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ORIGINAL RESEARCH ARTICLE

N-terminal pro BNP and galectin-3 are prognostic biomarkers of acute heart failure in sub-Saharan Africa: lessons from the BAHEF trial

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Abstract

Aims The relationship between N-terminal pro-brain natriuretic peptide (NT-pro-BNP) and galectin-3 and outcomes has not been studied in African patients with acute heart failure (AHF). The current analysis sought to describe the association between plasma levels of NT-pro-BNP and galectin-3 and cardiovascular (CV) death or heart failure (HF) hospitalization, as well as their associations with symptoms and echocardiography markers of left and right ventricular remodelling among AHF patientsv in sub-Saharan Africa.

Methods and results In a subset of 80 patients with complete data in a study assessing the effects of hydralazine and nitrates in patients with AHF (BAHEF trial; NCT01822808), NT-pro-BNP and galectin-3 analyses were performed, and the association with various characteristics and outcome measures assessed. The mean age of the patients for whom the aforementioned biomarkers were measured was 52.6 years, with 52.5% women. Galectin-3 at baseline predicted changes (Week 24 to baseline) in left ventricular ejection fraction, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, and tricuspid annular plane systolic excursion. Biomarkers and their changes were not associated with changes in 6 min walk test at 24 weeks. Baseline galectin-3 and change in NT-pro-BNP were associated with improvements in dyspnoea at 24 weeks. Nine patients had an HF readmission or died of CV causes through 24 weeks (11.6%). Both biomarkers at baseline predicted combined CV death or HF hospitalization through Week 24 (*P*-values = 0.0328 and 0.0001, respectively).

Conclusions In a cohort of patients with AHF from sub-Saharan Africa, NT-pro-BNP and galectin-3 at baseline and their changes were associated with some changes in dyspnoea, echocardiographic remodelling, and CV death or HF hospitalization through Week 24. These tests have potential of being used for risk stratification of AHF patients in sub-Saharan Africa where resources are scarce.

Keywords NT-pro-BNP; Galectin-3; Outcomes; Acute heart failure; Africa

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Introduction

Patients with recent hospitalizations for acute heart failure (AHF) are at high risk for future cardiovascular (CV) events and death.[1] African patients with AHF differ from those in the West, in that they are younger in their productive lives, present more acutely, have a more severe disease and higher mortality, and have predominantly hypertension and cardiomyopathy rather than ischaemic heart disease.[2–4]

Brain natriuretic peptide (BNP) and its cleavage equivalent N-terminal pro-brain natriuretic peptide (NT-pro-BNP) are established serum biomarkers for diagnosis and prognosis in AHF or chronic heart failure (HF).[5,6] These peptides have proven utility for confirming the diagnosis of AHF in breathless subjects and predict adverse outcomes in these patients.[7] In addition, high levels of natriuretic peptides are associated with recurrent hospitalization and risk of sudden death,[8] and pre-discharge BNP level appears to be a strong predictor for identifying subsequent death or hospital admission at 6 months.[5,9]

Galectin-3 is a soluble beta-galactoside binding lectin secreted by activated macrophages. It has been shown that cardiac macrophages are activated at an early stage in failure-prone, hypertrophied hearts and that these macrophages express galectin-3.[10] It has been recently identified to be involved in the pathophysiology of HF through mediation of myocardial fibrosis and inflammation, contributing to myocardial remodelling.[11] Because measurement of galectin-3 is readily feasible and reliable in stored plasma, and its value in diagnosis and prognostication of AHF patients, it becomes an important biomarker in the management of AHF patients. It is significantly increased in AHF and chronic HF, independent of aetiology.[12] While galectin-3 shows promise in detecting long-term outcomes, the role of galectin-3 levels at admission in diagnosis and early risk stratification in patients with AHF syndrome is undefined.[12,13] Plasma galectin-3 appears to be a prognostic marker of HF outcomes such as death and readmissions for HF[11,14–16] and is associated with increased risk for incident HF.[17]

The combination of NT-pro-BNP and galectin-3 has also been shown to identify those at greatest death risk among patients with AHF.[14] Patients with the highest quartile of both biomarkers had mortality rates as high as 15% within 10 days of presentation and twice the 30 days of mortality rate vs. the cohort with both markers being low.[14]

To the best of our knowledge, the relationship between NT-pro-BNP and galectin-3 and outcome was not studied in sub-Saharan African patients with AHF. From pre-specified secondary analyses of the Bi treatment with hydralazine/nitrates vs. placebo in Africans admitted with acute Heart Failure (BAHEF) study, which included assays of these biomarkers as part of patients' evaluation and follow-up, we set out to describe the association between plasma levels of NT-pro-BNP and galectin-3 and outcomes (CV death or HF hospitalization) through Week 24. We also aimed to identify the association between the plasma levels of these biomarkers and left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), which are markers of left ventricular (LV) remodelling, and tricuspid annular plane systolic excursion (TAPSE), a marker of right ventricular (RV) remodelling, in this cohort of AHF patients.

Methods

The BAHEF study[18] was a prospective, randomized, double-blind, placebo controlled trial comparing the combination of isosorbide dinitrate and hydralazine (HYIS) with placebo. The rationale and design of BAHEF have been previously reported.[18] In brief, patients were screened within 96 h of admission for AHF and recruited into the study if inclusion criteria were met. AHF was diagnosed based on symptoms and signs, supported by echocardiographic findings, and was confirmed by a cardiologist. Patients willing to participate in the study and who signed an informed consent were randomized to receive increasing doses of HYIS, starting with 25 mg hydralazine/10 mg isosorbide dinitrate and up-titrating to 50 mg hydralazine/20 mg isosorbide dinitrate TID (at 2 weeks depending on tolerability) or placebo. The dose selection and careful up-titration were performed in order to avoid hypotension in these patients during and immediately after AHF admission. Patients received standard HF therapy at the discretion of their treating physician and according to evidence-based guideline recommendations (angiotensin-converting inhibitors, angiotensin receptor antagonists, beta-blockers, aldosterone antagonists, and diuretics). Patients were followed up from randomization to discharge. Pre-discharge evaluations were conducted at the earlier of Day 7 or discharge. Post-admission follow-up included clinic visits every 4 weeks through to 24 weeks for the occurrence of readmissions and death. Evaluations at 8 and 24 weeks included dyspnoea assessment, physical examination, and laboratory assessments. Patients who withdrew from the study drug prior to 24 weeks were still followed up for 24 weeks. Patients who completed the 24 weeks of double-blind phase were given the option of continuing open-label treatment with active medication for up to 24 weeks. Approval was obtained from the ethics committee of each participating institution, and the study conformed to the principles of the Declaration of Helsinki. The study was governed by a Steering Committee and monitored by an independent Data and Safety Monitoring Committee.

Randomized patients underwent full clinical evaluation including physical examination, collection of patient's self-report of dyspnoea severity by a Visual analogue scale (VAS), 6 min walk test, and physician's assessment of HF signs and symptoms. Other information obtained included demographic data, date of diagnosis of HF and pre-admission history (previous HF-related admissions), New York Heart Association (NYHA) functional class, self-reported CV risk factors, co-morbidities, and medications history. Investigations performed included chest X-ray, 12-lead electrocardiogram, and echocardiography. Blood samples were drawn for fasting blood sugar, fasting lipid profile, electrolyte, urea and creatinine, and full blood count. In addition to the aforementioned blood tests, blood was collected from each patient for NT-pro-BNP and galectin-3 assays. A sensitive and specific

non-radioactive immunoluminometric (ILMA) assay based on competitive ligand binding was used. The blood was transfused into ethylenediaminetetraacetic acid tubes, and samples were immediately centrifuged; plasma was separated and then stored at −80°C until assayed. Samples were transported from the various centres in dry ice and shipped to the Hatter Institute for Cardiovascular Research in Africa for the assay. Plasma NT-pro-BNP was measured by a standard electrochemiluminescence immunoassay. NT-pro-BNP levels were measured from a banked aliquot from stored blood samples using BNP EIA fragment kit from Biomedica Gruppe. Galectin-3 was assayed using human galectin-3 enzyme linked immunosorbent assay for *in vitro* diagnostic use (Human Galectin-3 Platinum ELISA, eBiosciences). Both assays were performed at the Hatter Institute for Cardiovascular Research in Africa.

Statistical methods

The analysis population has been restricted to subjects with available baseline biomarker data. Summary statistics for continuous variables may include the number of non-missing observations, mean and standard deviation, median, first and third quartile (Q1, Q3), and minimum and maximum, as appropriate. Categorical variables are presented with absolute and/or relative frequencies (percentages). Relative frequencies are based on all non-missing observations for the corresponding variable if not stated otherwise. The summary statistics of the biomarker parameters additionally include the geometric mean and its corresponding 95% confidence interval (CI).

Missing values for the 6 min walk test distance and dyspnoea VAS were imputed by linear interpolation between non-missing observations at the closest visit before and after the missing value occurred; where no following non-missing value is available, the last available preceding value was carried forward. For subjects who died, values at visits following a death were imputed as zero for 6 min walk test distance and as the worst observed value for dyspnoea VAS. For echocardiographic parameters, values following a death were imputed as baseline plus or minus the worst observed change from baseline across all subjects. Clinically implausible values of TAPSE above 50 mm have been set to missing for the statistical analysis. Biomarker values below the limit of detection (LOD) have been replaced by 0.5*LOD, and values above the upper limit of quantification (ULOQ) have been replaced by 1.5*ULOQ.

Analysis of covariance methods have been applied to evaluate treatment differences for changes from baseline with treatment effect adjusted for the corresponding baseline values. Results are presented as least square mean differences with 95% CIs and *P*-value. For the biomarker parameters, analysis of covariance was applied on log-transformed values with adjustment for log-transformed baseline values. The resulting treatment difference is presented as the ratio of the baseline adjusted geometric means with corresponding 95% CIs.

Baseline biomarker values and changes from baseline have been further evaluated for their association with CV death or rehospitalization for HF through Week 24 and with CV death through Week 24 as well as with selected echocardiographic parameters. These associations were evaluated by fitting Cox proportional hazards models and presenting hazard ratios, 95% CIs, and *P*-values. In addition, number of events and the Kaplan–Meier estimate of the event rate are presented for each time-to-event endpoint. For change from Week 24 to baseline for 6 min walk test distance, dyspnoea VAS, LVEF, LVEDD, LVESD, and TAPSE, linear regression models have been applied to evaluate the association with baseline values as well as with change at Week 24 for the two biomarkers. Models evaluating the association with change from baseline have been adjusted for the baseline values of the respective biomarker. Effect sizes are presented as mean differences with 95% CIs and *P*-values.

All statistical analyses have been performed using SAS® 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

The BAHEF trial was performed in nine centres in six African countries (Mozambique, South Africa, Nigeria, Kenya, Uganda, and Senegal). Eighty patients had baseline biomarker data available for analysis, and their baseline characteristics are outlined in *Table 1*. Demographic characteristics of the patients were similar across participating countries. The randomization was blocked by study centre. Thus, randomization to the two study arms was balanced within country.

The mean age of the group (restricted biomarker subset) was 52.6 ± 15.8 years, with 52.5% being women. Seventy-three per cent were African/Black, and 24% were coloured or mixed race. The mean period from admission to randomization was 63.3 ± 27.6 h. Most of the patients had hypertension (65.8%) and idiopathic dilated cardiomyopathy (15.2%), while ischaemic heart disease was present in only 5.1%. Most patients (75.0%) also are in NYHA functional class III and IV. Baseline characteristics were similar in the active and placebo groups.[18]

The mean LVEF at baseline for the overall group was 24.1% with no difference between those on HYIS and placebo (*Table 2*). The baseline mean LVEDD was 62.7 ± 8.95 mm while the change from baseline to Week 24 was −0.01 ± 10.7 mm. For the LVESD, the mean was 55.8 ± 9.1 mm with a mean change from baseline to Week 24 of −5.8 ± 9.47 mm. The mean TAPSE at baseline was 20.9 ± 5.73 with a mean change between baseline and Week 24 of 0.2 ± 10.55. There was no

Table 1 Baseline characteristics of the study population by baseline biomarker median split (restricted to biomarker subset)

Characteristic	Statistic	NT-pro-BNP ≥ median (2882.25) (*N* = 40)	NT-pro-BNP < median (2882.25) (*N* = 40)	Galectin-3 ≥ median (5.805) (*N* = 40)	Galectin-3 < median (5.805) (*N* = 40)	Overall (*N* = 80)
Age (years)	Mean (SD)	52.5 (16.01)	52.8 (15.74)	48.7 (13.98)	56.6 (16.63)	52.6 (15.77)
Male sex	%	47.5	47.5	55.0	40.0	47.5
Weight (kg)	Mean (SD)	72.2 (16.12)	81.2 (21.10)	81.6 (21.29)	71.9 (15.66)	76.6 (19.12)
Primary cause of heart failure						
Ischaemic heart disease	%	5.0	5.3	10.0	0.0	5.1
Hypertension	%	65.0	66.7	65.0	66.7	65.8
Idiopathic	%	17.5	12.8	25.0	5.1	15.2
Valvular cause	%	2.5	0.0	0	2.6	1.3
NYHA class (screening)						
I	%	0	5.3	0	5.0	2.1
II	%	21.4	21.1	18.5	25.0	21.3
III	%	46.4	63.2	59.3	45.0	52.1
IV	%	32.1	10.5	22.2	25.0	22.9
Diabetes	%	15.0	5.1	10.0	10.3	10.1
Atrial fibrillation	%	10.3	10.5	10.0	10.8	10.4
Ejection fraction (% screening)	Mean (SD)	21.7 (9.60)	28.1 (9.31)	23.4 (10.70)	25.9 (9.15)	24.7 (9.86)
LVIDD (cm screening)	Mean (SD)	6.3 (0.92)	6.2 (0.88)	6.3 (0.96)	6.2 (0.83)	6.3 (0.89)
Blood pressure						
Systolic (mmHg)	Mean (SD)	128.9 (15.01)	137.2 (19.06)	133.2 (18.46)	132.8 (16.82)	133.0 (17.55)
Diastolic (mmHg)	Mean (SD)	85.7 (12.65)	89.8 (14.16)	86.2 (14.49)	89.2 (12.44)	87.7 (13.50)
Laboratory values						
Sodium (mmol/L)		134.6 (5.94)	137.3 (3.40)	135.4 (5.90)	136.4 (3.91)	135.9 (5.00)
Potassium (mmol/L)		4.4 (0.89)	4.4 (0.82)	4.4 (0.82)	4.4 (0.89)	4.4 (0.85)
Urea (mmol/L)		7.9 (3.68)	6.1 (2.72)	7.7 (3.49)	6.2 (3.03)	7.0 (3.34)
Creatinine (μmol/L)		112.4 (27.76)	106.4 (40.71)	112.2 (37.14)	106.5 (32.52)	109.4 (34.83)
Haemoglobin (g/L)		119.3 (19.39)	124.7 (19.43)	124.4 (19.73)	119.5 (19.15)	122.0 (19.48)
Medication for heart failure						
Diuretic	%	73.7	84.6	75.0	83.8	79.2
ACE inhibitor	%	89.5	94.9	85.0	100.0	92.2
ARB	%	7.9	0	7.5	0	3.9
Beta-blocker	%	21.1	38.5	32.5	27.0	29.9
Carvedilol	%	15.8	17.9	22.5	10.8	16.9
Digoxin	%	18.4	17.9	15.0	21.6	18.2
Spironolactone	%	13.2	7.7	20.0	0	10.4
Race						
African or Black	%	78.9	67.6	54.1	92.1	73.3
Coloured or mixed race	%	18.4	29.7	40.5	7.9	24.0
Caucasian or White	%	2.6	2.7	5.4	0	2.7
Time from presentation to randomization (h)	Mean (SD)	61.2 (25.46)	65.4 (29.76)	67.2 (28.86)	59.4 (26.06)	63.3 (27.60)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LVEDD, left ventricular end diastolic diameter; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

Table 2 Changes from baseline to Week 24 in echocardiographic parameter—imputed—full analysis set (restricted to biomarker subset)

Measure	Statistic	Placebo (n = 39)	HYIS (n = 41)	Overall (n = 80)	LS mean difference (95% CI)	P-value
LV ejection fraction (%)						
Baseline	Mean (SD)	23.5 (7.96)	24.8 (11.27)	24.1 (9.76)		
	Median (Q1, Q3)	24.0 (19.0, 29.0)	24.0 (15.0, 34.0)	24.0 (17.8, 32.0)		
Change to Week 24	Mean (SD)	12.7 (14.44)	11.0 (14.51)	11.8 (14.41)	−1.3 (−7.7, 5.0)	0.6750
	Median (Q1, Q3)	11.0 (0.0, 27.0)	13.0 (0.0, 20.0)	12.0 (0.0, 24.0)		
Left ventricular end-diastolic diameter (mm)						
Baseline	Mean (SD)	62.7 (9.77)	62.6 (8.20)	62.7 (8.95)		
	Median (Q1, Q3)	62.0 (57.0, 71.0)	62.0 (56.0, 67.3)	62.0 (57.0, 69.9)		
Change to Week 24	Mean (SD)	0.9 (9.57)	−0.9 (11.71)	−0.0 (10.69)	−1.8 (−6.5, 2.9)	0.4447
	Median (Q1, Q3)	0.0 (−5.0, 5.0)	−1.0 (−7.0, 1.0)	0.0 (−5.8, 3.3)		
Left ventricular end-systolic diameter (mm)						
Baseline	Mean (SD)	56.2 (8.81)	55.3 (9.47)	55.8 (9.10)		
	Median (Q1, Q3)	55.5 (50.0, 62.0)	55.5 (46.0, 64.0)	55.5 (48.0, 62.8)		
Change to Week 24	Mean (SD)	−4.5 (8.84)	−7.1 (10.01)	−5.8 (9.47)	−2.6 (−6.9, 1.8)	0.2407
	Median (Q1, Q3)	−5.0 (−11.0, 1.0)	−6.0 (−14.0, −1.0)	−5.5 (−13.0, 0.0)		
Tricuspid annular plane systolic excursion (mm)						
Baseline	Mean (SD)	20.8 (6.00)	21.0 (5.65)	20.9 (5.73)		
	Median (Q1, Q3)	19.0 (17.0, 24.0)	22.0 (18.0, 25.4)	20.7 (17.0, 25.0)		
Change to Week 24	Mean (SD)	1.2 (8.47)	−0.6 (12.12)	0.2 (10.55)	−1.7 (−8.6, 5.3)	0.6282
	Median (Q1, Q3)	5.0 (0.0, 7.0)	0.0 (−0.4, 3.0)	0.0 (0.0, 7.0)		

CI, confidence interval; HYIS, hydralazine/isosorbide dinitrate; LS, least square; LV, left ventricular; Q1, Q3, first and third quartile; SD, standard deviation.

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Table 3 Changes in biomarkers from baseline to follow-up by treatment—full analysis set (restricted to biomarker subset)

Measure	Statistic	Placebo (n = 39)	HYIS (n = 41)	Overall (n = 80)	Model-adjusted treatment difference (95% CI)	P-value
NT-pro-BNP (pmol/L)						
Baseline	*N*	39	41	80		
	Mean (SD)	4318.41 (2926.860)	3250.55 (2665.675)	3771.13 (2829.664)		0.0526
	Median	3476.00	2158.50	2882.25		
	Q1, Q3	2149.00, 6052.00	1246.00, 4461.00	1621.75, 4822.50		
	Min, max	358.5, 9600.0	430.5, 9600.0	358.5, 9600.0		
	Geom. mean	3332.18	2303.24	2757.58		
	95% CI of GM	2579.71, 4304.14	1742.88, 3043.76	2280.28, 3334.79		
	n (%) < LOD (171 pmol/L)	0 (0%)	0 (0%)	0 (0%)		
	n (%) > ULOQ (6400 pmol/L)	7 (17.9%)	4 (9.8%)	11 (13.8%)		
Follow-up	*N*	30	33	63		
	Mean (SD)	1484.23 (1629.811)	1172.05 (1136.942)	1320.71 (1390.800)		
	Median	711.25	679.00	703.50		
	Q1, Q3	449.00, 1608.50	397.50, 1815.50	418.00, 1815.50		
	Min, max	211.5, 6314.5	85.5, 4599.5	85.5, 6314.5		
	Geom. mean	931.22	771.32	843.71		
	95% CI of GM	653.14, 1327.70	551.43, 1078.89	664.99, 1070.47		
	n (%) < LOD (171 pmol/L)	0 (0%)	1 (3.0%)	1 (1.6%)		
	n (%) > ULOQ (6400 pmol/L)	0 (0%)	0 (0%)	0 (0%)		
Change to Week 24	*N*	30	33	63	1.10 (0.73, 1.66)	0.6425
	Mean (SD)	−2697.75 (2476.963)	−1859.82 (2467.246)	−2258.83 (2487.881)		
	Median	−2127.50	−983.00	−1472.00		
	Q1, Q3	−3615.00, −1097.00	−2450.00, −286.50	−3144.00, −513.50		
	Min, max	−9009.0, 717.5	−8712.0, 287.5	−9009.0, 717.5		
	Geom. mean	0.28	0.37	0.33		
	95% CI of GM	0.21, 0.39	0.28, 0.49	0.26, 0.40		
Galectin-3 (ng/mL)						
Baseline	*N*	39	41	80		
	Mean (SD)	7.42 (4.628)	9.06 (9.737)	8.26 (7.680)		0.8117
	Median	5.88	5.72	5.80		
	Q1, Q3	3.94, 10.20	3.70, 9.07	3.71, 9.65		
	Min, max	1.8, 24.1	1.9, 45.0	1.8, 45.0		
	Geom. mean	6.23	6.47	6.35		
	95% CI of GM	5.12, 7.58	5.09, 8.22	5.45, 7.40		
	n (%) < LOD (0.29 ng/mL) [1]	0 (0%)	0 (0%)	0 (0%)		
	n (%) > ULOQ (30 ng/mL)	0 (0%)	2 (4.9%)	2 (2.5%)		
Follow-up	*N*	30	32	62		
	Mean (SD)	6.69 (8.142)	5.99 (3.447)	6.33 (6.138)		
	Median	4.37	4.83	4.77		
	Q1, Q3	3.02, 7.09	3.64, 6.70	3.42, 6.80		
	Min, max	2.1, 45.0	2.8, 17.9	2.1, 45.0		
	Geom. mean	4.94	5.31	5.12		
	95% CI of GM	3.84, 6.35	4.48, 6.29	4.43, 5.93		
	n (%) < LOD (0.29 ng/mL)	0 (0%)	0 (0%)	0 (0%)		
	n (%) > ULOQ (30 ng/mL) [1]	1 (3.3%)	0 (0%)	1 (1.6%)		
Change to Week 24	*N*	30	32	62	1.05 (0.81, 1.36)	0.6997

(*Continues*)

Table 3 (continued)

Measure	Statistic	Placebo (n = 39)	HYIS (n = 41)	Overall (n = 80)	Model-adjusted treatment difference (95% CI)	P-value
	Mean (SD)	0.20 (6.696)	−1.59 (7.505)	−0.72 (7.125)		
	Median	−0.36	−0.28	−0.28		
	Q1, Q3	−3.06, 0.99	−1.60, 1.17	−2.78, 0.99		
	Min, max	−12.0, 26.1	−39.0, 9.4	−39.0, 26.1		
	Geom. mean	0.91	0.93	0.92		
	95% CI of GM	0.72, 1.16	0.76, 1.15	0.79, 1.08		

CI, confidence interval; HYIS, hydralazine/isosorbide dinitrate; LOD, limit of detection; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; ULOQ, upper limit of quantification; Q1, Q3, first and third quartile; SD, standard deviation.

difference between HYIS and placebo in terms of change from baseline to Week 24 for LVEF, LVEDD, LVESD, and TAPSE (*Table 2*).

The biomarker levels and their change from baseline to follow-up by treatment are shown in *Table 3*. The mean baseline NT-pro-BNP was 3771.13 ± 2829.66 pmol/L dropping down to 1320.71 ± 1390.80 pmol/L by Week 24. The mean change in NT-pro-BNP from baseline to Week 24 was −2258.83 ± 2487.88 with no difference between HYIS and placebo (P = 0.6425). For galectin-3, the mean at baseline was 8.26 ± 7.68 ng/mL and came down to 6.33 ± 6.14 by Week 24 of follow-up. The mean change in galectin-3 level was −0.72 ± 7.13, also with no difference between HYIS and placebo (P = 0.6997).

The total number of CV death or HF hospitalization through 24 weeks was 9/80 (11.6%) while CV deaths through Week 24 was 5/80 (6.8%). Using fitting Cox proportional hazards models, the associations of baseline biomarker values and changes at Week 24 with CV death or hospitalization for HF and with CV death are shown in *Table 4*. Higher baseline NT-pro-BNP and galectin-3 values were associated with higher risk of combined CV death or HF hospitalization through Week 24 (P-values = 0.0328 and 0.0001, respectively), but only galectin-3 at baseline predicted CV death through Week 24 (P = 0.0042). Galectin-3 at baseline and NT-pro-BNP change to 24 weeks predicted dyspnoea VAS change Week 24 to baseline using linear regression models.

For LVEF, LVEDD, LVESD, and TAPSE, linear regression models were applied to evaluate the association with baseline values as well as with change at Week 24 for the two biomarkers (*Table 5*). Models evaluating the association with change from baseline have been adjusted for the baseline values of the respective biomarker. While NT-pro-BNP at baseline only predicted change (Week 24 to baseline) in LVEDD, galectin-3 at baseline predicted changes (Week 24 to baseline) in all the tested markers of LV remodelling (LVEF, LVEDD, and LVESD) and RV remodelling (TAPSE).

Discussion

The BAHEF study showed that in sub-Saharan Africa, HF affects men and women who are relatively young (mid-50s) and is mostly caused by hypertension and not ischaemic heart disease, as is seen in Western countries.[19] Similar findings were recently reported in the sub-Saharan Africa Survey of Heart Failure (THESUS-HF) registry.[20] Both studies showed that these patients had predominantly systolic dysfunction and low incidence of atrial fibrillation.

The African-American Heart Failure Trial (A-HeFT)[21] was similar to BAHEF study but focused on chronic HF instead of AHF. Despite the difference in the study population, the mean ages of the patients were similar, both for the overall

Table 4 Associations of biomarker baseline values and changes at Week 24 with primary endpoints

Outcome[a]	Covariate	Effect size for a change of	Effect size (95% CI)	*P*-value	No. of events (KM rate)
CV death or HF hospitalization through Week 24	NT-pro-BNP at baseline	Doubling	2.12 (1.06, 4.22)	0.0328	9/80 (11.6%)
	Galectin-3 at baseline	Doubling	2.81 (1.65, 4.79)	0.0001	9/80 (11.6%)
CV death through Week 24	NT-pro-BNP at baseline	Doubling	2.21 (0.85, 5.71)	0.1027	5/80 (6.8%)
	Galectin-3 at baseline	Doubling	2.84 (1.39, 5.79)	0.0042	5/80 (6.8%)
6MWT change Week 24 to baseline (imputed)	NT-pro-BNP at baseline	Doubling	10.78 (−11.86, 33.43)	0.3538	
	NT-pro-BNP ratio Week 24 to baseline	Doubling	−14.91 (−34.60, 4.77)	0.1431	
	Galectin-3 at baseline	Doubling	−26.01 (−54.27, 2.25)	0.0754	
	Galectin-3 ratio Week 24 to baseline	Doubling	−16.34 (−43.50, 10.82)	0.2433	
Dyspnoea VAS change Week 24 to baseline (imputed)	NT-pro-BNP at baseline	Doubling	−2.27 (−7.65, 3.12)	0.4119	
	NT-pro-BNP ratio Week 24 to baseline	Doubling	−3.42 (−6.01, −0.82)	0.0122	
	Galectin-3 at baseline	Doubling	−14.01 (−19.94, −8.08)	<0.0001	
	Galectin-3 ratio Week 24 to baseline	Doubling	0.36 (−3.53, 4.24)	0.8583	

6MWT, 6 min walk test; CI, confidence interval; CV, cardiovascular; HF, heart failure; KM, Kaplan–Meier; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; VAS, visual analogue scale.
[a]Effect sizes shown are hazard ratios for time-to-event outcomes and mean differences for continuous outcomes. In case of continuous outcomes, estimates have been adjusted for the respective baseline value.

BAHEF patients and for the restricted biomarker subset group. They both had similar mean LVEF of 24% and had most of the patients in NYHA functional class III and IV. The mean LVEDD at recruitment was 62.7 ± 8.8 mm, similar to 65 ± 9 mm in A-HeFT. However, the A-HeFT patients had less hypertension and higher incidence of diabetes mellitus and ischaemic heart disease as compared with BAHEF.

We studied the relationship between NT-pro-BNP and galectin-3 and outcomes in this cohort. We are not aware of similar study from sub-Saharan Africa. We found both NT-pro-BNP and galectin-3 at baseline to predict the combined outcome of CV death or HF hospitalization through Week 24, with galectin-3 more predictive than NT-pro-BNP (*P*-values = 0.0001 and 0.0328, respectively). When the outcome of CV death alone was assessed, only galectin-3 at baseline predicted it through Week 24 (*P* = 0.0042). This is similar to the findings in the Pro-BNP Investigation of Dyspnea in the Emergency department (PRIDE) study.[14] They have shown that serum galectin-3 levels were elevated in patients with AHF and are prognostic of adverse outcomes over a 60 day period after presentation. Similar to our study, they also showed that galectin-3 was able to identify those HF patients at risk for short-term death or the combination of death or readmission within 60 days better than NT-pro-BNP.[14] In a meta-analysis of three studies and 892 patients that included 582 patients from Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) study, 181 patients from the PRIDE study, and 129 patients from University of Maryland Pro-BNP for Diagnosis and Prognosis in Patients Presenting with Dyspnea, de Boer *et al*.[22] reported that patients with elevated galectin-3 above 17.8 ng/mL were nearly three times as likely to suffer short-term rehospitalization (odds ratio 2.80, 95% CI 1.41–5.57, and 3.01, 95% CI 1.79–5.05, for 30 and 90 days of readmissions, respectively). Also, baseline galectin-3 was a predictor of rehospitalization even after adjustment for age, gender, estimated glomerular filtration rates, NYHA functional class, LVEF, and NT-pro-BNP levels. The authors of this meta-analysis concluded that in AHF, an elevated galectin-3 during an emergency department visit, hospital admission, or at hospital discharge is independently associated with early HF readmission. These findings are of clinical significance because the results of these studies suggest that galectin-3 may identify AHF patients with elevated risk for death and rehospitalization independent of the severity of signs and symptoms at presentation.

Identification of those AHF patients at highest risk by combined assessment of serum markers may help to tailor the most appropriate treatment strategy on a more individualized basis.

Galectin-3 at baseline also strongly predicted dyspnoea VAS change Week 24 to baseline using linear regression models in this study. In a study of 115 consecutive patients with acute dyspnoea, Shah and colleagues[15] found that dyspnoeic patients with HF and galectin-3 concentrations higher than the median value of 15.0 (11.1–19.7) had a 63% 4 years of mortality rate, compared with patients with concentrations lower than 11.0 (9.1–14.4) who had a 37% mortality rate (*P* = 0.003).

In this study, we also examined the associations between biomarker levels and cardiac structure and function through markers of LV and RV remodelling. While NT-pro-BNP at

Table 5 Association of biomarker baseline values and changes at Week 24 with echocardiographic parameters

Outcome[a]	Covariate	Effect size for a change of	Effect size (95% CI)	*P*-value
LVEF change Week 24 to baseline (imputed)	BNP at baseline	Doubling	−2.58 (−5.22, 0.06)	0.0589
	BNP ratio Week 24 to baseline	Doubling	−1.34 (−3.76, 1.08)	0.2811
	Galectin-3 at baseline	Doubling	−5.15 (−8.19, −2.10)	0.0014
	Galectin-3 ratio Week 24 to baseline	Doubling	0.04 (−3.48, 3.57)	0.9807
LVEDD change Week 24 to baseline (imputed)	BNP at baseline	Doubling	2.74 (0.94, 4.53)	0.0038
	BNP ratio Week 24 to baseline	Doubling	0.07 (−1.70, 1.85)	0.9359
	Galectin-3 at baseline	Doubling	4.95 (2.88, 7.02)	<0.0001
	Galectin-3 ratio Week 24 to baseline	Doubling	0.21 (−2.30, 2.71)	0.8719
LVESD change Week 24 to baseline (imputed)	BNP at baseline	Doubling	1.62 (−0.17, 3.41)	0.0795
	BNP ratio Week 24 to baseline	Doubling	−0.57 (−2.33, 1.18)	0.5251
	Galectin-3 at baseline	Doubling	3.51 (1.41, 5.61)	0.0016
	Galectin-3 ratio Week 24 to baseline	Doubling	−1.11 (−3.49, 1.27)	0.3633
TAPSE change Week 24 to baseline (imputed)	BNP at baseline	Doubling	−0.95 (−3.73, 1.82)	0.5049
	BNP ratio Week 24 to baseline	Doubling	−0.54 (−2.23, 1.15)	0.5365
	Galectin-3 at baseline	Doubling	−5.00 (−7.63, −2.38)	0.0007
	Galectin-3 ratio Week 24 to baseline	Doubling	−0.61 (−2.75, 1.53)	0.5802

BNP, brain natriuretic peptide; CI, confidence interval; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; TAPSE, tricuspid annular plane systolic excursion.
[a]Effect sizes shown are mean differences for continuous outcomes. Estimates have been adjusted for the respective baseline value.

baseline only predicted change (Week 24 to baseline) in LVEDD, galectin-3 at baseline predicted changes (Week 24 to baseline) in all the tested markers of LV remodelling (LVEF, LVEDD, and LVESD) and RV remodelling (TAPSE). In a study of hypertensive African subjects, Ojji and colleagues showed that NT-pro-BNP was significantly associated with LVEF ($P = 0.01$) but not with TAPSE.[23]

They also found that NT-pro-BNP concentrations were not associated with LV mass index, interventricular septal wall thickness, or posterior wall thickness in diastole, which is similar to findings of other workers.[24]

In the PRIDE study subanalysis,[15] to determine relationships between galectin-3 levels and cardiac structure, the authors showed that galectin-3 levels were significantly associated with echocardiographic markers of LV filling and diastolic function and valvular regurgitation. Similar to our study, they also observed significant association between galectin-3 and poor RV systolic function (as reflected in fractional area change). In this study, we used TAPSE to assess RV systolic dysfunction. Poor RV systolic function in AHF may reflect elevated LV filling pressures; thus, the associations between galectin-3 levels and markers of poor RV performance reflect similar associations between galectin-3 and elevated left-sided pressures. It is also possible that similar processes occurring in the LV (remodelling, fibrosis, and hypertrophy) may be occurring in the RV. Indeed, the role of RV structure and function in short-term and longer-term outcomes as well as remodelling in AHF is underappreciated, and our findings underscore the need for further research to determine the importance of the RV in AHF. As suggested there, galectin-3 may play a significant role in fibrosis modulation during the early phases of myocardial damage such as occurring in AHF, possibly explaining the association of galectin-3 and remodelling observed in the current study.

We suggest that our results provide bases for confirmation through a much bigger study on the role of these biomarkers in sub-Saharan African patients with AHF. Development of bedside kits for NT-pro-BNP and galectin-3 for risk stratification and referral to appropriate facility for immediate care will go a long way in improving morbidity and mortality in these patients, especially in Africa where resources are scarce.

This substudy shares the same limitations with the overall BAHEF study.[18] In addition and specific to biomarker analysis, the relatively small number of patients, with relatively limited numbers of events, may be a limitation, as a larger cohort would allow for increased scrutiny of short-term outcomes. Because of lack of complete data, we were unable to assess the relationship of these biomarkers with LV diastolic function. Finally, patients were enrolled based on admission diagnosis and treatment for AHF. While this is highly representative of clinical practice, bias may have been introduced in those patients where AHF was incorrectly diagnosed, as galectin-3 is known to be elevated in other causes of acute dyspnoea.[25]

Conclusions

In conclusion, we have shown that in sub-Saharan African patients with AHF, both NT-pro-BNP and galectin-3 at baseline predicted combined CV death or HF hospitalization. For cardiac remodelling, galectin-3 at baseline predicted changes

(Week 24 to baseline) in all the tested markers of LV remodelling and RV remodelling, whereas NT-pro-BNP at baseline only predicted change (Week 24 to baseline) in LVEDD. Galectin-3 provided important and significant prognostic value in identifying patients with AHF at elevated risk for subsequent HF morbidity and mortality.

Conflict of interest

None of the authors in this manuscript has any conflict of interest as regards this manuscript.

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