AVP=arginine-vasopressin.

Arginine-Vasopressin (AVP) was measured using a commercially available double antibody radioimmuno-assay (Bühlmann Laboratories AG, Switzerland). Normal values in a healthy population are <7.6 pg/ml with a lowest detection limit of 1.3 pg/ml (to convert into pmol/L multiply by 0.92).

2.2. Statistics

Descriptive statistics were calculated for demographic data, vital-parameters and NYHA-classification. All neurohumoral variables were non-normally distributed.

A significance level of 5% was used for all tests, which were performed using SAS (version 9.1).

With NT-pro-BNP being the best investigated neurohormone in CHF today we divided patients into quartiles according to baseline NT-pro-BNP. For demographic variables, a p-value for a trend amongst the quartile groups was calculated by using the Cochran-Armitage trend test (binary variables) or the Spearman's correlation coefficient (continuous variables).

The relationships between each baseline variable of interest and the primary endpoint (death or hospitalisation) were investigated by a series of univariate Cox regression models with each baseline variable considered as a two-level factor (≤median, >median). The hazard ratios (HR) were calculated with the associated 95% confidence intervals. A HR>1 indicated that there was a greater risk of the endpoint occurring within the subgroup having values ≤median. Similar models were also fitted for gender, presence of ischemic heart disease and treatment allocation according to randomisation. Two multivariate Cox models were also fitted including all the baseline variables in the same model, firstly with-

Table 2. Baseline Characteristics of Patients According to Quartiles of Baseline NT-pro-BNP Levels (pg/ml)

Variable	Quartile 1 (12-570)	Quartile 2 (571-1592)	Quartile 3 (1593-3596)	Quartile 4 (3597-16070)	p-Value for Trend
Patients, n (%)	23 (25)	23 (25)	23 (25)	23 (25)	
Median Age, yr (IQR)	73 (67-76)	74 (67-77)	76 (70-79)	72 (66-78)	0.96
Male, n (%)	15 (65)	16 (70)	15 (65)	18 (78)	0.42
Female, n (%)	8 (35)	7 (30)	8 (35)	5 (22)	0.42
Median Heart Rate, bpm (IQR)	72 (69-80)	75 (70-84)	76 (72-86)	83 (75-90)	0.0011 **
Median Systolic Blood Pressure, mm Hg (IQR)	142 (140-150)	140 (132-145)	130 (120-140)	130 (117-140)	<0.001 ***
Median Diastolic Blood Pressure, mm Hg (IQR)	85 (80-90)	80 (80-88)	80 (76-90)	80 (70-80)	0.007 **
Median LV-ejection fraction (IQR)	32 (30-35)	30 (24-33)	25 (24-30)	28 (25-30)	0.0048 **
NYHA class II, n (%)	11 (48)	17 (74)	13 (57)	8 (35)	0.22
NYHA class III, n (%)	12 (52)	6 (26)	10 (43)	15 (65)	0.22
Median BMI, kg/m^2 (IQR)	26.9 (23.9-29.9)	26.9 (24.8-28.4)	26.2 (23.5-28.5)	25.4 (23.7-28.3)	0.19
Median Creatinine clearance ml/min, (IQR)	63.2 (51.3-76.9)	64.8 (51.9-79.7)	57.4 (42.6-74.1)	52.2 (43.4-55.6)	0.006 **
Median Serum Sodium, mmol/l (IQR)	142 (139-144)	141 (140-142)	141 (137-143)	140 (138-142)	0.04 *
Cause of heart failure					
Ischemic heart disease, n (%)	17 (74)	11 (48)	12 (52)	11 (48)	0.11
Hypertension, n (%)	11 (48)	9 (39)	7 (30)	5 (22)	0.0502
Valvular disease, n (%)	-	-	2 (9)	1 (4)	0.19
Primary dilated cardiomyopathy, n (%)	1 (4)	2 (9)	2 (9)	6 (26)	0.03 *
Other, n (%)	-	6 (26)	4 (17)	6 (26)	0.049 *
Median NT-pro-BNP, pg/ml (IQR)	288 (161-503)	981 (704-1160)	2290 (1924-3161)	5387 (4069-7597)	<0.001 ***
Median NT-pro-ANP, nmol/l (IQR)	1.59 (0.44-2.59)	3.99 (2.02-5.10)	6.23 (5.12-8.01)	9.15 (7.55-13.15)	<0.001 ***
Median big-ET, fmol/ml (IQR)	0.49 (0.26-0.66)	0.38 (0.34-0.65)	0.64 (0.41-0.86)	0.69 (0.49-0.89)	0.011 *
Median AVP, pg/ml (IQR)	2.8 (2.2-6.1)	3.1 (2.3-5.3)	1.7 (1.4-4.3)	4.3 (3.0-6.0)	0.70

Abbreviations: IQR = Inter-Quartile Range; LV = left ventricular; BMI = body mass index; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; NT-pro-ANP = N-terminal pro-atrial natriuretic peptide; big-ET=big endothelin; AVP=arginine-vasopressin.
*: p<0.05; **: p<0.01; ***: p<0.001.

out regard to selection procedures and secondly using a stepwise regression procedure with a 5% significance level of entry into the model.

Changes of the four neurohumoral variables from baseline to the end of monotherapy and to the end of the study, respectively, were assessed using one-way analysis of covariance on ranked-transformed data with a factor for treatment group and baseline value as a covariate.

3. RESULTS

Overall 32 of 128 centres (25%) were able to participate in the neurohumoral substudy. These centres included 109 patients for analysis of neurohormones. Baseline characteristics of patients included in the neurohormonal analysis did not differ between the two treatment groups, with the exception of LVEF that was higher in the bisoprolol-first group (Table **1**). All neurohormones were clearly elevated at study entry and did not differ between treatment groups.

Patients (n=92) were divided into quartiles with regard to baseline levels of NT-pro-BNP. There was a statistically significant difference between quartiles regarding median resting heart rate, blood pressure, left ventricular ejection fraction, renal function and serum sodium concentration. With respect to neurohormones NT-pro-ANP and big-ET increased parallel to quartiles of NT-pro-BNP, while AVP did not show a significant trend (Table **2**).

The probabilities of reaching the primary endpoint according to quartiles of baseline NT-pro-BNP are shown in Fig. (**1**). Clearly, higher NT-pro-BNP levels at baseline were associated with poor prognosis.

In a univariate analysis of baseline parameters only NT-pro-BNP and big-ET above median statistically significantly predicted increased risk of the primary endpoint. All other parameters including age, heart rate, systolic blood pressure, body mass index (BMI), renal function, serum sodium concentration, NT-pro-ANP, AVP, gender, ischemic heart disease and treatment allocation (bisoprolol or enalapril first) were not statistically significant predictors (Table **3**).

However, the multivariate model showed that BMI below median (25.8 kg/m^2), big-ET above median (0.52 fmol/ml)

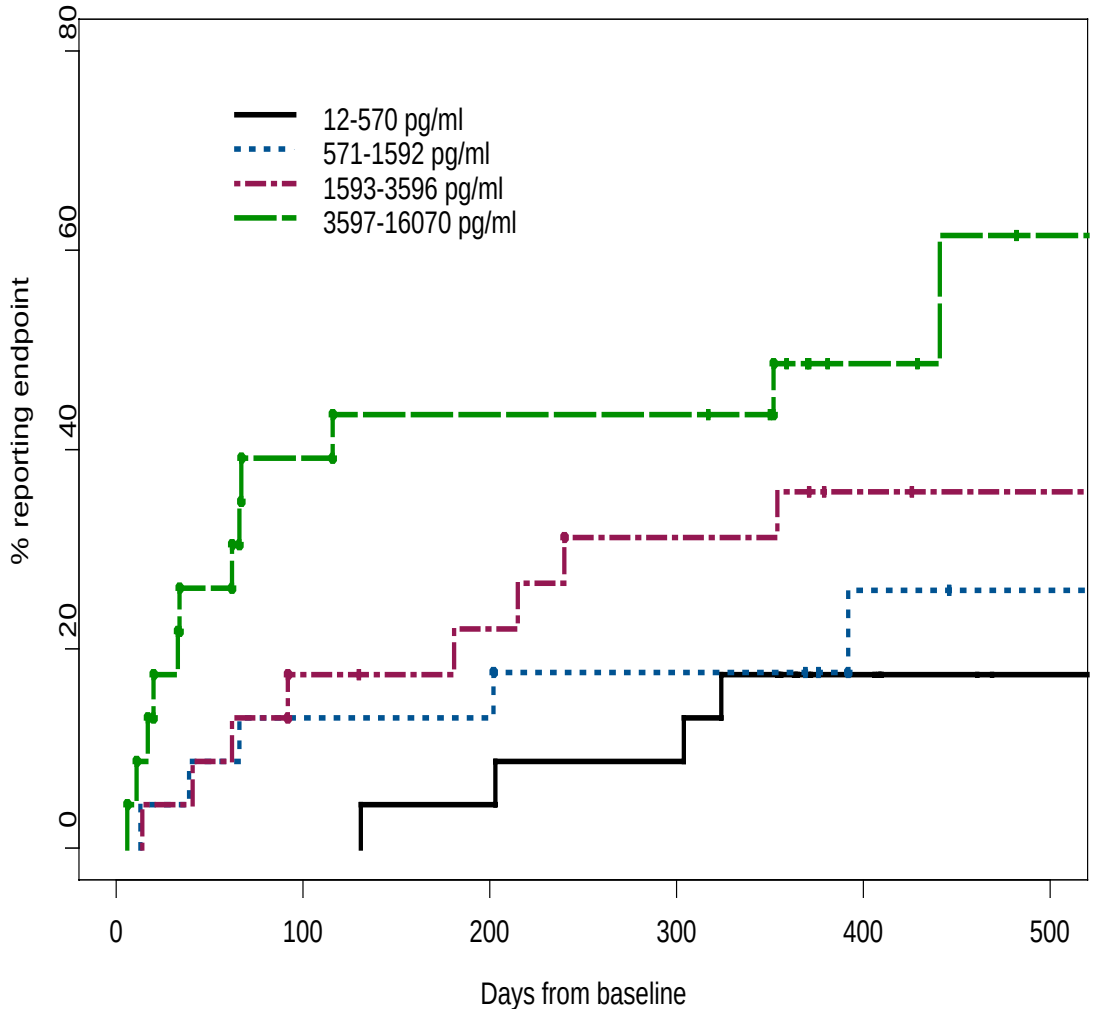

Fig. (1). Kaplan-Meier Curve for the combined primary endpoint (death or hospitalisation) according to Quartiles of baseline NT-pro-BNP levels (n=92) at study entry.

There was a significant between-quartile difference (p=0.02): the higher baseline NT-pro-BNP the higher the risk of death or hospitalisation. Kaplan-Meier mean estimates to time to reporting of endpoint in days were: 309.5 days (12-570 pg/ml), 337.3 days (571-1592 pg/ml), 282.0 days (1593-3596 pg/ml) and 263.5 days (3597-16070 pg/ml).

Table 3. Univariate Analysis of Baseline Predictors of the Primary Endpoint (Death or Hospitalisation)

Variable	Number (%) of Total Reporting Endpoint ≤ Median	Number (%) of Total Reporting Endpoint > Median	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-Value
Age (median = 73 years)	23/58 (40)	14/51 (27)	1.70	0.87, 3.31	0.12
Heart Rate (median = 76 bpm)	17/56 (30)	20/53 (38)	0.73	0.38, 1.40	0.35
Systolic Blood Pressure (median = 135 mmHg)	23/56 (41)	14/53 (26)	1.85	0.95, 3.59	0.07
BMI (median = 25.8 kg/m^2)	23/55 (42)	14/54 (26)	1.76	0.91, 3.42	0.10
Creatinine clearance (median = 57.3 ml/min)	22/55 (40)	15/54 (28)	1.62	0.84, 3.12	0.15
Serum Sodium (median = 141 mmol/l)	27/69 (39)	10/40 (25)	1.65	0.80, 3.42	0.18
NT-pro-BNP (median = 1592 pg/ml)	9/46 (20)	20/46 (43)	0.37	0.17, 0.81	0.013*
NT-pro-ANP (median = 5.3 nmol/l)	12/49 (24)	21/48 (44)	0.50	0.24, 1.01	0.053
Big-ET (median = 0.52 fmol/ml)	9/45 (20)	20/45 (44)	0.39	0.18, 0.86	0.02 *
AVP (median = 3.1 pg/ml)	20/54 (37)	15/53 (28)	1.48	0.76, 2.89	0.25
	Number (%) of Total Reporting Endpoint	**Number (%) of Total Reporting Endpoint**			
	male	**female**			
Gender	26/77 (34)	11/32 (34)	0.98	0.49, 1.99	0.96
	present	**absent**			
Ischemic heart disease	18/55 (33)	19/54 (35)	0.99	0.52, 1.88	0.97
	bisoprolol-first	**enalapril-first**			
Treatment allocation	23/60 (38)	14/49 (29)	1.37	0.70, 2.66	0.35

Abbreviations: BMI = body mass index; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; NT-pro-ANP = N-terminal pro-atrial natriuretic peptide; big-ET=big endothelin; AVP=arginine-vasopressin.
*: p<0.05; **: p<0.01; ***: p<0.001.

and presence of ischemic heart disease significantly predicted death or hospitalisation (Table **4**). Using a stepwise regression model, the factors kept in the model using a 5% significance level to predict the primary endpoint were a low BMI and an elevated big-ET.

Overall 37 (34%) patients who were included into the univariate analyses reached the primary endpoint throughout the study period. Due to missing data, 85 subjects were included in the multivariate analysis with 26 (31%) reporting the primary endpoint.

When looking at changes during the trial of the four tested neurohormones, we found no statistically significant changes. NT-pro-BNP decreased in both treatment groups during the six-month monotherapy phase and returned to baseline levels at the end of the trial. NT-pro-ANP decreased during monotherapy in the enalapril-first group only and returned to baseline levels at study end. Values for big-ET and AVP remained stable throughout the entire study period in both treatment arms.

4. DISCUSSION

This ancillary study of CIBIS III shows that, in elderly CHF patients naïve of ACE-inhibitors, ARBs and beta-blockers, baseline values of low BMI and high big-ET as well as presence of ischemic heart disease are independent predictors of all-cause death or hospitalisation.

Not surprisingly, NT-pro-BNP-data confirm that patients studied in CIBIS III suffered from mild to moderate CHF. However, while there were some patients with NT-pro-BNP-

Table 4. Multivariate Analysis of Baseline Predictors of the Primary Endpoint (Death or Hospitalisation)

Variable	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-Value
Age ≤ 73 years	2.46	0.90, 6.75	0.08
Male gender	0.71	0.25, 2.02	0.52
Heart Rate ≤ 76 bpm	0.94	0.39, 2.27	0.89
Systolic Blood Pressure ≤ 135 mHg	1.88	0.79, 4.50	0.16
BMI ≤ 25.8 kg/m^2	5.87	1.94, 17.80	0.002 **
Calculated creatinine clearance ≤ 57.3 ml/min	1.47	0.47, 4.60	0.51
Serum Sodium ≤ 141 mmol(l	1.50	0.59, 3.80	0.39
Ischemic heart disease	2.73	1.03, 7.22	0.04 *
Treatment allocation	1.68	0.66, 4.26	0.28
NT-pro-BNP ≤ 1592 pg/ml	0.55	0.15, 2.01	0.37
NT-pro-ANP ≤ 5.3 nmol/l	1.15	0.36, 3.68	0.81
Big-ET ≤ 0.52 fmol/ml	0.20	0.07, 0.59	0.004 **
AVP ≤ 3.1 pg/ml	2.20	0.86, 5.64	0.10

The factors kept in the model using stepwise regression model with 5% significance level

Variable	Number (%) of Total Reporting Endpoint ≤ Median	Number (%) of Total Reporting Endpoint > Median	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-Value
BMI ≤25.8 kg/m^2	16/38 (42)	10/47 (21)	2.82	1.26, 6.29	0.011 *
Big-ET ≤ 0.52 fmol/ml	7/43 (16)	19/42 (45)	0.26	0.11, 0.63	0.003 **

Abbreviations: BMI = body mass index; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; NT-pro-ANP = N-terminal pro-atrial natriuretic peptide; big-ET=big endothelin; AVP=arginine-vasopressin.
*: p<0.05; **: p<0.01; ***: p<0.001.

values suggesting mild CHF, there was a considerable proportion of patients with NT-pro-BNP-values suggesting moderate to severe heart failure as well (those in the highest quartile of baseline NT-pro-BNP).

Natriuretic peptides have a long history in HF. Both ANP and BNP have been thoroughly investigated. Nowadays, BNP together with its N-terminal fragment NT-pro-BNP are preferred over ANP for diagnosis and prognostication of CHF patients [1]. However, the foremost-discovered NT-pro-ANP correlates well with both clinical variables and with non-invasive measurements in CHF patients [7, 8]. BNP and NT-pro-BNP, which both can be measured easily by various commercially available ELISA-tests, are probably the best investigated laboratory parameters in CHF. They are helpful for diagnosis of patients with acute dyspnoea [9, 10], prognostication in patients with acute HF and CHF (**3-5**), and for monitoring therapeutic effects [11]. Recently it has been demonstrated that both intensified neurohumoral therapy and cardiac resynchronisation therapy can reduce NT-pro-BNP over the long-run [12-14]. Interestingly, in our cohort of patients with mild to moderate CHF, NT-pro-BNP was only a predictor of death or hospitalisation (the primary endpoint of CIBIS III) in the univariate analysis of baseline parameters. It lost its prognostic power in the multivariate analysis and was replaced by BMI.

Big-ET, the precursor of the potent vasoconstrictor endothelin 1, has been investigated in patients with moderate and advanced CHF. It is a potent prognostic marker for adverse outcome in the latter despite optimal chronic neurohumoral therapy [15-17]. Very recently, data from the Val-HeFT trial showed that big-ET was an independent marker of prognosis in a large population of patients with predominantly mild to moderate CHF [18], although its prognostic power was lower than that of BNP. In contrast, in our patient cohort multivariate analysis revealed that big-ET was better than NT-pro-BNP for prediction of death or hospitalisation. One possible reason for this discrepancy is that our patients were essentially untreated with ACE-inhibitors, ARBs and beta-blockers before randomisation. Another possible explanation is that our patients were substantially older than in almost all prior studies on the issue, including the Val-HeFT trial.

It is long known that cachexia is among the best predictors of adverse outcome in patients with CHF [19, 20]. The early observational reports have been confirmed by reports from large, randomised trials: Low BMI is consistently a marker of morbidity and mortality in patients with CHF [21,

22]. Therefore, our findings are in line with earlier reports. However, our patients with low BMI would correspond to the medium-risk group in the CHARM-population [22] and to the combined normal-weight and over-weight groups in the Val-HeFT-population, respectively [21]. Nevertheless, in our population, a BMI equal to or less than 25.8 kg/m^2 was associated with a 2.82-fold risk of death or hospitalisation, as compared with a BMI of more than 25.8 kg/m^2.

Treatment allocation at randomisation (i.e. bisoprolol-first or enalapril-first) had no influence on death or hospitalisation, as previously reported for the entire CIBIS III patient sample [2].

Limitations

The major limitation of our report is that only a minority of centres was willing and able to participate in this substudy. Therefore, only a limited percentage of patients taking part in the main-study could be included into this ancillary study. Hence, results can be valid only for this small population and one must be cautious about generalising them. However, BMI results are available for the entire study population, revealing very similar results.

5. CONCLUSION

In a cohort of elderly CHF patients naïve of ACE-inhibitors, ARBs and beta-blockers, the best predictors of death or hospitalisation were a low BMI and elevated levels of big-ET.

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