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Bi treatment with hydralazine/nitrates vs. placebo in Africans admitted with acute HEart Failure (BA-HEF)

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Aims Patients with acute heart failure in Africa are rarely being treated with a hydralazine/nitrates combination. Therefore the effect of this treatment was studied here

Methods and results The study was planned to enrol 500 patients during an acute heart failure (HF) admission, from nine sub-Saharan African countries. Patients were randomized in a double-blind manner to receive 50 mg hydralazine/20 mg isosorbide dinitrate (HYIS) t.i.d. or matching placebo for 24 weeks followed by open label HYIS for all patients. The study was terminated after 147 patients were enrolled due mostly to issues with recruitment into a prospective, placebo-controlled study. Most patients were recruited from Mozambique, South Africa, Kenya, and Uganda. The primary endpoint of death or HF readmission through 24 weeks was neutral [hazard ratio (HR) 1.05, 95% confidence interval (CI) 0.48–2.27, $P = 0.90$] in the 133 randomized patients included in the analyses. There were non-signficant effects in favour of HYIS in secondary endpoints including change in dyspnoea severity at day 7 or discharge, decrease in systolic blood pressure, greater decrease in weight, and increase in 6-min walk test distance at week 24. There were also small changes in echocardiographic indices of cardiac size and function in favour or HYIS, but none was significant.

Conclusion The BA-HEF trial demonstrated challenges in recruiting the expected number of patients with acute HF in a number of African countries, which highlights the need for strategic logistic support.
Trial registration: NCT01822808.

Keywords Treatment • Acute heart failure • Hydralazine • Nitrates • Africa

Introduction

Acute heart failure (AHF) is one of the most common reasons for admission to hospital and a major driver for health-related costs worldwide. A number of recent studies from Soweto, South Africa;[1] Abeokuta, Nigeria;[2] Abuja, Nigeria;[3] and Dar-es-Salaam, Tanzania[4] have shown the prevalence to be high, with a 6-month mortality >15%, despite the population being two decades younger than those in studies of higher income regions.[5,6]

Acute heart failure exacts a heavy social and economic burden on families and society in Africa.[2] In contrast to high-income countries where AHF affects patients with an average age of >70 years,

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the THESUS-HF registry[7] has shown that in sub-Saharan Africa AHF affects men and women in the most productive years of life, at an average age of 52.3 years, and is mostly caused by hypertension and not ischaemic heart disease (IHD). The THESUS-HF registry has also observed the use of a hydralazine/isosorbide dinitrate (HYIS) combination in <5% of patients, despite it being a Class IIb B indication for Black African patients with chronic HF,[8] and shown in previous studies to be especially effective in African Americans with chronic HF and reduced EF.[9–11]

The BA-HEF study was planned based on the limited evidence-based therapy for AHF altogether and because HYIS is available as a relatively affordable generic in most sub-Saharan countries. The purpose of the study was to examine the short-term (6 months) effects of HYIS in patients admitted for AHF in sub-Saharan Africa and treated with HYIS during the last days of admission through 6 months. The doses of HYIS used in the BA-HEF study were slightly lower than those used in the AHeFT study, and were introduced slowly through careful up-titration (see below) in order to avoid hypotension.

Methods

Patients and data collected

The BA-HEF study was a prospective, multicentre, randomized double-blind study which aimed to recruit a total of 500 patients during an admission for AHF from countries in the southern, eastern, central, and western regions of sub-Saharan Africa. AHF was diagnosed based on symptoms and signs, supported by echocardiographic findings, and was confirmed by a cardiologist. Inclusion criteria were presenting at ≥18 years of age, hospital admission for AHF, as defined by the presence of acute dyspnoea, and the presence of HF signs by physical examination with at least two of the following: rales, oedema, elevated jugular venous pressure (JVP), hepatomegaly, and ascites; LVEF <45% assessed by echocardiography or another method within the previous 12 months; background therapy with at least an ACE inhibitor or ARB and beta-blocker (unless a beta-blocker is contraindicated due to severe volume overload, low output HF, or cardiogenic shock); and availability for regular follow-up. Exclusion criteria were any intravenous treatment for HF, except i.v. furosemide (e.g. i.v. inotropes, vasopressors, nitrates, or nesiritide) at the time of screening; systolic blood pressure (BP) <100 mmHg; plan for revascularization; presentation >96 h after admission; reversible aetiology of AHF such as myocarditis, acute myocardial infarction, arrhythmia; hypertrophic obstructive cardiomyopathy, restrictive or constrictive cardiomyopathy, severe congenital heart disease, or significant stenotic valvular disease; marked renal impairment (defined by creatinine >3 mg/dL) at screening or on any type of dialysis; known cholestasis (total bilirubin >3 mg/dL) or increased ammonia levels at screening; known sensitivity or intolerance to ACE inhibitors or allergy to organic nitrates; severe cerebrovascular disease, including acute stroke or cerebral ischaemia; women who were pregnant or lactating; or history or presence of any other diseases (i.e. including malignancies or AIDS) with a life expectancy of <12 months.

Primary and secondary endpoints

The study was designed to investigate the effect of the combination of hydralazine/isosorbide dinitrate (HYIS) on the rate of the primary endpoint: all-cause death or re-admission for HF during 24 weeks of therapy. The intended sample size was estimated to provide 80% power to detect a hazard ratio (HR) of 0.61 assuming a 35% event rate in the placebo group.

The HYIS combination was also compared with placebo with respect to the following pre-specified secondary endpoints: (i) change in symptoms of HF from baseline to 7 days post-randomization or discharge, as assessed by dyspnoea severity and global well-being on a visual analogue scale (VAS); (ii) change in systolic BP from baseline to 7 days post-randomization or discharge, and at 8 weeks and 24 weeks post-randomization; (iii) functional status assessed by the 6-min walk test (6MWT) at 7 days post-randomization or discharge, and at 8 weeks and 24 weeks post-randomization; (iv) changes in markers of renal function [serum creatinine, urea, and estimated glomerular filtration rate (eGFR)] from baseline to 7 days post-randomization or discharge, and at 24 weeks post-randomization; and (v) change in LV dimensions and LVEF from baseline to 24 weeks post-randomization.

Approval was obtained from the ethics committee of each participating institution, and the study conformed to the principles of the Declaration of Helsinki. All patients gave written, informed consent prior to participation. The study was governed by a Steering Committee and monitored by an independent Data and Safety Monitoring Committee. The membership of both committees is detailed in Appendix 1. Investigators were trained through investigator meetings, and study personnel monitored study conduct through remote monitoring, telephone contacts, and site visits. The study is registered at Clinicaltrials.gov as NCT01822808.

Study visits

Within 96 h of admission for AHF, and during the admission, patients were screened and randomized into the study if the inclusion criteria were met. Patients' self-report of dyspnoea severity by VAS was measured and a 6MWT was performed. Patients 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 t.i.d. or placebo (*Figure 1*). The study drug was provided by Sandoz SA. The dose selection and careful up-titration were done in order to avoid hypotension in these patients during and immediately after an AHF admission. Patients received standard HF therapy at the discretion of their treating physician and according to evidence-based guideline recommendations (ACE inhibitors, ARBs, beta-blockers, aldosterone antagonists, and diuretics). Patients were followed by clinic visit through 6 months for the occurrence of readmissions and death. Patients who completed the 24-week double-blind phase were given the option of continuing open-label treatment with active medication for up to 24 weeks.

Statistical methods

Events reported by investigators were reviewed in a blinded manner by two independent cardiologists. Time-to-event endpoints, including the primary outcome, were compared between treatment groups on an intention-to-treat basis using a log-rank test. Kaplan–Meier estimates of event rates and associated 95% confidence intervals (CIs) are presented along with HRs and associated 95% CIs from Cox regression models that included only the treatment effect. The proportional hazards assumption was tested post-hoc through inclusion of a treatment × time interaction effect in the model. Patients were censored at the earlier of the last contact date or the time period of interest.

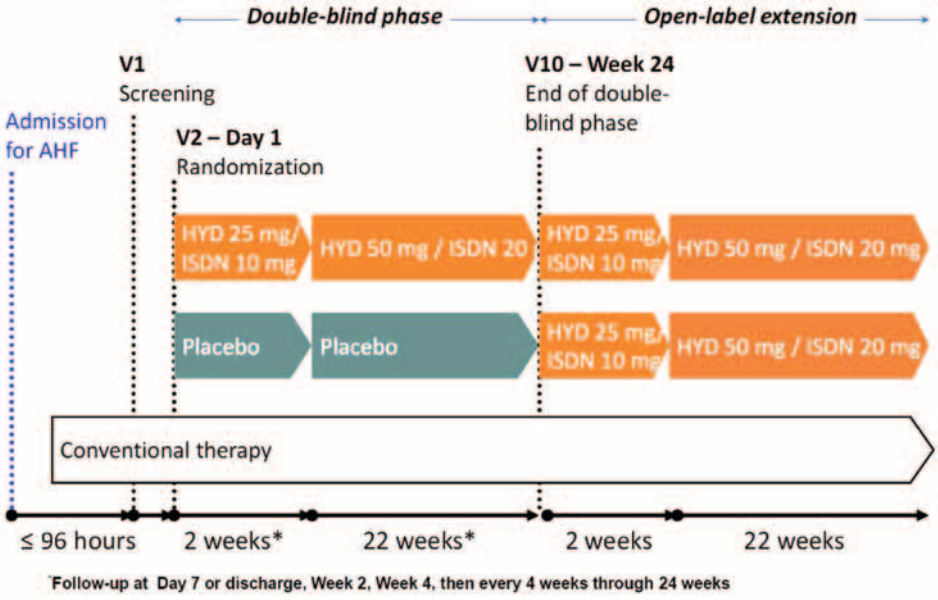

Figure 1 Schematic of the study design. AHF, acute heart failure.

For continuous outcomes, mean and standard deviation (SD) and/or median and first and third quartiles, and absolute and relative frequencies for categorical variables, are presented. The geometric mean and corresponding 95% CIs are also included for secondary laboratory endpoints that were log-transformed. Missing values were imputed using linear interpolation between nearest flanking non-missing values or through last observation carried forward (LOCF) where no following non-missing value was available. Values following a death were imputed as the worst reported score for dyspnoea and general well-being VAS, as zero for the 6MWT distance, as the LOCF for vital signs and laboratory values, and as the baseline plus or minus the worst reported change across all subjects for echocardiographic measures. Changes from baseline were compared between treatment groups using analysis of covariance with adjustment for the baseline value; least square mean differences and associated 95% CIs are presented, or the ratio of the geometric means with adjustment for the log-baseline result. Post-hoc analyses exploring effects on rehospitalizations included a comparison of the number of HF hospitalizations, where death was included as an event, using negative binomial regression. Additionally, days in hospital or dead from randomization through the earlier of 168 days or end of follow-up was compared between treatment groups using a *t*-test; length of hospital stay was imputed with the overall median (5.5 and 7 days, respectively) for three initial hospitalizations and one rehospitalization missing the discharge date. Data from one site in Senegal were excluded from the analyses due to major protocol non-compliance. SAS® 9.3 (SAS Institute, Inc., Cary, NC, USA) was used for analyses.

Results

Twelve centres from nine African countries were invited to paticipate, of which nine centres from six African countries (Mozambique, South Africa, Nigeria, Kenya, Uganda, and Senegal) participated. Data for 14 randomized patients from one centre in Senegal were excluded due to non-compliance with the protocol. This issue was reported to the site's local ethics committee after being discovered during routine monitoring. From March 2012 to March 2015, a total of 619 patients were screened and subsequently 133 patients were randomized (*Figure 2*) at the remaining eight centres. The primary reasons for exclusion from the study were (i) lack of test results, e.g. echo or laboratory, available within 96 h of admission; (ii) kidney function too poor; (iii) lack of background treatment with an ACE inhibitor and/or beta-blocker; (iv) liver function too poor; and (v) not eligible due to low BP. The study had to be terminated prematurely due to low recruitment and expiry of the study medication. Although as described below some patients screened failed to meet eligibility criteria, as seen in *Figure 2*, most of the lag in enrolment was related to lower than expected screening rates, in this double-blind, prospective, randomized study. Efforts were made to overcome these enrolment challenges including repeat investigators' meetings, frequent calls to the sites, and site visits by study personnel and the study Principal Investigator.

Demographic characteristics of the patients were rather similar across participating countries, except with a higher proportion of patients of race other than Black African enrolled in South Africa (Supplementary material online, *Table S1*). The randomization was blocked by study centre, however, so randomization to the two study arms was balanced within each country.

Baseline characteristics of the study population by treatment group are outlined in *Table 1*. For convenience of comparison, the last two columns of *Table 1* contain the baseline characteristics from the A-HeFT study.[11] The mean age of the entire group was 53.2 ± 14.8 years, with 49.2% being female. The majority (66.7%) of patients had hypertension, while few (5.3%) had a history of IHD.

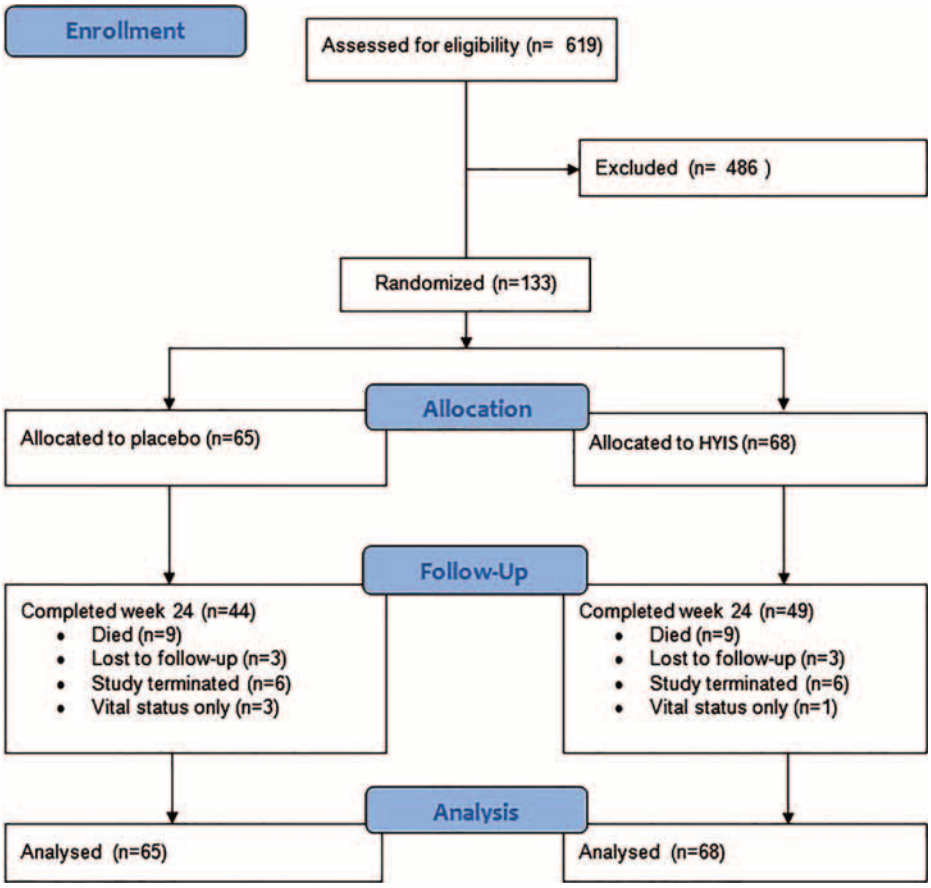

Figure 2 Study flow diagram. Excludes patients (25 screened, 14 randomized, 6 to placebo and 8 to hydralazine/isosorbide dinitrate) in one site in Senegal due to major protocol non-compliance.

Baseline characteristics were similar in the active and the placebo groups. Twenty-nine (22%) of the 133 patients were >65 years old, 26 (92.9%) of whom did not have a history of IHD. Of the 103 patients ≤65 years old, 98 (95.1%) had no history of IHD.

A total of 111 (83.5%) of the randomized patients either died or completed the study through week 24 (*Figure 2*). Twelve (9.0%) patients were discontinued prematurely when the study was terminated; 6 patients were lost to follow-up, and for 4 patients who had stopped attending visits, only the vital status at week 24 was obtained. The mean follow-up was 145.0 days. Over 60% of patients (63.5% and 67.6% in the placebo and HYIS groups, respectively) had a final dose of 50 mg hydralazine/20 mg isosorbide dinitrate t.i.d., while ~75% (73.8% and 77.9% in the placebo and HYIS groups, respectively) were on this dose at any point in the study.

The primary endpoint was not met, with a HR for death or HF readmission at 24 weeks of 1.05 (95% CI 0.48–2.27, $P = 0.90$). Fourteen patients in the HYIS arm died or had a HF readmission by week 24 as compared with 12 in the placebo arm. However, this was driven by an early potential benefit [at 60 days the HR was 0.49 (95% CI 0.18–1.32)] that decreased with time (*Figure 3A*). By day 60, 6 patients in the HYIS group and 11 patients in the placebo group had died or been hospitalized for HF, which was reflected by a statistically significant treatment × time interaction ($P = 0.0268$). Nine patients in each treatment group died by week 24: five in the HYIS group and nine in the placebo group from cardiovascular causes. One patient in the HYIS group and five patients in the placebo group died from a cardiovascular cause by day 60. There was a trend to benefit on cardiovascular mortality at 24 weeks where the HR was 0.51 (95% CI 0.17–1.52, $P = 0.22$) (*Figure 3B*).

In a post-hoc analysis we observed that patients in the placebo arm had more HF rehospitalizations per patient. The total number of events—deaths or HF readmissions—through week 24 was 18 in the HYIS arm vs. 26 in the placebo group, giving a rate ratio of 0.54 (95% CI 0.16–1.82, $P = 0.32$). Fifteen patients in the HYIS arm died or had a readmission for any cause by week 24 as compared with 17 in the placebo arm; however, patients in the placebo arm had more readmissions per patient. The total number of deaths or all-cause readmissions was 21 in the HYIS arm vs. 33 in the placebo arm ($P = 0.25$). The mean number of days dead or in hospital through 24 weeks was 18.3 ± 36.4 days [median 6.0, interquartile range (IQR) 3.0–8.5 days] in the HYIS group compared with 26.4 ± 45.9 days (median 7.0, IQR 5.0–15.0 days) in the placebo group ($P = 0.26$).

Table 1 Baseline characteristics of the study population

Characteristic	BA-HEF	AHeFT	
	Overall ($n = 133$)	Isosorbide dinitrate plus hydralazine ($n = 518$)	Placebo ($n = 532$)
Age, years, mean (SD)	53.2 (14.76)	56.7 (12.7)	56.9 (13.3)
Male sex, %	50.8	55.8	63.9
Weight, kg, mean (SD)	74.1 (19.1)	92.5 (21.4)	94.1 (25.5)
Primary cause of heart failure, %[a]			
Ischaemic heart disease	5.3	23.4	22.7
Hypertension	66.7	40.0	37.4
Idiopathic	13.7	24.5	27.6
Valvular cause	11.3	2.5	3.2
Other	–	9.7	9.0
NYHA class at screening, %			
I	1.1	0	0
II	22.2	0.2	0
III	55.6	96.7	94.7
IV	21.1	3.1	5.3
Diabetes, %	12.9	44.8	37.0
Atrial fibrillation, %	7.6	15.0	18.0
Cardiac resynchronization therapy, %	0.8	2.0	2.1
Implantable cardiac defibrillator, %	0	16.6	17.3
Ejection fraction at screening, %, mean (SD)	24.6 (10.2)	23.9 (7.3)	24.2 (7.5)
LVIDD, cm, at screening	6.3 (1.1)	6.5 (0.9)	6.5 (1.0)
Blood pressure, mmHg, mean (SD)			
Systolic	130.9 (19.6)	127.2 (17.4)	125.3 (18.1)
Diastolic	85.8 (14.8)	77.6 (10.3)	75.6 (10.5)
Medication for heart failure, %			
Diuretic	66.2	88.0	91.5
ACE inhibitor	85.7	69.4	69.5
ARB	9.8	17.2	16.5
Beta-blocker	43.6	74.1	73.5
Carvedilol	33.0	55.2	55.8
Digoxin	22.6	58.5	60.7
Spironolactone	27.8	40.2	37.6
Race, %			
African or Black	81.5	–	–
Coloured or mixed race	16.9	–	–
Caucasian or White	1.6	–	–
Time from presentation to randomization, hours, mean (SD)	73.1 (80.5)	–	–

LVIDD, left ventricular end-diastolic internal diameter.
[a]History of condition for BA-HEF.

The secondary endpoints showed non-significant trends in most outcomes in favour of HYIS vs. placebo. Dyspnoea improved by 1.6 mm more on a 100-mm VAS in the active group from an overall mean baseline of 57.7 mm, i.e. 3%, at day 7 or discharge ($P = 0.58$) (*Table 2*). General well-being improved to day 7 or discharge by 2.5 mm more in the active group ($P = 0.31$) from an overall mean baseline of 59.7 mm. The 6MWT distance improved at 24 weeks by 17.2 m more in the active group ($P = 0.48$) (*Table 2*). The overall mean baseline systolic BP was 126.7 mmHg, and decreased by 3.8 mmHg (95% CI −11.0 to 3.5) more in the active group ($P = 0.31$) at week 24 (*Figure 4*). The overall mean baseline weight was 73.7 kg and decreased by 2.7 kg (95% CI −5.52 to 0.13) more in the active group ($P = 0.06$) at 24 weeks (*Figure 5*). There was a similar drop in creatinine, a 13% larger drop in blood urea nitrogen (BUN; $P = 0.11$), and a 3.7 mL/min/1.73 m^2 greater improvement in eGFR ($P = 0.49$) at 24 weeks in the active group (*Table 3*). On echocardiographic evaluation, LVEF increased by 0.3% ($P = 0.92$), LV end-systolic diameter decreased by 2.0 mm ($P = 0.22$), and LV end-diastolic diameter decreased by 1.1 mm ($P = 0.55$) more in the active group (*Table 4*).

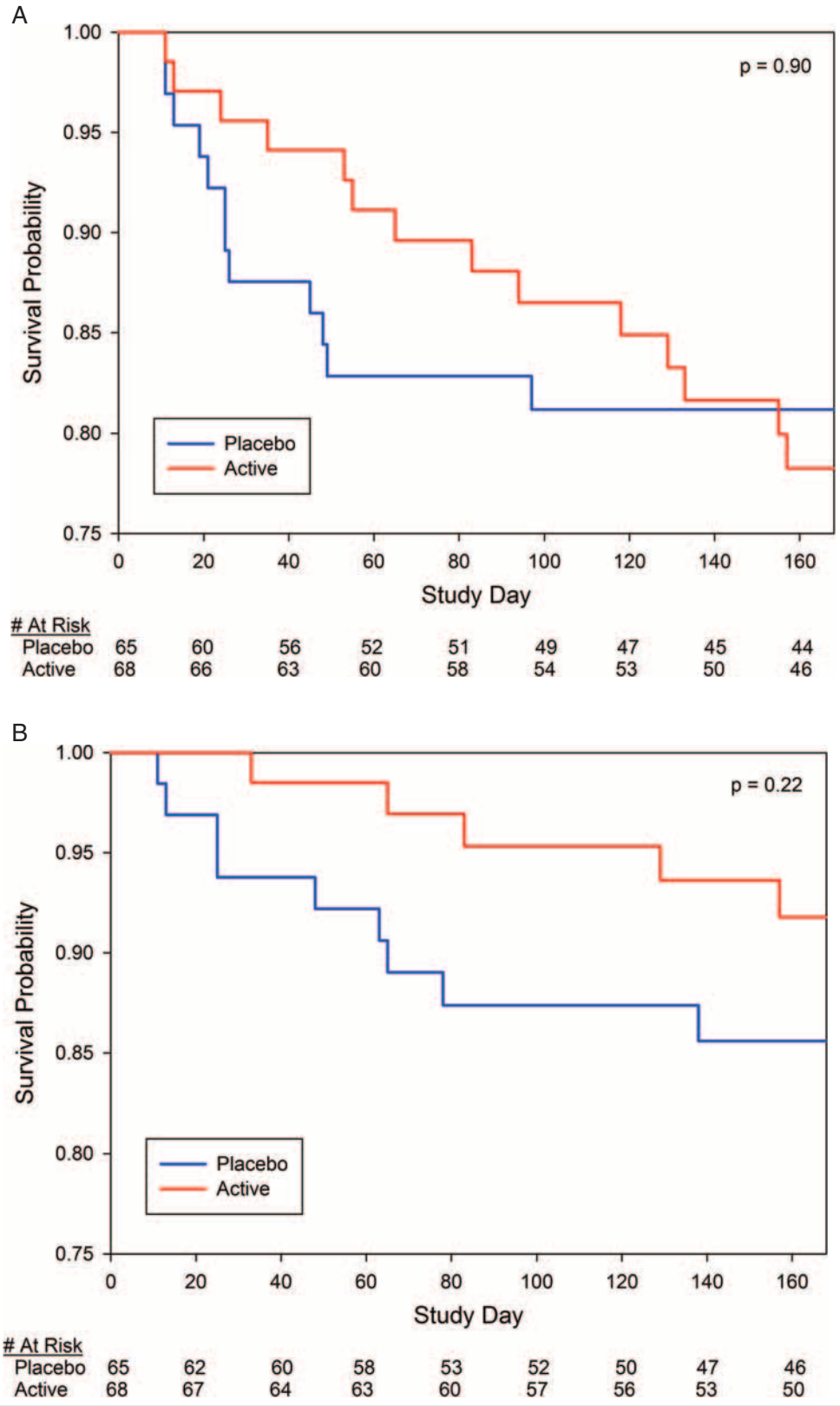

Figure 3 Kaplan–Meier curves for (*A*) all-cause death or heart failure rehospitalization through 24 weeks and (*B*) cardiovascular death trought week 24.

Table 2 Changes in dyspnoea, general well-being, and 6-min walk test distance

Measure	Statistic	Placebo ($n = 65$)	HYIS ($n = 68$)	LS mean difference (95% CI)	*P*-value
Dyspnoea VAS, mm					
Baseline	Mean (SD)	56.2 (18.24)	59.1 (21.58)		
	Median (Q1, Q3)	60.0 (50.0, 68.0)	60.0 (42.0, 73.0)		
Change to Day 7 or discharge	Mean (SD)	12.3 (18.57)	12.7 (19.91)	1.6 (−4.3, 7.5)	0.5842
	Median (Q1, Q3)	8.0 (0.0, 24.0)	7.0 (0.0, 20.5)		
Change to week 8	Mean (SD)	13.2 (25.41)	14.8 (27.29)	3.0 (−5.4, 11.5)	0.4804
	Median (Q1, Q3)	10.0 (0.0, 30.0)	12.5 (0.0, 30.0)		
Change to week 24	Mean (SD)	14.2 (31.79)	10.0 (32.81)	−2.9 (−13.6, 7.8)	0.5932
	Median (Q1, Q3)	20.0 (0.0, 36.0)	10.0 (0.0, 30.0)		
General well-being VAS, mm					
Baseline	Mean (SD)	59.2 (17.72)	60.3 (19.67)		
	Median (Q1, Q3)	60.0 (47.0, 72.0)	60.0 (50.0, 77.5)		
Change to Day 7 or discharge	Mean (SD)	9.0 (14.79)	11.2 (15.78)	2.5 (−2.4, 7.4)	0.3066
	Median (Q1, Q3)	5.0 (0.0, 19.0)	8.0 (0.0, 20.0)		
Change to week 8	Mean (SD)	12.4 (22.96)	14.6 (23.76)	2.9 (−4.1, 9.9)	0.4134
	Median (Q1, Q3)	15.0 (0.0, 24.0)	14.5 (0.0, 30.0)		
Change to week 24	Mean (SD)	12.3 (24.66)	10.6 (29.89)	−0.7 (−9.3, 7.8)	0.8661
	Median (Q1, Q3)	12.0 (0.0, 30.0)	13.0 (0.0, 30.0)		
6-min walk test distance, m					
Baseline	Mean (SD)	253.8 (115.60)	244.3 (123.37)		
	Median (Q1, Q3)	252.0 (170.0, 318.0)	229.0 (150.0, 333.0)		
Change to Day 7 or discharge	Mean (SD)	41.0 (52.93)	35.3 (101.42)	−6.7 (−35.0, 21.7)	0.6412
	Median (Q1, Q3)	28.0 (0.0, 74.0)	17.0 (0.0, 60.0)		
Change to week 8	Mean (SD)	42.3 (104.40)	66.7 (128.48)	23.0 (−18.1, 64.0)	0.2704
	Median (Q1, Q3)	45.0 (0.0, 114.0)	49.0 (8.0, 98.0)		
Change to week 24	Mean (SD)	48.1 (119.76)	65.7 (149.0)	17.2 (−30.5, 65.0)	0.4764
	Median (Q1, Q3)	37.0 (0.0, 129.0)	48.0 (0.0, 145.0)		

CI, confidence interval; HYIS, hydralazine/isosorbide dinitrate; LS, least squares; VAS, visual analogue scale.

Rates of reported serious adverse events were similar in the two treatment groups: 18 (27.7%) placebo and 19 (27.9%) HYIS patients. Adverse events leading to discontinuation of study drug were also similar and were reported for 4 (6.2%) placebo and 6 (8.8%) HYIS patients.

Discussion

The BA-HEF study was initiated on the heels of the THESUS-AF registry where we observed low use of a HYIS combination therapy in patients with HF in Africa.[7] Based on the screening and enrolment rates in the THESUS-AF registry, it was planned to enrol 500 patients during an AHF admission over a period of 12 months and test whether administration of HYIS would reduce the risk of death or HF readmission over 6 months. Regretfully, despite our best efforts, after 4 years we managed to enrol fewer than 150 patients and the study drug had expired and could not be renewed further. Hence, the study was terminated, all patients in the active part of the study crossed to active open-label HYIS, and the database was locked.

The primary endpoint was not met. However, in this limited data set, results for several secondary outcomes were consistent with expected effects of HYIS, including a lower rate of cardiovascular mortality through 24 weeks, a non-statistically significantly lower number of HF and all-cause admissions per patient, and fewer days dead or in hospital in the active arm. Other findings consistent with a benefit include that in the HYIS group compared with the placebo group, by 24 weeks systolic BP dropped more, weight decreased more, 6MWT improved more, and there was a larger drop in BUN. On echocardiographic evaluation, parameters such as improvement in the LVEF, and a decrease in LV end-systolic diameter and LV end-diastolic diameter all favoured the active group, although again in a statistically non-significant manner. The interpretation of these differences should be tempered by the fact that the study is small and recruitment was in a selected group of hospitals, mostly advanced medical centres in each country.

The combination of hydralazine and isosorbide dinitrate has been shown to reduce mortality, as compared with placebo, in patients with mild to moderate HF treated with digoxin and diuretics.[9] In V-HeFT II, enalapril improved survival to a greater extent than hydralazine and isosorbide dinitrate at 2 years, but the difference between the treatment groups was attenuated by the end of follow-up.[10] In A-HeFT, the fixed dose combination of hydralazine and isosorbide dinitrate improved survival, as compared with placebo (6.2% vs. 10.2%, HR 0.57, $P = 0.01$)[11] in African

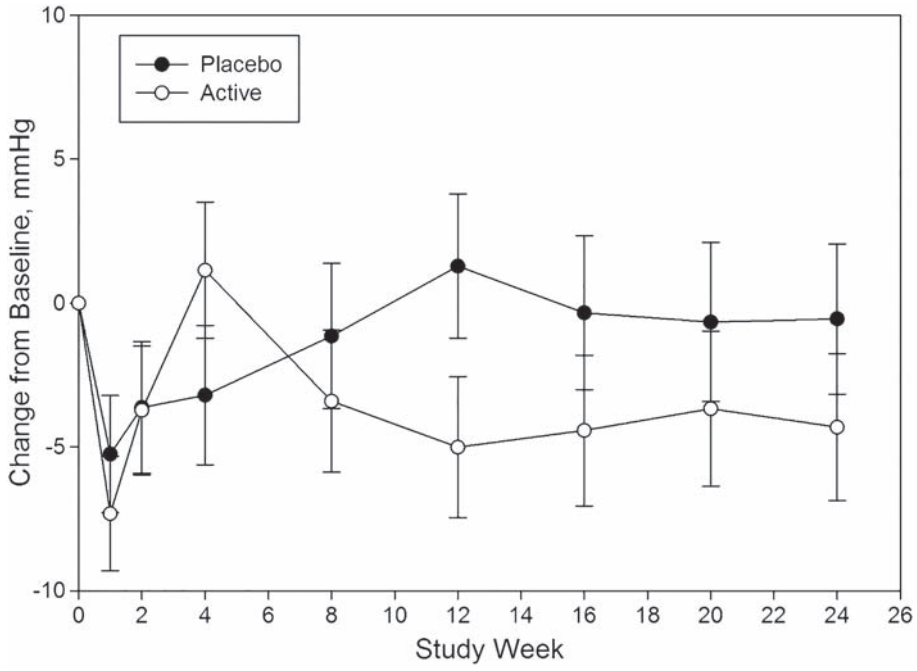

Figure 4 Changes in systolic blood pressure.

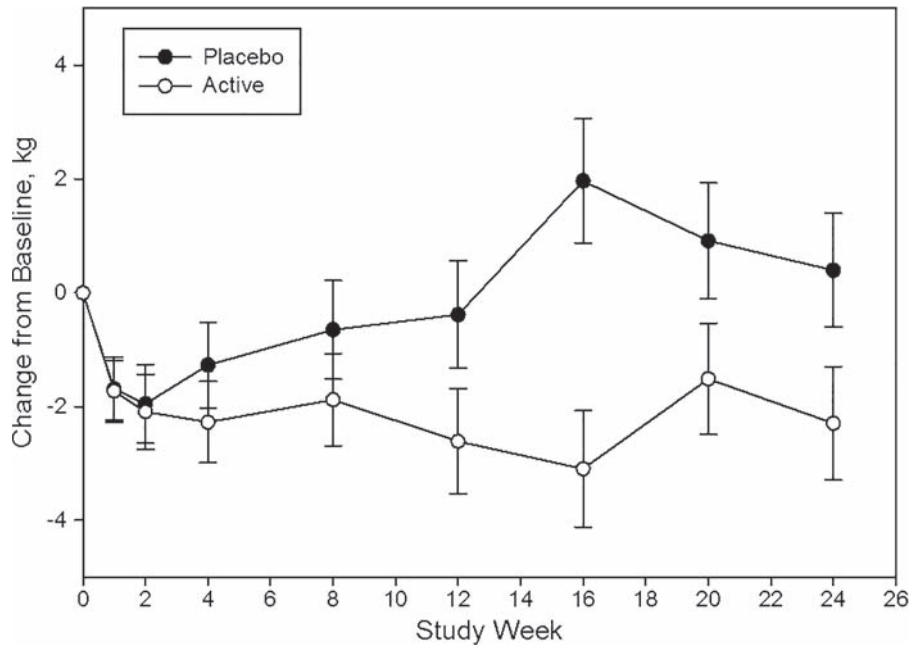

Figure 5 Changes in weight.

American patients. The rate of first HF hospitalization was also reduced in the hydralazine and isosorbide dinitrate group (16.4% vs. 24.4%, $P = 0.001$). Comparing the A-HeFT and BA-HEF studies highlights some important points, although one has to bear in mind that A-HeFT recruited chronic HF patients while BA-HEF recruited patients with AHF. Despite the above, the age of the patients was similar between the two studies (mid-50s). However, patients in A-HeFT were on average ~20 kg heavier than patients in BA-HEF. This may explained by the fact that patients in A-HeFT had a higher prevalence of diabetes mellitus and IHD as compared

Table 3 Changes in renal function markers

Measure	Statistic	Placebo ($n = 65$)	HYIS ($n = 68$)	Treatment effect (95% CI)[a]	*P*-value
Creatinine, μmol/L					
Baseline	Mean (SD)	106.20 (30.38)	120.08 (54.12)		
	Median (Q1, Q3)	104.0 (82.0, 125.0)	105.2 (88.4, 140.0)		
Change to week 24	Mean (SD)	4.50 (26.18)	1.78 (35.44)		
	Geometric mean (95% CI)	1.04 (0.98, 1.09)	1.01 (0.95, 1.09)	1.00 (0.92, 1.09)	0.9893
	Median (Q1, Q3)	0.0 (−8.5, 16.9)	0.0 (−14.6, 22.9)		
BUN, mmol/L					
Baseline	Mean (SD)	7.20 (3.40)	7.52 (4.76)		
	Median (Q1, Q3)	6.70 (4.60, 9.06)	6.53 (4.20, 8.50)		
Change to week 24	Mean (SD)	0.48 (3.71)	0.03 (4.99)		
	Geometric mean (95% CI)	1.06 (0.93, 1.22)	0.93 (0.81, 1.05)	0.87 (0.73, 1.03)	0.1082
	Median (Q1, Q3)	0.00 (−1.60, 2.59)	0.00 (−2.10, 1.20)		
eGFR, mL/min/1.73 m^2					
Baseline	Mean (SD)	79.21 (30.16)	73.41 (30.02)		
	Median (Q1, Q3)	74.56 (61.15, 90.70)	70.61 (51.37, 90.89)		
Change to week 24	Mean (SD)	−3.05 (20.11)	3.23 (41.50)	3.7 (−6.8, 14.3)	0.4865
	Median (Q1, Q3)	0.00 (−14.26, 5.15)	0.0 (−10.54, 16.01)		

BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; HYIS, hydralazine/isosorbide dinitrate.
[a]Treatment effect for creatinine and BUN is presented as the geometric least squares mean ratio. Treatment effect for eGFR is presented as the least squares mean difference.

Table 4 Changes in echocardiographic parameters

Measure	Statistic	Placebo ($n = 65$)	HYIS ($n = 68$)	LS mean difference (95% CI)	*P*-value
Ejection fraction, %					
Baseline	Mean (SD)	23.8 (9.07)	25.3 (11.26)		
	Median (Q1, Q3)	24.0 (18.0, 30.0)	25.0 (15.0, 34.0)		
Change to week 24	Mean (SD)	8.0 (14.18)	8.0 (14.13)	0.3 (−4.6, 5.1)	0.9187
	Median (Q1, Q3)	6.5 (0.0, 19.5)	4.0 (0.0, 19.5)		
Left ventricular size systole, mm					
Baseline	Mean (SD)	55.8 (10.72)	55.8 (10.71)		
	Median (Q1, Q3)	55.0 (50.0, 62.3)	56.0 (46.0, 63.3)		
Change to week 24	Mean (SD)	−2.2 (8.62)	−4.2 (9.58)	−2.0 (−5.2, 1.2)	0.2189
	Median (Q1, Q3)	0.0 (−7.0, 1.0)	−3.5 (−11.0, 0.0)		
Left ventricular size diastole, mm					
Baseline	Mean (SD)	62.7 (11.01)	63.1 (10.36)		
	Median (Q1, Q3)	63.0 (57.0, 71.0)	62.7 (55.1, 69.5)		
Change to week 24	Mean (SD)	2.1 (10.12)	1.0 (10.76)	−1.1 (−4.6, 2.5)	0.5502
	Median (Q1, Q3)	0.0 (−3.0, 5.0)	0.0 (−3.0, 1.0)		

CI, confidence interval; HYIS, hydralazine/isosorbide dinitrate; LS, least squares.

with BA-HEF. On the other hand, patients in BA-HEF had a higher incidence of valvular heart disease possibly due to a higher incidence of rheumatic heart disease. They also received on average less diuretics, beta-blockers, and aldosterone blockers at screening, although this may be in part related to the fact that some had new-onset HF, as reflected by the lower NYHA class at the same time (*Table 1*). Interestingly, in line with the findings from the THESUS registry,[7] patients in both studies were relatively young (mid-50s), had low prevalence of AF and IHD, and almost identical LVEF and LV end-diastolic diameter (*Table 1*).

Despite the encouraging results of A-HeFT, the THESUS-HF data show that patients in Africa are rarely treated with a combination of hydralazine and nitrates, or the fixed-dose combination BiDil that was used in A-HeFT, since this preparation is unavailable in Africa. The efficacy of combination hydralazine and isosorbide dinitrate is uncertain in Africans when given as individual generic agents. Finally, hydralazine and isosorbide dinitrate had not been evaluated in AHF.

There are a number of reasons for the poor recruitment into this study. There were only 21.5% of screened patients who were eligible for entry into the study, which reflects the difficulty in

recruiting patients for AHF trials in general. Screening failures were mostly due to renal and hepatic dysfunction, low BP, and procedural difficulties. Therefore, there was a need to screen 2500 patients to achieve the original sample size of 500 patients, which was not achieved due to the low screening at the enrolling sites and because some of the originally planned sites never screened patients at all.

Although other studies in which more sites were activated[12] have been able to reach their enrolment targets, this double-blind prospective randomized study seems to have been challenging for investigators, as have been other AHF studies of this kind. Many of the centres that participated in the BA-HEF study had limited clinical research facilities such as Good Clinical Practice-trained nurses and monitors, a dedicated research office or research equipment, and clinical staff with dedicated time to perform research. These factors made the recruitment of patients within the specified time interval extremely challenging. Obtaining ethics approval for centres that had limited experience with a placebo-controlled, multicentre randomized trial was a major challenge, causing delays of up to 2 years at some sites. Registries which do not have these short recruitment time intervals, or give study medication, are still possible under these circumstances, but require enthusiasm and large investment of after-hours time, as the recently published REMEDY study on rheumatic heart disease,[13] The Heart of Soweto Study,[14] and THESUS-HF[7] have demonstrated.

The shortage of trained physicians and cardiologists, plus inadequate specialized cardiac facilities and equipment, coupled with low levels of patient and public awareness, led to many patients not having ready access to basic diagnostic facilities such as electrocardiography and echocardiography, causing a delay in recruitment. It is therefore imperative that the research and developmental objectives be specifically focused and tailored towards those disease entities that are highly prevalent on the African continent (e.g. HF) and upon issues and obstacles in regard to documenting their epidemiology, treatment, and prevention.

As stated above, a cautious interpretation of the study results is warranted. However, this is the first study to examine the administration of the HYIS combination in patients with AHF. The limited results of the study suggest that HYIS treatment may be associated with an early decrease in cardiovascular mortality but offset by an increase in non-cardiovascular mortality and HF readmissions. A trend towards an increase in non-cardiovascular mortality while cardiovascular mortality decreases was observed in recent years in HF studies, although not to the point of a lack of decrease in all-cause mortality.[15] Nonetheless, the effects observed raise an important related question of what the effects of HYIS combination would be in all patients with AHF regardless of race and geographical region. As no new effective therapies have been developed in AHF in recent decades, would it be possible that some of the effects observed here may be replicated in larger and more diverse populations?

Limitations

The BA-HEF study enrolled patients in almost the same centres as in the THESUS-HF study and, as such, shares certain limitations with the original cohort. The majority of the patients were recruited in a limited number of hospitals—mainly in Kenya, Mozambique, Nigeria, South Africa, and Uganda. As the study had to be terminated early, it was underpowered. Loss to follow-up and missing laboratory data and assessments of clinical signs were higher than in studies conducted in other regions.

Conclusions

Extensive investment in research facilities in a number of African countries is needed which would allow randomized controlled studies for non-communicable diseases, including AHF studies.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline characteristics of the study population by country.

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Appendix

The Steering Committee included: Professor Sliwa, Professor Damasceno, Professor Mayosi, Dr Ojii, Dr Mondo, Dr Ogah, Dr Sani, Dr Davison, and Dr. Cotter.

The Data Monitoring Committee included: Professor Adrian A. Voors, Professor Justin Ezekowitz, Professor Faiez Zanad, and the DMC statistician Professor Jan Tijssen.

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